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Haematology

Evidence Update

May 2018

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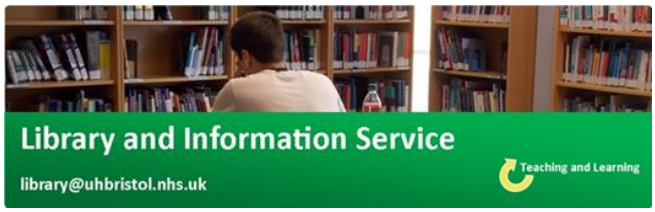

Lunchtime Drop-in Sessions

May (13.00-14.00)

3rd (Thu) Critical Appraisal

11th (Fri) Statistics

14th (Mon) Literature Searching

22nd (Tue) Critical Appraisal

30th (Wed) Statistics

June (12.00-13.00)

7th (Thu) Literature Searching

11th (Mon) Critical Appraisal

20th (Wed) Statistics

28th (Thu) Literature Searching

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Outreach: Your Outreach Librarian can help facilitate evidence-based practice for all in the team, as well as assisting with academic study and research. We also offer one-to-one or small group training in **literature searching, critical appraisal and medical statistics**. Get in touch: library@uhbristol.nhs.uk

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Contents

Current Journals: Tables of Contents

Click on journal title (+ Ctrl) for hyperlink. If you require full articles please email: library@uhbristol.nhs.uk

Journal	Month	Volume	Issue
Blood	May 3, 2018	131	18
Bone Marrow Transplantation	April 2018	53	4
British Journal of Haematology	May 2018	181	3
Experimental Hematology	May 2018	61	-
Haematologica	April 30, 2018	103	5
Journal of Clinical Oncology	May 2018	36	14
Journal of Thrombosis and Haemostatis	May 2018	16	5
Leukaemia Research	May 2018	68	-
New England Journal of Medicine	May 3, 2018	378	18

Latest Evidence

NICE National Institute for Health and Care Excellence

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma - guidance (TA510)

Source: National Institute for Health and Care Excellence - NICE - 14 March 2018

Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma - guidance (TA505)

Source: National Institute for Health and Care Excellence - NICE - 07 February 2018

A randomised phase II trial of selinexor with cyclophosphamide and prednisolone in relapsed or refractory multiplemyeloma (RRMM) patients

Source: UK Clinical Trials Gateway - UKCTG - 21 March 2018

British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding

Source: British Society for Haematology - 12 March 2018 - Publisher: British Society for Haematology

Cochrane Library

Preconception risk assessment for thalassaemia, **sickle cell** disease, cystic fibrosis and Tay-Sachs disease

Norita Hussein , Stephen F Weng , Joe Kai , Jos Kleijnen and Nadeem Qureshi
Online Publication Date: March 2018

Phytomedicines (medicines derived from plants) for **sickle cell** disease

Oluseyi Oniyangi and Damian H Cohall
Online Publication Date: February 2018

Interventions for treating neuropathic pain in people with **sickle cell** disease

Monika R Asnani , Damian K Francis , Amanda M Brandow , Christine EO Hammond Gabbadon and Amza Ali
Online Publication Date: February 2018

UpToDate®

OpenAthens login required. Register here: https://openathens.nice.org.uk/

What's new in hematology

Authors: Rebecca F Connor, MD; Jennifer S Tirnauer, MD; Alan G Rosmarin, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2018. | **This topic last updated:** Apr 17, 2018.

Overview of therapeutic monoclonal antibodies

Author: John P Manis, MD

Section Editor: Daniel E Furst, MD

Deputy Editors: Jennifer S Tirnauer, MD; Anna M Feldweg, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** Mar 26, 2018.

Neurologic complications of cancer treatment with biologic agents

Authors: Eudocia Quant Lee, MD, MPH; Patrick Y Wen, MD

Section Editor: Reed E Drews, MD

Deputy Editor: Diane MF Savarese, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** Aug 03, 2017.

Infusion-related reactions to therapeutic monoclonal antibodies used for cancer therapy

Authors: Ann S LaCasce, MD; Mariana C Castells, MD, PhD; Harold Burstein, MD, PhD; Jeffrey A Meyerhardt, MD, MPH

Section Editors: Reed E Drews, MD; N Franklin Adkinson, Jr, MD

Deputy Editors: Diane MF Savarese, MD; Anna M Feldweg, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Apr 2018. | **This topic last updated:** Mar 30, 2018.

Overview of the treatment of acute lymphoblastic leukemia in children and adolescents

Authors: Terzah M Horton, MD, PhD; C Philip Steuber, MD

Section Editor: Julie R Park, MD

Deputy Editor: Alan G Rosmarin, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2018. | **This topic last updated:** Mar 21, 2018.

Overview of the treatment of chronic lymphocytic leukemia

Authors: Kanti R Rai, MD; Stephan Stilgenbauer, MD

Section Editor:Richard A Larson, MD

Deputy Editor:Rebecca F Connor, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2018. | **This topic last updated:** Apr 09, 2018.

Clinical presentation, pathologic features, diagnosis, and differential diagnosis of chronic lymphocytic leukemia

Authors: Kanti R Rai, MD; Stephan Stilgenbauer, MD

Section Editor: Richard A Larson, MD

Deputy Editor: Rebecca F Connor, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2018. | **This topic last updated:** Feb 01, 2018.

Diagnosis of sickle cell disorders

Authors: Elliott P Vichinsky, MD; Donald H Mahoney, Jr, MD

Section Editor: Stanley L Schrier, MD

Deputy Editor: Jennifer S Tirnauer, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2018. | **This topic last updated:** Feb 26, 2018.

Routine comprehensive care for children with sickle cell disease

Author: Zora R Rogers, MD

Section Editor: Donald H Mahoney, Jr, MD

Deputy Editors: Jennifer S Tirnauer, MD; Carrie Armsby, MD, MPH

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2018. | **This topic last updated:** Feb 05, 2018

Pregnancy in women with sickle cell disease

Author: Elliott P Vichinsky, MD

Section Editors: Stanley L Schrier, MD; Lynn L Simpson, MD

Deputy Editors: Jennifer S Tirnauer, MD; Vanessa A Barss, MD, FACOG

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2018. | **This topic last updated:** Apr 03, 2018.

Overview of non-Hodgkin lymphoma in children and adolescents

Authors: Amanda M Termuhlen, MD; Thomas G Gross, MD, PhD

Section Editor: Julie R Park, MD

Deputy Editor: Alan G Rosmarin, MD

Contributor Disclosures

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2018. | **This topic last updated:** Mar 02, 2018.

New England Journal of Medicine

Gene Therapy in Patients with Transfusion-Dependent β-Thalassemia

Alexis A. Thompson, M.D., M.P.H., Mark C. Walters, M.D., Janet Kwiatkowski, M.D.,
April 19, 2018
N Engl J Med 2018; 378:1479-1493
DOI: 10.1056/NEJMoa1705342

Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma.

Roland Schmitz, Ph.D., George W. Wright, Ph.D., Da Wei Huang, M.D. et al.
April 12, 2018
N Engl J Med 2018; 378:1396-1407
DOI: 10.1056/NEJMoa1801445

Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

John F. Seymour, M.B., B.S., Ph.D., Thomas J. Kipps, M.D., Barbara Eichhorst, M.D. et al
March 22, 2018
N Engl J Med 2018; 378:1107-1120
DOI: 10.1056/NEJMoa1713976

Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma

María-Victoria Mateos, M.D., Meletios A. Dimopoulos, M.D., Michele Cavo, M.D. et al
February 8, 2018
N Engl J Med 2018; 378:518-528
DOI: 10.1056/NEJMoa1714678

Library Clinic

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March 7th: **Canteen (Level 9, BRI)** *12.00-14.00*

March 19th: **Welcome Centre, BRI** *10.00-16.00*

April 4th: **Foyer, Education Centre** *12.00-14.00*

April 11th: **Foyer, St Michael's Hospital** *12.00-14.00*

May 2nd: **Canteen (Level 9, BRI)** *12.00-14.00*

June 6th: **Terrace (Level 4, Education Centre)** *12.00-14.00*

June 19th: **Welcome Centre, BRI** *10.00-16.00*

July 3rd: **Welcome Centre, BRI** *10.00-16.00*

July 4th: **Canteen (Level 9, BRI)** *12.00-14.00*

August 8th: **Foyer, Education Centre** *12.00-14.00*

August 29th: **Foyer, St Michael's Hospital** *12.00-14.00*

September 5th: **Canteen (Level 9, BRI)** *12.00-14.00*

September 11th: **Welcome Centre, BRI** *10.00-16.00*

October 3rd: **Terrace (Level 4, Education Centre)** *12.00-14.00*

November 7th: **Canteen (Level 9, BRI)** *12.00-14.00*

December 5th: **Foyer, Education Centre** *12.00-14.00*

December 11th: **Welcome Centre, BRI** *10.00-16.00*

Recent Database Articles

Below is a selection of articles recently added to the healthcare databases on multiple myeloma, focusing this month on monoclonal antibody therapies in multiple myeloma. If you would like any of the articles in full text, or if you would like a more focused search on your own topic, please contact us: library@bristol.nhs.uk

Monoclonal antibody therapies in multiple myeloma

1. Elotuzumab for the Treatment of Relapsed or Refractory Multiple Myeloma, with Special Reference to its Modes of Action and SLAMF7 Signaling.

Author(s): Taniwaki, Masafumi; Yoshida, Mihoko; Matsumoto, Yosuke; Shimura, Kazuho; Kuroda, Junya; Kaneko, Hiroto

Source: Mediterranean journal of hematology and infectious diseases; 2018; vol. 10 (no. 1); p. e2018014

Publication Type(s): Journal Article Review

PubMedID: 29531651

Available at Mediterranean journal of hematology and infectious diseases - from Europe PubMed Central - Open Access

Available at Mediterranean journal of hematology and infectious diseases - from mjhid.org

Abstract: Elotuzumab, targeting signaling lymphocytic activation molecule family 7 (SLAMF7), has been approved in combination with lenalidomide and dexamethasone (ELd) for relapsed/refractory multiple myeloma (MM) based on the findings of the phase III randomized trial ELOQUENT-2 (NCT01239797). Four-year follow-up analyses of ELOQUENT-2 have demonstrated that progression-free survival was 21% in ELd versus 14% in Ld. Elotuzumab binds a unique epitope on the membrane IgC2 domain of SLAMF7, exhibiting a dual mechanism of action: natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) and enhancement of NK cell activity. The ADCC is mediated through engagement between Fc portion of elotuzumab and FcgRIIIa/CD16 on NK cells. Enhanced NK cell cytotoxicity results from phosphorylation of the immunoreceptor tyrosine-based switch motif (ITSM) that is induced via elotuzumab binding and recruits the SLAM-associated adaptor protein EAT-2. The coupling of EAT-2 to the phospholipase Cg enzymes SH2 domain leads to enhanced Ca2+ influx and MAPK/Erk pathway activation, resulting in granule polarization and enhanced exocytosis in NK cells. Elotuzumab does not stimulate the proliferation of MM cells due to a lack of EAT-2. The inhibitory effects of elotuzumab on MM cell growth are not induced by the lack of CD45, even though SHP-2, SHP-1, SHIP-1, and Csk may be recruited to phosphorylated ITSM of SLAMF7. ELd improves PFS in patients with high-risk cytogenetics, i.e. t(4;14), del(17p), and 1q21 gain/amplification. Since the immune state is paralytic in advanced MM, the efficacy of ELd with minimal toxicity may bring forward for consideration of its use in the early stages of the disease.

Database: Medline

2. Daratumumab resistance is frequent in advanced-stage multiple myeloma patients irrespective of CD38 expression and is related to dismal prognosis.

Author(s): Pick, Marjorie; Vainstein, Vladimir; Goldschmidt, Neta; Lavie, David; Libster, Diana; Gural, Alexander; Grisariu, Sigal; Avni, Batia; Ben Yehuda, Dina; Gatt, Moshe E

Source: European journal of haematology; May 2018; vol. 100 (no. 5); p. 494-501

Publication Type(s): Journal Article

PubMedID: 29453884

Abstract:OBJECTIVEDaratumumab is a promising new antimyeloma agent. We report a single center "real-world" series of multiple myeloma (MM) and amyloidosis (AL) patients treated with daratumumab.METHODSForty-one patients were included: 7 second-line MM, 30 heavily pretreated (median number of therapies of 5) advanced MM, and 4 with AL.RESULTSSecond-line patients and advanced AL showed high rate of durable overall responses. However, advanced MM patients had a dismal prognosis with an overall response rate (ORR) of 36%, and a short median progression-free and overall survival of 2.3 and 6.6 months, respectively. Responses were particularly poor in patients with extramedullary plasmacytomas. Neither the addition of another agent to daratumumab nor changing to the next line of therapy produced significant durable responses in this patient population. Flow cytometry analysis demonstrated that CD38 expression level was not predictive of response. We show that CD38 expression dynamics by a commercially available anti-CD38 antibody after daratumumab administration was hindered by competitive binding of daratumumab.CONCLUSIONSResponses to daratumumab and combinations in patients with advanced MM, particularly with extramedullary disease, are low and short-lived, stressing the administration of this agent should be early in the course of the disease.

Database: Medline

3. Adjusted comparison of daratumumab monotherapy versus real-world historical control data from the Czech Republic in heavily pretreated and highly refractory multiple myeloma patients.

Author(s): Jelínek, Tomáš; Maisnar, Vladimír; Pour, Luděk; Špička, Ivan; Minařík, Jiří; Gregora, Evžen; Kessler, Petr; Sýkora, Michal; Fraňková, Hana; Adamová, Dagmar; Wróbel, Marek; Mikula, Peter; Jarkovský, Jiří; Diels, Joris; Gatopoulou, Xenia; Veselá, Šárka; Besson, Hervé; Brožová, Lucie; Ito, Tetsuro; Hájek, Roman

Source: Current medical research and opinion; May 2018; vol. 34 (no. 5); p. 775-783

Publication Type(s): Journal Article

PubMedID: 29172760

Abstract:OBJECTIVESWe conducted an adjusted comparison of progression-free survival (PFS) and overall survival (OS) for daratumumab monotherapy versus standard of care, as observed in a real-world historical cohort of heavily pretreated multiple myeloma patients from Czech Republic.METHODSUsing longitudinal chart data from the Registry of Monoclonal Gammopathies (RMG) of the Czech Myeloma Group, patient-level data from the RMG was pooled with pivotal daratumumab monotherapy studies (GEN501 and SIRIUS; 16 mg/kg).RESULTSFrom the RMG database, we identified 972 treatment lines in 463 patients previously treated with both a proteasome inhibitor and an immunomodulatory drug. Treatment initiation dates for RMG patients were between March 2006 and March 2015. The most frequently used treatment regimens were lenalidomide-based regimens (33.4%), chemotherapy (18.1%), bortezomib-based regimens (13.6%), thalidomide-based regimens (8.0%), and bortezomib plus thalidomide (5.3%). Few patients were treated with carfilzomib-based regimens (2.5%) and pomalidomide-based regimens (2.4%). Median observed PFS for daratumumab and the RMG cohort was 4.0 and 5.8 months (unadjusted hazard

ratio [HR], 1.14; 95% confidence interval [CI], 0.94-1.39), respectively, and unadjusted median OS was 20.1 and 11.9 months (unadjusted HR, 0.61; 95% CI, 0.48-0.78), respectively. Statistical adjustments for differences in baseline characteristics were made using patient-level data. The adjusted HRs (95% CI) for PFS and OS for daratumumab versus the RMG cohort were 0.79 (0.56-1.12; p = .192) and 0.33 (0.21-0.52; p < .001), respectively.CONCLUSIONSAdjusted comparisons between trial data and historical cohorts can provide useful insights to clinicians and reimbursement decision makers on relative treatment efficacies in the absence of head-to-head comparison studies for daratumumab monotherapy.

Database: Medline

4. Current use of monoclonal antibodies in the treatment of multiple myeloma.

Author(s): Varga, Cindy; Maglio, Michelle; Ghobrial, Irene M; Richardson, Paul G

Source: British journal of haematology; Apr 2018

Publication Type(s): Journal Article Review

PubMedID: 29696629

Abstract: Multiple myeloma (MM) is the second most common haematological malignancy after non-Hodgkin lymphoma. Despite the improvement in outcomes over the last decade with the introduction of novel therapies, such as immunomodulatory agents (IMiDs) and proteasome inhibitors (PIs), MM remains an incurable disease. Patients who are both refractory to IMiDs and PIs carry a particularly dismal prognosis. The development of targeted therapy in the form of monoclonal antibodies has shifted the treatment paradigm of this disease, resulting in unprecedented response rates, even among the highest-risk patients. In this review, we will summarize the mechanism of action and provide an overview of the clinical trials that have led to the US Food and Drug Administration approval of Daratumumab and Elotuzumab, and their current use in the treatment of MM.

Database: Medline

5. Antibody dependent cellular phagocytosis by macrophages is a novel mechanism of action of elotuzumab.

Author(s): Kurdi, Ahmed T; Glavey, Siobhan V; Bezman, Natalie A; Jhatakia, Amy; Guerriero, Jennifer L; Manier, Salomon; Moschetta, Michele; Mishima, Yuji; Roccaro, Aldo; Detappe, Alexandre; Liu, Chia-Jen; Sacco, Antonio; Huynh, Daisy; Tai, Yu-Tzu; Robbins, Michael D; Azzi, Jamil; Ghobrial, Irene M

Source: Molecular cancer therapeutics; Apr 2018

Publication Type(s): Journal Article

PubMedID: 29654064

Abstract: Elotuzumab, a recently approved antibody for the treatment of multiple myeloma (MM), has been shown to stimulate Fcγ receptor (FcγR)-mediated antibody-dependent cellular cytotoxicity (ADCC) by natural killer (NK) cells towards myeloma cells. The modulatory effects of elotuzumab on other effector cells in the tumor microenvironment, however, has not been fully explored. Antibody dependent cellular phagocytosis (ADCP) is a mechanism by which macrophages contribute to anti-tumor potency of monoclonal antibodies. Herein, we studied the NK cell independent effect of elotuzumab on tumor associated macrophages (TAMs) using a xenograft tumor model deficient in NK and adaptive immune cells. We demonstrate significant anti-tumor efficacy of single agent

elotuzumab in immunocompromised xenograft models of multiple myeloma, which is in part mediated by Fc-FcγR interaction of elotuzumab with macrophages. Elotuzumab is shown in this study to induce phenotypic activation of macrophages in-vivo and mediates ADCP of myeloma cells though a FcγR dependent manner in-vitro. Together, these findings propose a novel immune mediated mechanism by which elotuzumab exerts anti-myeloma activity and helps to provide rationale for combination therapies that can enhance macrophage activity.

Database: Medline

6. Common Adverse Effects of Novel Therapies for Multiple Myeloma (MM) and Their Management Strategies.

Author(s): McCullough, Kristen B; Hobbs, Miriam A; Abeykoon, Jithma P; Kapoor, Prashant

Source: Current hematologic malignancy reports; Apr 2018; vol. 13 (no. 2); p. 114-124

Publication Type(s): Journal Article Review

PubMedID: 29450683

Abstract:PURPOSE OF REVIEWThe purpose of this review was to evaluate management strategies for common adverse effects of novel therapies in multiple myeloma (MM), including immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies, and a histone deacetylase inhibitor.RECENT FINDINGSThere are several adverse effects that occur across multiple classes of antimyeloma drugs, including rash, peripheral neuropathy, infusion reactions, and cardiotoxicity, but most can be managed without complete discontinuation of the agent or abandonment of the class. Additionally, several agents have critically important drug-drug interactions or dose-modification implications in hepatic or renal insufficiency that can be easily overlooked, and exacerbate adverse effects. As treatment of MM moves from fixed-duration traditional chemotherapy to novel agent-based regimens, commonly administered continuously until disease progression or intolerable toxicities, providers must adopt their management strategies for both acute and long-term adverse effects. Early and frequent monitoring for therapy-related complications, dose adjustments when needed, and timely treatment for toxicities are all important steps toward ensuring longevity of treatment from a limited array of therapeutic options that currently exist for a disease with a relapsing and remitting course.

Database: Medline

7. Influence of Disease and Patient Characteristics on Daratumumab Exposure and Clinical Outcomes in Relapsed or Refractory Multiple Myeloma.

Author(s): Yan, Xiaoyu; Clemens, Pamela L; Puchalski, Thomas; Lonial, Sagar; Lokhorst, Henk; Voorhees, Peter M; Usmani, Saad; Richardson, Paul G; Plesner, Torben; Liu, Kevin; Orlowski, Robert Z; Losic, Nedjad; Jansson, Richard; Ahmadi, Tahamtan; Lantz, Kristen; Ruixo, Juan Jose Perez; Zhou, Honghui; Xu, Xu Steven

Source: Clinical pharmacokinetics; Apr 2018; vol. 57 (no. 4); p. 529-538

Publication Type(s): Journal Article

PubMedID: 28983805

Available at Clinical Pharmacokinetics - from PubMed Central

Abstract:OBJECTIVEThe aim of this study was to understand the influence of disease and patient characteristics on exposure to daratumumab, an immunoglobulin Gκ (IgGκ) monoclonal antibody, and clinical outcomes in relapsed or refractory multiple myeloma (MM).PATIENTS AND

METHODSBaseline myeloma type, albumin levels, renal/hepatic function, age, sex, race, weight, Eastern Cooperative Oncology Group (ECOG) status, refractory status, and number of prior therapies were evaluated using data from two clinical studies-GEN501 (N = 104) and SIRIUS (N = 124).RESULTSDaratumumab clearance was approximately 110% higher in IgG myeloma patients than non-IgG myeloma patients, leading to significantly lower exposure in IgG myeloma patients based on maximum trough serum concentrations ($p < 0.0001$). However, the overall response rate was similar for IgG and non-IgG myeloma patients (odds ratio 1.08, 95% confidence interval 0.54-2.17, $p = 0.82$). For a given exposure, the drug effect was significantly higher (approximately two times) in IgG versus non-IgG patients ($p = 0.03$). The influence of other patient and disease characteristics on daratumumab exposure was minimal and no significant effect on efficacy was observed ($p \geq 0.1$). The incidences of infections and overall grade 3 or higher adverse events in subpopulations were generally consistent with that of the overall population.CONCLUSIONDue to competition with the MM-produced IgG M-protein for neonatal Fc receptor protection from clearance, IgG-based monoclonal antibodies in general may have significantly higher clearance and lower concentrations in IgG MM patients compared with non-IgG MM patients. Careful evaluation of the impact of exposure and patient and disease characteristics on safety and efficacy is warranted for all IgG-based monoclonal antibodies used in MM.

Database: Medline

8. Fratricide of NK Cells in Daratumumab Therapy for Multiple Myeloma Overcome by Ex Vivo Expanded Autologous NK Cells.

Author(s): Wang, Yufeng; Zhang, Yibo; Hughes, Tiffany; Zhang, Jianying; Caligiuri, Michael A; Benson, Don M; Yu, Jianhua

Source: Clinical cancer research : an official journal of the American Association for Cancer Research; Apr 2018

Publication Type(s): Journal Article

PubMedID: 29666301

Abstract:PURPOSEDaratumumab and its use in combination with other agents is becoming a new standard of care for treatment of multiple myeloma (MM). We mechanistically studied how daratumumab acts on NK cells.EXPERIMENTAL DESIGNQuantities of NK cells in peripheral blood (PB) and/or bone marrow (BM) of MM patients or healthy donors were examined by flow cytometry. NK cell apoptosis and the associated mechanism were assessed by flow cytometry and immunoblotting. Patients' NK cells were expanded in vitro using feeder cells. Combination treatment of daratumumab and expanded NK cells was performed using an MM.1S xenograft animal model. Results: CD38-/low NK cells survived, while CD38+ NK cells were almost completely eliminated, in PB and BM of daratumumab-treated MM patients. NK cell depletion occurred due to daratumumab-induced NK cell fratricide via antibody-dependent cellular cytotoxicity (ADCC). Consequently, CD38-/low NK cells were more effective for eradicating MM cells than were CD38+ NK cells in the presence of daratumumab. Blockade of CD38 with the F(ab)2 fragments of daratumumab inhibited the antibody-mediated NK cell fratricide. CD38-/low NK cells displayed a significantly better potential for expansion than CD38+ NK cells, and the expanded NK cells derived from the former population were more cytotoxic than those derived from the latter against MM cells. Therefore, infusion of ex vivo-expanded autologous NK cells from daratumumab-treated patients may improve the antibody therapy.CONCLUSIONSWe unravel a fratricide mechanism for daratumumab-mediated NK cell depletion and provide a potential therapeutic strategy to overcome this side effect in daratumumab-treated MM patients.

Database: Medline

9. Elotuzumab and dexamethasone for relapsed or refractory multiple myeloma patients: A retrospective study.

Author(s): Gross, Zachary; Rahbari, Ashkon; Wirtschafter, Eric; Spektor, Tanya M; Udd, Kyle A; Bujarski, Sean; Ghermezi, Michael; Nosrati, Jason D; Vidisheva, Aleksandra; Eades, Benjamin; Cecchi, Gary; Maluso, Tina; Swift, Regina; Berenson, James R

Source: European journal of haematology; Mar 2018

Publication Type(s): Case Reports

PubMedID: 29524348

Abstract:OBJECTIVETo evaluate the efficacy and safety of elotuzumab and dexamethasone (Ed) for relapsed or refractory multiple myeloma (RRMM) patients.METHODThis retrospective study evaluated the efficacy and safety of Ed treatment for 21 RRMM patients, 11 of whom were considered lenalidomide-refractory, and all of whom had progressed on at least 1 prior steroid-containing regimen. We also evaluated the efficacy of adding lenalidomide to a subset of patients following progression from Ed.RESULTSThe overall response rate (ORR) and clinical benefit rate (CBR) of Ed were 10% and 19%, respectively. An additional 52% of patients demonstrated stable disease as their best response. The median PFS was 1.8 months on Ed for all patients. Fifteen patients received ERd following progression on Ed, and 60% of these patients were lenalidomide-refractory. The ORR and CBR were 20% and 33%, respectively, and the median PFS was 3.4 months.CONCLUSIONOur results suggest that some patients can benefit from Ed without an accompanying immunomodulatory agent and that efficacy can be achieved with the addition of lenalidomide at the time of progression. No new safety signals were detected, except for thrombocytopenia in 1 patient on Ed.

Database: Medline

10. Development of a Targeted Mass-Spectrometry Serum Assay To Quantify M-Protein in the Presence of Therapeutic Monoclonal Antibodies.

Author(s): Zajec, Marina; Jacobs, Joannes F M; Groenen, Patricia J T A; de Kat Angelino, Corrie M; Stingl, Christoph; Luider, Theo M; De Rijke, Yolanda B; VanDuijn, Martijn M

Source: Journal of proteome research; Mar 2018; vol. 17 (no. 3); p. 1326-1333

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article

PubMedID: 29424538

Abstract:M-protein diagnostics can be compromised for patients receiving therapeutic monoclonal antibodies as treatment in multiple myeloma. Conventional techniques are often not able to distinguish between M-proteins and therapeutic monoclonal antibodies administered to the patient. This may prevent correct response assessment and can lead to overtreatment. We have developed a serum-based targeted mass-spectrometry assay to detect M-proteins, even in the presence of three therapeutic monoclonal antibodies (daratumumab, ipilimumab, and nivolumab). This assay can target proteotypic M-protein peptides as well as unique peptides derived from therapeutic monoclonal antibodies. We address the sensitivity in M-protein diagnostics and show that our mass-spectrometry assay is more than two orders of magnitude more sensitive than conventional M-protein diagnostics. The use of stable isotope-labeled peptides allows absolute quantification of the M-protein and increases the potential of assay standardization across multiple laboratories. Finally, we discuss the position of mass-spectrometry assays in monitoring minimal residual disease in multiple myeloma, which is currently dominated by molecular techniques based on plasma cell assessment that requires invasive bone marrow aspirations or biopsies.

Database: Medline

11. Comparative Efficacy of Daratumumab Monotherapy and Pomalidomide Plus Low-Dose Dexamethasone in the Treatment of Multiple Myeloma: A Matching Adjusted Indirect Comparison.

Author(s): Van Sanden, Suzy; Ito, Tetsuro; Diels, Joris; Vogel, Martin; Belch, Andrew; Oriol, Albert

Source: The oncologist; Mar 2018; vol. 23 (no. 3); p. 279-287

Publication Type(s): Journal Article

PubMedID: 29192016

Available at The Oncologist - from EBSCO (MEDLINE Complete)

Abstract:BACKGROUNDDaratumumab (a human CD38-directed monoclonal antibody) and pomalidomide (an immunomodulatory drug) plus dexamethasone are both relatively new treatment options for patients with heavily pretreated multiple myeloma. A matching adjusted indirect comparison (MAIC) was used to compare absolute treatment effects of daratumumab versus pomalidomide + low-dose dexamethasone (LoDex; 40 mg) on overall survival (OS), while adjusting for differences between the trial populations.MATERIALS AND METHODSThe MAIC method reduces the risk of bias associated with naïve indirect comparisons. Data from 148 patients receiving daratumumab (16 mg/kg), pooled from the GEN501 and SIRIUS studies, were compared separately with data from patients receiving pomalidomide + LoDex in the MM-003 and STRATUS studies.RESULTSThe MAIC-adjusted hazard ratio (HR) for OS of daratumumab versus pomalidomide + LoDex was 0.56 (95% confidence interval [CI], 0.38-0.83; p = .0041) for MM-003 and 0.51 (95% CI, 0.37-0.69; p < .0001) for STRATUS. The treatment benefit was even more pronounced when the daratumumab population was restricted to pomalidomide-naïve patients (MM-003: HR, 0.33; 95% CI, 0.17-0.66; p = .0017; STRATUS: HR, 0.41; 95% CI, 0.21-0.79; p = .0082). An additional analysis indicated a consistent trend of the OS benefit across subgroups based on M-protein level reduction (≥50%, ≥25%, and <25%).CONCLUSIONThe MAIC results suggest that daratumumab improves OS compared with pomalidomide + LoDex in patients with heavily pretreated multiple myeloma.IMPLICATIONS FOR PRACTICEThis matching adjusted indirect comparison of clinical trial data from four studies analyzes the survival outcomes of patients with heavily pretreated, relapsed/refractory multiple myeloma who received either daratumumab monotherapy or pomalidomide plus low-dose dexamethasone. Using this method, daratumumab conferred a significant overall survival benefit compared with pomalidomide plus low-dose dexamethasone. In the absence of head-to-head trials, these indirect comparisons provide useful insights to clinicians and reimbursement authorities around the relative efficacy of treatments.

Database: Medline

12. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study.

Author(s): Raje, Noopur; Terpos, Evangelos; Willenbacher, Wolfgang; Shimizu, Kazuyuki; García-Sanz, Ramón; Durie, Brian; Legieć, Wojciech; Krejčí, Marta; Laribi, Kamel; Zhu, Li; Cheng, Paul; Warner, Douglas; Roodman, G David

Source: The Lancet. Oncology; Mar 2018; vol. 19 (no. 3); p. 370-381

Publication Type(s): Journal Article

PubMedID: 29429912

Available at The Lancet. Oncology - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract:BACKGROUNDMultiple myeloma is characterised by monoclonal paraprotein production and osteolytic lesions, commonly leading to skeletal-related events (spinal cord compression, pathological fracture, or surgery or radiotherapy to affected bone). Denosumab, a monoclonal antibody targeting RANKL, reduces skeletal-related events associated with bone lesions or metastases in patients with advanced solid tumours. This study aimed to assess the efficacy and safety of denosumab compared with zoledronic acid for the prevention of skeletal-related events in patients with newly diagnosed multiple myeloma.METHODSIn this international, double-blind, double-dummy, randomised, active-controlled, phase 3 study, patients in 259 centres and 29 countries aged 18 years or older with symptomatic newly diagnosed multiple myeloma who had at least one documented lytic bone lesion were randomly assigned (1:1; centrally, by interactive voice response system using a fixed stratified permuted block randomisation list with a block size of four) to subcutaneous denosumab 120 mg plus intravenous placebo every 4 weeks or intravenous zoledronic acid 4 mg plus subcutaneous placebo every 4 weeks (both groups also received investigators' choice of first-line antimyeloma therapy). Stratification was by intent to undergo autologous transplantation, antimyeloma therapy, International Staging System stage, previous skeletal-related events, and region. The clinical study team and patients were masked to treatment assignments. The primary endpoint was non-inferiority of denosumab to zoledronic acid with respect to time to first skeletal-related event in the full analysis set (all randomly assigned patients). All safety endpoints were analysed in the safety analysis set, which includes all randomly assigned patients who received at least one dose of active study drug. This study is registered with ClinicalTrials.gov, number NCT01345019.FINDINGSFrom May 17, 2012, to March 29, 2016, we enrolled 1718 patients and randomly assigned 859 to each treatment group. The study met the primary endpoint; denosumab was non-inferior to zoledronic acid for time to first skeletal-related event (hazard ratio 0·98, 95% CI 0·85-1·14; pnon-inferiority=0·010). 1702 patients received at least one dose of the investigational drug and were included in the safety analysis (850 patients receiving denosumab and 852 receiving zoledronic acid). The most common grade 3 or worse treatment-emergent adverse events for denosumab and zoledronic acid were neutropenia (126 [15%] vs 125 [15%]), thrombocytopenia (120 [14%] vs 103 [12%]), anaemia (100 [12%] vs 85 [10%]), febrile neutropenia (96 [11%] vs 87 [10%]), and pneumonia (65 [8%] vs 70 [8%]). Renal toxicity was reported in 85 (10%) patients in the denosumab group versus 146 (17%) in the zoledronic acid group; hypocalcaemia adverse events were reported in 144 (17%) versus 106 (12%). Incidence of osteonecrosis of the jaw was not significantly different between the denosumab and zoledronic acid groups (35 [4%] vs 24 [3%]; p=0·147). The most common serious adverse event for both treatment groups was pneumonia (71 [8%] vs 69 [8%]). One patient in the zoledronic acid group died of cardiac arrest that was deemed treatment-related.INTERPRETATIONIn patients with newly diagnosed multiple myeloma, denosumab was non-inferior to zoledronic acid for time to skeletal-related events. The results from this study suggest denosumab could be an additional option for the standard of care for patients with multiple myeloma with bone disease.FUNDINGAmgen.

Database: Medline

13. CD38-targeting antibodies in multiple myeloma: mechanisms of action and clinical experience.

Author(s): Frerichs, Kristine A; Nagy, Noemi Anna; Lindenbergh, Pieter L; Bosman, Patty; Marin Soto, Jhon; Broekmans, Marloes; Groen, Richard W J; Themeli, Maria; Nieuwenhuis, Louise; Stege, Claudia; Nijhof, Inger S; Mutis, Tuna; Zweegman, Sonja; Lokhorst, Henk M; van de Donk, Niels W C J

Source: Expert review of clinical immunology; Mar 2018; vol. 14 (no. 3); p. 197-206

Publication Type(s): Journal Article

PubMedID: 29465271

Abstract:INTRODUCTIONMultiple myeloma (MM) is generally an incurable hematological malignancy with heterogeneous overall survival rates ranging from a few months to more than 10 years. Survival is especially poor for patients who developed disease that is refractory to immunomodulatory drugs and proteasome inhibitors. Areas covered: This review will discuss the importance of CD38-targeting antibodies for the treatment of MM patients to improve their outcome. Expert commentary: Intense immuno-oncological laboratory research has resulted in the development of functionally active monoclonal antibodies against cell surface markers present on MM cells. In this respect, CD38-targeting antibodies such as daratumumab, MOR202, and isatuximab, have high single agent activity in heavily pretreated MM patients by virtue of their pleiotropic mechanisms of action including Fc-dependent effector mechanisms and immunomodulatory activities. Importantly, CD38-targeting antibodies are well tolerated, with infusion reactions as most frequent adverse event. Altogether, this makes them attractive combination partners with other anti-MM agents. Daratumumab is already approved as monotherapy and in combination with lenalidomide-dexamethasone as well as bortezomib-dexamethasone in pretreated MM patients. Furthermore, results from studies evaluating CD38-targeting antibodies in newly diagnosed MM patients are also promising, indicating that CD38-targeting antibodies will be broadly used in MM, resulting in further improvements in survival.

Database: Medline

14. Comparative Efficacy of Treatments for Previously Treated Multiple Myeloma: A Systematic Literature Review and Network Meta-analysis.

Author(s): Maiese, Eric M; Ainsworth, Claire; Le Moine, Jean-Gabriel; Ahdesmäki, Outi; Bell, Judith; Hawe, Emma

Source: Clinical therapeutics; Mar 2018; vol. 40 (no. 3); p. 480

Publication Type(s): Journal Article Review

PubMedID: 29500140

Abstract:PURPOSENew therapies, including daratumumab plus lenalidomide plus dexamethasone (DRd) and daratumumab plus bortezomib plus dexamethasone (DVd), have recently been approved in the United States for patients with multiple myeloma (MM) who have received at least 1 prior line of therapy. However, few treatments have been compared in head-to-head clinical trials to determine the most efficacious therapy. In an update of the POLLUX (Phase 3 Study Comparing DRd Versus Rd in Subjects with Relapsed or Refractory Multiple Myeloma [RRMM]) trial, median progression-free survival (PFS) for DRd was not reached; the hazard ratio compared with Rd was 0.41. In an update of the CASTOR (Phase 3 Study Comparing DVd Versus Vd in Subjects with RRMM) trial, median PFS for DVd was 16.7 months, compared with 7.1 months for Vd with a PFS hazard ratio of 0.31. A systematic literature review and network meta-analysis (NMA) was performed to estimate the relative efficacy of treatments for previously treated patients with MM.METHODSA systematic search of MEDLINE, EMBASE, BioSciences Information Service, and the Cochrane Library databases was conducted from initiation to September 2016. Abstracts published by international congresses (2014-2016) and bibliographies of pertinent systematic reviews and meta-analyses were also searched. Eligible studies consisted of randomized controlled trials (RCTs) or long-term follow-up studies with >1 treatment arm assessing the efficacy or safety of MM therapies. An NMA was conducted by using Bayesian fixed effect mixed-treatment comparisons. Outcomes considered were hazard ratios for PFS and odds ratios for overall response rate (ORR).FINDINGSIn total, 108 articles reporting 27 RCTs were included in the NMA. Data formed 2 evidence networks: RCTs with DRd and RCTs with DVd. Primary analysis of PFS found that DRd and DVd had a higher probability of being the

best treatments (probability, 0.997 and 0.999, respectively) and had the lowest risk of progression or death than other treatments approved by the US Food and Drug Administration for the treatment of MM. Results from sensitivity analyses using time to progression as a proxy for missing PFS data were consistent. DRd and DVd also showed improved ORR compared with other treatments. Subgroup analyses of PFS in patients treated with only 1 prior therapy were like the results of the primary analyses.IMPLICATIONSThis NMA provides comparative efficacy for MM treatments not studied in head-to-head RCTs. The NMA suggests that, compared with other approved MM treatments in the United States, DRd and DVd have a higher probability of providing the longest PFS in patients who have received at least 1 prior therapy and in patients who have received only 1 prior therapy.

Database: Medline

15. The Clinical Pharmacology of Elotuzumab.

Author(s): Passey, Chaitali; Sheng, Jennifer; Mora, Johanna; Tendolkar, Amol; Robbins, Michael; Dodge, Robert; Roy, Amit; Bello, Akintunde; Gupta, Manish

Source: Clinical pharmacokinetics; Mar 2018; vol. 57 (no. 3); p. 297-313

Publication Type(s): Journal Article Review

PubMedID: 28779463

Abstract: Novel treatment options are needed to improve long-term outcomes for patients with multiple myeloma (MM). In this article, we comprehensively review the clinical pharmacology of elotuzumab, a first-in-class monoclonal anti-SLAMF7 antibody approved in combination with lenalidomide and dexamethasone (ELd) for the treatment of patients with MM and one to three prior therapies. Elotuzumab has a dual mechanism of action to specifically kill myeloma cells: binding SLAMF7 on myeloma cells facilitates natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC), and direct engagement of SLAMF7 on NK cells further enhances NK cell activity. Elotuzumab administration causes transient elevations of selected cytokines (tumor necrosis factor-α, interferon-γ-induced protein-10 and monocyte chemoattractant protein-1). The temporary nature of these elevations (greatest after the first dose, with a trend to return to baseline by day 7) suggests a low likelihood of facilitating clinically meaningful drug-drug interactions. Elotuzumab exposure increases more than proportionally to dose and >80% SLAMF7 receptor occupancy is achieved with the approved elotuzumab 10 mg/kg regimen. Population pharmacokinetic data from 375 patients demonstrated weight-based dosing is appropriate for elotuzumab, and that ethnicity and hepatic/renal function have minimal effects on exposure. Exposure-response analysis of patients treated with ELd demonstrated that increased elotuzumab exposure does not elevate the risk of grade 3+ adverse events (AEs) or AEs leading to discontinuation/death. Elotuzumab antidrug antibodies occurred in 18.5% of patients treated with ELd or elotuzumab plus bortezomib and dexamethasone, but were generally transient and did not affect elotuzumab efficacy or safety. A monotherapy study indicated elotuzumab does not have clinically relevant effects on QT intervals.

Database: Medline

16. A Comparison of the Efficacy of Immunomodulatory-containing Regimens in Relapsed/Refractory Multiple Myeloma: A Network Meta-analysis.

Author(s): Dimopoulos, Meletios Athanasios; Kaufman, Jonathan L; White, Darrell; Cook, Gordon; Rizzo, Maria; Xu, Yingxin; Fahrbach, Kyle; Gaudig, Maren; Slavcev, Mary; Dearden, Lindsay; Lam, Annette

Source: Clinical lymphoma, myeloma & leukemia; Mar 2018; vol. 18 (no. 3); p. 163

Publication Type(s): Journal Article

PubMedID: 29456035

Abstract:BACKGROUNDPrevious network meta-analyses combined studies of immunomodulatory drug (IMiD)-containing and IMiD-free regimens, despite a lack of head-to-head randomized controlled trials to robustly link them. However, patients with relapsed or refractory multiple myeloma (RRMM) treated with IMiD-containing regimens differ from those treated with IMiD-free regimens, especially relating to treatment history, which is an important treatment-effect modifier requiring clinical consideration when evaluating the most appropriate subsequent treatment options. A need exists to separately assess the efficacy of treatment regimens for patients who are suitable candidates for IMiD-containing and IMiD-free regimens. The presented analyses will enable clinicians to assess the best regimens to use in patients suitable for IMiD-containing regimens.MATERIALS AND METHODSWe used a Bayesian network meta-analysis to compare IMiD-containing regimens in patients with RRMM. Additionally, subgroup analyses were conducted stratified by previous therapy line, previous bortezomib therapy, and previous lenalidomide therapy.RESULTSThe results indicated that triplet combinations are more effective than doublet combinations. Of the triplet combinations, daratumumab, lenalidomide, dexamethasone (DRd) was significantly better in improving progression-free survival in patients with RRMM than were other IMiD-containing regimens (lenalidomide, dexamethasone [Rd]: hazard ratio [HR], 0.37; carfilzomib, Rd: HR, 0.54; elotuzumab, Rd: HR, 0.54; ixazomib, Rd: HR, 0.50). Similar trends were observed for overall survival and overall response. DRd showed the greatest probability of being the best treatment for all clinical efficacy outcomes. The subgroup analyses results were consistent with the base-case results.CONCLUSIONIn patients with RRMM who are suitable for an IMiD-containing regimen, DRd showed clear advantages in survival and response outcomes compared with other IMiD-containing regimens.

Database: Medline

17. Elotuzumab(E) in combination with carfilzomib, lenalidomide and dexamethasone(E-KRd) versus KRd prior to and following autologous stem cell transplant in newly diagnosed multiple myeloma + subsequent maintenance with elotuzumab + lenalidomide versus single agent lenalidomide

Author(s): Willenbacher W.

Source: Memo - Magazine of European Medical Oncology; Mar 2018; vol. 11 (no. 1)

Publication Type(s): Conference Abstract

Abstract: Start of study: Q2 2018 (in Austria) End of recruitment: Q2 2020 Design: This is an interventional, multicentre, open-label, randomized phase III trial with two parallel arms to compare two different regimens. Quadruple elotuzumab in combination with carfilzomib, lenalidomide, and dexamethasone [E-KRd] versus triple carfilzomib, lenalidomide, and dexamethasone [KRd] is given during induction treatment prior to ASCT and as consolidation treatment after ASCT in patients suffering from newly diagnosed multiple myeloma according to the updated IMWG criteria. Consolidation treatment is followed by maintenance treatment (elotuzumab in combination with lenalidomide versus lenalidomide monotherapy). Patients are randomized in a 1:1 ratio to be administered 6 cycles induction treatment, either E-KRd (Arm A) or KRd (Arm B). Primary objective: To compare the rate of MRD negativity in patients with VGPR or better response according to IMWG criteria following two different induction regimens (quadruple [E-KRd] vs. triple [KRd]) in newly diagnosed multiple myeloma patients and to determine progression-free survival (PFS) following maintenance treatment. Patients: 576 patients will be randomized into this phase III trial. It is

planned that the study will be performed in up to 45 German trial centres and 10 Austrian trial centres.

Database: EMBASE

18. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma.

Author(s): Mateos, María-Victoria; Dimopoulos, Meletios A; Cavo, Michele; Suzuki, Kenshi; Jakubowiak, Andrzej; Knop, Stefan; Doyen, Chantal; Lucio, Paulo; Nagy, Zsolt; Kaplan, Polina; Pour, Ludek; Cook, Mark; Grosicki, Sebastian; Crepaldi, Andre; Liberati, Anna M; Campbell, Philip; Shelekhova, Tatiana; Yoon, Sung-Soo; Iosava, Genadi; Fujisaki, Tomoaki; Garg, Mamta; Chiu, Christopher; Wang, Jianping; Carson, Robin; Crist, Wendy; Deraedt, William; Nguyen, Huong; Qi, Ming; San-Miguel, Jesus; ALCYONE Trial Investigators

Source: The New England journal of medicine; Feb 2018; vol. 378 (no. 6); p. 518-528

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Multicenter Study Journal Article Clinical Trial, Phase Iii

PubMedID: 29231133

Available at The New England Journal of Medicine - from ProQuest (Hospital Premium Collection) - NHS Version

Available at The New England Journal of Medicine - from Ovid (Journals @ Ovid) - Remote Access

Abstract:BACKGROUNDThe combination of bortezomib, melphalan, and prednisone is a standard treatment for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation. Daratumumab has shown efficacy in combination with standard-of-care regimens in patients with relapsed or refractory multiple myeloma.METHODSIn this phase 3 trial, we randomly assigned 706 patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation to receive nine cycles of bortezomib, melphalan, and prednisone either alone (control group) or with daratumumab (daratumumab group) until disease progression. The primary end point was progression-free survival.RESULTSAt a median follow-up of 16.5 months in a prespecified interim analysis, the 18-month progression-free survival rate was 71.6% (95% confidence interval [CI], 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group (P<0.001), and the rate of complete response or better (including stringent complete response) was 42.6%, versus 24.4% (P<0.001). In the daratumumab group, 22.3% of the patients were negative for minimal residual disease (at a threshold of 1 tumor cell per 105 white cells), as compared with 6.2% of those in the control group (P<0.001). The most common adverse events of grade 3 or 4 were hematologic: neutropenia (in 39.9% of the patients in the daratumumab group and in 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anemia (in 15.9% and 19.8%, respectively). The rate of grade 3 or 4 infections was 23.1% in the daratumumab group and 14.7% in the control group; the rate of treatment discontinuation due to infections was 0.9% and 1.4%, respectively. Daratumumab-associated infusion-related reactions occurred in 27.7% of the patients.CONCLUSIONSAmong patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation, daratumumab combined with bortezomib, melphalan, and prednisone resulted in a lower risk of disease progression or death than the same regimen without daratumumab. The daratumumab-containing regimen was associated with more grade 3 or 4 infections. (Funded by Janssen Research and Development; ALCYONE ClinicalTrials.gov number, NCT02195479 .).

Database: Medline

19. Daratumumab for untreated multiple myeloma.

Author(s): Stirrups, Robert

Source: The Lancet. Oncology; Feb 2018; vol. 19 (no. 2); p. e80

Publication Type(s): Journal Article

PubMedID: 29276025

Database: Medline

20. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond.

Author(s): Chim, C S; Kumar, S K; Orlowski, R Z; Cook, G; Richardson, P G; Gertz, M A; Giralt, S; Mateos, M V; Leleu, X; Anderson, K C

Source: Leukemia; Feb 2018; vol. 32 (no. 2); p. 252-262

Publication Type(s): Journal Article Review

PubMedID: 29257139

Available at Leukemia - from PubMed Central

Abstract: Despite enormous advances, management of multiple myeloma (MM) remains challenging. Multiple factors impact the decision to treat or which regimen to use at MM relapse/progression. Recent major randomized controlled trials (RCTs) showed widely varying progression-free survivals (PFS), ranging from a median of 4 months (MM-003) to 23.6 months (ASPIRE). Based on these RCTs, next-generation proteasome inhibitors (carfilzomib and ixazomib), next-generation immunomodulatory agent (pomalidomide), and monoclonal antibodies (elotuzumab and daratumumab) were approved for relapsed and refractory MM. Daratumumab, targeting CD38, has multiple mechanisms of action including modulation of the immunosuppressive bone marrow micro-environment. In addition to the remarkable single agent activity in refractory MM, daratumumab produced deep responses and superior PFS in MM when combined with lenalidomide/dexamethasone, or bortezomib/dexamethasone. Other anti-CD38 antibodies, such as isatuximab and MOR202, are undergoing assessment. Elotuzumab, targeting SLAMF7, yielded superior response rates and PFS when combined with lenalidomide/dexamethasone. New combinations of these next generation novel agents and/or antibodies are undergoing clinical trials. Venetoclax, an oral BH3 mimetic inhibiting BCL2, showed single agent activity in MM with t(11;14), and is being studied in combination with bortezomib/dexamethasone. Selinexor, an Exportin-1 inhibitor, yielded promising results in quad- or penta-refractory MM including patients resistant to daratumumab. Pembrolizumab, an anti-PD1 check-point inhibitor, is being tested in combination with lenalidomide/dexamethasone or pomalidomide/dexamethasone. Chimeric antigen receptor-T cells targeting B-cell maturation antigen have yielded deep responses in RRMM. Finally, salvage autologous stem cell transplantation (ASCT) remains an important treatment in MM relapsing/progressing after a first ASCT. Herein, the clinical trial data of these agents are summarized, cautious interpretation of RCTs highlighted, and algorithm for salvage treatment of relapse/refractory MM proposed.

Database: Medline

21. Considerations for pre-transfusion immunohaematology testing in patients receiving the anti-CD38 monoclonal antibody daratumumab for the treatment of multiple myeloma.

Author(s): Quach, Hang; Benson, Simon; Haysom, Helen; Wilkes, Anne-Marie; Zacher, Nicole; Cole-Sinclair, Merrole; Miles Prince, Henry; Mollee, Peter; Spencer, Andrew; Joy Ho, Phoebe; Harrison, Simon J; Lee, Cindy; Augustson, Bradley; Daly, James

Source: Internal medicine journal; Feb 2018; vol. 48 (no. 2); p. 210-220

Publication Type(s): Journal Article

PubMedID: 29415351

Abstract: In recent years, the anti-CD38 monoclonal antibody daratumumab (Darzalex; Janssen-Cilag Pty Ltd) has been shown to be highly efficacious in relapsed and refractory multiple myeloma, with the final results of treatment in newly diagnosed patients awaited. Despite awareness of the potential interference of daratumumab in pre-transfusion immunohaematology testing during phase I and II clinical studies, there was a degree of unpreparedness in the community upon the introduction of this drug into the clinics, particularly the impact that it has on the operational processes in hospital transfusion laboratories and timely issue of red blood cells (RBCs). Anti-CD38 interference in pre-transfusion immunohaematology tests is a particular problem in patients being treated with daratumumab for multiple myeloma as many will require RBC transfusions during their disease treatment. Panagglutination caused by anti-CD38 monoclonal antibody during the indirect antiglobulin test may mask the presence of a clinically significant RBC alloantibody in the patient's plasma during the antibody screen and identification process, which may be overlooked, particularly in urgent situations, subsequently resulting in a delayed or acute haemolytic transfusion reaction. Here, we summarise daratumumab's effects on pre-transfusion immunohaematology testing and its impact on clinical practice and make practical recommendations based on a consensus from medical and scientific transfusion experts and myeloma specialists on behalf of the Australian and New Zealand Society of Blood Transfusion and Myeloma Scientific Advisory Group to Myeloma Australia, respectively.

Database: Medline

22. Emerging immune targets for the treatment of multiple myeloma.

Author(s): Sohail, Atif; Mushtaq, Adeela; Iftikhar, Ahmad; Warraich, Zabih; Kurtin, Sandra E; Tenneti, Pavan; McBride, Ali; Anwer, Faiz

Source: Immunotherapy; Feb 2018; vol. 10 (no. 4); p. 265-282

Publication Type(s): Journal Article

PubMedID: 29421983

Abstract: We reviewed emerging immune strategies for multiple myeloma (MM) therapy excluding US FDA approved drugs. In relapsed refractory MM, isatuximab (anti-CD38) monotherapy achieved overall response (OR) of 24%. Other monoclonal antibodies that have shown efficacy in combination therapy include siltuximab (OR: 66%), indatuximab (OR: 78%), isatuximab (OR: 64.5%), pembrolizumab (OR: 60%), bevacizumab (OR: 70%), dacetuzumab (OR: 39%) and lorvotuzumab (OR: 56.4%). No OR was observed with monotherapy using BI-505, siltuximab, bevacizumab, AVE-1642, figitumumab, atacicept, milatuzumab, dacetuzumab, lucatumumab, IPH2101, lorvotuzumab, BT062 and nivolumab. We included seven clinical trials on chimeric antigen receptor (CAR) T cells. CAR T-cell targets include BCMA, CD19, KLC and CD138. A recent experience of CAR T-cell (B-cell maturation antigen) therapy in advanced MM has shown global response of 100%. The future of monoclonal antibodies and adoptive T cells for MM treatment seems promising.

Database: Medline

23. A review discussing elotuzumab and its use in the second-line plus treatment of multiple myeloma.

Author(s): Offidani, Massimo; Corvatta, Laura

Source: Future oncology (London, England); Feb 2018; vol. 14 (no. 4); p. 319-329

Publication Type(s): Journal Article

PubMedID: 29091475

Abstract: Monoclonal antibodies (mAb) represent a new frontier to treat newly diagnosed and relapsed-refractory multiple myeloma (MM). Elotuzumab, an mAb targeted SLAM7 in the plasma cells and natural killer cells surface, is the first mAb approved for the treatment of relapsed-refractory MM in combination with lenalidomide and dexamethasone. This approval was the final result of several preclinical and Phase I-II clinical studies leading to ELOQUENT-2 Phase III trial that demonstrated that elotuzumab adds a significant and durable value to standard therapy, paved the way of this new treatment strategy for MM. In this review we will describe elotuzumab mechanisms of action, clinical pharmacology and clinical studies that have led to these developments.

Database: Medline

24. EMA Review of Daratumumab for the Treatment of Adult Patients with Multiple Myeloma.

Author(s): Tzogani, Kyriaki; Penninga, Elisabeth; Schougaard Christiansen, Marie Louise; Hovgaard, Doris; Sarac, Sinan B; Camarero Jimenez, Jorge; Garcia, Isabel; Lafuente, Marta; Sancho-López, Arantxa; Salmonson, Tomas; Gisselbrecht, Christian; Pignatti, Francesco

Source: The oncologist; Jan 2018

Publication Type(s): Journal Article

PubMedID: 29371479

Available at The oncologist - from EBSCO (MEDLINE Complete)

Abstract: On May 20, 2016, a conditional marketing authorization valid through the European Union (EU) was issued for daratumumab as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD) and who had demonstrated disease progression on the last therapy. The review of daratumumab was conducted under the EMA's accelerated assessment program for drugs that are of major interest for public health, especially from the point of view of therapeutic innovation.Daratumumab monotherapy achieved an overall response rate of 29.2% (95% confidence interval [CI] 20.8 to 38.9) in patients with multiple myeloma who had received at least three prior lines of therapy (including a PI and IMiD) or were double refractory to a PI and an IMiD (Study MMY2002). In patients with multiple myeloma relapsed from or refractory to two or more different prior therapies, including IMiDs (e.g., thalidomide, lenalidomide) and PI, an overall response was observed in 15 patients (35.7%, 95% CI: 21.6 to 52.0) (Study GEN501).On April 28, 2017, the therapeutic indication was extended to include the use of daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. This was based on two subsequent phase III studies of daratumumab in combination with lenalidomide/low-dose dexamethasone (MMY3003) and bortezomib/low dose dexamethasone (MMY3004).The most common side effects (grade 3-4) associated with daratumumab included neutropenia (37%), thrombocytopenia (23%), anemia (16%), pneumonia (10%), lymphopenia (8%), infusion-related reactions (6%), upper respiratory tract infection (5%), and fatigue (5%).The objective of this study was to summarize the scientific review done by the CHMP of the application leading to regulatory approval in the EU. The full scientific assessment report and product information, including the

Summary of Product Characteristics (SmPC), are available on the EMA website (www.ema.europa.eu).IMPLICATIONS FOR PRACTICEA conditional Marketing authorization was issued in the European Union for daratumamb as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, based on the response rate data from two single-agent studies. Darzalex, a novel monoclonal antibody targeted against CD38, demonstrated a durable response rate in a heavily pre-treated population with limited treatment options based on the response rate data from two single-agent studies. The addition of daratumumab to lenalidomide and dexamethasone (study MMY3003), or bortezomib and dexamethasone (MMY3004), demonstrated a positive effect on progression-free survival in patients with multiple myeloma who had received at least one prior therapy. Following submission of the controlled data of the MMY3003 and MMY3004 studies, the efficacy and safety of daratumumab was confirmed and the approval of daratumumab was converted to standard approval.

Database: Medline

25. The role of elotuzumab in the treatment of relapsed or refractory multiple myeloma.

Author(s): Comeau, Jill M; Kelly, Katherine; Jean, Gary W

Source: American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists; Jan 2018; vol. 75 (no. 2); p. 55-66

Publication Type(s): Journal Article Review

PubMedID: 29317395

Available at American Journal of Health-System Pharmacy - from EBSCO (MEDLINE Complete)

Available at American Journal of Health-System Pharmacy - from EBSCO (CINAHL Plus with Full Text)

Abstract:PURPOSEThe pharmacology, pharmacokinetics, clinical efficacy and safety, cost, and place in therapy of elotuzumab for treatment of relapsed or refractory multiple myeloma (MM) are reviewed.SUMMARYElotuzumab is a humanized monoclonal antibody that targets the signaling lymphocytic activation molecule (SLAM) protein SLAMF7 and facilitates an antibody-dependent cellular cytotoxicity interaction between myeloma cells and natural killer cells. Elotuzumab has U.S. marketing approval for use in combination with lenalidomide and dexamethasone in patients with relapsed or refractory MM who have received 1-3 previous therapies; this regimen is among the preferred regimens for relapsed or refractory MM recommended by the National Comprehensive Cancer Network (NCCN). A Phase III trial involving 321 patients demonstrated a median progression-free survival duration of 19.4 months with elotuzumab plus lenalidomide and dexamethasone versus 14.9 months with lenalidomide and dexamethasone alone (hazard ratio for progression or death, 0.70; 95% confidence interval, 0.57-0.85; $p < 0.001$). Common adverse effects of elotuzumab-lenalidomide-dexamethasone therapy include hematologic toxicities, fatigue, pyrexia, diarrhea, constipation, muscle spasms, and cough. Elotuzumab plus bortezomib and dexamethasone is an NCCN-recommended alternative option for relapsed or refractory MM.CONCLUSIONWhile elotuzumab plus lenalidomide and dexamethasone is a promising regimen for patients with MM, it is only one of several regimens recommended by NCCN for relapsed or refractory MM. Key factors in patient selection for elotuzumab therapy include adverse effects, prior treatments received, and cost considerations.

Database: Medline

26. CD38 antibodies in multiple myeloma: back to the future.

Author(s): van de Donk, Niels W C J; Richardson, Paul G; Malavasi, Fabio

Source: Blood; Jan 2018; vol. 131 (no. 1); p. 13-29

Publication Type(s): Journal Article Review

PubMedID: 29118010

Abstract:CD38 is highly and uniformly expressed on multiple myeloma (MM) cells, and at relatively low levels on normal lymphoid and myeloid cells, and in some tissues of nonhematopoietic origin. CD38 is a transmembrane glycoprotein with ectoenzymatic activity, and also functions as a receptor and adhesion molecule. Altogether, this has triggered the development of several CD38 antibodies including daratumumab (fully human), isatuximab (chimeric), and MOR202 (fully human). CD38 antibodies have pleiotropic mechanisms of action including Fc-dependent immune-effector mechanisms, direct apoptotic activity, and immunomodulatory effects by the elimination of CD38+ immune-suppressor cells. CD38-targeting antibodies are generally well tolerated and induce partial response or better in ∼30% of heavily pretreated MM patients as monotherapy. Based on their distinct mechanisms of action, favorable toxicity profile, and single-agent activity, CD38 antibodies are attractive partners in combination regimens. Indeed, deep responses and prolonged progression-free survival can be achieved in relapsed/refractory MM patients when CD38 antibodies are combined with immunomodulatory agents or proteasome inhibitors. Infusion-related reactions, which typically occur during the first infusion, are the most frequent adverse events. Attention should also be paid to the interference of CD38 antibodies with certain laboratory assays, which may complicate response evaluation and blood compatibility testing. Several studies are currently examining the role of CD38-based therapies in newly diagnosed and high-risk smoldering MM. Furthermore, CD38 antibodies are currently also under investigation in other hematologic malignancies, including acute lymphoblastic leukemia, natural killer/T-cell lymphoma, and acute myeloid leukemia, as well as in solid tumors.

Database: Medline

27. Blood Transfusion Management and Transfusion-Related Outcomes in Daratumumab-Treated Patients With Relapsed or Refractory Multiple Myeloma.

Author(s): Chari, Ajai; Arinsburg, Suzanne; Jagannath, Sundar; Satta, Toshihisa; Treadwell, Ivey; Catamero, Donna; Morgan, Gillian; Feng, Huaibao; Uhlar, Clarissa; Khan, Imran; Doshi, Parul; Usmani, Saad

Source: Clinical lymphoma, myeloma & leukemia; Jan 2018; vol. 18 (no. 1); p. 44-51

Publication Type(s): Journal Article

PubMedID: 29054515

Abstract:INTRODUCTIONDaratumumab, a human CD38 monoclonal antibody approved for multiple myeloma (MM) treatment, binds red blood cells (RBCs), resulting in panagglutination in compatibility tests. Published mitigation methods avoid additional testing, ensuring timely release of blood products. Blood transfusion management and transfusion-related outcomes of daratumumab-treated patients in the SIRIUS study are reported, with emphasis on 2 clinical sites.PATIENTS AND METHODSPatients had MM treated with ≥ 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or were refractory to a proteasome inhibitor and an immunomodulatory drug. RBC typing and alloantibody screening were performed in gel cards. Antibody identification using RBC panels was performed on patients with positive antibody screens. Hematology panels and serum chemistry were analyzed ≤ 2 days before each daratumumab infusion and the first daratumumab dose within each treatment cycle, respectively. Pre- and posttransfusion

hemoglobin values were analyzed retrospectively.RESULTSAt clinical cutoff, patients received 236 transfusions; 47 (37.9%) of 124 patients received 147 packed RBC transfusions, and 17 (13.7%) received 89 platelet transfusions. No hemolysis was reported, and 1 platelet transfusion reaction was observed. At Mount Sinai, no transfusion adverse events were observed, no new unexpected RBC alloantibodies were identified, and transfusions increased hemoglobin values (median, 1.2 g/dL). At Levine Cancer Institute, 6 of 7 patients responded to transfusions, with a median hemoglobin change of 1.7 g/dL.CONCLUSIONIn SIRIUS, no RBC transfusion reactions, including hemolysis, were observed. Observations from Mount Sinai and Levine Cancer Institute confirm that transfusions may be administered safely to daratumumab-treated patients.

Database: Medline

28. Treatment of multiple myeloma with monoclonal antibodies and the dilemma of false positive M-spikes in peripheral blood.

Author(s): Murata, Kazunori; McCash, Samuel I; Carroll, Brittany; Lesokhin, Alexander M; Hassoun, Hani; Lendvai, Nikoletta; Korde, Neha S; Mailankody, Sham; Landau, Heather J; Koehne, Guenther; Chung, David J; Giralt, Sergio A; Ramanathan, Lakshmi V; Landgren, Ola

Source: Clinical biochemistry; Jan 2018; vol. 51 ; p. 66-71

Publication Type(s): Journal Article

PubMedID: 27664535

Abstract:OBJECTIVESTo characterize the effect of three humanized IgG κ monoclonal antibodies (daratumumab, isatuximab, and elotuzumab) on the interpretation of results generated by protein electrophoresis, immunofixation, free light chain, and heavy/light chain assays performed on human serum.METHODSHealthy volunteer serum and serum from multiple myeloma patients were supplemented with clinically relevant concentrations of each of the three monoclonal antibodies. These specimens then underwent analysis via serum protein electrophoresis, immunofixation, serum free light chain quantification, heavy/light chain quantification, total IgG, and total protein. In addition, serum specimens from patients who had undergone treatment with elotuzumab for multiple myeloma underwent similar analysis.RESULTSAddition of the study drugs to serum from both the healthy donor as well as multiple myeloma patients resulted in a visible and quantifiable M-protein on SPEP and a visible IgGκ band by IFE. Increases were also noted in total IgG, IgGκ, and IgGκ/IgGλ-ratios. Analysis of serum from multiple myeloma patients receiving study drug showed similar findings with an additional IgGκ band and quantifiable M-protein with similar migration patterns in specimens drawn after administration.CONCLUSIONThe treatment of multiple myeloma patients with monoclonal antibodies results in a visible and quantifiable M-protein that has the potential to falsely indicate poor response to therapy.

Database: Medline

29. New monoclonal antibodies on the horizon in multiple myeloma

Author(s): O'Donnell E.K.; Raje N.S.

Source: Therapeutic Advances in Hematology; 2017; vol. 8 (no. 2); p. 41-53

Publication Type(s): Review

Available at Therapeutic Advances in Hematology - from Europe PubMed Central - Open Access

Available at Therapeutic Advances in Hematology - from PubMed Central

Abstract: Across all cancers, monoclonal antibodies have emerged as a potential strategy for cancer therapy. Monoclonal antibodies target antigens expressed on the surface of cancer cells and accessory cells. This targeted approach uses the host's immune system to promote the killing of cancer cells. Multiple myeloma (MM) is the second most common hematologic malignancy that remains incurable in the majority of patients. The treatment of MM has evolved dramatically over the past decade and continues to evolve with the approval of four new drugs in 2015. Most recently the United States Food and Drug Administration (US FDA) approved two monoclonal antibodies for the treatment of this disease. Monoclonal antibodies are generally well-tolerated and offer a novel method of action for treated relapsed and refractory disease and are now being studied in the upfront setting. In this article, we review the evidence for the existing approved monoclonal antibodies and discuss promising targeted therapies and innovative strategies for the treatment of MM.

Database: EMBASE

30. Optimizing current and emerging therapies in multiple myeloma: a guide for the hematologist

Author(s): Raza S.; Safyan R.A.; Rosenbaum E.; Bowman A.S.; Lentzsch S.

Source: Therapeutic Advances in Hematology; 2017; vol. 8 (no. 2); p. 55-70

Publication Type(s): Review

Available at Therapeutic Advances in Hematology - from Europe PubMed Central - Open Access

Available at Therapeutic Advances in Hematology - from PubMed Central

Abstract: Multiple myeloma (MM) is the second most common hematologic malignancy. The diagnosis of MM requires 10% clonal plasma cells in the bone marrow or biopsy-proven plasmacytoma, plus evidence of end-organ damage (hypercalcemia, renal failure, anemia, and lytic bone lesions). The definition of MM has recently been expanded to include a 60% clonal plasma cell burden in the bone marrow, serum involved/uninvolved light chain ratio of 100, or more than one focal lesion on magnetic resonance imaging 5 mm in the absence of end-organ damage. MM is an incurable malignancy previously associated with poor survival rates. However, over the past two decades, the introduction of novel treatment options has resulted in a dramatic improvement in response rates and overall survival (OS). The combination of a proteasome inhibitor and an immunomodulator (IMiD) is the preferred induction treatment for newly diagnosed transplant-eligible MM patients. After induction, high-dose therapy with autologous stem cell transplant (ASCT) is still the standard of care for these patients. In patients who are transplant ineligible, dose adjusted IMiDs or proteasome inhibitor-based combinations are the preferred treatment option. With the recent approval of novel drugs like carfilzomib, ixazomib, pomalidomide, panobinostat, and monoclonal antibodies (elotuzumab and daratumumab), as well as improved understanding of risk stratification, management of comorbidities and treatment side effects, clinicians can optimize anti-MM therapy, particularly in relapse/refractory MM patients. In this review, we outline the current therapeutic approach to the management of MM.

Database: EMBASE

31. Clinical potential of SLAMF7 antibodies - focus on elotuzumab in multiple myeloma.

Author(s): Friend, Reed; Bhutani, Manisha; Voorhees, Peter M; Usmani, Saad Z

Source: Drug design, development and therapy; 2017; vol. 11 ; p. 893-900

Publication Type(s): Journal Article Review

PubMedID: 28356715

Available at Drug Design, Development and Therapy - from Europe PubMed Central - Open Access

Available at Drug Design, Development and Therapy - from EBSCO (MEDLINE Complete)

Available at Drug Design, Development and Therapy - from PubMed Central

Abstract: Elotuzumab is one of the first monoclonal antibodies to be approved for the treatment of multiple myeloma. It is a humanized immunoglobulin G kappa (IgGκ) antibody that targets signaling lymphocytic activation molecule family member 7 (SLAMF7), a surface marker that is highly expressed on normal and malignant plasma cells. This review summarizes the preclinical and clinical data that led to the approval of elotuzumab, along with a discussion on the ongoing and future clinical investigations.

Database: Medline

32. Functional Imaging with 18F-FDG PET/CT and Diffusion Weighted Imaging (DWI) in Early Response Evaluation of Combination Therapy of Elotuzumab, Lenalidomide, and Dexamethasone in a Relapsed Multiple Myeloma Patient.

Author(s): Sachpekidis, Christos; Dimitrakopoulou-Strauss, Antonia; Delorme, Stefan; Goldschmidt, Hartmut

Source: Diagnostics (Basel, Switzerland); Dec 2017; vol. 7 (no. 4)

Publication Type(s): Journal Article

PubMedID: 29244720

Available at Diagnostics - from Europe PubMed Central - Open Access

Available at Diagnostics - from PubMed Central

Abstract: Elotuzumab is the first monoclonal antibody approved for the treatment of relapsed-refractory multiple myeloma (MM) in combination with lenalidomide, an immunodulatory drug, and dexamethasone. We report on a multiply pre-treated MM patient with disease progression due to appearance of new focal lesions on imaging modalities, who was started on a combination treatment of elotuzumab, lenalidomide, and dexamethasone. After completion of three cycles of the new therapy the patient responded very well with a major decline of serological myeloma activity parameters serum monoclonal protein, kappa light chains, free light chains (FLC) ratio. The patient was also monitored with the functional imaging modalities 18F-FDG PET/CT and diffusion weighted imaging (DWI), which exhibited a mismatch of almost complete metabolic remission on positron emission tomography/computed tomography (PET/CT) with 18F-fluoro-2-deoxy-d-glucose (18F-FDG) (consistent with the serological response), and signal elevation persistence on DWI. This case demonstrates the potentially superior performance of 18F-FDG PET/CT over DWI in early response evaluation of combined treatment with a monoclonal antibody, an immunomodulatory drug, and dexamethasone in MM.

Database: Medline

33. Monocytes and Granulocytes Reduce CD38 Expression Levels on Myeloma Cells in Patients Treated with Daratumumab.

Author(s): Krejcik, Jakub; Frerichs, Kris A; Nijhof, Inger S; van Kessel, Berris; van Velzen, Jeroen F; Bloem, Andries C; Broekmans, Marloes E C; Zweegman, Sonja; van Meerloo, Johan; Musters, René J P; Poddighe, Pino J; Groen, Richard W J; Chiu, Christopher; Plesner, Torben; Lokhorst, Henk M; Sasser, A Kate; Mutis, Tuna; van de Donk, Niels W C J

Source: Clinical cancer research : an official journal of the American Association for Cancer Research; Dec 2017; vol. 23 (no. 24); p. 7498-7511

Publication Type(s): Journal Article

PubMedID: 29025767

Abstract: Purpose: Daratumumab treatment results in a marked reduction of CD38 expression on multiple myeloma cells. The aim of this study was to investigate the clinical implications and the underlying mechanisms of daratumumab-mediated CD38 reduction.Experimental Design: We evaluated the effect of daratumumab alone or in combination with lenalidomide-dexamethasone, on CD38 levels of multiple myeloma cells and nontumor immune cells in the GEN501 study (daratumumab monotherapy) and the GEN503 study (daratumumab combined with lenalidomide-dexamethasone). In vitro assays were also performed.Results: In both trials, daratumumab reduced CD38 expression on multiple myeloma cells within hours after starting the first infusion, regardless of depth and duration of the response. In addition, CD38 expression on nontumor immune cells, including natural killer cells, T cells, B cells, and monocytes, was also reduced irrespective of alterations in their absolute numbers during therapy. In-depth analyses revealed that CD38 levels of multiple myeloma cells were only reduced in the presence of complement or effector cells, suggesting that the rapid elimination of CD38high multiple myeloma cells can contribute to CD38 reduction. In addition, we discovered that daratumumab-CD38 complexes and accompanying cell membrane were actively transferred from multiple myeloma cells to monocytes and granulocytes. This process of trogocytosis was also associated with reduced surface levels of some other membrane proteins, including CD49d, CD56, and CD138.Conclusions: Daratumumab rapidly reduced CD38 expression levels, at least in part, through trogocytosis. Importantly, all these effects also occurred in patients with deep and durable responses, thus excluding CD38 reduction alone as a mechanism of daratumumab resistance.The trials were registered at www.clinicaltrials.gov as NCT00574288 (GEN501) and NCT1615029 (GEN503).

Database: Medline

34. Daratumumab: A Review in Relapsed and/or Refractory Multiple Myeloma.

Author(s): Blair, Hannah A

Source: Drugs; Dec 2017; vol. 77 (no. 18); p. 2013-2024

Publication Type(s): Journal Article

PubMedID: 29127588

Abstract: Intravenous daratumumab (DARZALEX®) is a first-in-class human IgG1κ monoclonal antibody against CD38 available for use in patients with relapsed and/or refractory multiple myeloma. In phase I/II and II trials and a pooled analysis of these studies, daratumumab monotherapy induced an overall response (partial response or better) in approximately one-third of patients; responses were rapid, deep and durable. An overall survival (OS) benefit was seen with daratumumab monotherapy, including in patients with a minimal response or stable disease. In phase III trials, daratumumab in combination with either bortezomib plus dexamethasone or lenalidomide plus dexamethasone significantly prolonged progression-free survival and induced deep and durable responses compared with bortezomib plus dexamethasone or lenalidomide plus dexamethasone. An OS benefit with daratumumab triple combination therapy is yet to be demonstrated (as the OS data were not mature at the time of the last analysis). Daratumumab was generally well tolerated when used as monotherapy and had a generally manageable tolerability profile when used in combination therapy. Infusion-related reactions (IRRs) were the most common adverse events; these were predominantly grade 1 or 2 and mostly occurred during the first infusion. The most common grade 3-4 adverse events associated with daratumumab triple

combination therapy were thrombocytopenia, neutropenia and anaemia. Although final OS data are awaited, current evidence indicates that daratumumab is a valuable addition to the treatment options currently available for patients with relapsed or refractory multiple myeloma.

Database: Medline

35. Incorporating monoclonal antibodies into the management of multiple myeloma.

Author(s): Mark, Tomer M

Source: Clinical advances in hematology & oncology : H&O; Dec 2017; vol. 15 (no. 12); p. 919-922

Publication Type(s): Journal Article

PubMedID: 29315283

Available at Clinical advances in hematology & oncology : H&O - from EBSCO (MEDLINE Complete)

Database: Medline

36. Monoclonal antibody: A new treatment strategy against multiple myeloma

Author(s): Cho S.-F.; Lin L.; Xing L.; Yu T.; Wen K.; Anderson K.C.; Tai Y.-T.

Source: Antibodies; Dec 2017; vol. 6 (no. 4)

Publication Type(s): Review

Available at Antibodies - from mdpi.com

Abstract:2015 was a groundbreaking year for the multiple myeloma community partly due to the breakthrough approval of the first two monoclonal antibodies in the treatment for patients with relapsed and refractory disease. Despite early disappointments, monoclonal antibodies targeting CD38 (daratumumab) and signaling lymphocytic activation molecule F7 (SLAMF7) (elotuzumab) have become available for patients with multiple myeloma in the same year. Specifically, phase 3 clinical trials of combination therapies incorporating daratumumab or elotuzumab indicate both efficacy and a very favorable toxicity profile. These therapeutic monoclonal antibodies for multiple myeloma can kill target cells via antibody-dependent cell-mediated cytotoxicity, complementdependent cytotoxicity, and antibody-dependent phagocytosis, as well as by direct blockade of signaling cascades. In addition, their immunomodulatory effects may simultaneously inhibit the immunosuppressive bone marrow microenvironment and restore the key function of immune effector cells. In this review, we focus on monoclonal antibodies that have shown clinical efficacy or promising preclinical anti-multiple myeloma activities that warrant further clinical development. We summarize mechanisms that account for the in vitro and in vivo anti-myeloma effects of these monoclonal antibodies, as well as relevant preclinical and clinical results. Monoclonal antibodybased immunotherapies have already and will continue to transform the treatment landscape in multiple myeloma.

Database: EMBASE

37. Efficacy of daratumumab-based therapies in patients with relapsed, refractory multiple myeloma treated outside of clinical trials.

Author(s): Lakshman, Arjun; Abeykoon, Jithma P; Kumar, Shaji K; Rajkumar, S Vincent; Dingli, David; Buadi, Francis K; Gonsalves, Wilson I; Leung, Nelson; Dispenzieri, Angela; Kourelis, Taxiarchis V; Go, Ronald S; Lacy, Martha Q; Hobbs, Miriam A; Lin, Yi; Warsame, Rahma; Lust, John; Fonder, Amie L; Hwa, Yi L; Hayman, Suzanne R; Russell, Stephen J; Kyle, Robert A; Gertz, Morie A; Kapoor, Prashant

Source: American journal of hematology; Nov 2017; vol. 92 (no. 11); p. 1146-1155

Publication Type(s): Journal Article

PubMedID: 28799231

Abstract: Outside of clinical trials, experience with daratumumab-based combination therapies (DCTs) using bortezomib (V)/lenalidomide (R)/pomalidomide (P), and dexamethasone (d) in relapsed/refractory multiple myeloma (RRMM) is limited. We reviewed the outcomes of 126 patients who received ≥ 1 cycle of any DCT. Median age at DCT initiation was 67 (range, 43-93) years. High-risk cytogenetics was present in 33% patients. Median number of prior therapies was 4 (range, 1-14) and time to first DCT from diagnosis was 4.3 years (range, 0.4-13.0). Seventeen (13%) patients were refractory to single agent daratumumab. Fifty-two (41%), 34 (27%), 23 (18%), and 17 (14%) received DPd, DRd, DVd and "other" DCTs, respectively. Overall response rate was 47%. Median follow-up was 5.5 months (95% CI, 4.2-6.1). Median progression-free survival (PFS) was 5.5 months (95% CI, 4.2-7.8). Median overall survival was not reached (NR) with any regimen. Median PFS (months) was worst for penta-refractory MM (n = 8) vs quadruple refractory MM (n = 18) and others (n = 100) (2.2 [95% CI, 1-2.4] vs 3.1 [95% CI, 2.1-NR] vs 5.9 [95% CI, 5.0-NR]; P 2 prior therapies vs others (5.0 months [95% CI, 3.7-5.9] vs NR [95% CI, NR-NR]; P = .002). Non-hematologic toxicities included infections (38%), fatigue (32%), and infusion reactions (18%). Grade 3 or higher hematological toxicities were seen in 41% of patients. DCTs are effective in RRMM. ORR and PFS in heavily pretreated patients are lower than those reported in clinical trials.

Database: Medline

38. Daratumumab, lenalidomide, and dexamethasone (DRD) vs lenalidomide and dexamethasone (RD) in relapsed or refractory multiple myeloma (RRMM): Update on pollux

Author(s): Bahlis N.J.; Moreau P.; Nahi H.; Plesner T.; Goldschmidt H.; Suzuki K.; Orlowski R.Z.; Rabin N.; Leiba M.; Oriol A.; Chari A.; San-Miguel J.; Richardson P.G.; Usmani S.Z.; O'Rourke L.M.; Wu K.; Chiu C.; Qin X.; Casneuf T.; Dimopoulos M.A.

Source: Indian Journal of Hematology and Blood Transfusion; Nov 2017; vol. 33 (no. 1)

Publication Type(s): Conference Abstract

Abstract: Introduction: Daratumumab (DARA), a human CD38-targeting antibody, demonstrated a significant benefit to progression-free survival (PFS) when combined with standard of care in patients (pts) with RRMM. Objectives: To update data from a phase 3 study of DRd vs Rd in RRMM (POLLUX [NCT02076009]). Material and Methods: Eligible pts had received >= 1 prior line of therapy (LOT) and were not refractory to lenalidomide. Rd (25 mg PO lenalidomide on Days 1-21; 40 mg dexamethasone weekly) +/- DARA (16 mg/kg IV qw for Cycles 1 and 2, q2w for Cycles 3-6, then q4w until disease progression) was given in 28-day cycles. Pts were assessed for minimal residual disease (MRD) at sensitivities of 10-4, 10-5, and 10-6 via next-generation sequencing at time of suspected complete response (CR) and at 3 and 6 months after suspected CR. Results: Pts received a median (range) of 1 (1-11) prior LOT and 55% of pts had received prior treatment with IMiDs (18% lenalidomide). At a median follow-up of 25.4 months, DRd significantly prolonged PFS (median: not reached vs 17.5 months; HR, 0.41; 95% CI, 0.31-0.53; P<0.0001). Overall response rate (ORR) was significantly higher with DRd vs Rd (ORR; 93% vs 76%, P<0.0001). The rates of very good partial response or better (79% vs 48%) and CR or better (51% vs 21%) were also higher with DRd vs Rd (P<0.0001). MRD negativity was>3-fold higher across all sensitivity thresholds with DRd vs Rd (26% vs 6% at the 10-5 threshold; P<0.000001). PFS was prolonged in MRD-negative pts compared with MRD-positive pts. With follow up ongoing, 63 (22%) and 79 (28%) deaths had occurred in the DRd and Rd arms, respectively. Consistent with earlier analyses, no new safety signals were identified. Conclusions: At 25 months of follow up, a significant benefit to PFS, ORR, and MRD negativity was

observed with DRd vs Rd. The favorable safety profile of DRd was maintained with longer follow up. These data support the use of DRd in pts with RRMM who have received >= 1 prior LOT.

Database: EMBASE

39. A systematic literature review and network meta-analysis evaluating the efficacy of daratumumab-based regimens in patients with relapsed/refractory multiple myeloma

Author(s): Dimopoulos M.A.; Weisel K.; Kaufman J.; Sonneveld P.; Rizzo M.; Xu Y.; Fahrbach K.; Gaudig M.; Slavcev M.; Dearden L.; Lam A.

Source: Indian Journal of Hematology and Blood Transfusion; Nov 2017; vol. 33 (no. 1)

Publication Type(s): Conference Abstract

Abstract: Introduction: Daratumumab (DARA) is a monoclonal antibody for the treatment of relapsed or refractory multiple myeloma (RRMM). Two randomized controlled trials (RCTs) demonstrated that addition of DARA to standard of care significantly reduced risk of progression or death (POLLUX: DARA plus lenalidomide and dexamethasone [DRd] vs Rd; CASTOR: DARA plus bortezomib and dexamethasone [DVd] vs Vd). Objective: To compare DRd and DVd with relevant treatment options using a network meta-analysis (NMA). Material and Methods: In order to identify and assess RCTs of treatments for RRMM, a systematic literature review (SLR) was conducted. Data from trials that met the SLR's inclusion criteria and the most recent data from POLLUX and CASTOR were extracted and included in a Bayesian NMA to allow for indirect comparisons. Results: Data from RCTs identified by the SLR allowed formulation of two evidence networks. Network 1 included DRd and other immunomodulatory agent (IMiD)-containing regimens and Network 2 contained DVd and other IMiD-free regimens. Analysis using a fixed-effects model found that, among patients RRMM, DRd and DVd prolonged PFS compared with regimens in Networks 1 and 2, respectively, and there was a trend toward prolonged OS with both DRd and DVd (see Table 1). Conclusions: This NMA suggests that the combinations of DRd and DVd improve PFS in patients with RRMM when compared with other established and novel regimens; similar trends were found for OS.

Database: EMBASE

40. Daratumumab, bortezomib and dexamethasone (DVD) vs bortezomib and dexamethasone (VD) in relapsed or refractory multiple myeloma (RRMM): Efficacy and safety update (CASTOR)

Author(s): Weisel K.; Lentzsch S.; Mateos M.-V.; Hungria V.; Munder M.; Nooka A.K.; Mark T.; Quach H.; Scott E.C.; Lee J.-J.; Sonneveld P.; Casneuf T.; Chiu C.; Qin X.; Qi M.; Amin H.; Schecter J.M.; Thiyagarajah P.; Spencer A.

Source: Indian Journal of Hematology and Blood Transfusion; Nov 2017; vol. 33 (no. 1)

Publication Type(s): Conference Abstract

Abstract: Introduction: Daratumumab (DARA), a human, CD38-targeting antibody, is well tolerated and induces deep and durable responses in patients (pts) with RRMM. Objectives: To provide an update on the phase 3 study of DVd vs Vd (CASTOR [NCT02136134]) in RRMM. Material and Methods: Bortezomib-refractory pts were ineligible and all pts had received >= 1 prior line of therapy (LOT). Pts received Vd (1.3 mg/m2 bortezomib on Days 1, 4, 8, and 11; 20 mg dexamethasone on Days 1-2, 4-5, 8-9, and 11-12) +/- DARA (16 mg/kg IV weekly in Cycles 1-3, every 3 weeks for Cycles 4-8, then every 4 weeks until progression) for 8 21-day cycles. Minimal residual disease (MRD) was evaluated at sensitivities of 10-4, 10-5, and 10-6 using the ClonoSEQ assay at suspected complete response (CR) and at 6 and 12 months after the first dose of study treatment. Results: Pts had received a median (range) of 2 (1-10) prior LOTs. 21% of pts were refractory to

lenalidomide as their last prior LOT and 66% of pts had prior bortezomib exposure. At a median follow-up of 19.4 months, there was a significant benefit to progression-free survival (PFS) with DVd versus Vd (median: 16.7 vs 7.1 months; HR, 0.31; 95% CI, 0.24-0.39; P<0.0001), regardless of number of prior LOTs received. However, the greatest benefit to PFS occurred in pts with 1 prior LOT (median: not reached vs 7.9 months; HR, 0.19; 95% CI, 0.12-0.29; P<0.0001). Regardless of number of prior LOTs, the overall response rate was significantly higher with DVd vs Vd (84% vs 63%), along with very good partial response or better (62% vs 29%) and CR or better (29% vs 10%; P<0.0001 for all). At all sensitivities, MRD-negative rates were >= 4-fold higher with DVd vs Vd (12% vs 2% at 10-5). Prolonged PFS was observed in pts achieving MRD negativity versus those that remained MRD-positive. Thrombocytopenia was the most common grade 3/4 TEAE and occurred in 46% and 33% of pts who received DVd and Vd, respectively. Conclusions: Significant benefits to PFS, response, and MRD-negativity were observed in pts who received DVd compared with Vd. No new safety signals were reported. These data support the use of DVd in pts with RRMM, particularly those with 1 prior LOT.

Database: EMBASE

41. Effects of daratumumab on natural killer cells and impact on clinical outcomes in relapsed or refractory multiple myeloma.

Author(s): Casneuf, Tineke; Xu, Xu Steven; Adams, Homer C; Axel, Amy E; Chiu, Christopher; Khan, Imran; Ahmadi, Tahamtan; Yan, Xiaoyu; Lonial, Sagar; Plesner, Torben; Lokhorst, Henk M; van de Donk, Niels W C J; Clemens, Pamela L; Sasser, A Kate

Source: Blood advances; Oct 2017; vol. 1 (no. 23); p. 2105-2114

Publication Type(s): Journal Article

PubMedID: 29296857

Available at Blood advances - from PubMed Central

Abstract: Daratumumab, a human CD38 imunoglobulin G 1κ monoclonal antibody, has demonstrated clinical activity and a manageable safety profile in monotherapy and combination therapy clinical trials in relapsed and/or refractory multiple myeloma. CD38 is expressed at high levels on myeloma cells and, to a lesser extent, on immune effector cells, including natural killer (NK) cells, which are important for daratumumab-mediated antibody-dependent cellular cytotoxicity (ADCC). Here, the pharmacodynamic effects of daratumumab monotherapy on NK cells, and the effect of NK cell dynamics on daratumumab efficacy and safety, were assessed. Daratumumab, like other CD38 antibodies, reduced NK-cell counts in peripheral blood mononuclear cells (PBMCs) of healthy donors in vitro. Data on NK-cell counts, clinical efficacy, and adverse events were pooled from two single-agent daratumumab studies, GEN501 and SIRIUS. In daratumumab-treated myeloma patients, total and activated NK-cell counts reduced rapidly in peripheral blood after the first dose, remained low over the course of treatment, and recovered after treatment ended. There was a clear maximum effect relationship between daratumumab dose and maximum reduction in NK cells. Similar reductions were observed in bone marrow. PBMCs from daratumumab-treated patients induced lysis by ADCC of CD38+ tumor cells in vitro, suggesting that the remaining NK cells retained cytotoxic functionality. There was no relationship between NK-cell count reduction and the efficacy or safety profile of daratumumab. Furthermore, although NK cell numbers are reduced after daratumumab treatment, they are not completely depleted and may still contribute to ADCC, clinical efficacy, and infection control.

Database: Medline

42. Recent progress in relapsed multiple myeloma therapy: implications for treatment decisions.

Author(s): Moreau, Philippe; de Wit, Edwin

Source: British journal of haematology; Oct 2017; vol. 179 (no. 2); p. 198-218

Publication Type(s): Research Support, Non-u.s. Gov't Journal Article Review

PubMedID: 28556890

Abstract: The availability of novel therapies for the treatment of multiple myeloma has had a dramatic impact on the depth of response that can be expected on initial treatment. Despite these advances, disease relapse remains inevitable in most patients and brings with it a different set of priorities for therapy. The most recent wave of novel agents may have a particular impact in the relapsed setting. In this review, we examine the evidence currently available from clinical trials for the use of novel agents, particularly in the formation of triplet therapy. We consider data supporting the addition of the proteasome inhibitors carfilzomib and ixazomib, or the monoclonal antibodies elotuzumab or daratumumab, to a treatment backbone of lenalidomide and dexamethasone. The clinical data set is less well developed for the addition of a third agent to the combination of bortezomib and dexamethasone; nonetheless, data are presented supporting the addition of the histone deacetylase inhibitor panobinostat, or elotuzumab or daratumumab. While acknowledging the lack of head-to-head data on which to base comparisons between the numerous regimens, we collate the latest data in order to provide a basis on which to make clinical decisions in this rapidly advancing field.

Database: Medline

43. Emerging drugs and combinations to treat multiple myeloma.

Author(s): Larocca, Alessandra; Mina, Roberto; Gay, Francesca; Bringhen, Sara; Boccadoro, Mario

Source: Oncotarget; Sep 2017; vol. 8 (no. 36); p. 60656-60672

Publication Type(s): Journal Article Review

PubMedID: 28948001

Available at Oncotarget - from Europe PubMed Central - Open Access

Available at Oncotarget - from PubMed Central

Abstract: In the past few years, multiple targeted therapies and immunotherapies including second generation immunomodulatory drugs (pomalidomide) and proteasome inhibitors (carfilzomib, ixazomib), monoclonal antibodies and checkpoint inhibitors were approved for the treatment of myeloma or entered advanced phases of clinical testing. These agents showed significant activity in advanced myeloma and increased the available treatment strategies. Pomalidomide is well-tolerated and effective in patients with relapsed/refractory multiple myeloma who have exhausted any possible treatment with lenalidomide and bortezomib. Carfilzomib, a second-generation proteasome inhibitor, is active as a single agent and in combination with other anti-myeloma agents. Ixazomib is the first oral proteasome inhibitor to be evaluated in myeloma and is associated with a good safety profile and anti-myeloma activity in relapsed/refractory patients, even in those refractory to bortezomib. Monoclonal antibodies and immune checkpoint inhibitors are likely to play a major role in the treatment of myeloma over the next decade. In phase 3 studies, triplet regimens based on these agents combined with a backbone therapy (including lenalidomide, pomalidomide or bortezomib) were more efficacious than doublet regimens in patients with relapsed/refractory multiple myeloma, with limited additional toxic effects. This paper aims to provide an overview of the recent use of these agents for the treatment of myeloma, in particular focusing on the role of multi-agent combinations.

Database: Medline

44. Monoclonal Antibodies in Multiple Myeloma: A New Wave of the Future.

Author(s): Sherbenou, Daniel W; Mark, Tomer M; Forsberg, Peter

Source: Clinical lymphoma, myeloma & leukemia; Sep 2017; vol. 17 (no. 9); p. 545-554

Publication Type(s): Journal Article Review

PubMedID: 28734795

Abstract: In 2015, 2 monoclonal antibodies were approved for the treatment of relapsed or refractory multiple myeloma (RRMM), elotuzumab and daratumumab. Elotuzumab is a monoclonal IgG-κ antibody directed against SLAMF7 (signaling lymphocytic activation molecule F7), a cell surface receptor involved in natural killer cell activation. Daratumumab is a monoclonal IgG-κ antibody that binds to CD38, a transmembrane protein found on the surface of myeloma cells and responsible for cellular adhesion and ectoenzymatic activity. Both elotuzumab and daratumumab act through recruitment of the immune system to enhance cellular cytotoxicity directed against myeloma cells. Elotuzumab requires lenalidomide and dexamethasone combined to enhance progression-free survival in patients with RRMM, and daratumumab has both single-agent and combination activity with either lenalidomide or the proteasome inhibitor bortezomib in RRMM. The adverse effect profile of both agents mainly consists of allergic-type infusion reactions. Other considerations for monoclonal antibody use in the treatment of MM include the potential for interference in serum protein electrophoresis testing and cross-reactivity of daratumumab with CD38 present on red blood cells. In the present report, we discussed the clinical development of daratumumab and elotuzumab and newer immunologic approaches to the treatment of MM.

Database: Medline

45. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth.

Author(s): Dimopoulos, Meletios A; Lonial, Sagar; White, Darrell; Moreau, Philippe; Palumbo, Antonio; San-Miguel, Jesus; Shpilberg, Ofer; Anderson, Kenneth; Grosicki, Sebastian; Spicka, Ivan; Walter-Croneck, Adam; Magen, Hila; Mateos, Maria-Victoria; Belch, Andrew; Reece, Donna; Beksac, Meral; Bleickardt, Eric; Poulart, Valerie; Sheng, Jennifer; Sy, Oumar; Katz, Jessica; Singhal, Anil; Richardson, Paul

Source: British journal of haematology; Sep 2017; vol. 178 (no. 6); p. 896-905

Publication Type(s): Research Support, Non-u.s. Gov't Randomized Controlled Trial Journal Article Clinical Trial, Phase Iii

PubMedID: 28677826

Abstract: The randomized phase III ELOQUENT-2 study (NCT01239797) evaluated the efficacy and safety of elotuzumab + lenalidomide/dexamethasone (ELd) versus lenalidomide/dexamethasone (Ld) in relapsed/refractory multiple myeloma. ELd reduced the risk of disease progression/death by 30% versus Ld (hazard ratio [HR] 0·70). Median time from diagnosis was 3·5 years. We present extended 3-year follow-up data. Endpoints included progression-free survival (PFS), overall response rate (ORR) and interim overall survival (OS). Exploratory post-hoc analyses included impact of time from diagnosis and prior lines of therapy on PFS, and serum M-protein dynamic modelling. ORR was 79% (ELd) and 66% (Ld) (P = 0·0002). ELd reduced the risk of disease progression/death by 27% versus Ld (HR 0·73; P = 0·0014). Interim OS demonstrated a trend in favour of ELd (P = 0·0257); 1-, 2- and 3-year rates with ELd versus Ld were: 91% versus 83%, 73% versus 69% and 60% versus 53%. In

patients with ≥ median time from diagnosis and one prior therapy, ELd resulted in a 53% reduction in the risk of progression/death versus Ld (HR 0·47). Serum M-protein dynamic modelling showed slower tumour regrowth with ELd. Adverse events were comparable between arms. ELd provided a durable and clinically relevant improvement in efficacy, with minimal incremental toxicity.

Database: Medline

46. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma.

Author(s): Chari, Ajai; Suvannasankha, Attaya; Fay, Joseph W; Arnulf, Bertrand; Kaufman, Jonathan L; Ifthikharuddin, Jainulabdeen J; Weiss, Brendan M; Krishnan, Amrita; Lentzsch, Suzanne; Comenzo, Raymond; Wang, Jianping; Nottage, Kerri; Chiu, Christopher; Khokhar, Nushmia Z; Ahmadi, Tahamtan; Lonial, Sagar

Source: Blood; Aug 2017; vol. 130 (no. 8); p. 974-981

Publication Type(s): Research Support, Non-u.s. Gov't Clinical Trial, Phase I Multicenter Study Journal Article

PubMedID: 28637662

Available at Blood - from PubMed Central

Abstract: Daratumumab plus pomalidomide and dexamethasone (pom-dex) was evaluated in patients with relapsed/refractory multiple myeloma with ≥2 prior lines of therapy who were refractory to their last treatment. Patients received daratumumab 16 mg/kg at the recommended dosing schedule, pomalidomide 4 mg daily for 21 days of each 28-day cycle, and dexamethasone 40 mg weekly. Safety was the primary end point. Overall response rate (ORR) and minimal residual disease (MRD) by next-generation sequencing were secondary end points. Patients (N = 103) received a median (range) of 4 (1-13) prior therapies; 76% received ≥3 prior therapies. The safety profile of daratumumab plus pom-dex was similar to that of pom-dex alone, with the exception of daratumumab-specific infusion-related reactions (50%) and a higher incidence of neutropenia, although without an increase in infection rate. Common grade ≥3 adverse events were neutropenia (78%), anemia (28%), and leukopenia (24%). ORR was 60% and was generally consistent across subgroups (58% in double-refractory patients). Among patients with a complete response or better, 29% were MRD negative at a threshold of 10-5 Among the 62 responders, median duration of response was not estimable (NE; 95% confidence interval [CI], 13.6-NE). At a median follow-up of 13.1 months, the median progression-free survival was 8.8 (95% CI, 4.6-15.4) months and median overall survival was 17.5 (95% CI, 13.3-NE) months. The estimated 12-month survival rate was 66% (95% CI, 55.6-74.8). Aside from increased neutropenia, the safety profile of daratumumab plus pom-dex was consistent with that of the individual therapies. Deep, durable responses were observed in heavily treated patients. The study was registered at www.clinicaltrials.gov as #NCT01998971.

Database: Medline

47. Novel Immunotherapies for Multiple Myeloma.

Author(s): D'Agostino, Mattia; Boccadoro, Mario; Smith, Eric L

Source: Current hematologic malignancy reports; Aug 2017; vol. 12 (no. 4); p. 344-357

Publication Type(s): Journal Article Review

PubMedID: 28819882

Abstract:PURPOSE OF REVIEWThe treatment landscape of multiple myeloma is rapidly changing; however, despite improvement in patients' survival, it still remains a largely incurable disease. One hallmark of myeloma is substantial immune dysfunction leading to an increased infection rate and the inability of immune surveillance to detect neoplastic cells. Here, we critically analyze clinical approaches to harness the immune system to overcome this defect with a focus on antibody based and adoptive cellular therapies.RECENT FINDINGSClinical trials exploring these immunotherapies to treat myeloma are now well underway and show promising results. In relapsed myeloma, monoclonal antibodies directed against plasma cell antigens and immune checkpoints have already shown substantial efficacy. In parallel, trials of adoptive cellular therapy have exciting promise in myeloma, having induced dramatic responses in a handful of early study participants. Taken together, immunotherapeutic approaches hold enormous potential in the field of multiple myeloma and in the near future can be combined with or even replace the current standard of care.

Database: Medline

48. Pharmacokinetics of Daratumumab Following Intravenous Infusion in Relapsed or Refractory Multiple Myeloma After Prior Proteasome Inhibitor and Immunomodulatory Drug Treatment.

Author(s): Clemens, Pamela L; Yan, Xiaoyu; Lokhorst, Henk M; Lonial, Sagar; Losic, Nedjad; Khan, Imran; Jansson, Richard; Ahmadi, Tahamtan; Lantz, Kristen; Zhou, Honghui; Puchalski, Thomas; Xu, Xu Steven

Source: Clinical pharmacokinetics; Aug 2017; vol. 56 (no. 8); p. 915-924

Publication Type(s): Clinical Trial, Phase I Clinical Trial, Phase Ii Multicenter Study Journal Article

PubMedID: 27896689

Available at Clinical Pharmacokinetics - from PubMed Central

Abstract: Daratumumab is a CD38 monoclonal antibody recently approved for the treatment of multiple myeloma (MM). We report daratumumab pharmacokinetic data from GEN501, a phase I/II dose-escalation (0.005-24 mg/kg) and dose-expansion (8 or 16 mg/kg) study, and SIRIUS, a phase II study (8 or 16 mg/kg), in relapsed or refractory MM. Noncompartmental analysis was conducted to characterize daratumumab pharmacokinetics, and, in both studies, daratumumab exhibited nonlinear pharmacokinetic characteristics. Decreasing daratumumab clearance with increasing dose suggests saturation of target-mediated clearance at higher dose levels, whereas decreasing clearance over time with repeated dosing may be due to tumor burden reductions as CD38-positive cells are eliminated. These and other pharmacokinetic data analyses support the use of the recommended dose regimen of daratumumab (16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter) to rapidly saturate target-mediated clearance during weekly dosing and maintain saturation when dosing every 2 or 4 weeks.

Database: Medline

49. Daratumumab monotherapy compared with historical control data in heavily pretreated and highly refractory patients with multiple myeloma: An adjusted treatment comparison.

Author(s): Usmani, Saad Z; Diels, Joris; Ito, Tetsuro; Mehra, Maneesha; Khan, Imran; Lam, Annette

Source: American journal of hematology; Aug 2017; vol. 92 (no. 8); p. E146

Publication Type(s): Journal Article

PubMedID: 28474745

Available at American Journal of Hematology - from PubMed Central

Abstract: Daratumumab is a human CD38-directed monoclonal antibody approved in the United States as monotherapy for patients with multiple myeloma (MM) who have received ≥3 prior lines of therapy (LOTs), including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double refractory to a PI and an IMiD, and in combination with lenalidomide/dexamethasone or bortezomib/dexamethasone for patients with MM who have received ≥1 prior LOT. This study compared the efficacy of daratumumab monotherapy versus historical controls through adjusted treatment comparison. Patient-level data were pooled from two daratumumab monotherapy studies (16 mg/kg; GEN501 and SIRIUS) and two independent US databases (IMS LifeLink and OPTUM), which reflect treatments used in real-world patients with MM who received ≥3 prior LOTs or were double refractory to a PI and an IMiD. Using a multivariate proportional hazards regression model, the relative treatment effect of daratumumab versus historical controls was estimated, adjusting for imbalances in characteristics between cohorts. Baseline characteristics that differed between patients treated with daratumumab (N = 148) and historical control (N = 658) were prior treatment with pomalidomide (55% vs 15%) or carfilzomib (41% vs 28%) and triple/quadruple refractory status (64% vs 14%). The adjusted overall survival-hazard ratio (OS-HR) for daratumumab versus historical control was 0.33 (95% confidence interval, 0.24-0.46) compared with 0.46 (0.35-0.59) for unadjusted HR. Impact of adjustment was mainly driven by refractory status and prior pomalidomide/carfilzomib exposure. This adjusted treatment comparison suggests that daratumumab demonstrates improved OS compared with historical control data in heavily pretreated and highly refractory MM patients.

Database: Medline

50. Daratumumab for the treatment of multiple myeloma.

Author(s): Touzeau, Cyrille; Moreau, Philippe

Source: Expert opinion on biological therapy; Jul 2017; vol. 17 (no. 7); p. 887-893

Publication Type(s): Journal Article Review

PubMedID: 28434255

Abstract:INTRODUCTIONProteasome inhibitors and immunomodulatory drugs have contributed to the dramatic improvement in survival for patients with myeloma over the past decades. However, the disease typically relapses and new classes of drugs are needed. In 2015, two monoclonal antibodies were approved for the treatment of patients with relapsed multiple myeloma, and immunotherapy has rapidly become indispensable in the management of myeloma patients. Areas covered: Here, the authors discuss the published data regarding the mechanism of action, safety and clinical efficacy of the CD38-targeted monoclonal antibody daratumumab for the treatment of patients with multiple myeloma. Expert opinion: Daratumumab is indicated for myeloma patients who have received at least 3 prior therapies, including bortezomib, lenalidomide and pomalidomide. In 2016, daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone was approved for the treatment of patients with multiple myeloma who have received at least one prior therapy. Daratumumab displays an excellent safety profile. Moderate-grade infusion-related reactions occurring mostly during the first infusion are the main treatment-emergent adverse event. In the context of daratumumab therapy, attention should be paid to interference with blood compatibility testing and response assessment. Daratumumab-based combination therapies are currently under evaluation in relapsed and newly diagnosed patients.

Database: Medline

51. Emerging combination therapies for the management of multiple myeloma: The role of elotuzumab

Author(s): Chen W.-C.; Petros W.P.; Hazlehurst L.A.; Kanate A.S.; Craig M.

Source: Cancer Management and Research; Jul 2017; vol. 9 ; p. 307-314

Publication Type(s): Review

Available at Cancer management and research - from Europe PubMed Central - Open Access

Available at Cancer management and research - from PubMed Central

Abstract: Treatment options for patients with multiple myeloma (MM) have increased during the past decade. Despite the significant advances, challenges remain on which combination strategies will provide the optimal response for any given patient. Defining optimal combination strategies and corresponding companion diagnostics, that will guide clinical decisions are required to target relapsed or refractory multiple myeloma (RRMM) in order to improve disease progression, survival and quality of life for patients with MM. Elotuzumab is a humanized monoclonal antibody that targets signaling lymphocytic activation molecule F7 (SLAMF7), approved by the US Food and Drug Administration (FDA) in 2015 and the European Medicines Agency in 2016 for the treatment of MM. SLAMF7 is expressed in normal and malignant plasma cells and has lower expression on natural killer (NK) cells. Experimental evidence indicates that elotuzumab exhibits anti-myeloma activity through 1) antibody-dependent cell-mediated cytotoxicity, 2) enhancing NK cells cytotoxicity and 3) interfering with adhesion of MM cells to bone marrow stem cells (BMSCs). Although elotuzumab has no single agent activity in patients with RRMM who have received one to three prior therapies, the combination of elotuzumab with anti-myeloma agents, such as immunomodulatory drugs-lenalidomide, or proteasome inhibitors (PIs)-bortezomib, remarkably improved the overall response rates and progressionfree survival in MM patients with only minimal incremental toxicity. In brief, the clinical data for elotuzumab indicate that targeting SLAMF7 in combination with the use of conventional therapies is feasible and effective with a tolerable safety profile for the treatment of RRMM.

Database: EMBASE

52. The safety of daratumumab for the treatment of multiple myeloma.

Author(s): Cejalvo, María J; Ribas, Paz; de la Rubia, Javier

Source: Expert opinion on drug safety; Jun 2017; vol. 16 (no. 6); p. 753-760

Publication Type(s): Journal Article Review

PubMedID: 28490215

Abstract:INTRODUCTIONThe overall survival of patients with multiple myeloma (MM) has changed dramatically in the last decade. MM remains an incurable plasma cell disorder but immunotherapy with monoclonal antibodies (MoAbs) has emerged as a promising treatment. Areas covered: Fully published, clinical trials including patients with relapsed or refractory MM were reviewed. Safety data of daratumumab (DARA) single-agent or in combination regimens have been addressed. Additionally, infusion-related reactions, data on special populations, and DARA-interference with laboratory testing, including assessment of MM response in patients have also been addressed. Expert opinion: Daratumumab both as single agent and in combination regimens has shown a favorable safety profile without significant increase in toxicities. Extensive clinical development of DARA is currently ongoing and given the efficacy that has been seen with this drug in clinical trials, DARA is likely to change the landscape of myeloma treatment.

Database: Medline

53. Clinical Implications of Complex Pharmacokinetics for Daratumumab Dose Regimen in Patients With Relapsed/Refractory Multiple Myeloma.

Author(s): Xu, X S; Yan, X; Puchalski, T; Lonial, S; Lokhorst, H M; Voorhees, P M; Plesner, T; Liu, K; Khan, I; Jansson, R; Ahmadi, T; Ruixo, Jj Perez; Zhou, H; Clemens, P L

Source: Clinical pharmacology and therapeutics; Jun 2017; vol. 101 (no. 6); p. 721-724

Publication Type(s): Journal Article

PubMedID: 27859027

Available at Clinical Pharmacology & Therapeutics - from PubMed Central

Abstract: New therapeutic strategies are urgently needed to improve clinical outcomes in patients with multiple myeloma (MM). Daratumumab is a first-in-class, CD38 human immunoglobulin G1κ monoclonal antibody approved for treatment of relapsed or refractory MM. Identification of an appropriate dose regimen for daratumumab is challenging due to its target-mediated drug disposition, leading to time- and concentration-dependent pharmacokinetics. We describe a thorough evaluation of the recommended dose regimen for daratumumab in patients with relapsed or refractory MM.

Database: Medline

54. The multi-faceted potential of CD38 antibody targeting in multiple myeloma.

Author(s): Shallis, Rory M; Terry, Christopher M; Lim, Seah H

Source: Cancer immunology, immunotherapy : CII; Jun 2017; vol. 66 (no. 6); p. 697-703

Publication Type(s): Journal Article

PubMedID: 28341874

Abstract:CD38, an adenine dinucleotide phosphate (ADP) ribose cyclase and a cyclic ADP ribose hydrolase, is widely expressed on the surface of multiple myeloma (MM) cells. It is known to play a pivotal role in the downstream pathways that mediate MM cell growth, signal transduction, and adhesion. The clinical use of CD38 monoclonal antibodies (MoAbs), such as daratumumab, either as monotherapy or in combination with other anti-MM agents, has produced impressive results in patients who have failed standard MM therapy. CD38 MoAbs exhibit several cytotoxic mechanisms on MM cells. In addition to the classical effector mechanisms associated with antibody therapy, CD38 MoAbs induce MM apoptosis and clonal T-cell expansion. Here, we summarize the results of some pivotal clinical studies using a human CD38 MoAb, daratumumab, in patients with MM, discuss the anti-MM effector mechanisms induced by CD38 MoAbs, and review the potential tumor antigens that may be suitable targets for immunotherapy of MM. Finally, we present a paradigm of immunotherapy for MM patients using CD38 MoAbs followed by GM-CSF and an immune checkpoint inhibitor in patients who have undergone high dose chemotherapy and autologous stem cell transplant. CD38 MoAbs have emerged as a novel and ultimately very promising immunotherapeutic agent for MM because of its ability to induce MM cytotoxicity through both arms of the adaptive immune responses.

Database: Medline

55. Systematic review and meta-analysis of the efficacy and safety of novel monoclonal antibodies for treatment of relapsed/refractory multiple myeloma.

Author(s): Zhang, Tiantian; Wang, Sen; Lin, Tengfei; Xie, Jingmei; Zhao, Lina; Liang, Zhuoru; Li, Yangqiu; Jiang, Jie

Source: Oncotarget; May 2017; vol. 8 (no. 20); p. 34001-34017

Publication Type(s): Meta-analysis Journal Article Review

PubMedID: 28454113

Available at Oncotarget - from Europe PubMed Central - Open Access

Available at Oncotarget - from PubMed Central

Abstract: Although two newly launched monoclonal antibodies (mAbs), elotuzumab and daratumumab, performed well in patients with relapsed or relapsed/refractory multiple myeloma (RRMM), their efficacy and safety remain uncertain. We therefore performed a systematic review and meta-analysis of the most recent clinical trials that evaluated elotuzumab and/or daratumumab for the treatment of patients with RRMM. Our meta-analysis included 13 clinical trials with 2,402 patients participating. The overall response rate (ORR) was 57% (95% confidence interval [CI]: 38-76%), and the at least very good partial response rate (VGPR) was 32% (95% CI: 19-46%). mAb-based regimens prolonged progression-free survival (PFS, hazard ratio: 0.52, 95% CI: 0.36-0.75) compared to non-mAb-based regimens. Additionally, the efficacy of triplet regimens was superior to that of single or doublet regimens. The same trend was observed in a subgroup analysis of daratumumab and elotuzumab. The most common grade 3/4 adverse events included neutropenia, lymphopenia, thrombocytopenia, anemia, leukopenia, pneumonia, and fatigue. Elotuzumab and daratumumab improved the ORR, at least VGPR, and PFS compared to non-mAb-based regimens. In a pooled analysis, both mAbs had promising efficacy and safety profiles, particularly in triplet regimens. The same trend was observed in daratumumab- and elotuzumab-based regimens. Daratumumab triplet therapy (daratumumab, lenalidomide, and dexamethasone) was superior to other triplet regimens for the treatment of RRMM, and daratumumab monotherapy was more effective than either single agent in heavily pretreated MM patients, suggesting CD38 is an effective target for treatment of RRMM. Additional clinical studies of elotuzumab and daratumumab will be required to validate these results.

Database: Medline

56. A phase 2 safety study of accelerated elotuzumab infusion, over less than 1 h, in combination with lenalidomide and dexamethasone, in patients with multiple myeloma.

Author(s): Berenson, James; Manges, Robert; Badarinath, Suprith; Cartmell, Alan; McIntyre, Kristi; Lyons, Roger; Harb, Wael; Mohamed, Hesham; Nourbakhsh, Ali; Rifkin, Robert

Source: American journal of hematology; May 2017; vol. 92 (no. 5); p. 460-466

Publication Type(s): Clinical Trial, Phase Ii Journal Article

PubMedID: 28213943

Available at American Journal of Hematology - from Wiley Online Library Free Content - NHS

Abstract: Elotuzumab, an immunostimulatory SLAMF7-targeting monoclonal antibody, induces myeloma cell death with minimal effects on normal tissue. In a previous phase 3 study in patients with relapsed/refractory multiple myeloma (RRMM), elotuzumab (10 mg/kg, ~3-h infusion), combined with lenalidomide and dexamethasone, demonstrated durable efficacy and acceptable safety; 10% (33/321) of patients had infusion reactions (IRs; Grade 1/2: 29; Grade 3: 4). This phase 2 study (NCT02159365) investigated an accelerated infusion schedule in 70 patients with newly diagnosed multiple myeloma or RRMM. The primary endpoint was cumulative incidence of Grade 3/4 IRs by completion of treatment Cycle 2. Dosing comprised elotuzumab 10 mg/kg intravenously (weekly, Cycles 1-2; biweekly, Cycles 3+), lenalidomide 25 mg (daily, Days 1-21), and dexamethasone (28 mg orally and 8 mg intravenously, weekly, Cycles 1-2; 40 mg orally, weekly, Cycles 3+), in 28-day cycles. Premedication with diphenhydramine, acetaminophen, and ranitidine (or their equivalents)

was given as in previous studies. If no IRs occurred, infusion rate was increased in Cycle 1 from 0.5 to 2 mL/min during dose 1 (~2 h 50 min duration) to 5 mL/min for the entire infusion by dose 3 and also during all subsequent infusions (~1-h duration). Median number of treatment cycles was six. No Grade 3/4 IRs occurred; only one Grade 1 and one Grade 2 IR occurred, both during the first infusion. These data support the safety of a faster infusion of elotuzumab administered over ~1 h by the third dose, providing a more convenient alternative dosing option for patients.

Database: Medline

57. Monoclonal antibody therapy in multiple myeloma.

Author(s): Touzeau, C; Moreau, P; Dumontet, C

Source: Leukemia; May 2017; vol. 31 (no. 5); p. 1039-1047

Publication Type(s): Journal Article Review

PubMedID: 28210004

Available at Leukemia - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract: The therapeutic landscape of multiple myeloma (MM) has evolved spectacularly over the past decade with the discovery and validation of proteasome inhibitors and immunomodulatory agents as highly active agents, both in front-line therapy as well as in the relapse and maintenance settings. Although previous attempts to apply available monoclonal antibodies (Mabs) to the treatment of patients with MM has until recently been disappointing, novel targets specifically explored in the context of MM have recently lead to the first approvals of Mabs for the treatment of patients with MM. We have performed a literature search to identify preclinical targeting of MM, including in vitro and in vivo models using monoclonal antibodies, as well as clinical trials of monoclonal antibodies in patients with MM. Sources used were peer-reviewed publications, congress abstracts and on-line clinical trials data (such as clinicaltrials.gov). Several targets have been evaluated in preclinical models and a growing number of agents are being evaluated in clinical trials, as single agents or in combination and under various antibody formats. Two agents, targeting for the first time CD38 and SLAMF7, respectively, have recently been approved for the treatment of patients with MM. The recent approval of these two antibodies is expected to have a strong impact on treatment modalities and outcome in patients with MM, including both transplant eligible and elderly patients.

Database: Medline

58. Systematic Literature Review and Network Meta-Analysis of Treatment Outcomes in Relapsed and/or Refractory Multiple Myeloma.

Author(s): van Beurden-Tan, Chrissy H Y; Franken, Margreet G; Blommestein, Hedwig M; Uyl-de Groot, Carin A; Sonneveld, Pieter

Source: Journal of clinical oncology : official journal of the American Society of Clinical Oncology; Apr 2017; vol. 35 (no. 12); p. 1312-1319

Publication Type(s): Meta-analysis Journal Article Review

PubMedID: 28240968

Available at Journal of clinical oncology : official journal of the American Society of Clinical Oncology - from American Society of Clinical Oncology

Available at Journal of clinical oncology : official journal of the American Society of Clinical Oncology - from EBSCO (MEDLINE Complete)

Abstract: Purpose Since 2000, many new treatment options have become available for relapsed and/or refractory multiple myeloma (R/R MM) after a long period in which dexamethasone and melphalan had been the standard treatment. Direct comparisons of these novel treatments, however, are lacking. This makes it extremely difficult to evaluate the relative added value of each new treatment. Our aim was to synthesize all efficacy evidence, enabling a comparison of all current treatments for R/R MM. Methods We performed a systematic literature review to identify all publicly available phase III randomized controlled trial evidence. We searched Embase, MEDLINE, MEDLINE In-Process, Cochrane Central Register of Controlled Clinical Trials, and the Web site www.ClinicalTrials.gov . In addition, two trials presented at two international hematology congresses (ie, ASCO 2016 and European Hematology Association 2016) were added to include the most recent evidence. In total, 17 randomized controlled trials were identified, including 18 treatment options. The evidence was synthesized using a conventional network meta-analysis. To include all treatments within one network, two treatment options were combined: (1) bortezomib monotherapy and bortezomib plus dexamethasone, and (2) thalidomide monotherapy and thalidomide plus dexamethasone. Results The combination of daratumumab, lenalidomide, and dexamethasone was identified as the best treatment. It was most favorable in terms of (1) hazard ratio for progression-free survival (0.13; 95% credible interval, 0.09 to 0.19), and (2) probability of being best (99% of the simulations). This treatment combination reduced the risk of progression or death by 87% versus dexamethasone, 81% versus bortezomib plus dexamethasone, and 63% versus lenalidomide plus dexamethasone. Conclusion Our network meta-analysis provides a complete overview of the relative efficacy of all available treatments for R/R MM. Until additional data from randomized studies are available, on the basis of this analysis, the combination of daratumumab, lenalidomide, and dexamethasone seems to be the best treatment option.

Database: Medline

59. New developments in the treatment of multiple myeloma - Clinical utility of daratumumab

Author(s): McEllistrim C.; Krawczyk J.; O'Dwyer M.E.

Source: Biologics: Targets and Therapy; Apr 2017; vol. 11 ; p. 31-43

Publication Type(s): Review

Available at Biologics : targets & therapy - from Europe PubMed Central - Open Access

Available at Biologics : targets & therapy - from PubMed Central

Abstract: Multiple myeloma is a clonal disorder of plasma cells that is currently considered incurable. CD38 is a 46 kDa type II transmembrane glycoprotein that is highly expressed on myeloma cells. Daratumumab is a first in-class human IgG1 monoclonal antibody that targets CD38, and has antimyeloma effects through several mechanisms. Single-agent trials show surprising activity in heavily pretreated myeloma patients. Trials in the relapsed setting, where daratumumab is added to lenalidomide and dexamethasone or bortezomib and dexamethasone, have demonstrated significantly improved progression-free survival with acceptable toxicity. In this review, we discuss the mechanism of action, pharmacology and pharmacokinetics of daratumumab and review the available clinical data in detail. We examine how daratumumab interferes with transfusion testing due to the expression of CD38 on the red blood cells, leading to potential difficulties releasing blood products. Daratumumab also affects disease assessments in multiple myeloma, including serum protein electrophoresis, immunofixation and flow cytometry. Strategies to mitigate these effects are discussed. The optimal use of daratumumab has yet to be decided, and several trials are ongoing in the relapsed and upfront setting. We discuss the potential upfront role of this exciting therapy, which has significant potential for increased minimal residual disease negativity and improved progression-free survival even in high-risk groups. **Database:** EMBASE

Multiple myeloma

1. Prognostic role of neutrophil-lymphocyte ratio in multiple myeloma: a dose-response meta-analysis.

Author(s): Mu, Shidai; Ai, Lisha; Fan, Fengjuan; Sun, Chunyan; Hu, Yu

Source: OncoTargets and therapy; 2018; vol. 11 ; p. 499-507

Publication Type(s): Journal Article

PubMedID: 29416350

Available at OncoTargets and therapy - from Europe PubMed Central - Open Access

Available at OncoTargets and therapy - from PubMed Central

Abstract: BackgroundThe neutrophil-lymphocyte ratio (NLR), a biomarker for systematic inflammation, has been recently identified as a prognostic factor for various types of both solid and hematologic malignancies. Our study presented here was the first meta-analysis assessing the prognostic role of NLR in multiple myeloma (MM).MethodsWe systematically searched PubMed, Embase, and ISI Web of Science for relevant studies. Odds ratios (ORs) or hazards ratios (HRs) with corresponding 95% CIs are pooled to estimate the association between NLR and clinicopathological parameters or survival of MM patients.ResultsSeven trials with 1,971 MM patients were enrolled in the meta-analysis, and the results indicated that elevated pretreatment NLR was significantly associated with advanced tumor stages (International Staging System [ISS] III vs ISS I-II: OR 2.427, 95% CI: 1.268-4.467; and Durie-Salmon III vs Durie-Salmon I-II: OR 1.738, 95% CI: 1.133-2.665). Moreover, increased NLR also predicted poorer overall survival (HR 2.084, 95% CI: 1.341-3.238) and progression-free survival (HR 1.029, 95% CI: 1.016-1.042). And two-stage dose-response meta-analysis revealed linear association between increased NLR and risk of mortality in MM patients.ConclusionWe can conclude that MM patients with higher NLR are more likely to have poorer prognosis than those with lower NLR.

Database: Medline

2. Efficacy and safety of subcutaneous bortezomib versus intravenous bortezomib in patients with multiple myeloma: A systematic review and meta-analysis

Author(s): Zhang S.; Li J.; Liu P.

Source: International Journal of Clinical and Experimental Medicine; 2018; vol. 11 (no. 2); p. 445-452

Publication Type(s): Review

Abstract: Purpose: To compare the efficacy and safety of subcutaneous (SC) bortezomib versus intravenous (IV) bortezomib in multiple myeloma (MM) patients. Methods: A systematic literature search was performed from databases including the Cochrane Library, Embase, Medline, the Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Service System (CBM) and Wan Fang Database. Odds ratio (OR), and 95% confidence interval (CI) were calculated by RevMan 5.3. Subgroup analysis and publication bias were also conducted. Results: The meta-analysis included seven randomized controlled trials and six retrospective cohort studies, altogether involving 1,198 patients. Patients in SC administration group had lower risk of peripheral neuropathy (PN), both all grades (OR = 0.40, 95% CI 0.27 to 0.59, P < 0.001) and 3-4 grades (OR = 0.45, 95% CI 0.25 to 0.82, P < 0.001). Complete response (CR) and overall response rate (ORR) had no significant differences between the two groups (OR = 0.78, 95% CI 0.56 to 1.10, P = 0.17; OR = 0.82, 95% CI 0.63 to 1.07, P = 0.14, respectively). Conclusion: The efficacy of SC bortezomib was similar to IV bortezomib for MM patients and has a significant improved safety profile. **Database:** EMBASE

3. Proteasome inhibitor-based therapy for treatment of newly diagnosed multiple myeloma

Author(s): Vandross A.

Source: Seminars in Oncology; 2018

Publication Type(s): Article In Press

Abstract: Multiple myeloma is a hematologic malignancy that is unable to be cured and has significant impact throughout the world. Front line treatment has shifted but ultimately has landed on a bortezomib-based combination therapy. Carfilzomib is a next-generation proteasome inhibitor shown to improve both progression-free and overall survival in relapsed and refractory multiple myeloma in combination with lenalidomide and dexamethasone (KRd). Given the favorable response rates seen in phase II trials treating newly diagnosed myeloma, this combination is listed as a viable option for upfront treatment. This systematic review compares pharmacologic properties, clinical efficacy, and toxicities of carfilzomib- and bortezomib-based regimens.

Database: EMBASE

4. Efficacy and toxicity profile of carfilzomib based regimens for treatment of multiple myeloma: A systematic review.

Author(s): Mushtaq, Adeela; Kapoor, Vikas; Latif, Azka; Iftikhar, Ahmad; Zahid, Umar; McBride, Ali; Abraham, Ivo; Riaz, Irbaz Bin; Anwer, Faiz

Source: Critical reviews in oncology/hematology; May 2018; vol. 125 ; p. 1-11

Publication Type(s): Journal Article Review

PubMedID: 29650268

Abstract: Standard induction therapy for multiple myeloma is three-drug combination based on following classes of drugs: proteasome inhibitors, immunomodulators and steroids. Despite its notable efficacy, bortezomib has side effects like peripheral neuropathy (PNP) with reported incidence of grade ≥3 PNP between 2%-23% Schlafer et al., 2017. Carfilzomib (CFZ) has high selectivity and minimal off-target adverse effects including lower rates of PNP. CFZ is already approved for treatment of relapsed and refractory multiple myeloma (RRMM) as single agent as well as in combination with lenalidomide and/or dexamethasone. Extensive literature search identified a total of 1839 articles. Twenty-six articles (n = 5980) met the inclusion criteria, 15 in newly diagnosed multiple myeloma (NDMM) and 11 in RRMM group. CFZ demonstrates comparable or even better efficacy to bortezomib with much favorable AE profile. Deep, rapid and sustainable response using KRd with safer toxicity profile supports extension of KRd therapy to frontline therapy for all risk categories of MM. High incidence of grade ≥3 HTN underscores the importance of serial BP monitoring. In RRMM, CFZ has documented efficacy with standard 20-27mg/m2 dose. Further large-scale trials are needed to study benefit-to-risk profile of 20-56 and 20-70 mg/m2 dose of CFZ vs standard 20-27 mg/m2 dose in NDMM and RRMM.

Database: Medline

5. Use of depth of response to predict progression-free survival in relapsed or refractory multiple myeloma: Evaluation of results from 102 clinical trials.

Author(s): Mangal, Naveen; Salem, Ahmed Hamed; Menon, Rajeev M; Freise, Kevin J

Source: Hematological oncology; Apr 2018

Publication Type(s): Journal Article

PubMedID: 29672885

Abstract: Progression-free survival (PFS) is the standard endpoint for demonstration of clinical effectiveness of novel therapies in relapsed or refractory multiple myeloma (RRMM). However, the long evaluation times for PFS limits its usefulness in the development of new therapies. Therefore, the objective of this analysis was to determine the relationship between response rates and median PFS in RRMM. A database was systematically developed from 268 identified RRMM trials reported from 1999 to 2016. Evaluated covariates for the relationship between response rates and PFS included age, sex, drug class(es), and number of drug classes. One-hundred two (102) trials involving 136 cohorts were included in the meta-analysis, representing 13 322 patients in total. Regression analysis using response rates and median PFS indicated that the correlation between very good partial response (VGPR) or better and median PFS was higher (R^2 = 0.63) than the separately analyzed correlations between clinical benefit, overall response, or complete response rate and median PFS (R^2 = 0.47 - 0.52). Subsequent covariate analysis revealed that treatment with an immunomodulatory imide drug (IMiD) further improved the relationship (R^2 = 0.69), with a longer median PFS at a given VGPR or better rate when at least 1 drug treatment was an IMiD. Number of drug classes was not found to alter this relationship. In conclusion, VGPR or better rate can be used to predict the median PFS, with adjustment for the additional PFS provided by an IMiD.

Database: Medline

6. Prognostic Biomarkers in the Progression From MGUS to Multiple Myeloma: A Systematic Review.

Author(s): Cosemans, Charlotte; Oben, Bénedith; Arijs, Ingrid; Daniëls, Annick; Declercq, Jeroen; Vanhees, Kimberly; Froyen, Guy; Maes, Brigitte; Mebis, Jeroen; Rummens, Jean-Luc

Source: Clinical lymphoma, myeloma & leukemia; Apr 2018; vol. 18 (no. 4); p. 235-248

Publication Type(s): Journal Article Review

PubMedID: 29506935

Abstract: Multiple myeloma (MM), characterized by malignant plasma cells in the bone marrow, is consistently preceded by asymptomatic premalignant stage monoclonal gammopathy of undetermined significance (MGUS). These MGUS patients have an annual risk of 1% to progress to MM. Clinical, imaging, and genomic (genetic and epigenetic) factors were identified, whose presence increased the risk of progression from MGUS to MM. In this systematic review we summarize the currently identified clinical, imaging, and genomic biomarkers suggested to increase the progression risk or shown to be differentially expressed/present between both cohorts of patients. Despite the wide range of proposed markers, there are still no reliable biomarkers to individually predict which MGUS patient will progress to MM and which will not. Research on biomarkers in the progression from MGUS to MM will give more insight in the unknown pathogenesis of this hematological malignancy. This would improve research by elucidating new pathways and potential therapeutic targets as well as clinical management by closer follow-up and earlier treatment of high-risk MGUS patients.

Database: Medline

7. Health-Related Quality of Life after Autologous Stem Cell Transplantation for Multiple Myeloma.

Author(s): Chakraborty, Rajshekhar; Hamilton, Betty K; Hashmi, Shahrukh K; Kumar, Shaji K; Majhail, Navneet S

Source: Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation; Apr 2018

Publication Type(s): Journal Article Review

PubMedID: 29626515

Abstract: Autologous stem cell transplantation (ASCT) is an integral part of the frontline therapy in eligible multiple myeloma (MM) patients. The impact of ASCT on health-related quality of life (HRQoL) in myeloma has not been well described. We performed a systematic literature search to identify studies evaluating the impact of ASCT on HRQoL. Our search retrieved 12 relevant studies: 10 manuscripts and 2 conference abstracts. There was a widespread heterogeneity across studies in instruments used to measure HRQoL, time-points of measurement and statistical analysis. Only one study was a randomized controlled trial with HRQoL as a prespecified secondary end-point. The common theme that emerged from most studies is that ASCT leads to an immediate deterioration in HRQoL and increase in symptom burden. However, baseline HRQoL and symptom scores are regained as early as 1-2 months post-transplantation. Furthermore, an improvement in HRQoL and pain on long-term follow-up was noted in some studies. We describe opportunities for further research in this area, including routine incorporation of HRQoL as an end-point in transplant related clinical trials and need for trials investigating interventions that may improve short and long-term HRQoL in myeloma ASCT recipients.

Database: Medline

8. Microfluidic enrichment of plasma cells improves treatment of multiple myeloma.

Author(s): Gao, Li; Zeng, Yunjing; Luo, Xiaoqing; Chen, Yan; Kabeer, Mustafa H; Chen, Xuelian; Stucky, Andres; Loudon, William G; Li, Shengwen Calvin; Zhang, Xi; Zhong, Jiang F

Source: Molecular oncology; Apr 2018

Publication Type(s): Journal Article

PubMedID: 29638042

Abstract: Cytogenetic alterations form the basis for risk stratification for multiple myeloma (MM) and guide the selection of therapy; however, current pathology assays performed on bone marrow samples can produce false negatives due to the unpredictable distribution and rarity of MM cells. Here, we report on a microfluidic device used to facilitate CD45 depletion to enhance the detection of cytogenetic alterations in plasma cells. Bone marrow samples from 48 MM patients were each divided into two aliquots. One aliquot was subjected to classic flow cytometry and FISH. The other first went through CD45+ cell depletion, further enriched by microfluidic size selection. The enriched samples were then analyzed using flow cytometry and FISH, and compared to those analyzed using the classic method only. Unlike the traditional method, the microfluidic device removed the CD45+ leukocytes and specifically selected plasma cells from the remaining white blood cells. Therefore, the microfluidic method (MF-CD45-TACs) significantly increased the percentage of CD38+/CD138+ cells to 37.7%±20.4% (P<0.001) from 10.3%±8.5% in bone marrow. After the MF-CD45-TACs enrichment, the detection rate of IgH rearrangement, del(13q14), del(17p) and 1q21 gains rose to 56.3%(P<0.001), 37.5%(P<0.001), 22.9%(P<0.001) and 41.7% (P=0.001), respectively; all rates of detection were significantly increased compared to the classically analyzed samples. In this clinical trial, this microfluidic-assisted assay provided a precise detection of cytogenetic alterations in plasma cells (PCs) and improved clinical outcomes.

Database: Medline

9. Lenalidomide versus lenalidomide + dexamethasone prolonged treatment after second-line lenalidomide + dexamethasone induction in multiple myeloma.

Author(s): Lund, Johan; Gruber, Astrid; Lauri, Birgitta; Duru, Adil Doganay; Blimark, Cecilie; Swedin, Agneta; Hansson, Markus; Forsberg, Karin; Ahlberg, Lucia; Carlsson, Conny; Waage, Anders; Gimsing, Peter; Vangsted, Annette Juul; Frølund, Ulf; Holmberg, Erik; Gahrton, Gösta; Alici, Evren; Hardling, Mats; Mellqvist, Ulf-Henrik; Nahi, Hareth

Source: Cancer medicine; Apr 2018

Publication Type(s): Journal Article

PubMedID: 29673108

Available at Cancer medicine - from Wiley Online Library Free Content - NHS

Available at Cancer medicine - from Europe PubMed Central - Open Access

Abstract: Lenalidomide (Len) plus dexamethasone (Dex) is approved for the treatment of relapsed or refractory multiple myeloma (RRMM). It is possible that single-agent Len may be effective as prolonged treatment regimen in RRMM once patients demonstrate an initial response to Len+Dex induction. Patients with RRMM who responded to first-line Len+Dex in an observational study (NCT01430546) received up to 24 cycles of either Len (25 mg/day) or Len+Dex (25 mg/day and 40 mg/week) as prolonged treatment in a subsequent phase 2 clinical trial (NCT01450215). In the observational study (N = 133), median time to response was 1.7 (range 0.6-9.6) months. A complete response to all treatments received in both studies was observed in 11% of patients; very good partial response and partial response rates were 31% and 38%, respectively. Corresponding response rates in the subgroup of patients who did not enter the phase 2 trial (n = 71) were 3%, 18%, and 39%, respectively. Rates of disease progression at 2 years in the phase 2 trial were 47% versus 31% for Len versus Len+Dex (P = 0.14). After 36 months median follow-up in surviving patients, median time to progression was not reached with Len+Dex and was 24.9 months (95% confidence interval 12.5-not calculable, P < 0.001) with Len. Three-year OS among the total observational study population was 61% (95% CI, 52-69%). The corresponding rate among patients who entered the phase 2 clinical trial was 73% (95% CI, 60-83%) and was significantly lower among those patients who achieved ≥PR but did not proceed into the phase 2 trial (55%; P = 0.01). In the phase 2 trial, OS was 73% in both treatment arms (P = 0.70). Neutropenia and thrombocytopenia were more common with prolonged (phase 2 trial) versus short-term (observational study) Len administration but remained manageable. Prolonged treatment with Len with or without Dex provides sustained, clinically relevant responses and demonstrates an acceptable safety profile.

Database: Medline

10. Allogeneic stem-cell transplantation for multiple myeloma: A systematic review and meta-analysis from 2007 to 2017

Author(s): Yin X.; Tang L.; Fan F.; Sun C.; Hu Y.; Jiang Q.

Source: Cancer Cell International; Apr 2018; vol. 18 (no. 1)

Publication Type(s): Article

Available at Cancer Cell International - from BioMed Central

Available at Cancer Cell International - from Europe PubMed Central - Open Access

Abstract: Background: Despite recent advances, multiple myeloma (MM) remains incurable. However, the appearance of allogeneic stem cell transplantation (allo-SCT) through graft-versus-myeloma effect provides a potential way to cure MM to some degree. This systematic review aimed to evaluate the outcome of patients receiving allo-SCT and identified a series of prognostic factors

that may affect the outcome of allo-SCT. Patients/methods: We systematically searched PubMed, Embase, and the Cochrane Library from 2007.01.01 to 2017.05.03 using the keywords 'allogeneic' and 'myeloma'. Results: A total of 61 clinical trials involving 8698 adult patients were included. The pooled estimates (95% CI) for overall survival (OS) at 1, 2, 3 and 5 years were 70 (95% CI 56-84%), 62 (95% CI 53-71%), 52 (95% CI 44-61%), and 46 (95% CI 40-52%), respectively; for progression-free survival were 51 (95% CI 38-64%), 40 (95% CI 32-48%), 34 (95% CI 27-41%), and 27 (95% CI 23-31%), respectively; and for treatment-related mortality (TRM) were 18 (95% CI 14-21%), 21 (95% CI 17-25%), 20 (95% CI 13-26%), and 27 (95% CI 21-33%), respectively. Additionally, the pooled 100-day TRM was 12 (95% CI 5-18%). The incidences of grades II-IV acute graft-versus-host disease (GVHD) and chronic GVHD were 34 (95% CI 30-37%) and 51 (95% CI 46-56%), respectively. The incidences of relapse rate (RR) and death rate were 50 (95% CI 45-55%) and 51 (95% CI 45-57%), respectively. Importantly, disease progression was the most major cause of death (48%), followed by TRM (44%). The results failed to show an apparent benefit of allo-SCT for standard risk patients, compared with tandem auto-SCT. In contrast, all 14 trials in our study showed that patients with high cytogenetic risk after allo-SCT had similar OS and PFS compared to those with standard risk, suggesting that allo-SCT may overcome the adverse prognosis of high cytogenetic risk. Conclusion: Due to the lack of consistent survival benefit, allo-SCT should not be considered as a standard of care for newly diagnosed and relapsed standard-risk MM patients. However, for patients with high-risk MM who have a poor long-term prognosis, allo-SCT may be a strong consideration in their initial course of therapy or in first relapse after chemotherapy, when the risk of disease progression may outweigh the transplant-related risks. A large number of prospective randomized controlled trials were needed to prove the benefits of these therapeutic options.

Database: EMBASE

11. Autologous Transplantation for Newly Diagnosed Multiple Myeloma in the Era of Novel Agent Induction: A Systematic Review and Meta-analysis.

Author(s): Dhakal, Binod; Szabo, Aniko; Chhabra, Saurabh; Hamadani, Mehdi; D'Souza, Anita; Usmani, Saad Z; Sieracki, Rita; Gyawali, Bishal; Jackson, Jeffrey L; Asimakopoulos, Fotis; Hari, Parameswaran N

Source: JAMA oncology; Mar 2018; vol. 4 (no. 3); p. 343-350

Publication Type(s): Journal Article

PubMedID: 29302684

Abstract: ImportanceThe role of high-dose therapy with melphalan followed by autologous stem cell transplant (HDT/ASCT) in patients with multiple myeloma continues to be debated in the context of novel agent induction.ObjectiveTo perform a systematic review, conventional meta-analysis, and network meta-analysis of all phase 3 randomized clinical trials (RCTs) evaluating the role of HDT/ASCT.Data SourcesWe performed a systematic literature search of Cochrane Central, MEDLINE, and Scopus from January 2000 through April 2017 and relevant annual meeting abstracts from January 2014 to December 2016. The following search terms were used: "myeloma" combined with "autologous," "transplant," "myeloablative," or "stem cell."Study SelectionPhase 3 RCTs comparing HDT/ASCT with standard-dose therapy (SDT) using novel agents were assessed. Studies comparing single HDT/ASCT with bortezomib, lenalidomide, and dexamethasone consolidation and tandem transplantation were included for network meta-analysis.Data Extraction And SynthesisFor the random effects meta-analysis, we used hazard ratios (HRs) and corresponding 95% CIs.Main Outcomes and MeasuresThe primary outcome was progression-free survival (PFS). Overall survival (OS), complete response, and treatment-related mortality were secondary outcomes.ResultsA total of 4 RCTs (2421 patients) for conventional meta-analysis and 5 RCTs (3171 patients) for network

meta-analysis were selected. The combined odds for complete response were 1.27 (95% CI, 0.97-1.65; P = .07) with HDT/ASCT when compared with SDT. The combined HR for PFS was 0.55 (95% CI, 0.41-0.74; P < .001) and 0.76 for OS (95% CI, 0.42-1.36; P = .20) in favor of HDT. Meta-regression showed that longer follow-up was associated with superior PFS (HR/mo, 0.98; 95% CI, 0.96-0.99; P = .03) and OS (HR/mo, 0.90; 95% CI, 0.84-0.96; P = .002). For PFS, tandem HDT/ASCT had the most favorable HR (0.49; 95% CI, 0.37-0.65) followed by single HDT/ASCT with bortezomib, lenalidomide, and dexamethasone (HR, 0.53; 95% CI, 0.37-0.76) and single HDT/ASCT alone (HR, 0.68; 95% CI, 0.53-0.87) compared with SDT. For OS, none of the HDT/ASCT-based approaches had a significant effect on survival. Treatment-related mortality with HDT/ASCT was minimal (<1%).Conclusions and RelevanceThe results of the conventional meta-analysis and network meta-analysis of all the phase 3 RCTs showed that HDT/ASCT was associated with superior PFS with minimal toxic effects compared with SDT. Both tandem HDT/ASCT and single HDT/ASCT with bortezomib, lenalidomide, and dexamethasone were superior to single HDT/ASCT alone and SDT for PFS, but OS was similar across the 4 approaches. Longer follow-up may better delineate any OS benefit; however, is likely to be affected by effective postrelapse therapy.

Database: Medline

12. Multidrug resistance 1 (MDR1/ABCB1) gene polymorphism (rs1045642 C > T) and susceptibility to multiple myeloma: a systematic review and meta-analysis.

Author(s): Razi, Bahman; Anani Sarab, Gholamreza; Omidkhoda, Azadeh; Alizadeh, Shahab

Source: Hematology (Amsterdam, Netherlands); Mar 2018 ; p. 1-7

Publication Type(s): Journal Article

PubMedID: 29495954

Available at Hematology (Amsterdam, Netherlands) - from EBSCO (MEDLINE Complete)

Abstract:INTRODUCTIONSeveral studies have evaluated the association between the multidrug resistance 1 (MDR1) polymorphism (rs1045642 C > T) and multiple myeloma (MM). However, the results were not consistent. Therefore, to reach a comprehensive and reliable answer we determined the association of the MDR1 (rs1045642 C > T) polymorphism and MM in the context of meta-analysis.METHODSAll eligible studies published in EMBASE, PubMed, and Web of Science databases before July 2017 were reviewed. Subsequently, to assess the strength of association in the dominant model, recessive model, allelic model, homozygotes contrast, and heterozygotes contrast, pooled odds ratios and 95% confidence intervals (CIs) were calculated by the fixed effects model.RESULTSA total of four case-control studies with 395 MM cases and 418 healthy controls were included in the meta-analysis. The overall results showed no significant association between the MDR1 (rs1045642 C > T) polymorphism and the risk of MM in genetic models (dominant model: OR = 1.04, 95% CI = 0.78-1.38; recessive model: OR = 0.74, 95% CI = 0.52-1.06; allelic model: OR = 0.90, 95% CI = 0.73-1.11; TT vs. CC: OR = 0.80, 95% CI = 0.51-1.25; and CT vs. CC: OR = 1.12, 95% CI = 0.77-1.62). No evidence of publication bias was detected except for the analysis of the recessive model.CONCLUSIONThis meta-analysis suggests that the MDR1 C > T polymorphism was not associated with the risk of MM. To confirm these findings, further comprehensive and well-designed studies are needed.

Database: Medline

13. Carfilzomib-Associated Cardiovascular Adverse Events: A Systematic Review and Meta-analysis.

Author(s): Waxman, Adam J; Clasen, Suparna; Hwang, Wei-Ting; Garfall, Alfred; Vogl, Dan T; Carver, Joseph; O'Quinn, Rupal; Cohen, Adam D; Stadtmauer, Edward A; Ky, Bonnie; Weiss, Brendan M

Source: JAMA oncology; Mar 2018; vol. 4 (no. 3); p. e174519

Publication Type(s): Journal Article

PubMedID: 29285538

Abstract: ImportanceCardiovascular adverse events (CVAE) with carfilzomib in patients with multiple myeloma can be potentially life-threatening and remain incompletely characterized. We performed the first systematic review and meta-analysis of carfilzomib-associated CVAE.ObjectiveTo determine the incidence of carfilzomib-associated CVAE and to compare the rates of carfilzomib CVAE among different doses and companion therapies.Data SourcesPubMed, EMBASE, Web of Science, and clinicaltrials.gov were queried for the keywords "carfilzomib," "Kyprolis," and "PX-171" through January 1, 2017.Study SelectionPhase 1 to 3 prospective clinical trials of carfilzomib in patients with multiple myeloma with evaluable toxic effects data were eligible for meta-analysis.Data Extraction and SynthesisData were independently extracted by 2 reviewers following Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Pooled incidence rates and relative risks (for randomized trials) and 95% confidence intervals were calculated using a random effects model. Subgroup analyses were performed to assess study-level characteristics associated with CVAE.Main Outcomes and MeasuresCardiovascular adverse events were defined as heart failure, hypertension, ischemia, and arrhythmia. All-grade and grades 3 or higher AEs and study characteristics were recorded.ResultsA total of 514 studies were assessed for eligibility. Of those, 24 studies were eligible, including a total of 2594 patients with multiple myeloma. All-grade and grades 3 and higher CVAE were seen in 617 (18.1%) and 274 (8.2%), respectively. Phase 2 or 3 studies and carfilzomib doses of 45 mg/m2 or higher were associated with high-grade CVAE. Median age older than 65 years, prior myeloma therapies, and concurrent myeloma therapies were not associated with CVAE. For the 3 randomized clinical trials, the summary relative risk of all-grade and grade 3 or higher CVAE for patients receiving carfilzomib compared with noncarfilzomib-receiving control patients were 1.8 and 2.2, respectively.Conclusions and RelevanceCarfilzomib was associated with a significant incidence of CVAE, with higher rates seen with higher doses of carfilzomib. Phase 1 studies may be underdetecting CVAE. Future studies are needed to identify patients at high risk for CVAE, develop optimal monitoring strategies, and explore strategies to mitigate these risks.

Database: Medline

14. A Comparison of the Efficacy of Immunomodulatory-containing Regimens in Relapsed/Refractory Multiple Myeloma: A Network Meta-analysis.

Author(s): Dimopoulos, Meletios Athanasios; Kaufman, Jonathan L; White, Darrell; Cook, Gordon; Rizzo, Maria; Xu, Yingxin; Fahrbach, Kyle; Gaudig, Maren; Slavcev, Mary; Dearden, Lindsay; Lam, Annette

Source: Clinical lymphoma, myeloma & leukemia; Mar 2018; vol. 18 (no. 3); p. 163

Publication Type(s): Journal Article

PubMedID: 29456035

Abstract:BACKGROUNDPrevious network meta-analyses combined studies of immunomodulatory drug (IMiD)-containing and IMiD-free regimens, despite a lack of head-to-head randomized controlled trials to robustly link them. However, patients with relapsed or refractory multiple myeloma (RRMM) treated with IMiD-containing regimens differ from those treated with IMiD-free

regimens, especially relating to treatment history, which is an important treatment-effect modifier requiring clinical consideration when evaluating the most appropriate subsequent treatment options. A need exists to separately assess the efficacy of treatment regimens for patients who are suitable candidates for IMiD-containing and IMiD-free regimens. The presented analyses will enable clinicians to assess the best regimens to use in patients suitable for IMiD-containing regimens.MATERIALS AND METHODSWe used a Bayesian network meta-analysis to compare IMiD-containing regimens in patients with RRMM. Additionally, subgroup analyses were conducted stratified by previous therapy line, previous bortezomib therapy, and previous lenalidomide therapy.RESULTSThe results indicated that triplet combinations are more effective than doublet combinations. Of the triplet combinations, daratumumab, lenalidomide, dexamethasone (DRd) was significantly better in improving progression-free survival in patients with RRMM than were other IMiD-containing regimens (lenalidomide, dexamethasone [Rd]: hazard ratio [HR], 0.37; carfilzomib, Rd: HR, 0.54; elotuzumab, Rd: HR, 0.54; ixazomib, Rd: HR, 0.50). Similar trends were observed for overall survival and overall response. DRd showed the greatest probability of being the best treatment for all clinical efficacy outcomes. The subgroup analyses results were consistent with the base-case results.CONCLUSIONIn patients with RRMM who are suitable for an IMiD-containing regimen, DRd showed clear advantages in survival and response outcomes compared with other IMiD-containing regimens.

Database: Medline

15. Comparative Efficacy of Treatments for Previously Treated Multiple Myeloma: A Systematic Literature Review and Network Meta-analysis.

Author(s): Maiese, Eric M; Ainsworth, Claire; Le Moine, Jean-Gabriel; Ahdesmäki, Outi; Bell, Judith; Hawe, Emma

Source: Clinical therapeutics; Mar 2018; vol. 40 (no. 3); p. 480

Publication Type(s): Journal Article Review

PubMedID: 29500140

Available at Clinical therapeutics - from ProQuest (Hospital Premium Collection) - NHS Version

Abstract:PURPOSENew therapies, including daratumumab plus lenalidomide plus dexamethasone (DRd) and daratumumab plus bortezomib plus dexamethasone (DVd), have recently been approved in the United States for patients with multiple myeloma (MM) who have received at least 1 prior line of therapy. However, few treatments have been compared in head-to-head clinical trials to determine the most efficacious therapy. In an update of the POLLUX (Phase 3 Study Comparing DRd Versus Rd in Subjects with Relapsed or Refractory Multiple Myeloma [RRMM]) trial, median progression-free survival (PFS) for DRd was not reached; the hazard ratio compared with Rd was 0.41. In an update of the CASTOR (Phase 3 Study Comparing DVd Versus Vd in Subjects with RRMM) trial, median PFS for DVd was 16.7 months, compared with 7.1 months for Vd with a PFS hazard ratio of 0.31. A systematic literature review and network meta-analysis (NMA) was performed to estimate the relative efficacy of treatments for previously treated patients with MM.METHODSA systematic search of MEDLINE, EMBASE, BioSciences Information Service, and the Cochrane Library databases was conducted from initiation to September 2016. Abstracts published by international congresses (2014-2016) and bibliographies of pertinent systematic reviews and meta-analyses were also searched. Eligible studies consisted of randomized controlled trials (RCTs) or long-term follow-up studies with >1 treatment arm assessing the efficacy or safety of MM therapies. An NMA was conducted by using Bayesian fixed effect mixed-treatment comparisons. Outcomes considered were hazard ratios for PFS and odds ratios for overall response rate (ORR).FINDINGSIn total, 108 articles reporting 27 RCTs were included in the NMA. Data formed 2 evidence networks: RCTs with DRd and

RCTs with DVd. Primary analysis of PFS found that DRd and DVd had a higher probability of being the best treatments (probability, 0.997 and 0.999, respectively) and had the lowest risk of progression or death than other treatments approved by the US Food and Drug Administration for the treatment of MM. Results from sensitivity analyses using time to progression as a proxy for missing PFS data were consistent. DRd and DVd also showed improved ORR compared with other treatments. Subgroup analyses of PFS in patients treated with only 1 prior therapy were like the results of the primary analyses.IMPLICATIONSThis NMA provides comparative efficacy for MM treatments not studied in head-to-head RCTs. The NMA suggests that, compared with other approved MM treatments in the United States, DRd and DVd have a higher probability of providing the longest PFS in patients who have received at least 1 prior therapy and in patients who have received only 1 prior therapy.

Database: Medline

16. Role of Bone-Modifying Agents in Multiple Myeloma: American Society of Clinical Oncology Clinical Practice Guideline Update.

Author(s): Anderson, Kenneth; Ismaila, Nofisat; Flynn, Patrick J; Halabi, Susan; Jagannath, Sundar; Ogaily, Mohammed S; Omel, Jim; Raje, Noopur; Roodman, G David; Yee, Gary C; Kyle, Robert A

Source: Journal of clinical oncology : official journal of the American Society of Clinical Oncology; Mar 2018; vol. 36 (no. 8); p. 812-818

Publication Type(s): Journal Article

PubMedID: 29341831

Abstract: Purpose To update guideline recommendations on the role of bone-modifying agents in multiple myeloma. Methods An update panel conducted a targeted systematic literature review by searching PubMed and the Cochrane Library for randomized controlled trials, systematic reviews, meta-analyses, clinical practice guidelines, and observational studies. Results Thirty-five relevant studies were identified, and updated evidence supports the current recommendations. Recommendations For patients with active symptomatic multiple myeloma that requires systemic therapy with or without evidence of lytic destruction of bone or compression fracture of the spine from osteopenia on plain radiograph(s) or other imaging studies, intravenous administration of pamidronate 90 mg over at least 2 hours or zoledronic acid 4 mg over at least 15 minutes every 3 to 4 weeks is recommended. Denosumab has shown to be noninferior to zoledronic acid for the prevention of skeletal-related events and provides an alternative. Fewer adverse events related to renal toxicity have been noted with denosumab compared with zoledronic acid and may be preferred in this setting. The update panel recommends that clinicians consider reducing the initial pamidronate dose in patients with preexisting renal impairment. Zoledronic acid has not been studied in patients with severe renal impairment and is not recommended in this setting. The update panel suggests that bone-modifying treatment continue for up to 2 years. Less frequent dosing has been evaluated and should be considered in patients with responsive or stable disease. Continuous use is at the discretion of the treating physician and the risk of ongoing skeletal morbidity. Retreatment should be initiated at the time of disease relapse. The update panel discusses measures regarding osteonecrosis of the jaw. Additional information is available at www.asco.org/hematologic-malignancies-guidelines and www.asco.org/guidelineswiki .

Database: Medline

17. Model-Based Meta-Analysis for Multiple Myeloma: A Quantitative Drug-Independent Framework for Efficient Decisions in Oncology Drug Development.

Author(s): Teng, Zhaoyang; Gupta, Neeraj; Hua, Zhaowei; Liu, Guohui; Samnotra, Vivek; Venkatakrishnan, Karthik; Labotka, Richard

Source: Clinical and translational science; Mar 2018; vol. 11 (no. 2); p. 218-225

Publication Type(s): Journal Article

PubMedID: 29168990

Available at Clinical and Translational Science - from Europe PubMed Central - Open Access

Available at Clinical and Translational Science - from EBSCO (MEDLINE Complete)

Available at Clinical and Translational Science - from PubMed Central

Abstract: The failure rate for phase III trials in oncology is high; quantitative predictive approaches are needed. We developed a model-based meta-analysis (MBMA) framework to predict progression-free survival (PFS) from overall response rates (ORR) in relapsed/refractory multiple myeloma (RRMM), using data from seven phase III trials. A Bayesian analysis was used to predict the probability of technical success (PTS) for achieving desired phase III PFS targets based on phase II ORR data. The model demonstrated a strongly correlated (R2 = 0.84) linear relationship between ORR and median PFS. As a representative application of the framework, MBMA predicted that an ORR of ~66% would be needed in a phase II study of 50 patients to achieve a target median PFS of 13.5 months in a phase III study. This model can be used to help estimate PTS to achieve gold-standard targets in a target product profile, thereby enabling objectively informed decision-making.

Database: Medline

18. Ixazomib for Relapsed or Refractory Multiple Myeloma: Review from an Evidence Review Group on a NICE Single Technology Appraisal.

Author(s): Armoiry, Xavier; Connock, Martin; Tsertsvadze, Alexander; Cummins, Ewen; Melendez-Torres, G J; Royle, Pam; Clarke, Aileen

Source: PharmacoEconomics; Mar 2018

Publication Type(s): Journal Article Review

PubMedID: 29582405

Abstract: Ixazomib is an oral proteasome inhibitor used in combination with lenalidomide plus dexamethasone (IXA-LEN-DEX) and licensed for relapsed or refractory multiple myeloma. As part of a single technology appraisal (ID807) undertaken by the National Institute of Health and Care Excellence, the Evidence Review Group, Warwick Evidence was invited to independently review the evidence submitted by the manufacturer of ixazomib, Takeda UK Ltd. The main source of clinical effectiveness data about IXA-LEN-DEX came from the Tourmaline-MM1 randomized controlled trial in which 771 patients with relapsed or refractory multiple myeloma received either IXA-LEN-DEX or placebo-LEN-DEX as their second-, third-, or fourth-line treatment. Takeda estimated the cost effectiveness of IXA-LEN-DEX using a de-novo partitioned-survival model with three health states (pre-progression, post-progression, and dead). In their first submission, this model was used to estimate the cost effectiveness of IXA-LEN-DEX vs. bortezomib plus dexamethasone (BORT-DEX) in second-line treatment, and of IXA-LEN-DEX vs. LEN-DEX in third-line treatment. To estimate the relative clinical performance of IXA-LEN-DEX vs. BORT-DEX, Takeda conducted network meta-analyses for important outcomes. The network meta-analysis for overall survival was found to be flawed in several respects, but mainly because a hazard ratio input for one of the studies in the network had been inverted, resulting in a large inflation of the claimed superiority of IXA-LEN-DEX

over BORT-DEX and a considerable overestimation of its cost effectiveness. In subsequent submissions, Takeda withdrew second-line treatment as an option for IXA-LEN-DEX. The manufacturer's first submission comparing IXA-LEN-DEX with LEN-DEX for third-line therapy employed Tourmaline-MM1 data from third- and fourth-line patients as proxy for a third-line population. The appraisal committee did not consider this reasonable because randomization in Tourmaline-MM1 was stratified according to one previous treatment and two or more previous treatments. A further deficiency was considered to be the manufacturer's use of interim survival data rather than the most mature data available. A second submission from the company focussed on IXA-LEN-DEX vs. LEN-DEX as third- or fourth-line treatment (the two or more previous lines population) and a new patient access scheme was introduced. Covariate modeling of survival outcomes was proposed using the most mature survival data. The Evidence Review Group's main criticisms of the new evidence included: the utility associated with the pre-progression health state was overestimated, treatment costs of ixazomib were underestimated, survival models were still associated with great uncertainty, leading to clinically implausible anomalies and highly variable incremental cost-effectiveness ratio estimates, and the company had not explored a strong assumption that the survival benefit of IXA-LEN-DEX over LEN-DEX would be fully maintained for a further 22 years beyond the observed data, which encompassed only approximately 2.5 years of observation. The appraisal committee remained unconvinced that ixazomib represented a cost-effective use of National Health Service resources. Takeda's third submission offered new base-case parametric models for survival outcomes, a new analysis of utilities, and proposed a commercial access agreement. In a brief critique of the third submission, the Evidence Review Group agreed that the selection of appropriate survival models was problematic and at the request of the National Institute for Health Care and Excellence investigated external sources of evidence regarding survival outcomes. The Evidence Review Group considered that some cost and utility estimates in the submission may have remained biased in favor of ixazomib. As a result of their third appraisal meeting, the committee judged that for the two to three prior therapies population, and at the price agreed in a commercial access agreement, ixazomib had the potential to be cost effective. It was referred to the Cancer Drugs Fund so that further data could accrue with the aim of diminishing the clinical uncertainties.

Database: Medline

19. Pomalidomide-dexamethasone in refractory multiple myeloma: long-term follow-up of a multi-cohort phase II clinical trial.

Author(s): Ailawadhi, S; Mikhael, J R; LaPlant, B R; Laumann, K M; Kumar, S; Roy, V; Dingli, D; Bergsagel, P L; Buadi, F K; Rajkumar, S V; Fonseca, R; Gertz, M A; Kapoor, P; Sher, T; Hayman, S R; Stewart, A K; Dispenzieri, A; Kyle, R A; Gonsalves, W I; Reeder, C B; Lin, Y; Go, R S; Leung, N; Kourelis, T; Lust, J A; Russell, S J; Chanan-Khan, A A; Lacy, M Q

Source: Leukemia; Mar 2018; vol. 32 (no. 3); p. 719-728

Publication Type(s): Journal Article

PubMedID: 28860655

Abstract: Despite therapeutic advances, multiple myeloma remains incurable, with limited options for patients with refractory disease. We conducted a large, multi-cohort clinical trial testing various doses and treatment schedules of pomalidomide and dexamethasone (Pom/dex) in patients with refractory multiple myeloma. Overall, 345 patients were enrolled to six cohorts based on number and type of prior lines of therapy, pomalidomide dose and schedule. Median prior lines of therapy were three with near universal prior exposure to proteasome inhibitors and/or immunomodulatory drugs. A confirmed response rate of 35% was noted for all cohorts (range 23-65%) with higher

responses in cohorts with fewer prior lines of therapy. Median time to confirmed response was ⩽2 months and the longest progression-free survival and overall survival seen in any cohort were 13.1 and 47.9 months, respectively. Observed adverse reactions were as expected, with myelosuppression and fatigue being the most common hematologic and non-hematologic adverse events (AEs), respectively. Longer durations of treatment and response, higher response rates and fewer AEs were noted with the 2 mg pomalidomide dose. This is the longest follow-up data for Pom/dex in refractory multiple myeloma and will help shape the real-world utilization of this regimen.

Database: Medline

20. Patient-reported outcomes in relapsed/refractory multiple myeloma: a systematic review.

Author(s): Sparano, Francesco; Cavo, Michele; Niscola, Pasquale; Caravita, Tommaso; Efficace, Fabio

Source: Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer; Mar 2018

Publication Type(s): Journal Article Review

PubMedID: 29560502

Abstract:PURPOSEWe performed a systematic review to quantify the amount of evidence-based data available on patient-reported outcomes (PRO) in Relapsed/Refractory Multiple Myeloma (RRMM) patients and to examine the added value of such studies in supporting clinical decision-making.METHODSWe conducted a search in PubMed/Medline and the Cochrane Library to identify studies published between January 1990 and May 2017. All studies, regardless of the design, including patients with RRMM and also evaluating PRO were considered. For each study, we collected both PRO and traditional clinical outcomes, such as survival and toxicity information, based on a predefined data extraction form.RESULTSAfter having screened 1680 records, 11 studies were identified and these included six randomized controlled trials (RCT). Overall, there were five studies focusing on proteasome inhibitors (PIs), four on immunomodulatory drugs (IMiDs), one on both PIs and IMiDs, and one on monoclonal antibodies. Considering only RCTs, it was found that primary clinical efficacy endpoints frequently favored experimental arms, while (physician-reported) toxicity data did not. However, inspection of PRO data revealed novel information that often contrasted with standard toxicity, for example, by not indicating worse quality of life outcomes or symptom severity for patients enrolled in the experimental arms.CONCLUSIONSThere is paucity of evidence-based data regarding the impact of therapies on quality of life and symptom burden of patients with RRMM. Inclusion of PRO in future studies of patients with RRMM is needed to better inform clinical decision-making.

Database: Medline

21. Is it feasible to conduct a randomised controlled trial of pretransplant exercise (prehabilitation) for patients with multiple myeloma awaiting autologous haematopoietic stem cell transplantation? Protocol for the PREeMPT study.

Author(s): Keen, Carol; Skilbeck, Julie; Ross, Helen; Smith, Lauren; Collins, Karen; Dixey, Joanne; Walters, Stephen; Greenfield, Diana M; Snowden, John A; Mawson, Susan

Source: BMJ open; Mar 2018; vol. 8 (no. 3); p. e021333

Publication Type(s): Journal Article

PubMedID: 29525775

Available at BMJ Open - from HighWire - Free Full Text

Available at BMJ Open - from Europe PubMed Central - Open Access

Available at BMJ Open - from PubMed Central

Abstract:INTRODUCTIONWhile myeloma is an incurable malignancy, developments in disease management have led to increased life expectancy in recent years. Treatment typically involves stem-cell transplantation. Increased survival rates equate to more patients living with the burden of both the disease and its treatment for increasing number of years, rendering myeloma a long-term condition.Evidence exists to demonstrate the benefits of exercise for patients recovering from stem-cell transplantation, and prehabilitation-exercise before treatment-has been shown to be effective in other disease areas. To date there has been no research into prehabilitation in patients with myeloma awaiting transplantation treatment.Our objective is to determine whether it is feasible to conduct a randomised controlled trial into pretransplant exercise for patients with multiple myeloma who are awaiting autologous stem-cell transplantation.METHODS AND ANALYSISThis mixed methods study identifies patients with diagnosis of multiple myeloma who have been assigned to the autologous transplantation list and invites them to participate in six weekly sessions of individualised, supervised exercise while awaiting transplantation.Quantitative data to determine feasibility targets include rates of recruitment, adherence and adverse events, and outcome measures including 6 min walking distance test and quality of life.Qualitative interviews are undertaken with a purposive sample of patients to capture their experiences of the study and the intervention.ETHICS AND DISSEMINATIONEthics committee approval has been obtained. Dissemination will be through open-access publications and presentations and will seek to reach multiprofessional bases as well as patients and carer groups, addressing the widespread interest in this area of research.TRIAL REGISTRATION NUMBERNCT03135925; Pre-results.

Database: Medline

22. The role of ixazomib as an augmented conditioning therapy in salvage autologous stem cell transplant (ASCT) and as a post-ASCT consolidation and maintenance strategy in patients with relapsed multiple myeloma (ACCoRd [UK-MRA Myeloma XII] trial): study protocol for a Phase III randomised controlled trial.

Author(s): Striha, Alina; Ashcroft, A John; Hockaday, Anna; Cairns, David A; Boardman, Karen; Jacques, Gwen; Williams, Cathy; Snowden, John A; Garg, Mamta; Cavenagh, Jamie; Yong, Kwee; Drayson, Mark T; Owen, Roger; Cook, Mark; Cook, Gordon

Source: Trials; Mar 2018; vol. 19 (no. 1); p. 169

Publication Type(s): Journal Article

PubMedID: 29514706

Available at Trials - from BioMed Central

Available at Trials - from Europe PubMed Central - Open Access

Available at Trials - from EBSCO (MEDLINE Complete)

Available at Trials - from PubMed Central

Abstract:BACKGROUNDMultiple myeloma (MM) is a plasma cell tumour with an approximate annual incidence of 4500 in the UK. Therapeutic options for patients with MM have changed in the last decade with the arrival of proteasome inhibitors and immunomodulatory drugs. Despite these options, almost all patients will relapse post first-line autologous stem cell transplantation (ASCT). First relapse management (second-line treatment) has evolved in recent years with an expanding portfolio of novel agents, driving response rates influencing the durability of response. A second

ASCT, as part of relapsed disease management (salvage ASCT), has been shown to prolong the progression-free survival and overall survival following a proteasome inhibitor-containing re-induction regimen, in the Cancer Research UK-funded National Cancer Research Institute Myeloma X (Intensive) study. It is now recommended that salvage ASCT be considered for suitable patients by the International Myeloma Working Group and the National Institute for Health and Care Excellence NG35 guidance.METHODS/DESIGNACCoRd (Myeloma XII) is a UK-nationwide, individually randomised, multi-centre, multiple randomisation, open-label phase III trial with an initial single intervention registration phase aimed at relapsing MM patients who have received ASCT in first-line treatment. We will register 406 participants into the trial to allow 284 and 248 participants to be randomised at the first and second randomisations, respectively. All participants will receive re-induction therapy until maximal response (four to six cycles of ixazomib, thalidomide and dexamethasone). Participants who achieve at least stable disease will be randomised (1:1) to receive either ASCTCon, using high-dose melphalan, or ASCTAug, using high-dose melphalan with ixazomib. All participants achieving or maintaining a minimal response or better, following salvage ASCT, will undergo a second randomisation (1:1) to consolidation and maintenance or observation. Participants randomised to consolidation and maintenance will receive consolidation with two cycles of ixazomib, thalidomide and dexamethasone, and maintenance with ixazomib until disease progression.DISCUSSIONThe question of how best to maximise the durability of response to salvage ASCT warrants clinical investigation. Given the expanding scope of oral therapeutic agents, patient engagement with long-term maintenance strategies is a real opportunity. This study will provide evidence to better define post-relapse treatment in MM.TRIAL REGISTRATIONISRCTN, ISRCTN10038996 . Registered on 15 December 2016.

Database: Medline

23. Autologous/Allogeneic Hematopoietic Cell Transplantation versus Tandem Autologous Transplantation for Multiple Myeloma: Comparison of Long-Term Postrelapse Survival.

Author(s): Htut, Myo; D'Souza, Anita; Krishnan, Amrita; Bruno, Benedetto; Zhang, Mei-Jie; Fei, Mingwei; Diaz, Miguel Angel; Copelan, Edward; Ganguly, Siddhartha; Hamadani, Mehdi; Kharfan-Dabaja, Mohamed; Lazarus, Hillard; Lee, Cindy; Meehan, Kenneth; Nishihori, Taiga; Saad, Ayman; Seo, Sachiko; Ramanathan, Muthalagu; Usmani, Saad Z; Gasparetto, Christina; Mark, Tomer M; Nieto, Yago; Hari, Parameswaran

Source: Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation; Mar 2018; vol. 24 (no. 3); p. 478-485

Publication Type(s): Journal Article

PubMedID: 29079457

Abstract: We compared postrelapse overall survival (OS) after autologous/allogeneic (auto/allo) versus tandem autologous (auto/auto) hematopoietic cell transplantation (HCT) in patients with multiple myeloma (MM). Postrelapse survival of patients receiving an auto/auto or auto/allo HCT for MM and prospectively reported to the Center for International Blood and Marrow Transplant Research between 2000 and 2010 were analyzed. Relapse occurred in 404 patients (72.4%) in the auto/auto group and in 178 patients (67.4%) in the auto/allo group after a median follow-up of 8.5 years. Relapse occurred before 6 months after a second HCT in 46% of the auto/allo patients, compared with 26% of the auto/auto patients. The 6-year postrelapse survival was better in the auto/allo group compared with the auto/auto group (44% versus 35%; P = .05). Mortality due to MM was 69% (n = 101) in the auto/allo group and 83% (n = 229) deaths in auto/auto group. In multivariate analysis, both cohorts had a similar risk of death in the first year after relapse (hazard ratio [HR], .72; P = .12); however, for time points beyond 12 months after relapse, overall survival

was superior in the auto/allo cohort (HR for death in auto/auto =1.55; P = .005). Other factors associated with superior survival were enrollment in a clinical trial for HCT, male sex, and use of novel agents at induction before HCT. Our findings shown superior survival afterrelapse in auto/allo HCT recipients compared with auto/auto HCT recipients. This likely reflects a better response to salvage therapy, such as immunomodulatory drugs, potentiated by a donor-derived immunologic milieu. Further augmentation of the post-allo-HCT immune system with new immunotherapies, such as monoclonal antibodies, checkpoint inhibitors, and others, merit investigation.

Database: Medline

24. Bortezomib maintenance therapy in transplant-ineligible myeloma patients who plateaued after bortezomib-based induction therapy: a multicenter phase II clinical trial.

Author(s): Isoda, Atsushi; Murayama, Kayoko; Ito, Shigeki; Kohara, Yoichi; Iino, Masaki; Miyazawa, Yuri; Matsumoto, Morio; Handa, Hiroshi; Imai, Yosuke; Ishiguro, Takuro; Izumita, Wataru; Kitano, Kiyoshi; Hirabayashi, Yukio; Nakazawa, Hideyuki; Ishida, Fumihiro; Mitsumori, Toru; Kirito, Keita; Chou, Takaaki; Murakami, Hirokazu; Kanshinetsu Multiple Myeloma Study Group

Source: International journal of hematology; Mar 2018

Publication Type(s): Journal Article

PubMedID: 29594921

Abstract: In the era of novel therapeutic agents for multiple myeloma (MM), both the significance of achieving the plateau phase and the efficacy of subsequent maintenance therapy remain unclear. In the present study, we evaluated the efficacy and safety of bortezomib maintenance therapy (biweekly for 1 year) in transplant-ineligible MM patients who plateaued after bortezomib-based induction therapy. Of 36 evaluable patients, the overall response rate during induction therapy was 61%, with a stringent complete response in 6%, a complete response in 6%, a very good partial response in 17%, and a partial response in 33%. Twenty patients achieved the plateau phase and subsequently received bortezomib maintenance therapy. Median progression-free survival from the induction and maintenance therapies was 13.8 months (95% confidence interval, 11.4-23.7 months) and 10.7 months (95% confidence interval, 3.7-10.7 months), respectively. During maintenance therapy, there were no cases with grade ≥ 2 peripheral neuropathy, nor was there any improvement in the quality of the response. In conclusion, although maintenance therapy with biweekly bortezomib for up to 1 year was feasible, plateau-oriented bortezomib induction therapy followed by bortezomib maintenance therapy was not adequate in newly diagnosed transplant-ineligible MM patients.

Database: Medline

25. Immunomodulatory drugs and the risk of serious infection in multiple myeloma: systematic review and meta-analysis of randomized and observational studies

Author(s): Chen M.; Xu C.; Wang X.; Zhang X.; Zhao Y.; Mao B.

Source: Annals of Hematology; Mar 2018 ; p. 1-20

Publication Type(s): Article In Press

Abstract: The effect of immunomodulatory drugs (IMiDs) on serious infection remains uncertain. We therefore conducted a systematic review and meta-analysis to assess the possible impact of IMiDs on serious infection in patients with multiple myeloma (MM). We searched randomized controlled trials (RCTs) and observational studies from databases that addressed the effect of IMiDs on serious infection in patients with MM. We pooled data from RCTs and observational studies separately and

used the GRADE approach to rate the quality of evidence. Rates in patients with individual IMiDs at different treatment status ranged from 7.00 to 23.00%. The use of thalidomide- or lenalidomide-based regimen induction therapy for autologous stem cell transplantation (ASCT)-ineligible patients suggests increase in serious infection (RR = 1.59, 95% CI 1.31-1.93, p < 0.01). Compared to conventional therapy, IMiDs' induction in ASCT-eligible patients significantly decreases the risk of serious infection (RR = 0.82, 95% CI 0.72-0.94, p < 0.01). Lenalidomide-based therapy was associated with a significant increase in risk of serious infection in patients treated compared with conventional therapy (RR = 2.45, 95% CI 1.57-3.83, p < 0.01). The current evidence suggests that patients with MM treated with IMiDs are at a high risk of serious infection.

Database: EMBASE

26. Cardiotoxicity associated with carfilzomib: systematic review and meta-analysis.

Author(s): Shah, Chintan; Bishnoi, Rohit; Jain, Ankur; Bejjanki, Harini; Xiong, Sican; Wang, Yu; Zou, Fei; Moreb, Jan S

Source: Leukemia & lymphoma; Feb 2018 ; p. 1-13

Publication Type(s): Journal Article

PubMedID: 29465266

Abstract: Carfilzomib is a second-generation proteasome inhibitor (PI) that is approved for patients with relapsed or refractory multiple myeloma (RRMM) who failed ≥1 prior lines of therapy. We performed a systematic review of carfilzomib literature with meta-analysis to determine cumulative incidence of cardiotoxicity. After the literature search, we included a total of 29 eligible phase I/II, phase II and phase III clinical trials which used carfilzomib. The cumulative incidence and overall odds ratios (OR) were calculated with random effect model, using 'R' software with metaphor package. A total of 4164 patients with various malignancies were included. The overall estimated cumulative incidence of cardiotoxicity was 8.68% and 4.92%, respectively, for all-grade and high-grade (≥ grade 3) toxicity, which seems higher than other PIs. Compared to control group, the odds of developing cardiotoxicity due to carfilzomib was significantly higher with OR of 2.03 (95% CI: 1.19-3.46, p = .010) and 2.04 (95% CI: 1.31-3.17, p = .002) for all-grades and high grades, respectively. Concomitant immunomodulatory agents seem to increase the risk of cardiotoxicity (high-grade cardiotoxicity 6.45% and 4.34% with and without concomitant immunomodulatory agents, respectively (p = .033)). There was no variation in the incidence of cardiotoxicity among newly diagnosed versus RRMM (p = .38), and high versus standard dose carfilzomib (p = .86).

Database: Medline

27. Acupuncture for reduction of symptom burden in multiple myeloma patients undergoing autologous hematopoietic stem cell transplantation: a randomized sham-controlled trial.

Author(s): Deng, Gary; Giralt, Sergio; Chung, David J; Landau, Heather; Siman, Jonathan; Search, Benjamin; Coleton, Marci; Vertosick, Emily; Shapiro, Nathan; Chien, Christine; Wang, Xin S; Cassileth, Barrie; Mao, Jun J

Source: Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer; Feb 2018; vol. 26 (no. 2); p. 657-665

Publication Type(s): Journal Article

PubMedID: 28920142

Abstract:PURPOSEHematopoietic stem cell transplantation (HCT) is potentially curative for a number of hematologic malignancies, but is associated with high symptom burden. We conducted a randomized sham-controlled trial (RCT) to evaluate efficacy and safety of acupuncture as an integrative treatment for managing common symptoms during HCT.METHODSAdult patients with multiple myeloma undergoing high-dose melphalan followed by autologous HCT (AHCT) were randomized to receive either true or sham acupuncture once daily for 5 days starting the day after chemotherapy. Patients and clinical evaluators, but not acupuncturists, were blinded to group assignment. Symptom burden, the primary outcome was assessed with the MD Anderson Symptom Inventory (MDASI) at baseline, during transplantation, and at 15 and 30 days post transplantation.RESULTSAmong 60 participants, true acupuncture produced nonsignificant reductions in overall MDASI core symptom scores and symptom interference scores during transplantation (P = .4 and .3, respectively), at 15 days (P = .10 and .3), and at 30 days posttransplantation (P = .2 and .4) relative to sham. However, true acupuncture was significantly more efficacious in reducing nausea, lack of appetite, and drowsiness at 15 days (P = .042, .025, and .010, respectively). Patients receiving sham acupuncture were more likely to increase pain medication use posttransplantation (odds ratio 5.31, P = .017).CONCLUSIONSAcupuncture was well tolerated with few attributable adverse events. True acupuncture may prevent escalation of symptoms including nausea, lack of appetite, and drowsiness experienced by patients undergoing AHCT, and reduce the use of pain medications. These findings need to be confirmed in a future definitive study.TRIAL REGISTRATIONNCT01811862.

Database: Medline

28. Phase II clinical trial of lenalidomide and dexamethasone therapy in Japanese elderly patients with newly diagnosed multiple myeloma to determine optimal plasma concentration of lenalidomide.

Author(s): Kobayashi, Takahiro; Miura, Masatomo; Niioka, Takenori; Abumiya, Maiko; Ito, Fumiko; Kobayashi, Isuzu; Ikeda, Sho; Yoshioka, Tomoko; Kameoka, Yoshihiro; Takahashi, Naoto

Source: Therapeutic drug monitoring; Feb 2018

Publication Type(s): Journal Article

PubMedID: 29494421

Abstract:BACKGROUNDThe authors conducted a phase II clinical trial of lenalidomide and dexamethasone combination therapy in Japanese elderly patients with newly diagnosed multiple myeloma to evaluate its safety and efficacy and to determine whether safety and efficacy correlate with the plasma concentration of lenalidomide.METHODSForty patients received oral lenalidomide on days 1-21 of a 28-day cycle in addition to weekly doses of dexamethasone. Plasma concentrations of lenalidomide were measured, and the area under the concentration-time curve from 0 to 24 h (AUC0-24) of lenalidomide was predicted using a formula the authors previously reported in this journal.RESULTSThe median age was 75.5 years. Twenty-one patients had renal impairment severe enough to require dose adjustment of lenalidomide. The median initial doses of lenalidomide and dexamethasone were 12.5 and 20 mg, respectively. The overall response rate was 68.6%, and the 2-year overall survival rate was 88.5%. There was no correlation between the response rate and plasma concentration of lenalidomide. Grade 3 to 4 adverse events were observed in 57.5% of patients. The AUC0-24 of lenalidomide was significantly higher in patients with grade 3 to 4 adverse events than in those who did not suffer from adverse events (median = 4852.0 ng h/mL vs. 2464.9 ng h/mL, P = 0.027). Receiver-operating characteristic (ROC) curve analysis showed that the AUC0-24 of lenalidomide was a good predictor of grade 3 to 4 adverse events, with an area under the ROC curve of 0.758 (95% CI = 0.572-0.943, P = 0.027). The cutoff value for best prediction of grade 3 to 4

adverse events was 2613.5 ng h/mL (sensitivity 86.7%, specificity 54.5%). Multivariate logistic analysis confirmed the significance of this cutoff value.CONCLUSIONSThese data suggest that overexposure to lenalidomide could contribute to toxicity. Furthermore, the predicted cutoff value of AUC0-24 can be clinically used to prevent severe adverse events.

Database: Medline

29. Bortezomib plus dexamethasone vs thalidomide plus dexamethasone for relapsed or refractory multiple myeloma.

Author(s): Iida, Shinsuke; Wakabayashi, Masashi; Tsukasaki, Kunihiro; Miyamoto, Kenichi; Maruyama, Dai; Yamamoto, Kazuhito; Takatsuka, Yoshifusa; Kusumoto, Shigeru; Kuroda, Junya; Ando, Kiyoshi; Kikukawa, Yoshitaka; Masaki, Yasufumi; Kobayashi, Miki; Hanamura, Ichiro; Asai, Hiroaki; Nagai, Hirokazu; Shimada, Kazuyuki; Tsukamoto, Norifumi; Inoue, Yoshiko; Tobinai, Kensei

Source: Cancer science; Feb 2018

Publication Type(s): Journal Article

PubMedID: 29478257

Available at Cancer science - from Europe PubMed Central - Open Access

Available at Cancer science - from EBSCO (MEDLINE Complete)

Abstract:A randomized phase II selection design study (JCOG0904) was carried out to evaluate the more promising regimen between bortezomib (Bor) plus dexamethasone (Dex; BD) and thalidomide (Thal) plus Dex (TD) in Bor and Thal-naïve patients with relapsed or refractory multiple myeloma (RRMM). Patients ≥20 and <80 years old with a documented diagnosis of symptomatic multiple myeloma (MM) who received one or more prior therapies were randomized to receive BD (Bor 1.3 mg/m2) or TD (Thal 200 mg/d). In both arms, 8 cycles of induction (3-week cycle) were followed by maintenance phase (5-week cycle) until disease progression, unacceptable toxicity, or patient refusal. The primary end-point was 1-year progression-free survival (PFS). Forty-four patients were randomized and assigned to receive BD and TD (n = 22, each group). At a median follow-up of 34.3 months, the 1-year PFS in the BD and TD arms were 45.5% (95% confidence interval (CI), 24.4%-64.3%) and 31.8% (95% CI, 14.2%-51.1%), respectively, and the overall response rates were 77.3% and 40.9%, respectively. The 3-year overall survival (OS) was 70.0% (95% CI, 44.9%-85.4%) in the BD, and 48.8% (95% CI, 25.1%-69.0%) in the TD arm. Among grade 3/4 adverse events, thrombocytopenia (54.5% vs 0.0%) and sensory peripheral neuropathy (22.7% vs 9.1%) were more frequent in BD when compared with the TD arm. Patients treated with BD had better outcomes than those treated with TD with regard to 1-year PFS and 3-year OS. Thus, BD was prioritized over TD for further investigations in Bor and Thal-naïve RRMM patients. (Clinical trial registration no. UMIN000003135.).

Database: Medline

30. Pomalidomide with Dexamethasone for Treating Relapsed and Refractory Multiple Myeloma Previously Treated with Lenalidomide and Bortezomib: An Evidence Review Group Perspective of an NICE Single Technology Appraisal.

Author(s): Büyükkaramikli, Nasuh C; de Groot, Saskia; Fayter, Debra; Wolff, Robert; Armstrong, Nigel; Stirk, Lisa; Worthy, Gill; Albuquerque de Almeida, Fernando; Kleijnen, Jos; Al, Maiwenn J

Source: PharmacoEconomics; Feb 2018; vol. 36 (no. 2); p. 145-159

Publication Type(s): Journal Article Review

PubMedID: 29086363

Available at PharmacoEconomics - from PubMed Central

Abstract: The National Institute for Health and Care Excellence (NICE), as part of the institute's single technology appraisal (STA) process, invited the manufacturer of pomalidomide (POM; Imnovid®, Celgene) to submit evidence regarding the clinical and cost effectiveness of the drug in combination with dexamethasone (POM + LoDEX) for the treatment of relapsed and refractory multiple myeloma (RRMM) after at least two regimens including lenalidomide (LEN) and bortezomib (BOR). Kleijnen Systematic Reviews Ltd (KSR) and Erasmus University Rotterdam were commissioned as the Evidence Review Group (ERG) for this submission. The ERG reviewed the evidence submitted by the manufacturer, validated the manufacturer's decision analytic model, and conducted exploratory analyses in order to assess the robustness and validity of the presented clinical and cost-effectiveness results. This paper describes the company submission, the ERG assessment, and NICE's subsequent decisions. The company conducted a systematic review to identify studies comparing POM with comparators outlined in the NICE scope: panobinostat with bortezomib and dexamethasone (PANO + BOR + DEX), bendamustine with thalidomide and dexamethasone (BTD) and conventional chemotherapy (CC). The main clinical effectiveness evidence was obtained from MM-003, a randomized controlled trial (RCT) comparing POM + LoDEX with high-dose dexamethasone (HiDEX; used as a proxy for CC). Additional data from other studies were also used as nonrandomized observational data sources for the indirect treatment comparison of POM + LoDEX with BTD and PANO + BOR + DEX. Covariate or treatment switching adjustment methods were used for each comparison. The model developed in Microsoft® Excel 2010 using a semi-Markov partitioned survival structure, submitted in the original submission to NICE for TA338, was adapted for the present assessment of the cost effectiveness of POM + LoDEX. Updated evidence from the clinical-effectiveness part was used for the survival modelling of progression-free survival and overall survival. For POM + LoDEX, the patient access scheme (PAS) discount was applied to the POM price. Three separate comparisons were conducted for each comparator, each comparison using a different dataset and adjustment methods. The ERG identified and corrected some errors, and the corrected incremental cost-effectiveness ratios (ICERs) for POM + LoDEX versus each comparator were presented: approximately £45,000 per quality-adjusted life-year (QALY) gained versus BTD, savings of approximately £143,000 per QALY lost versus PANO + BOR + DEX, and approximately £49,000 per QALY gained versus CC. The ERG also conducted full incremental analyses, which revealed that CC, POM + LoDEX and PANO + BOR + DEX were on the cost-effectiveness frontier. The committee's decision on the technology under analysis deemed that POM + LoDEX should be recommended as an option for treating multiple myeloma in adults at third or subsequent relapse of treatments including both LEN and BOR, contingent on the company providing POM with the discount agreed in the PAS.

Database: Medline

31. Management of relapsed and refractory multiple myeloma: Novel agents, antibodies, immunotherapies and beyond

Author(s): Chim C.S.; Kumar S.K.; Gertz M.A.; Orlowski R.Z.; Cook G.; Richardson P.G.; Anderson K.C.; Giralt S.; Mateos M.V.; Leleu X.

Source: Leukemia; Feb 2018; vol. 32 (no. 2); p. 252-262

Publication Type(s): Review

Available at Leukemia - from PubMed Central

Abstract: Despite enormous advances, management of multiple myeloma (MM) remains challenging. Multiple factors impact the decision to treat or which regimen to use at MM relapse/progression.

Recent major randomized controlled trials (RCTs) showed widely varying progression-free survivals (PFS), ranging from a median of 4 months (MM-003) to 23.6 months (ASPIRE). Based on these RCTs, next-generation proteasome inhibitors (carfilzomib and ixazomib), next-generation immunomodulatory agent (pomalidomide), and monoclonal antibodies (elotuzumab and daratumumab) were approved for relapsed and refractory MM. Daratumumab, targeting CD38, has multiple mechanisms of action including modulation of the immunosuppressive bone marrow micro-environment. In addition to the remarkable single agent activity in refractory MM, daratumumab produced deep responses and superior PFS in MM when combined with lenalidomide/dexamethasone, or bortezomib/dexamethasone. Other anti-CD38 antibodies, such as isatuximab and MOR202, are undergoing assessment. Elotuzumab, targeting SLAMF7, yielded superior response rates and PFS when combined with lenalidomide/dexamethasone. New combinations of these next generation novel agents and/or antibodies are undergoing clinical trials. Venetoclax, an oral BH3 mimetic inhibiting BCL2, showed single agent activity in MM with t(11;14), and is being studied in combination with bortezomib/dexamethasone. Selinexor, an Exportin-1 inhibitor, yielded promising results in quad- or penta-refractory MM including patients resistant to daratumumab. Pembrolizumab, an anti-PD1 check-point inhibitor, is being tested in combination with lenalidomide/dexamethasone or pomalidomide/dexamethasone. Chimeric antigen receptor-T cells targeting B-cell maturation antigen have yielded deep responses in RRMM. Finally, salvage autologous stem cell transplantation (ASCT) remains an important treatment in MM relapsing/progressing after a first ASCT. Herein, the clinical trial data of these agents are summarized, cautious interpretation of RCTs highlighted, and algorithm for salvage treatment of relapse/ refractory MM proposed.

Database: EMBASE

32. Pooled analysis of the reports of carfilzomib/ixazomib combinations for relapsed/refractory multiple myeloma.

Author(s): Xu, Wenjun; Sun, Xuedong; Wang, Baohong; Guo, Hui

Source: Annals of hematology; Feb 2018; vol. 97 (no. 2); p. 299-307

Publication Type(s): Meta-analysis Journal Article

PubMedID: 29159498

Abstract: We sought to evaluate the activity and safety of carfilzomib-/ixazomib-containing combinations for patients with relapsed/refractory multiple myeloma (RRMM). We searched published reports including carfilzomib-/ixazomib-containing combinations for RRMM. Finally, we identified 11 prospective studies covering 2845 relapsed/refractory patients. Carfilzomib- and ixazomib-containing combinations respectively resulted in an impressive overall response rate (ORR 77 vs. 64%, P = 0.14), very good partial response or better (≥ VGPR 48 vs. 21%, P = 0.001), complete response or better (≥ CR 14 vs. 7%, P = 0.23), and clinical benefit rate (CBR 84 vs. 59%, P = 0.0002). Subgroup analysis showed that the carfilzomib (CFZ) +lenalidomide (LEN) + dexamethasone (DEX) triplet regimen resulted into similar response outcomes to those from CFZ + DEX doublet regimen in ORR (77 vs. 78%, P = 0.91), ≥VGPR (50 vs. 53%, P = 0.84), and ≥ CR (13 vs. 12%, P = 0.96) analysis in these previously heavily pretreated population. And, there were no statistically significant differences between IXA + LEN + DEX triplet regimen and CFZ + LEN + DEX triplet regimen in ORR (85 vs. 78%, P = 0.55), ≥ VGPR (37 vs. 53%, P = 0.19), and ≥ CR (18 vs. 12%, P = 0.70) analysis. There were favorable trend towards proteasome inhibitors (PIs) + IMiDs + DEX in comparison with PIs + alkylating agent + Dex in ORR (79 vs 49%, P < 0.00001), ≥ VGPR analysis (36 vs. 16%, P = 0.008), and ≥ CR (16 vs. 3%, P < 0.00001). Compared with current standard chemotherapy, carfilzomib containing combinations clearly improved overall survival (HR, 0.79; P = 0.01), progression free survival (HR,

0.61; P = 0.0001). Carfilzomib-/ixazomib-containing combinations produced clinical benefit for patients with R/RMM. PIs + IMiDs + DEX triplet regimens could be good options for such relapsed/refractory patients.

Database: Medline

33. Prediction of outcome in newly diagnosed myeloma: a meta-analysis of the molecular profiles of 1905 trial patients.

Author(s): Shah, V; Sherborne, A L; Walker, B A; Johnson, D C; Boyle, E M; Ellis, S; Begum, D B; Proszek, P Z; Jones, J R; Pawlyn, C; Savola, S; Jenner, M W; Drayson, M T; Owen, R G; Houlston, R S; Cairns, D A; Gregory, W M; Cook, G; Davies, F E; Jackson, G H; Morgan, G J; Kaiser, M F

Source: Leukemia; Jan 2018; vol. 32 (no. 1); p. 102-110

Publication Type(s): Journal Article

PubMedID: 28584253

Available at Leukemia - from PubMed Central

Abstract: Robust establishment of survival in multiple myeloma (MM) and its relationship to recurrent genetic aberrations is required as outcomes are variable despite apparent similar staging. We assayed copy number alterations (CNA) and translocations in 1036 patients from the NCRI Myeloma XI trial and linked these to overall survival (OS) and progression-free survival. Through a meta-anlysis of these data with data from MRC Myeloma IX trial, totalling 1905 newly diagnosed MM patients (NDMM), we confirm the association of t(4;14), t(14;16), t(14;20), del(17p) and gain(1q21) with poor prognosis with hazard ratios (HRs) for OS of 1.60 (P=4.77 × 10-7), 1.74 (P=0.0005), 1.90 (P=0.0089), 2.10 (P=8.86 × 10-14) and 1.68 (P=2.18 × 10-14), respectively. Patients with 'double-hit' defined by co-occurrence of at least two adverse lesions have an especially poor prognosis with HRs for OS of 2.67 (P=8.13 × 10-27) for all patients and 3.19 (P=1.23 × 10-18) for intensively treated patients. Using comprehensive CNA and translocation profiling in Myeloma XI we also demonstrate a strong association between t(4;14) and BIRC2/BIRC3 deletion (P=8.7 × 10-15), including homozygous deletion. Finally, we define distinct sub-groups of hyperdiploid MM, with either gain(1q21) and CCND2 overexpression (P<0.0001) or gain(11q25) and CCND1 overexpression (P<0.0001). Profiling multiple genetic lesions can identify MM patients likely to relapse early allowing stratification of treatment.

Database: Medline

34. A phase 1 clinical trial evaluating marizomib, pomalidomide and low-dose dexamethasone in relapsed and refractory multiple myeloma (NPI-0052-107): final study results.

Author(s): Spencer, Andrew; Harrison, Simon; Zonder, Jeffrey; Badros, Ashraf; Laubach, Jacob; Bergin, Krystal; Khot, Amit; Zimmerman, Todd; Chauhan, Dharminder; Levin, Nancy; MacLaren, Ann; Reich, Steven D; Trikha, Mohit; Richardson, Paul

Source: British journal of haematology; Jan 2018; vol. 180 (no. 1); p. 41-51

Publication Type(s): Clinical Trial, Phase I Multicenter Study Journal Article

PubMedID: 29076150

Abstract: Marizomib (MRZ) is an irreversible, pan-subunit proteasome inhibitor (PI) in clinical development for relapsed/refractory multiple myeloma (RRMM) and glioma. This study analysed MRZ, pomalidomide (POM) and low-dose dexamethasone (Lo-DEX) [PMD] in RRMM to evaluate safety and determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose

(RP2D). Intravenous MRZ (0·3-0·5 mg/m2) was administered over 2 h on days 1, 4, 8, 11; POM (3-4 mg) on days 1-21; and Lo-DEX (5 or 10 mg) on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 16, 22 and 23 of every 28-day cycle. Thirty-eight patients were enrolled that had received a median of 4 (range 1-10) prior lines of therapy; all patients received prior lenalidomide and bortezomib. No dose-limiting toxicities (DLTs) were observed and 0·5 mg/m2 MRZ was determined to be the RP2D. The most common treatment-related ≥Grade 3 adverse events were: neutropenia (11/38 patients: 29%), pneumonia (4/38 patients 11%), anaemia (4/38 patients; 11%) and thrombocytopenia (4/38 patients; 11%). The overall response rate and clinical benefit rate was 53% (19/36) and 64% (23/36), respectively. In conclusion, PMD was well tolerated and demonstrated promising activity in heavily pre-treated, high-risk RRMM patients.

Database: Medline

35. Pharmacogenetic study of the impact of ABCB1 single-nucleotide polymorphisms on lenalidomide treatment outcomes in patients with multiple myeloma: results from a phase IV observational study and subsequent phase II clinical trial.

Author(s): Jakobsen Falk, Ingrid; Lund, Johan; Gréen, Henrik; Gruber, Astrid; Alici, Evren; Lauri, Birgitta; Blimark, Cecilie; Mellqvist, Ulf-Henrik; Swedin, Agneta; Forsberg, Karin; Carlsson, Conny; Hardling, Mats; Ahlberg, Lucia; Lotfi, Kourosh; Nahi, Hareth

Source: Cancer chemotherapy and pharmacology; Jan 2018; vol. 81 (no. 1); p. 183-193

Publication Type(s): Journal Article

PubMedID: 29177954

Available at Cancer Chemotherapy and Pharmacology - from PubMed Central

Abstract:PURPOSEDespite therapeutic advances, patients with multiple myeloma (MM) continue to experience disease relapse and treatment resistance. The gene ABCB1 encodes the drug transporter P-glycoprotein, which confers resistance through drug extrusion across the cell membrane. Lenalidomide (Len) is excreted mainly via the kidneys, and, given the expression of P-gp in the renal tubuli, single-nucleotide polymorphisms (SNPs) in the ABCB1 gene may influence Len plasma concentrations and, subsequently, the outcome of treatment. We, therefore, investigated the influence of ABCB1 genetic variants on Len treatment outcomes and adverse events (AEs).METHODSNinety patients with relapsed or refractory MM, who received the second-line Len plus dexamethasone in the Rev II trial, were genotyped for the ABCB1 SNPs 1199G>A (Ser400Asn, rs2229109), 1236C>T (silent, rs1128503), 2677G>T/A (Ala893Ser, rs2032582), and 3435C>T (silent, rs1045642) using pyrosequencing, and correlations to response parameters, outcomes, and AEs were investigated.RESULTSNo significant associations were found between genotype and either best response rates or hematological AEs, and 1236C>T, 2677G>T or 3435C>T genotypes had no impact on survival. There was a trend towards increased time to progression (TTP) in patients carrying the 1199A variant, and a significant difference in TTP between genotypes in patients with standard-risk cytogenetics.CONCLUSIONSOur findings show a limited influence of ABCB1 genotype on lenalidomide treatment efficacy and safety. The results suggest that 1199G>A may be a marker of TTP following Len treatment in standard-risk patients; however, larger studies are needed to validate and clarify the relationship.

Database: Medline

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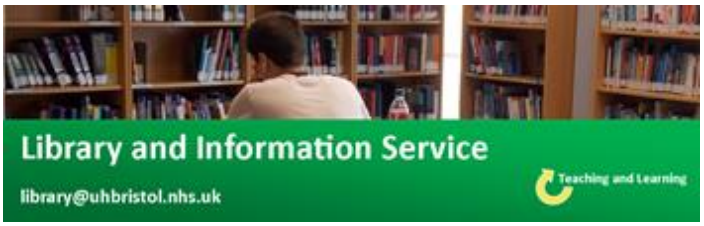
Relapse in teenage and young adult patients treated on a paediatric minimal residual disease stratified ALL treatment protocol is associated with a poor outcome: results from UKALL2003.
Sellar RS, Rowntree C, Vora AJ, **Furness CL**, Goulden N, Mitchell C, Moorman AV, Hough R.
Br J Haematol. 2018 Apr 24. doi: 10.1111/bjh.15208. [Epub ahead of print]
PMID: 29687881

The subclonal complexity of STIL-TAL1+ T-cell acute lymphoblastic leukaemia.
Furness CL, Mansur MB, Weston VJ, Ermini L, van Delft FW, Jenkinson S, Gale R, Harrison CJ, Pombo-de-Oliveira MS, Sanchez-Martin M, Ferrando AA, Kearns P, Titley I, Ford AM, Potter NE, Greaves M.
Leukemia. 2018 Mar 20. doi: 10.1038/s41375-018-0046-8. [Epub ahead of print]
PMID: 29556024

Early morphological response is significantly associated with, but does not accurately predict, relapse in teenagers and young adults aged 10-24 years with acute lymphoblastic leukaemia (ALL): results from UKALL2003.
Furness CL, Kirkwood A, Rowntree C, Vora A, Mitchell C, Samarasinghe S, Goulden N, Moorman A, Hough R.
Br J Haematol. 2018 Feb 22. doi: 10.1111/bjh.15150. [Epub ahead of print] No abstract available.
PMID: 29468646



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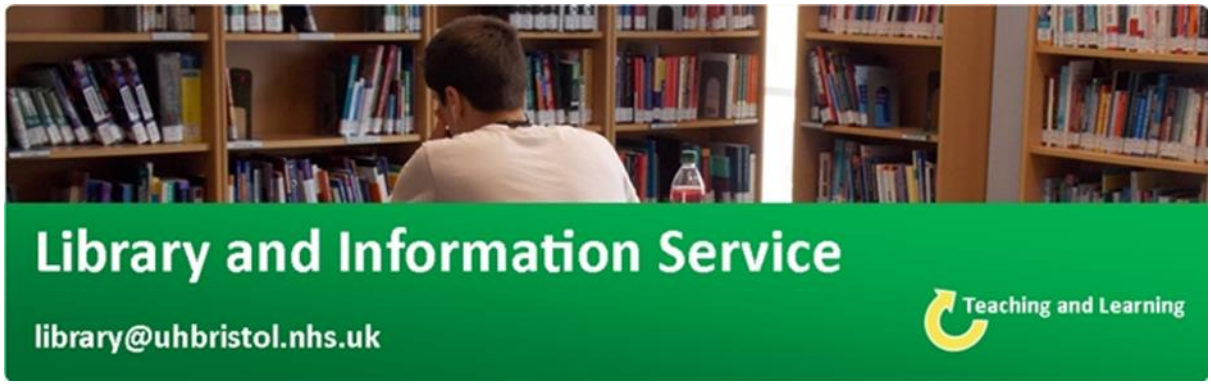

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