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Radiotherapy

Evidence Update

August 2017

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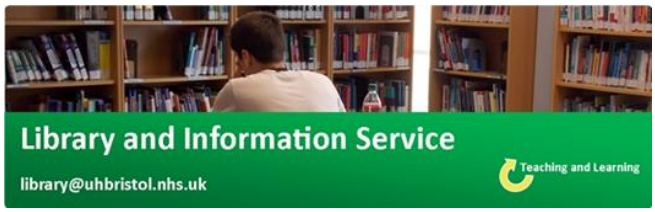

Lunchtime Drop-in Sessions

All sessions last one hour

September (13.00-14.00)

1st (Fri) Literature Searching

4th (Mon) Critical Appraisal

12th (Tues) Interpreting Statistics

20th (Wed) Literature Searching

28th (Thu) Critical Appraisal

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Contents

Current Journals: Tables of Contents

Click on journal title (+ Ctrl) for hyperlink

Journal	Month	Volume	Issue
Radiotherapy and Oncology	August	124	2
International Journal of Radiation Oncology Biology and Physics	September	99	1
Clinical Oncology	September	29	9

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Latest Evidence

NICE National Institute for Health and Care Excellence

Biodegradable spacer insertion to reduce rectal toxicity during radiotherapy for prostate cancer (IPG590)

Evidence-based recommendations on biodegradable spacer insertion (gel or balloon) to reduce rectal toxicity during radiotherapy for prostate cancer in adults.

Interventional procedures guidance Published August 2017

Cochrane Library

Riley P, Glenny AM, Hua F, Worthington HV. **Pharmacological interventions for preventing dry mouth and salivary gland dysfunction following radiotherapy**. Cochrane Database of Systematic Reviews 2017, Issue 7. Art. No.: CD012744. DOI: 10.1002/14651858.CD012744.

Vellayappan BA, Soon YY, Ku GY, Leong CN, Lu JJ, Tey JCS. **Chemoradiotherapy versus chemoradiotherapy plus surgery for esophageal cancer.** Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD010511. DOI: 10.1002/14651858.CD010511.pub2.

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

Radiation therapy techniques in cancer treatment

Author: Timur Mitin, MD, PhD

Literature review current through: Jul 2017. | **This topic last updated:** Aug 01, 2017.

Bone metastases in advanced prostate cancer: Management

Authors: A Oliver Sartor, MD; Steven J DiBiase, MD

Literature review current through: Jul 2017. | **This topic last updated:** Jul 11, 2017.

Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer

Author: Jennifer F De Los Santos, MD

Literature review current through: Jul 2017. | **This topic last updated:** Aug 17, 2017.

Guidelines

Royal College of Radiologists

Society of Radiographers

Institute of Physics and Engineering in Medicine

Horton P, Eaton D (2017). **Design and Shielding of Radiotherapy Treatment Facilities.** Institute of Physics and Engineering in Medicine.

Physics Aspects of Quality Control in Radiotherapy (update of Report 81)
Expected: 2017

Database Articles

Below is a selection of articles recently added to the healthcare databases, grouped in the categories:

- **Liver SABR (Stereotactic Ablative Radiotherapy)**
- **Radium 223 – prostate and breast metastases**

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

Liver SABR (Stereotactic Ablative Radiotherapy)

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1. Survival and prognostic factors for patients with advanced hepatocellular carcinoma after stereotactic ablative radiotherapy.

Author(s): Lo, Cheng-Hsiang; Yang, Jen-Fu; Liu, Ming-Yueh; Jen, Yee-Min; Lin, Chun-Shu; Chao, Hsing-Lung; Huang, Wen-Yen

Source: PloS one; 2017; vol. 12 (no. 5); p. e0177793

Publication Date: 2017

Publication Type(s): Journal Article

PubMedID: 28545098

Available in full text at PLoS ONE - from National Library of Medicine

Available in full text at PLoS One - from ProQuest

Abstract:OBJECTIVETo evaluate the survival outcomes and prognostic factors of patients with advanced hepatocellular carcinoma (HCC) who underwent stereotactic ablative radiotherapy (SABR).METHODSThis retrospective study evaluated patients with advanced HCC who underwent SABR between December 2007 and July 2015. All patients had Barcelona Clinic Liver Cancer stage C disease and Child-Turcotte-Pugh (CTP) class A-B function. In-field control (IFC), overall survival (OS), prognostic factors, and toxicity were evaluated.RESULTSIn this study of 89 patients, the 3-year IFC rate was 78.1%, and the 1-year and 3-year OS rates were 45.9% and 24.3%, respectively. The multivariate analysis revealed that CTP class, the presence of main portal vein tumor thrombosis, and the presence of extrahepatic spread were independent predictors of OS. The expected median OS values among patients with ≥2, 1, and 0 predictors were 4.2, 8.6, and 26.4 months, respectively (p <0.001).CONCLUSIONSSABR may be useful for patients with advanced HCC, and patient selection could be based on the CTP classification, main portal vein tumor thrombosis, and extrahepatic spread.

Database: Medline

2. Comparison Between Child-Turcotte-Pugh and Albumin-Bilirubin Scores in Assessing the Prognosis of Hepatocellular Carcinoma After Stereotactic Ablative Radiation Therapy.

Author(s): Lo, Cheng-Hsiang; Liu, Ming-Yueh; Lee, Meei-Shyuan; Yang, Jen-Fu; Jen, Yee-Min; Lin, Chun-Shu; Chao, Hsing-Lung; Shen, Po-Chien; Huang, Wen-Yen

Source: International journal of radiation oncology, biology, physics; Sep 2017; vol. 99 (no. 1); p. 145-152

Publication Date: Sep 2017

Publication Type(s): Journal Article

PubMedID: 28816140

Abstract:PURPOSETo evaluate the prognostic performance of the Child-Turcotte-Pugh (CTP) score and the albumin-bilirubin (ALBI) score in hepatocellular carcinoma (HCC) patients treated using stereotactic ablative radiation therapy (SABR).METHODS AND MATERIALSThis retrospective study evaluated the data of patients with HCC who underwent SABR between December 2007 and June 2015. We collected pretreatment CTP and ALBI scores and analyzed their correlation with survival and liver toxicity.RESULTSThis study included 152 HCC patients: 78.3% of CTP class A and 21.7% of CTP class B. The median ALBI score was -2.49 (range, -3.67 to -0.84) with 39.5% of grade 1, 56.6% of grade 2, and 3.9% of grade 3. The CTP classification and ALBI grade were significantly associated with overall survival (P<.001). Albumin-bilirubin grade (1 vs 2) had a trend to stratify CTP class A patients into 2 risk groups of mortality (P=.061). Combined CTP class and ALBI score could predict development of radiation-induced liver disease (2.4% in CTP A-ALBI < -2.76, 15.1% in CTP A-ALBI ≥ -2.76, and 25.8% in CTP B).CONCLUSIONAlbumin-bilirubin score is a potential predictor for both survival and liver toxicity. Complementary use of CTP and ALBI score could predict the risk of post-SABR liver toxicity. Further prospective studies are necessary before use of the ALBI score can become part of daily practice.

Database: Medline

3. Long-Term Survival Analysis of Stereotactic Ablative Radiotherapy Versus Liver Resection for Small Hepatocellular Carcinoma.

Author(s): Su, Ting-Shi; Liang, Ping; Liang, Jian; Lu, Huan-Zhen; Jiang, Hua-Yan; Cheng, Tao; Huang, Yong; Tang, Yang; Deng, Xin

Source: International journal of radiation oncology, biology, physics; Jul 2017; vol. 98 (no. 3); p. 639-646

Publication Date: Jul 2017

Publication Type(s): Comparative Study Journal Article

PubMedID: 28581406

Abstract:PURPOSETo compare the efficacy of stereotactic ablative radiation therapy (SABR) versus liver resection for small hepatocellular carcinoma (HCC) ≤5 cm with Child-Pugh A cirrhosis.METHODS AND MATERIALSThis retrospective study included 117 patients with small HCCs with 1 or 2 nodules. Eighty-two patients received SABR (SABR group), and 35 patients underwent liver resection (resection group). Overall survival (OS) and progression-free survival (PFS) were analyzed. One-to-one matched pairs between the 2 groups were created using propensity score matching to reduce the potential confounding effect of treatment and selection bias.RESULTSThere was no between-group difference in OS and PFS. Before propensity score matching, the 1-, 3-, and 5-year OS was 96.3%, 81.8%, and 70.0% in the SABR group and 93.9%, 83.1%, and 64.4% in the resection group, respectively (P=.558). The 1-, 3- and 5-year PFS was 81.4%, 50.2%, and 40.7% in the SABR group and

68.0%, 58.3%, and 40.3% in the resection group, respectively (P=.932). After propensity score matching, 33 paired patients were selected from the SABR and resection groups. The 1-, 3-, and 5-year OS was 100%, 91.8%, and 74.3% in the SABR group and 96.7%, 89.3%, and 69.2% in the resection group, respectively (P=.405). The 1-, 3-, and 5-year PFS was 84.4%, 59.2%, and 43.9% in the SABR group and 69.0%, 62.4%, and 35.9% in the resection group, respectively (P=.945). There was a similarity of hepatotoxicity between the 2 groups. The SABR group showed fewer complications, such as hepatic hemorrhage, hepatic pain, and weight loss. Acute nausea was significantly more frequent in the SABR group than in the resection group.CONCLUSIONFor patients with small primary HCC with 1 or 2 nodules and Child-Pugh A cirrhosis, SABR has local effects that are similar to those with liver resection. Stereotactic ablative radiation therapy has an advantage over resection in being less invasive.

Database: Medline

4. State of the ablation nation: a review of ablative therapies for cure in the treatment of hepatocellular carcinoma.

Author(s): Salati, Umer; Barry, Aisling; Chou, Frank Y; Ma, Roy; Liu, David M

Source: Future oncology (London, England); Jul 2017; vol. 13 (no. 16); p. 1437-1448

Publication Date: Jul 2017

Publication Type(s): Journal Article

PubMedID: 28685607

Abstract: Primary liver cancer, mainly hepatocellular carcinoma, is one of the most common malignancies worldwide. Surgical management, either resection or transplantation, is considered definitive treatment, however, less than 20% of patients are ultimately candidates. Thermal ablation modalities such as radiofrequency ablation and microwave ablation have evolved such that these modalities have been applied with curative intent. Moreover, thermal ablation has demonstrated efficacy in treating early-stage tumors and can be offered as first-line treatment in patients with uncomplicated disease. Attributing to refinements in technology and techniques, recent studies evaluating stereotactic ablative body radiotherapy have shown promising results, while irreversible electroporation, an emerging modality, may further expand the role of ablative therapy in treating potentially resectable hepatocellular carcinoma.

Database: Medline

5. Systematic review of patient reported quality of life following stereotactic ablative radiotherapy for primary and metastatic liver cancer.

Author(s): Mutsaers, Adam; Greenspoon, Jeffrey; Walker-Dilks, Cindy; Swaminath, Anand

Source: Radiation oncology (London, England); Jun 2017; vol. 12 (no. 1); p. 110

Publication Date: Jun 2017

Publication Type(s): Journal Article Review

PubMedID: 28662680

Available in full text at Radiation Oncology - from National Library of Medicine

Available in full text at Radiation Oncology - from BioMed Central

Available in full text at Radiation Oncology - from ProQuest

Abstract:BACKGROUNDStereotactic ablative radiotherapy (SABR) is a safe and effective modality in patients with liver cancer who are ineligible for other local therapies. However SABR is not current standard of practice and requires further validation. Patient reported quality of life (QOL) is key to this validation, yet no systematic reviews to date have been performed to analyse QOL following liver SABR. QOL is a critical part of therapy evaluation, particularly in disease states with short life expectancy. The purpose of this study was to conduct a systematic review of QOL outcomes for liver SABR.MATERIALS AND METHODSMEDLINE and EMBASE databases from 1996 to October 2015 were queried to obtain English language studies analysing QOL following liver SABR. Included studies described patient-reported QOL as either a primary or secondary endpoint, and analysed QOL change over time. Studies were screened, and relevant data were abstracted and analysed.RESULTSOf 2181 initially screened studies, 5 met all inclusion criteria. Extracted studies included a total of 392 eligible patients with hepatocellular carcinoma, liver metastases and intrahepatic cholangiocarcinoma. Four studies were prospective in design, and only one study was a conference abstract. Extracted studies were heterogeneous in dose prescription used (11-70 Gy in 3-30 fractions), in addition to reported QOL metrics (EORTC QLQ C-15 PAL,/C-30/LM-21, EuroQol 5D, FACT-Hep, FLIC) and final endpoints (range 6 weeks to 12 months). Despite this there were few statistically significant declines in QOL scores following SABR. Four studies demonstrated transient fatigue in the first 1-4 weeks, while 2 studies showed transient worsening of appetite at 1 month. In all but one instance (loss of appetite at 6 weeks), levels returned to insignificant difference baseline by the final endpoints. All studies showed no significant QOL decline in any domain at their respective endpoints. In studies with overlapping QOL tools, estimates of 3-month post SABR global QOL were similar.CONCLUSIONResults of this systematic review demonstrate well-preserved post liver SABR QOL. These findings strengthen the argument for liver SABR, and should aim to support future comparative effectiveness trials with other local modalities including surgery, chemoembolization and radiofrequency ablation, with a focus on QOL outcomes as an important endpoint.

Database: Medline

6. Stereotactic ablative radiotherapy for patients with unresectable or medically inoperable cholangiocarcinoma.

Author(s): Liu, Ming-Yueh; Lo, Cheng-Hsiang; Lin, Chun-Shu; Chao, Hsing-Lung; Yang, Jen-Fu; Lin, Kuen-Tze; Fan, Chao-Yueh; Su, Yu-Fu; Huang, Wen-Yen

Source: Tumori; May 2017; vol. 103 (no. 3); p. 236-241

Publication Date: May 2017

Publication Type(s): Journal Article

PubMedID: 28058710

Abstract:PURPOSEThe role of stereotactic ablative radiotherapy (SABR) in patients with unresectable or medically inoperable cholangiocarcinoma remains unclear. We examined the efficacy and safety of SABR in this group of patients.METHODSFrom January 2008 to December 2014, 15 patients with 17 lesions were included in this study. The lesions included 14 intrahepatic, 1 hilar, and 2 distal bile duct tumors. Three patients were classified as medically inoperable because of old age or multiple comorbidities. Tumors measured 0.8-13 cm (median, 3.6 cm). The median prescribed dose was 45 Gy delivered in 5 fractions over 5 consecutive days.RESULTSThe median follow-up period for surviving patients was 29.9 months. Objective responses were observed for 10 of 17 tumors (58.8%), including 3 complete responses (17.6%). The median survival duration was 12.6 months, and the 1- and 2-year overall survival rates were 50.3% and 14.4%, respectively. The 1- and 2-year in-field failure-free rates were 61.5% and 30.8%, respectively. For patients with biologically effective doses

(BEDs) exceeding 75 Gy10, the 1- and 2-year overall survival rates were 58.3% and 33.3%, respectively, compared to 20.0% and 0%, respectively for those with BEDs lower than 75 Gy10. Radiation-induced liver disease did not develop in any patient. Acute toxicities were generally mild and tolerable.CONCLUSIONSStereotactic ablative radiotherapy could be an alternative treatment for unresectable or medically inoperable cholangiocarcinoma. Further dose escalation may be considered to optimize local control.

Database: Medline

7. Ipilimumab with Stereotactic Ablative Radiation Therapy: Phase I Results and Immunologic Correlates from Peripheral T Cells.

Author(s): Tang, Chad; Welsh, James W; de Groot, Patricia; Massarelli, Erminia; Chang, Joe Y; Hess, Kenneth R; Basu, Sreyashi; Curran, Michael A; Cabanillas, Maria E; Subbiah, Vivek; Fu, Siqing; Tsimberidou, Apostolia M; Karp, Daniel; Gomez, Daniel R; Diab, Adi; Komaki, Ritsuko; Heymach, John V; Sharma, Padmanee; Naing, Aung; Hong, David S

Source: Clinical cancer research : an official journal of the American Association for Cancer Research; Mar 2017; vol. 23 (no. 6); p. 1388-1396

Publication Date: Mar 2017

Publication Type(s): Journal Article

PubMedID: 27649551

Available in full text at Clinical Cancer Research - from Highwire Press

Abstract: Purpose: Little prospective data are available on clinical outcomes and immune correlates from combination radiation and immunotherapy. We conducted a phase I trial (NCT02239900) testing stereotactic ablative radiotherapy (SABR) with ipilimumab.Experimental Design: SABR was given either concurrently (1 day after the first dose) or sequentially (1 week after the second dose) with ipilimumab (3 mg/kg every 3 weeks for 4 doses) to five treatment groups: concurrent 50 Gy (in 4 fractions) to liver; sequential 50 Gy (in 4 fractions) to liver; concurrent 50 Gy (in 4 fractions) to lung; sequential 50 Gy (in 4 fractions) to lung; and sequential 60 Gy (in 10 fractions) to lung or liver. MTD was determined with a 3 + 3 dose de-escalation design. Immune marker expression was assessed by flow cytometry.Results: Among 35 patients who initiated ipilimumab, 2 experienced dose-limiting toxicity and 12 (34%) grade 3 toxicity. Response outside the radiation field was assessable in 31 patients. Three patients (10%) exhibited partial response and 7 (23%) experienced clinical benefit (defined as partial response or stable disease lasting ≥6 months). Clinical benefit was associated with increases in peripheral CD8+ T cells, CD8+/CD4+ T-cell ratio, and proportion of CD8+ T cells expressing 4-1BB and PD1. Liver (vs. lung) irradiation produced greater T-cell activation, reflected as increases in the proportions of peripheral T cells expressing ICOS, GITR, and 4-1BB.Conclusions: Combining SABR and ipilimumab was safe with signs of efficacy, peripheral T-cell markers may predict clinical benefit, and systemic immune activation was greater after liver irradiation. Clin Cancer Res; 23(6); 1388-96. ©2016 AACR.

Database: Medline

8. Stereotactic Ablative Body Radiotherapy (SABR) for liver tumours-the Peter MacCallum Cancer Centre experience

Author(s): Thomas R.

Source: Journal of Medical Radiation Sciences; Mar 2017; vol. 64 ; p. 37

Publication Date: Mar 2017

Publication Type(s): Conference Abstract

Abstract: Introduction: Stereotactic Ablative Body Radiotherapy (SABR) techniques offer the ability to deliver significantly higher effective biological radiation therapy (RT) doses to discrete regions. SABR is ideally suited to treat disease within radiosensitive structures such as the liver. The risk of radiation induced liver disease, coupled with the high therapeutic doses required to treat cancer in this region, necessitates a highly conformal approach to RT planning and delivery. With modern technological advances in stereotactic treatment delivery and image verification, it has become possible to deliver ablative doses to liver lesions using plans characterised by rapid dose fall-off and acceptable doses to critical structures. Discussion: Delivering SABR techniques to the liver involves complex challenges, with treatment outcomes heavily reliant on accurate definition of target volumes and confidence in treatment verification. Targets are often delineated using several imaging modalities, requiring multiple scans and image fusion accounting for breathing motion in this readily deformable organ. Furthermore, treatment verification is confounded by difficulty in visualising the lesions on cone-beam computed tomography (CBCT) alone. A personalised workflow developed at our centre has been a result of maximising clinical experience, to obtain a consistent and yet personalised method for each patient. This presentation will detail our approach to treatment Liver SBRT patients, data gained thus far, and demonstrate the advantages of a patient-centred approach. Conclusion: We have developed a process of triaging our patients at simulation to define the optimal motion management strategy, managing the complexities of motion during treatment delivery and the delivery of acceptable dose.

Database: EMBASE

9. Liver SABR end expiration breath hold-reaching beyond to overcome the challenges

Author(s): McMaster A.; Foo J.

Source: Journal of Medical Radiation Sciences; Mar 2017; vol. 64 ; p. 31

Publication Date: Mar 2017

Publication Type(s): Conference Abstract

Abstract: The addition of Liver Stereotactic Ablative Body Radiotherapy (SABR) to Nepean Cancer Care Centre's SABR service for patients with hepatocellular carcinoma and liver metastases, provided multiple challenges. Radiation treatment for liver can be a clinical challenge due to multiple lesions, respiratory motion, liver organ deformation and difficulty visualising the tumour on CT and CBCT scans. These multiple challenges required the collaboration of an interdisciplinary team of Radiation Therapists, Radiation Oncologists and Medical Physicists to enhance the radiation therapy imaging, planning and treatment process. Collaboration was also necessary with MRI Radiographers and Nuclear Medicine Technologists to ensure their images were optimal for Liver SABR. We will detail how the Nepean team needed to reach beyond our previous SABR experience utilising our existing equipment in new ways to overcome the following challenges for Liver SABR: I. Patient immobilisation II. Respiratory motion management using End Expiration Breath Hold III. Acquisition of triple phase IV contrast planning CTs IV. Image registration of multiple CT, MRI and PET scans V. PTV delineation between multimodality imaging with liver deformation VI. Achieving the highest prescribed dose using a highly conformal VMAT technique, while sparing the nearby radiosensitive gastrointestinal tissues and remaining healthy liver VII. Optimising the image quality for IGRT and the use of tumour surrogates for localisation in daily IGRT VIII. Treatment delivery Future goals in developing a motion management assessment tool to ascertain the most optimal motion management strategy for Liver SABR patients will also be discussed.

Database: EMBASE

Radium 223 - prostate and breast metastases

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1. Treatment of metastatic prostate cancer patients with RA-223 dichloride (XOFIGO)

Author(s): Kepes Z.; Garai I.; Ilyes M.; Vanczku A.; Kaplar A.; Szegedi-Szabo J.; Deak A.; Santha O.

Source: Nuclear Medicine Review; 2017; vol. 20 (no. 2); p. 115

Publication Date: 2017

Publication Type(s): Conference Abstract

Available in full text at Nuclear medicine review. Central & Eastern Europe [Nucl Med Rev Cent East Eur] NLMUID: 100886103 - from EBSCOhost

Abstract:INTRODUCTION: Ra-223 dichloride is approved for the treatment of patients with castration-resistant prostate cancer suffering from symptomatic bone metastases and no evidence of visceral metastatic disease. Ra-223 dichloride is the first alpha-particle emitting radiotherapeutic drug for systemic use. As calcium analogue, it forms complexes with hydroxyapatit crystals especially in the areas of increased bone turnover. In our study we analysed efficacy of the therapy on bone pain and on the survival of the patients treated with Ra-223 dichloride. METHODS: We treated 51 patients (mean age 68.51 year, 44-89 y) with 271 cycles of Ra-223 dichloride therapy matching the approved inclusion criteria for the treatment. The mean follow-up period was 15 months (6-29 months). The time from the diagnosis of bone metastases to the therapy was mean 3.3 years (1-16 y). Every patient had at least 3 bone metastases especially in the axial skeleton. 50 kBq/kg Ra223 dichloride was administered iv. in 6 cycles, with 4-week intervals. During the follow-up we controlled the hematological status with lab tests and the intensity of the pain using 10-point visual scale. 22 patients got chemotherapy (Docetaxel) before Ra-223 therapy. All statistical calculations were carried out by IBM SPSS statistics software. RESULTS: 36/51 patients completed 6 cycles of radioisotope therapy. We had to discontinue the treatment in 15 cases. The median overall survival after Ra-223 therapy was 11 months. Kaplan-Meier analysis proved that there is no significant difference in survival time between patients who underwent chemotherapy prior to Ra-223 therapy or did not (12 months vs. 11 months). The significance was calculated by Breslow (Generalized Wilcoxon) test, p = 0.506. We could not find significant changes in laboratory parameters (Mann-Whitney test) during the therapy. Jonckheere-Terpstra test was applied to examine trends in pain response during the treatment. The p = 0.000 indicated the differences in pain (the median of pain value changed from score 6 to score 2). CONCLUSION: Radium-223 dichloride is the first systematic a-emitter therapeutic agent that has shown significant benefits to soothe bone pain in prostatic cancer patients having bone metastases.

Database: EMBASE

2. Using external beam radiation treatment as an adjunct in radium-223 treatment

Author(s): Ganesh V.; Agarwal A.; Vuong S.; Barakat T.; Borean M.; Wan A.; Chow E.

Source: Supportive Care in Cancer; 2017; vol. 25 (no. 2)

Publication Date: 2017

Publication Type(s): Conference Abstract

Abstract: Introduction Castrate-resistant prostate cancer (CRPC) commonly metastasizes to the bone, afflicting 90% of these patients. Radium-223 dichloride (223Ra) has proven promising in the treatment of CRPC patients, prolonging life and reducing bone-turnover systemically. However, many patients undergoing 223Ra treatment require further palliation of pain. External beam

radiation treatment (EBRT) may therefore be used in between 223Ra injections to provide accelerated pain relief. This can allow patients to continue their 223Ra regimens and gain its associated benefits (i.e., im-proved overall survival, and delayed time to PSA progression or skeletal-related events). Objectives To report the case of a 65-year-old male whose pain persisted after his first cycle of 223Ra, and was successfully treated with a single fraction of EBRT. Methods A retrospective chart review was conducted. Results The patient was diagnosed with prostate cancer in 2013. In 2015, he received the first dose of 223Ra but reported severe pain in his right ischium in 2015 and was referred to the Rapid Response Radiotherapy Program (RRRP). Imaging results revealed significant sclerotic bone lesions. The patient subsequently delayed his second 223Ra injection and underwent a single fraction of EBRT at a dose of 8Gy. He received significant pain reduction ten days post-EBRT, and resumed 223Ra treatment. Conclusions The clinically significant benefits observed with both treatments support the use of EBRT as an adjunct therapy with 223Ra.

Database: EMBASE

3. Radium-223 is a well tolerated and safe treatment for metastatic castration resistant prostate cancer (mcrpc): Real world data from a single cancer center

Author(s): Tsoukalas N.; Saigi Morgui M.; Dudek A.; Pouptsis A.; Nikolaou C.; Enting D.; Chowdhury S.; Rudman S.; Mills C.; Lewington V.

Source: Supportive Care in Cancer; 2017; vol. 25 (no. 2)

Publication Date: 2017

Publication Type(s): Conference Abstract

Abstract: Introduction Radium-223 is an alpha emitter that selectively targets bone metastases. It has been approved for the treatment of CRPC with bone metastases and without visceral involvement. Objectives We present real world data for the first two years of Radium-223 administration at Guy's Hospital. Methods CRPC patients with bone metastases received Radium-223 for a period of two years. 50kBq/kg Radium-223 was given intravenously every 28 days for 6 cycles. Results 60 patients with median age 75 years (49-86) were studied. ECOG PS was 0-1 in 55% and 2 in 45%. 80% had > 6 bone metastases while 20 % had a superscan. 63.3% had bone pain WHO score 2 or more and 30% were receiving concurrent bisphosphonates. The majority (71.7%) had received 2 or more lines of prior treatments. 49 (81.7%) had finished treatment while the remaining 11 patients continue Radium-223. 22 of 49 (45%) completed all 6 cycles of treatment, while disease progression was the main cause for treatment interruption (26 patients) and 1 stopped due to toxicity. Patients with 2 or less previous lines of treatment had an increased likelihood of completing 5 or 6 cycles of therapy (p=0.013). There was a trend for patients PS 0-1 to complete 5-6 cycles of Radium-223 compared to patients PS 2 (p=0.79). Treatment was well tolerated and safe. Most of adverse events were grade 1-2 while incidence of grade 3-4 events was less than 3% (anaemia). Conclusions Radium-223 is well tolerated and safe treatment. Optimal patient selection remains crucial in order to ensure effective treatment delivery.

Database: EMBASE

4. An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223

Author(s): Sartor O.; Coleman R.E.; Nilsson S.; Heinrich D.; Helle S.I.; O'Sullivan J.M.; Vogelzang N.J.; Bruland OO.; Kobina S.; Wilhelm S.; Xu L.; Shan M.; Kattan M.W.; Parker C.

Source: Annals of Oncology; 2017; vol. 28 (no. 5); p. 1090-1097

Publication Date: 2017

Publication Type(s): Article

Abstract: Background: Baseline clinical variables are prognostic for overall survival (OS) in patients with castration-resistant prostate cancer (CRPC). Their prognostic and predictive value with agents targeting bone metastases, such as radium-223, is not established. Patients and methods: The radium-223 ALSYMPCA trial enrolled patients with CRPC and symptomatic bone metastases. Prognostic potential of baseline variables was assessed using Cox models. Percentage changes in biomarker levels from baseline were evaluated during the trial period; changes from baseline to week 12 were evaluated for association with OS and surrogacy. Results: Eastern Cooperative Oncology Group performance status, total alkaline phosphatase (tALP), lactate dehydrogenase (LDH), and prostate-specific antigen (PSA) at baseline were associated with OS (P =3 weeks from week 12) had 55% lower risk of death (hazard ratio=0.45; 95% CI 0.34-0.61) versus those with no confirmed tALP decline. Proportional treatment effect (PTE) values for tALP, LDH, and PSA changes from baseline at week 12 as OS surrogate markers were 0.34 (95% CI: 0-0.746), 0.07 (95% CI: 0-0.211), and 0 (95% CI: 0-0.082), respectively. Conclusions: Significant tALP declines (versus placebo) occurred as early as 4 weeks after beginning radium-223 therapy. tALP or LDH declines at 12 weeks correlated with longer OS, but did not meet statistical surrogacy requirements. Dynamic changes in tALP and LDH during radium-223 treatments may be useful to monitor, but do not serve as surrogates for survival.

Database: EMBASE

5. Practical recommendations for radium-223 treatment of metastatic castration-resistant prostate cancer.

Author(s): Du, Yong; Carrio, Ignasi; De Vincentis, Giuseppe; Fanti, Stefano; Ilhan, Harun; Mommsen, Caroline; Nitzsche, Egbert; Sundram, Francis; Vogel, Wouter; Oyen, Wim; Lewington, Val

Source: European journal of nuclear medicine and molecular imaging; Sep 2017; vol. 44 (no. 10); p. 1671-1678

Publication Date: Sep 2017

Publication Type(s): Journal Article

PubMedID: 28631036

Abstract:PURPOSERadium Ra 223 dichloride (radium-223, Xofigo®) is the first targeted alpha therapy for patients with castration-resistant prostate cancer and symptomatic bone metastases. Radium-223 provides a new treatment option for this setting, but also necessitates a new treatment management approach. We provide straightforward and practical recommendations for European nuclear medicine centres to optimize radium-223 service provision.METHODSAn independent research consultancy agency observed radium-223 procedures and conducted interviews with all key staff members involved in radium-223 treatment delivery in 11 nuclear medicine centres across six countries (Germany, Italy, the Netherlands, Spain, Switzerland and the UK) experienced in administering radium-223. The findings were collated and discussed at a meeting of experts from these centres, during which key consensus recommendations were defined.RESULTSThe recommendations cover centre organization and preparation; patient referral; radium-223 ordering, preparation and disposal; radium-223 treatment delivery/administration; and patient experience. Guidance includes structured coordination and communication within centres and multidisciplinary teams, focusing on sharing best practice to provide high-quality, patient-centred care throughout the treatment pathway.CONCLUSIONSThese expert recommendations are intended to complement

existing management guidelines. Sharing best practice and experience will help nuclear medicine centres to optimize radium-223 service provision and improve patient care.

Database: Medline

6. Imaging response during therapy with radium-223 for castration-resistant prostate cancer with bone metastases-analysis of an international multicenter database.

Author(s): Keizman, D; Fosboel, M O; Reichegger, H; Peer, A; Rosenbaum, E; Desax, M-C; Neiman, V; Petersen, P M; Mueller, J; Cathomas, R; Gottfried, M; Dresler, H; Sarid, D; Mermershtain, W; Rouvinov, K; Mortensen, J; Gillessen, S; Daugaard, G; Omlin, A

Source: Prostate cancer and prostatic diseases; Sep 2017; vol. 20 (no. 3); p. 289-293

Publication Date: Sep 2017

Publication Type(s): Journal Article

PubMedID: 28244493

Abstract:BACKGROUNDThe imaging response to radium-223 therapy is at present poorly described. We aimed to describe the imaging response to radium-223 treatment.METHODSWe retrospectively evaluated the computed tomography (CT) and bone scintigraphy response of metastatic castration-resistant prostate cancer (CRPC) patients treated with radium-223, in eight centers in three countries.RESULTSA total of 130 patients were included, the majority (n=84, 65%) received radium-223 post docetaxel. Thirty-four of 99 patients with available data (34%) received concomitant abiraterone or enzalutamide. A total of 54% (n=70) patients completed the planned six injections of radium-223. In patients with available data, a transient increase in bone metastases-related pain was observed in 27% (n=33/124) and an improvement of bone metastases-related pain on treatment with radium-223 was noted in 49% of patients (n=61/124). At 3 and 6 months of treatment with radium-223, bone imaging showed stable disease in 74% (n=84/113) and 94% of patients (n=93/99) with available data, respectively. An increase in the number of bone lesions was documented at 3 months compared with baseline in 26% (n=29/113) and at 6 months compared with 3 months in 6% of patients (n=6/99), respectively. Radiological extraskeletal disease progression occurred in 46% of patients (n=57/124) with available CT data at 3 and/or 6 months.CONCLUSIONSProgression of bone metastases during radium-223 therapy is uncommon. A bone flare (pain and/or radiological) may be noted during the first 3 months, and should not be confused with progression. Imaging by CT scan should be considered after three and six doses of radium-223 to rule out extraskeletal disease progression.

Database: Medline

7. Hematologic Toxicity of Concurrent Administration of Radium-223 and Next-generation Antiandrogen Therapies.

Author(s): Dan, Tu D; Eldredge-Hindy, Harriet B; Hoffman-Censits, Jean; Lin, Jianqing; Kelly, William K; Gomella, Leonard G; Lallas, Costas D; Trabulsi, Edouard J; Hurwitz, Mark D; Dicker, Adam P; Den, Robert B

Source: American journal of clinical oncology; Aug 2017; vol. 40 (no. 4); p. 342-347

Publication Date: Aug 2017

Publication Type(s): Clinical Trial Journal Article

PubMedID: 25723740

Abstract:PURPOSE/OBJECTIVESRadium-223 is a first-in-class radiopharmaceutical recently approved for the treatment of castration-resistant prostate cancer in patients with symptomatic bone metastases. Initial studies investigating Radium-223 primarily used nonsteroidal first-generation antiandrogens. Since that time, newer antiandrogen therapies have demonstrated improved survival in patients with castration-resistant prostate cancer. It has been suggested that the rational combination of these newly approved agents with Radium-223 may lead to improved response rates and clinical outcomes. Currently, there is lack of information regarding the safety of concurrent administration of these agents with radiopharmaceuticals. Here, we report on hematologic toxicity findings from our institution in patients receiving concurrent Radium-223 and next-generation antiandrogen therapies with either enzalutamide or abiraterone.MATERIALS/METHODSIn a retrospective study, we analyzed patients who received Radium-223 as part of an early-access trial, and following FDA approval in May 2013, patients receiving Radium-223 as part of standard care. Radium-223 was given at standard dosing of 50 kBq/kg each month for 6 total cycles. Complete blood counts were performed before treatment monthly and following each injection. Blood counts from patients receiving Radium alone and concurrently with next-generation antiandrogens were compared. To date, 25 total patients were analyzed, with a median of 5 monthly doses received per patient. Fourteen patients received concurrent therapy during monthly Radium-223 with either enzalutamide (n=8) or abiraterone (n=6).RESULTSSix patients expired due to disease progression. Two patients discontinued treatment due to grade 3 myelosuppression. For patients receiving either Radium alone and with concurrent next-generation antiandrogen therapy, there did not appear to be any statistically significant differences between initial and nadir blood counts. Mean change from initial neutrophil count to nadir was 1.9×10/L in patients receiving Radium alone, versus 2.3×10/L in patients receiving concurrent therapy (P=0.77). Mean change from initial hemoglobin value to nadir was 1.5 g/L in patients receiving Radium alone, versus 1.8 g/L in patients receiving concurrent therapy (P=0.31). Mean change from initial platelet count to nadir was 52.3×10 cells/L in patients receiving Radium alone versus 70.6×10 cells/L in patients receiving concurrent therapy (P=0.39). Individual blood counts for each measured laboratory are included in the supplemental data. PSA was stable or decreased in 22% of patients receiving Radium alone versus 35% of patients receiving combination treatment (P=0.24).CONCLUSIONSConcurrent administration of Radium-223 and next-generation antiandrogen therapies appears to be well tolerated with similar toxicities to standard administration of Radium-223 alone. This particular cohort of patients represents a high-risk, heavily pretreated group of patients with advanced metastatic disease and significant marrow burden. Despite these risk factors, hematologic toxicity was modest and was in the range expected for this risk group based on previous trials. To date, this is the first study investigating the toxicity of combination treatment. Further studies investigating the safety and efficacy of combination treatments are warranted.

Database: Medline

8. Radium-223 Inhibits Osseous Prostate Cancer Growth by Dual Targeting of Cancer Cells and Bone Microenvironment in Mouse Models.

Author(s): Suominen, Mari I; Fagerlund, Katja M; Rissanen, Jukka P; Konkol, Yvonne M; Morko, Jukka P; Peng, ZhiQi; Alhoniemi, Esa J; Laine, Salla K; Corey, Eva; Mumberg, Dominik; Ziegelbauer, Karl; Käkönen, Sanna-Maria; Halleen, Jussi M; Vessella, Robert L; Scholz, Arne

Source: Clinical cancer research : an official journal of the American Association for Cancer Research; Aug 2017; vol. 23 (no. 15); p. 4335-4346

Publication Date: Aug 2017

Publication Type(s): Journal Article

PubMedID: 28364014

Available in full text at Clinical Cancer Research - from Highwire Press

Abstract: Purpose: Radium-223 dichloride (radium-223, Xofigo), a targeted alpha therapy, is currently used for the treatment of patients with castration-resistant prostate cancer (CRPC) with bone metastases. This study examines the mode-of-action and antitumor efficacy of radium-223 in two prostate cancer xenograft models.Experimental Design: Mice bearing intratibial LNCaP or LuCaP 58 tumors were randomized into groups (n = 12-17) based on lesion grade and/or serum PSA level and administered radium-223 (300 kBq/kg) or vehicle, twice at 4-week intervals. X-rays and serum samples were obtained biweekly. Soft tissue tumors were observed macroscopically at sacrifice. Tibiae were analyzed by gamma counter, micro-CT, autoradiography and histology.Results: Radium-223 inhibited tumor-induced osteoblastic bone growth and protected normal bone architecture, leading to reduced bone volume in LNCaP and abiraterone-resistant LuCaP 58 models. Furthermore, radium-223 resulted in lower PSA values and reduced total tissue and tumor areas, indicating that treatment constrains prostate cancer growth in bone. In addition, radium-223 suppressed abnormal bone metabolic activity as evidenced by decreased number of osteoblasts and osteoclasts and reduced level of the bone formation marker PINP. Mode-of-action studies revealed that radium-223 was deposited in the intratumoral bone matrix. DNA double-strand breaks were induced in cancer cells within 24 hours after radium-223 treatment, and PSA levels were significantly lower 72 hours after treatment, providing further evidence of the antitumor effects.Conclusions: Taken together, radium-223 therapy exhibits a dual targeting mode-of-action that induces tumor cell death and suppresses tumor-induced pathologic bone formation in tumor microenvironment of osseous CRPC growth in mice. Clin Cancer Res; 23(15); 4335-46. ©2017 AACR.

Database: Medline

9. Radium-223 dichloride for the treatment of castration-resistant prostate cancer with symptomatic bone metastases.

Author(s): Vogelzang, Nicholas J

Source: Expert review of clinical pharmacology; Aug 2017; vol. 10 (no. 8); p. 809-819

Publication Date: Aug 2017

Publication Type(s): Journal Article Review

PubMedID: 28649893

Abstract:INTRODUCTIONCastration-resistant prostate cancer (CRPC) is associated with the development of bone metastases, increased mortality, and a reduction in the patient's quality of life (QOL). The management of metastatic CRPC (mCRPC) has rapidly evolved over the past decade, with a number of available therapeutic agents improving overall survival. Radium-223 dichloride (radium-223), the first targeted alpha therapy, improves survival accompanied by QOL benefits with a favorable safety profile. It is approved in over 40 countries for the treatment of patients with CRPC with symptomatic bone metastases and no known visceral metastatic disease. Areas covered: The current management of CRPC in men with bone metastases, and in particular the role of radium-223 in this setting, is reviewed and discussed. A search of bibliographic databases for peer-reviewed literature and major meetings was conducted. Expert commentary: In treating patients with mCRPC, the best sequencing and/or combination of radium-223 with other agents has yet to be fully elucidated. The role of radium-223 in treating patients with hormone-sensitive metastatic prostate cancer who are candidates for chemotherapy should also be investigated in well-designed trials. The ability to tailor radium-223 therapy to both the clinical and genetic profiles of CRPC patients would be a promising development.

Database: Medline

10. Imaging and dosimetry for radium-223: the potential for personalized treatment.

Author(s): Flux, Glenn D

Source: The British journal of radiology; Aug 2017; vol. 90 (no. 1077); p. 20160748

Publication Date: Aug 2017

Publication Type(s): Journal Article

PubMedID: 28654303

Abstract: Radium-223 (223Ra) offers a new option for the treatment of bone metastases from prostate cancer. As cancer treatment progresses towards personalization, the potential for an individualized approach is exemplified in treatments with radiotherapeutics due to the unique ability to image in vivo the uptake and retention of the therapeutic agent. This is unmatched in any other field of medicine. Currently, 223Ra is administered according to standard fixed administrations, modified according to patient weight. Although gamma emissions comprise only 1% of the total emitted energy, there are increasing reports that quantitative imaging is feasible and can facilitate patient-specific dosimetry. The aim of this article is to review the application of imaging and dosimetry for 223Ra and to consider the potential for treatment optimization accordingly, in order to ensure clinical and cost effectiveness of this promising agent.

Database: Medline

11. Comparative efficacy and safety of second-line treatment for castration-resistant prostate cancer via a network metaanalysis of randomized controlled trials

Author(s): Chen C.; Liu H.; Huang H.; Lin T.; Huang J.

Source: International Journal of Urology; Aug 2017; vol. 24 ; p. 38-39

Publication Date: Aug 2017

Publication Type(s): Conference Abstract

Abstract: Introduction and objectives At the initiation of this study the standard therapy that had been shown to prolong survival in patients with CRPC was docetaxel-based chemotherapy. Treatment options for patients whose disease progresses after docetaxel treatment was an unmet medical need. We evaluated the comparative efficacy and safety of the second-line treatments for CRPC via a network meta-analysis of randomized controlled trials (RCTs). Materials and methods The systematic search of the literature was applied and identified RCTs that compared the abilities of placebo combination with prednisone/prednisolone (P) vs other chemotherapy regimens, immunotherapy and AR-targeting. The Bayesian network meta-analysis was conducted to combine direct and indirect evidence and estimate the relative effects of treatment. Results We identified 20 trials, comprising 11779 participants comparing with 15 treatment strategies. We compared with 15 different therapies for CRPC in overall survival (OS), 13 treatments in progression free survival (PFS). Enzalutamide Qd (Hazard Ratio [HR]: 0.633,95% CI: 0.531-0.752) was the most efficacious agent in OS, probability of ranking among the top 3 agents, followed by Cabazitaxel+P Q3w (HR:0.710,95% CI: 0.536,0.922), Radium-223 Q3w (HR: 0.697,95% CI: 0.606,0.804). For PFS, Enzalutamide Qd (HR: 0.401,95% CI: 0.344,0.463) was superior to others in PFS, followed by Cabozantinib Qd (HR: 0.482,95% CI: 0.404, 0.573) and Cabazitaxel+P Q3w (HR: 0.521,95% CI :0.402,0.668). Conclusion Treatment with Enzalutamide Qd is the most efficacious second-line agents for improving OS and

PFS in patients with CRPC, based. on existing RCTs. Cabazitaxel+P Q3w also showed the significant efficacy benefit.

Database: EMBASE

12. Phase II study of radium-223 dichloride in Japanese patients with symptomatic castration-resistant prostate cancer

Author(s): Matsubara N.; Nagamori S.; Wakumoto Y.; Uemura H.; Kimura G.; Yokomizo A.; Kikukawa H.; Mizokami A.; Kosaka T.; Masumori N.; Kawasaki Y.; Yonese J.; Nasu Y.; Fukasawa S.; Sugiyama T.; Kinuya S.; Hosono M.; Yamaguchi I.; Tsutsui H.

Source: International Journal of Clinical Oncology; Aug 2017 ; p. 1-8

Publication Date: Aug 2017

Publication Type(s): Article In Press

Abstract: Background: Radium-223 dichloride (radium-223) is the first targeted alpha therapy approved for the treatment of castration-resistant prostate cancer (CRPC) with bone metastases. This study investigated the efficacy and safety of radium-223 in Japanese patients with symptomatic CRPC and bone metastases. Methods: In this open-label, multicenter, phase II study, patients with progressive, symptomatic CRPC and bone metastases were treated with radium-223 (55 kBq/kg, intravenously) in a 4-week cycle for six cycles. The primary endpoint was the percent change in total alkaline phosphatase (ALP) from baseline at 12 weeks. Secondary endpoints included the percent ALP change from baseline to end of treatment (EOT), ALP response rates, percent change in prostate-specific antigen (PSA) from baseline to 12 weeks and EOT, PSA response rates, overall survival (OS), and time to symptomatic skeletal events (SSEs). Adverse events were monitored throughout the study period. Results: Of the 49 Japanese patients (median age 74 years), 28 completed all infusions. Mean percent change in total ALP and PSA from baseline to 12 weeks was -19.3 and +97.4%, respectively. One-year OS and SSE-free rate at the end of active follow-up were 78 and 89%, respectively. The ALP response rate was 31%, while the PSA response rate was 6%. Grade 3/4 treatment-emergent adverse events observed in >=10% of patients included decreased lymphocyte count (14%), anemia (14%), anorexia (10%), and bone pain (10%). Conclusions: Radium-223 is effective and well tolerated in Japanese patients with CRPC and bone metastases. Results were comparable with the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial. Clinical trial registration: ClinicalTrials.gov NCT01929655.

Database: EMBASE

13. Three-year Safety of Radium-223 Dichloride in Patients with Castration-resistant Prostate Cancer and Symptomatic Bone Metastases from Phase 3 Randomized Alpharadin in Symptomatic Prostate Cancer Trial.

Author(s): Parker, Christopher C; Coleman, Robert E; Sartor, Oliver; Vogelzang, Nicholas J; Bottomley, David; Heinrich, Daniel; Helle, Svein I; O'Sullivan, Joe M; Fosså, Sophie D; Chodacki, Aleš; Wiechno, Paweł; Logue, John; Seke, Mihalj; Widmark, Anders; Johannessen, Dag Clement; Hoskin, Peter; James, Nicholas D; Solberg, Arne; Syndikus, Isabel; Kliment, Jan; Wedel, Steffen; Boehmer, Sibylle; Dall'Oglio, Marcos; Franzén, Lars; Bruland, Øyvind S; Petrenciuc, Oana; Staudacher, Karin; Li, Rui; Nilsson, Sten

Source: European urology; Jul 2017

Publication Date: Jul 2017

Publication Type(s): Journal Article

PubMedID: 28705540

Abstract:BACKGROUNDIn Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial, radium-223 versus placebo prolonged overall survival with favorable safety in castration-resistant prostate cancer patients with symptomatic bone metastases. Long-term radium-223 monitoring underlies a comprehensive safety and risk/benefit assessment.OBJECTIVETo report updated ALSYMPCA safety, including long-term safety up to 3 yr after the first injection.DESIGN, SETTING, AND PARTICIPANTSSafety analyses from phase 3 randomized ALSYMPCA trial included patients receiving ≥1 study-drug injection (600 radium-223 and 301 placebo). Patients (405 radium-223 and 167 placebo) entered long-term safety follow-up starting 12 wk after the last study-drug injection, to 3 yr from the first injection. Forty-eight of 405 (12%) radium-223 and 12/167 (7%) placebo patients completed follow-up, with evaluations every 2 mo for 6 mo, then every 4 mo until 3 yr.OUTCOME MEASUREMENTS AND STATISTICAL ANALYSISAll adverse events (AEs) were collected until 12 wk after the last injection; subsequently, only treatment-related AEs were collected. Additional long-term safety was assessed by development of acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), aplastic anemia, and secondary malignancies. Data analysis used descriptive statistics.RESULTS AND LIMITATIONSDuring treatment to 12 wk following the last injection, 564/600 (94%) radium-223 and 292/301 (97%) placebo patients had treatment-emergent AEs (TEAEs). Myelosuppression incidence was low. Grade 3/4 hematologic TEAEs in radium-223 and placebo groups were anemia (13% vs 13%), neutropenia (2% vs 1%), and thrombocytopenia (7% vs 2%). Ninety-eight of 600 (16%) radium-223 and 68/301 (23%) placebo patients experienced grade 5 TEAEs. Long-term follow-up showed no AML, MDS, or new primary bone cancer; secondary non-treatment-related malignancies occurred in four radium-223 and three placebo patients. One radium-223 patient had aplastic anemia 16 mo after the last injection. No other cases were observed. Limitations include short (3-yr) follow-up.CONCLUSIONSFinal long-term safety ALSYMPCA analysis shows that radium-223 remained well tolerated, with low myelosuppression incidence and no new safety concerns.PATIENT SUMMARYUpdated Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial findings show that radium-223 remained well tolerated during treatment and up to 3 yr after each patient's first injection.

Database: Medline

14. Radium-223 in the therapeutic sequence of metastatic castration-resistant prostate cancer.

Author(s): Unda-Urzaiz, M; Sousa-Campo, R; Rodríguez-Antolín, A; Silva-Marins, C; Juárez-Soto, A; Miñana-López, B; Figueiredo-de Castro, A; Cozar-Olmos, J M

Source: Actas urologicas espanolas; Jul 2017

Publication Date: Jul 2017

Publication Type(s): Journal Article

PubMedID: 28711312

Abstract:CONTEXTRadium-223 is an □ -particle transmitter with specific action on bone metastases. The Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study showed that radium-223 extended overall survival and delayed the onset of bone events in patients with symptomatic castration-resistant prostate cancer with bone metastases (mCRPC) and without visceral metastases, with a good safety profile.OBJECTIVETo review the new scientific evidence on radium-223 based on prespecified and post-hoc analyses of the ALSYMPCA study and on early-access programs after the publication of the ALSYMPCA study, thereby providing new data on the management of patients with mCRPC.ACQUISITION OF EVIDENCEWe searched for evidence on PubMed and in the abstracts of international urology and oncology congresses, as well as ongoing clinical trials (ClinicalTrials.gov).SYNTHESIS OF THE EVIDENCEThe results of the reviewed studies offer promising

results that will broaden the therapeutic benefits of radium-223 to patients with mild symptoms and those with no symptoms. The results also provide preliminary evidence on the benefit of radium-223 treatment after the failure of docetaxel, enzalutamide or abiraterone or the combination of radium-223 with these agents or other therapeutic agents such as bone-targeted agents and immunotherapy.CONCLUSIONRadium-223 can be a treatment option for patients with mild symptoms and can provide a therapeutic benefit after failure of currently available treatments or in combination with these treatments. This evidence should be corroborated in clinical trials before being added to clinical practice.

Database: Medline

15. Radium-223 for primary bone metastases in patients with hormone-sensitive prostate cancer after radical prostatectomy.

Author(s): Wenter, Vera; Herlemann, Annika; Fendler, Wolfgang P; Ilhan, Harun; Tirichter, Natalia; Bartenstein, Peter; Stief, Christian G; la Fougère, Christian; Albert, Nathalie L; Rominger, Axel; Gratzke, Christian

Source: Oncotarget; Jul 2017; vol. 8 (no. 27); p. 44131-44140

Publication Date: Jul 2017

Publication Type(s): Journal Article

PubMedID: 28484088

Abstract: Radium-223 dichloride (Ra-223) is the first bone-targeting agent showing improvement in overall survival in patients with castration-resistant prostate cancer (CRPC) and bone metastases. We aimed to assess feasibility of Ra-223 treatment in patients with metastatic hormone-sensitive prostate cancer (mHSPC). Ten patients with primary bone metastases received Ra-223 following radical prostatectomy (RP). Changes in alkaline phosphatase (ALP) and prostate-specific antigen (PSA) were recorded, while pain intensity was evaluated using the self-reporting Brief Pain Inventory (BPI) questionnaire. Bone scintigraphy (BS) was performed to assess treatment response. Seven patients completed six cycles of Ra-223. Discontinuation was due to leuko- and lymphopenia, progressive lymph node metastasis or newly diagnosed liver metastasis. Treatment-related adverse events occurred in three patients and included leuko- and lymphopenia, fatigue, abdominal discomfort and nausea. Overall, a median decrease of 28% in ALP and a median decrease of 83% in PSA were noted at follow-up. However, PSA progressed in five patients at follow-up. Improvement of pain was observed in all patients (median decrease of 36% after 3 cycles and of 40% at the end of therapy). On BS, three patients showed remission, four had stable disease, and one showed progressive disease at follow-up. Our results suggest that Ra-223 for primary bone metastases in patients with mHSPC after RP is feasible and alleviates pain. ALP, rather than PSA, may be a good marker for assessing treatment response. Ra-223 could therefore be taken into consideration as part of a multimodal approach for carefully selected patients with advanced prostate cancer.

Database: Medline

16. Comparing Clinical Outcomes for Radium-223: Do Older Patients Do Worse?

Author(s): Song, Yee Pei; Ellis, Tracey; Walshaw, Richard; Mbanu, Peter; Parikh, Omi; Logue, John; Choudhury, Ananya

Source: International journal of radiation oncology, biology, physics; Jul 2017; vol. 98 (no. 4); p. 955-957

Publication Date: Jul 2017

Publication Type(s): Comparative Study Multicenter Study Journal Article

PubMedID: 28365163

Available in full text at International Journal of Radiation Oncology*Biology*Physics - from Elsevier

Abstract:PURPOSETo examine the clinical benefits and toxicities of 223Ra in 2 different age groups of patients with castrate-resistant prostate cancer.METHODS AND MATERIALSThis was a retrospective study of patients treated with 223Ra in 2 tertiary centers. Patients were divided into 2 different groups based on their age (≥72 years old and <72 years old). Treatment toxicities were graded according to Common Terminology Criteria for Adverse Events version 4.0. Comparison of characteristics and outcome was carried out with the Mann-Whitney test and analysis of overall survival with the log-rank test.RESULTSIn all, 129 patients were treated during the study period. Clinical benefit was similar in both groups. However, a statistically significant higher proportion of patients in the younger group had previously been treated with docetaxel. There was a higher rate of grade 3 anemia in younger patients.CONCLUSIONSIn line with other studies, 223Ra was well tolerated with minimum toxicities. The significantly higher rate of grade 3 anemia in younger patients may be due to more cautious patient selection in the elderly population.

Database: Medline

17. Emerging role of Radium-223 in the growing therapeutic armamentarium of metastatic castration-resistant prostate cancer.

Author(s): Picciotto, Maria; Franchina, Tindara; Russo, Alessandro; Ricciardi, Giuseppina Rosaria Rita; Provazza, Giusy; Sava, Serena; Baldari, Sergio; Caffo, Orazio; Adamo, Vincenzo

Source: Expert opinion on pharmacotherapy; Jun 2017; vol. 18 (no. 9); p. 899-908

Publication Date: Jun 2017

Publication Type(s): Journal Article

PubMedID: 28449621

Abstract:INTRODUCTIONDuring the last few years, the therapeutic armamentarium of castration resistant prostate cancer (mCRPC) has been enriched with the introduction of new effective therapies with proved survival benefit and quality of life gain, including cabazitaxel, abiraterone, enzalutamide, and Radium-223. Areas covered: Bone metastases represent a substantial cause of morbidity in mCRPC with a high rate of related skeletal events (SREs). In case of multifocal pain due to diffuse osteoblastic metastases, treatment with bone-targeting radiopharmaceutical agents can provide palliation from pain. Radium-223, a calcium-mimetic, is the first α-particle emitting radiopharmaceutical that prolonged overall survival, delayed symptomatic skeletal events and improved quality of life in mCRPC. Expert opinion: In this therapeutic scenario, no clear evidences support the best way to sequence these available agents and there is an urgent need for prospective studies to define it. 223Ra is a firmly established therapeutic option in CRPC with symptomatic bone metastases and no visceral/bulky nodal involvement, with an undeniable advantage over new hormonal agents, given its peculiar mechanism of action. Current ongoing randomized clinical trials will clarify the optimal use of this effective therapy in the therapeutic armamentarium of CRPC either alone or combined with other new approved agents and whether there is a role in patients with asymptomatic disease.

Database: Medline

18. Acute Promyelocytic Leukemia After Treatment of Metastatic Castration-Resistant Prostate Cancer With Radium-223.

Author(s): Odo, Ugochukwu; Vasudevamurthy, Ashwin K; Sartor, Oliver

Source: Clinical genitourinary cancer; Jun 2017; vol. 15 (no. 3); p. e501

Publication Date: Jun 2017

Publication Type(s): Journal Article

PubMedID: 28111175

Database: Medline

19. Computational modeling of radiobiological effects in bone metastases for different radionuclides.

Author(s): Liberal, Francisco D C Guerra; Tavares, Adriana Alexandre S; Tavares, João Manuel R S

Source: International journal of radiation biology; Jun 2017; vol. 93 (no. 6); p. 627-636

Publication Date: Jun 2017

Publication Type(s): Comparative Study Journal Article

PubMedID: 28276897

Abstract:PURPOSEComputational simulation is a simple and practical way to study and to compare a variety of radioisotopes for different medical applications, including the palliative treatment of bone metastases. This study aimed to evaluate and compare cellular effects modelled for different radioisotopes currently in use or under research for treatment of bone metastases using computational methods.METHODSComputational models were used to estimate the radiation-induced cellular effects (Virtual Cell Radiobiology algorithm) post-irradiation with selected particles emitted by Strontium-89 (89Sr), Samarium-153 (153Sm), Lutetium-177 (177Lu), and Radium-223 (223Ra).RESULTSCellular kinetics post-irradiation using 89Sr β- particles, 153Sm β- particles, 177Lu β- particles and 223Ra α particles showed that the cell response was dose- and radionuclide-dependent. 177Lu beta minus particles and, in particular, 223Ra alpha particles, yielded the lowest survival fraction of all investigated particles.CONCLUSIONS223Ra alpha particles induced the highest cell death of all investigated particles on metastatic prostate cells in comparison to irradiation with β- radionuclides, two of the most frequently used radionuclides in the palliative treatment of bone metastases in clinical routine practice. Moreover, the data obtained suggest that the used computational methods might provide some perception about cellular effects following irradiation with different radionuclides.

Database: Medline

20. Analysis of real-world use of radium-223 in Ontario

Author(s): Emmenegger U.; Cheng S.; Rowbottom L.; McDonald R.; Chow R.; Chow E.; Fleshner N.E.; Zalewski P.; Kapoor A.

Source: Canadian Urological Association Journal; Jun 2017; vol. 11 (no. 6)

Publication Date: Jun 2017

Publication Type(s): Conference Abstract

Available in full text at Canadian Urological Association Journal - from National Library of Medicine

Abstract: Introduction: Radium-223 (Ra223) improves survival and delays symptomatic skeletal events in patients with metastatic castration-resistant prostate cancer (mCRPC) to bone. In the ALSYMPCA registration trial, 63% of patients received the maximum of six cycles of Ra223. Because patients treated outside of clinical trials typically are older and present with more comorbidities, we

decided to study the real-world use of Ra223 in Ontario. Methods: In this retrospective chart review, we studied mCRPC patients receiving >=1 dose of provincially funded Ra223 at Odette Cancer Centre from January 2015 to April 2016. Primary endpoints were the median number of Ra223 cycles and reasons for treatment discontinuations at =3 cycles of Ra223, PSA30 was 5%, and ALP normalization was seen in 4/9 (44.5%) patients with baseline ALP elevation. There were no unexpected adverse events. Conclusions: In an older, real-world patient population with similar, if not better baseline disease characteristics than in ALSYMPCA, Ra223 can be administered efficaciously and safely, but the rate of patients completing six cycles of Ra223 is lower. We are in the process of collecting data from three additional centres (Princess Margaret Cancer Centre, Lakeridge Health, Juravinski Hospital) to analyze factors predicting early treatment termination.

Database: EMBASE

21. Bone scan index at baseline as a tool for predicting hematologic toxicity in metastatic castration-resistant prostate cancer patients eligible for radium-223 treatment

Author(s): Kothari S.; Sharif-Tabrizi A.; Attwood K.; Lamonica D.M.; Levine E.G.; George S.

Source: Journal of Clinical Oncology; Jun 2017; vol. 35 (no. 15)

Publication Date: Jun 2017

Publication Type(s): Conference Abstract

Available in full text at Journal of clinical oncology: official journal of the American Society of Clinical Oncology [J Clin Oncol] NLMUID: 8309333 - from EBSCOhost

Available in full text at Journal of Clinical Oncology - from American Society of Clinical Oncology

Abstract: Background: The prognosis of castration-resistant prostate cancer with skeletal metastasis (CRPCSM) is poor. The ALSYMPCA trial led to the approval of radium-223 (Ra223) in such patients. Factors that could predict hematologic toxicities associated with Ra223 remain poorly defined. We analyzed the utility of bone scan index (BSI) at baseline (BSI-B) as a predictive marker for such toxicities. Methods: This is a retrospective study of CRPCSM patients without visceral metastasis who received Ra223 at Roswell Park Cancer Institute from 2013 to 2015. BSI was defined utilizing the estimation of a numerical index (max, 70.8% for diffuse skeletal involvement) that expresses the fractional involvement of each bone by tumor. BSI-B values were classified into third quartile (> Q3). The associations between BSI-B and different hematologic parameters [hemoglobin (Hgb), platelets (Plt), absolute neutrophil count (ANC)] over the Ra223 treatment duration were evaluated using linear mixed models. Results: A total of 79 patients were included in this analysis. The median Gleason score was 8 (range: 4-10) and the median age at first Ra223 was 71 years. Seventy percent of patients received 5 or more doses of Ra223. There was a significant association between BSI-B and Hgb (p = 0.005) and Plt (p = 0.011) levels at baseline and at all time points. The > Q3 BSIB was associated with a greater drop in Plt from an elevated baseline with subsequent treatments of Ra223 [drop from a mean of 293.5+/-21.3 x109/L (n = 19) to 132.2+/-48.8 x109/L (n = 9) after sixth Ra223]; while such a decline was not observed for lower BSI-B (p Q3 BSI-B but not in the ones with lower BSI-B (p = 0.003). Conclusions: Our work demonstrates that hematologic parameters at baseline and during Ra223 treatment are associated with higher BSI-B values, raising the possibility of BSI-B as a valuable tool for predicting the risk of cytopenias before initiating Ra223 in CRPCSM patients. Prospective validation is needed to confirm the utility of our findings.

Database: EMBASE

22. Management of metastatic castration-resistant prostate cancer: A focus on radium-223: Opinions and suggestions from an expert multidisciplinary panel.

Author(s): Baldari, Sergio; Boni, Giuseppe; Bortolus, Roberto; Caffo, Orazio; Conti, Giario; De Vincentis, Giuseppe; Monari, Fabio; Procopio, Giuseppe; Santini, Daniele; Seregni, Ettore; Valdagni, Riccardo

Source: Critical reviews in oncology/hematology; May 2017; vol. 113 ; p. 43-51

Publication Date: May 2017

Publication Type(s): Journal Article Review

PubMedID: 28427521

Abstract: Radium-223, a calcium mimetic bone-seeking radionuclide that selectively targets bone metastases with alpha particles, is approved for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) and symptomatic bone metastases. In patients with mCRPC, treatment with radium-223 has been associated with survival benefit, regardless of prior docetaxel use, and also has a positive impact on symptomatic skeletal events and quality of life. Radium-223 is best suited for patients with symptomatic mCRPC and bone-predominant disease and no visceral metastases, and may lead to better outcomes when given early in the course of the disease. An expert multidisciplinary panel convened in Milan, Italy to review the current best-evidence literature on radium-223 and to convey their personal expertise with the use of radium-223 and identify possible strategies for best practice. This article summarizes the best available evidence for the use of radium-223, discusses the essential role of the multidisciplinary team in delivering effective treatment for mCRPC, clarifies pre- and post-treatment evaluation and monitoring, and outlines future scenarios for radium-223 in the treatment of men with MCRPC.

Database: Medline

23. Exploring New Multimodal Quantitative Imaging Indices for the Assessment of Osseous Tumour Burden in Prostate Cancer using 68Ga-PSMA-PET/CT.

Author(s): Bieth, Marie; Krönke, Markus; Tauber, Robert; Dahlbender, Marielena; Retz, Margitta; Nekolla, Stephan G; Menze, Bjoern; Maurer, Tobias; Eiber, Matthias; Schwaiger, Markus

Source: Journal of nuclear medicine : official publication, Society of Nuclear Medicine; May 2017

Publication Date: May 2017

Publication Type(s): Journal Article

PubMedID: 28546330

Available in full text at Journal of nuclear medicine: official publication, Society of Nuclear Medicine [J Nucl Med] NLMUID: 0217410 - from EBSCOhost

Abstract: Positron-emission-tomography (PET) combined with computed-tomography (CT) and prostate-specific-membrane-antigen (PSMA) ligands has gained significant interest for staging prostate cancer (PC). In this study, we propose two multimodal quantitative indices as imaging biomarker for the assessment of osseous tumour burden using 68Ga-PSMA-PET/CT and present preliminary clinical data. We define two Bone-PET-Indices (BPI) that incorporate anatomical information from CT and functional information from 68Ga-PSMA-PET: BPIVOL is the percental bone volume affected by tumour. BPISUV additionally considers the level of PSMA-expression. We describe a semi-automatic computation method based on segmentation of bones in CT and of lesions in PET. Data from 45 patients with castration-resistant PC and bone metastases during Radium-223-dichloride were retrospectively analysed. We evaluated the computational stability and reproducibility of the proposed indices, and explored their relation to the prostate-specific-antigen

(PSA) blood value, the Bone-Scan-Index (BSI) and disease classification using the PET response criteria in solid tumours (PERCIST). On the technical side, BPIVOL and BPISUV showed an inter-observer maximum difference of 3.5% and their computation took only a few minutes. On the clinical side, BPIVOL and BPISUV showed significant correlations with BSI (r=0.76 and 0.74 respectively, p<0.001) and PSA-values (r=0.57 and 0.54 respectively, p<0.01). When comparing the proposed indices against expert rating using PERCIST, BPIVOL and BPISUV showed better agreement than BSI, indicating their potential for objective response evaluation. We propose the evaluation of BPIVOL and BPISUV as imaging biomarkers for 68Ga-PSMA-PET/CT in a prospective study exploring their potential for outcome prediction in patients with bone metastases from PC.

Database: Medline

24. Impact of collimator on ²²³Ra imaging: A monte-carlo study

Author(s): Sasaki M.; Oshima R.; Takahashi A.; Baba S.; Himuro K.

Source: Journal of Nuclear Medicine; May 2017; vol. 58

Publication Date: May 2017

Publication Type(s): Conference Abstract

Available in full text at Society of Nuclear Medicine Annual Meeting Abstracts - from Highwire Press

Abstract: Objectives: Radium-223 (223Ra) is an alpha-emitting radionuclide used in unsealed radionuclide therapy for bone-metastatic prostate cancer. Alpha rays have a short range and high energy. Thus, it is important to comprehend their movement in a patient's body. In this study, we investigated the impact of collimator on 223Ra abdominal imaging using Monte Carlo simulation. Methods: The Monte Carlo codes are HEXAGON and NAI; these were developed by Tanaka and Uehara. The HEXAGON code simulates the behavior of the photon and electron in the phantom and collimator, and then, the NAI code simulates their behavior in the gamma camera, including the optical components and scintillator, producing projection images. We installed a numeric phantom that was created using computed tomography (CT) images of an abdominal phantom. 223Ra was distributed in the third lumbar vertebral region, and 22 X-rays and gamma rays were installed. The width of the energy window was determined to be 20 % of 84 keV-photopeak (76-92 keV), in accordance with previous studies. We examined two low-energy, general-purpose (LEGP) collimators (Collimators I and II) and two medium-energy, general-purpose (MEGP) collimators (Collimators III and IV). The collimator dimensions, i.e., septal thickness and hole diameter, were 0.017 cm and 0.178 cm for Collimator I, 0.025 cm and 0.190 cm for Collimator II, 0.084 cm and 0.260 cm for Collimator III, and 0.11 cm and 0.337 cm for Collimator IV, respectively. The collimator height was 4.0 cm. The event number of decay was 108. Results: As the septal thickness increased, the simulated projection images seemed clearer. Detection sensitivity (cps/MBq) is an important factor in imaging. We simulated energy spectra for each image from which sensitivities were derived. The total sensitivities of the gamma camera were 131 cps/MBq for Collimator I, 80.1 cps/MBq for Collimator II, 41.9 cps/MBq for Collimator III, and 69.5 cps/MBq Collimator IV. The fractions of sensitivity due to unscattered photons, indicating the image quality, were 6.35 (I), 11.0 (II), 27.4 (III), and 29.4 % (IV). The sensitivities for LEGP were much larger than those for MEGP; however, the fractions of unscattered photons for MEGP were larger than those for LEGP. This is because thick septa effectively removed scattered photons and lead fluorescence. Conclusion: In this investigation, the most favorable collimator for superior image quality was the Collimator IV, which had the thickest septum and the largest hole diameter. However, an excessively large hole diameter increases photon scatter and degrades spatial resolution. Therefore, other collimators need to be investigated for various 223Ra distributions.

Database: EMBASE

25. Oral administration of barium sulfate reduces radiation exposure to the large intestine during alpha therapy with radium-223 dichloride

Author(s): Washiyama K.; Yoshimoto M.; Hanadate S.; Tsuji A.; Higashi T.; Yoshii Y.; Matsumoto H.

Source: Journal of Nuclear Medicine; May 2017; vol. 58

Publication Date: May 2017

Publication Type(s): Conference Abstract

Available in full text at Society of Nuclear Medicine Annual Meeting Abstracts - from Highwire Press

Abstract: Objectives: Radium-223 dichloride (223RaCl2) is an FDA-approved alpha-emitting drug for patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. 223Ra is a calcium analogue and forms complexes with hydroxyapatite in activated osteoblastic regions near metastases. Clinical studies have demonstrated that gastrointestinal disorders, such as nausea, abdominal discomfort and diarrhea, were the most frequent adverse events due to the high radiation doses to the large intestine caused by intravenous injection of 223RaCl2. Here, we proposed a novel strategy to reduce accumulation of 223Ra in the large intestine by oral administration of barium sulfate (BaSO4) known as a coprecipitating agent of Ra. Methods: 223RaCl2 (10 kBq/mouse) was intravenously injected in ddY mice with or without oral administration of BaSO4 (150 mg/mouse) at 1 h before 223RaCl2 injection. The biodistribution study was conducted at 1, 2, 4, 6, and 24 h after 223RaCl2 injection. In addition, for laxative treatment, 50% glycerin enema solution (0.3 mL) was administered rectally at 3 h after 223RaCl2 injection, with or without BaSO4 administration in a manner described above, and the biodistribution study was conducted at 1 h after glycerin enema (4 h after 223RaCl2 injection). The organs of interest (blood, liver, kidney, small intestine, large intestine, spleen, and femur) were collected and weighed and urine and feces were also collected. Radioactivity was counted with a gamma-counter. The biodistribution data were shown as the %ID/g for the organs and the %ID for the urine and feces (n = 4). Results: BaSO4 significantly reduced 223Ra accumulation in the large intestine at 1, 2 and 4 h after 223RaCl2 injection (P 223Ra activity of the urine and feces was found in the BaSO4 group at 24 h after 223RaCl2 injection, compared to the control group. Glycerin enema also decreased 223Ra accumulation in the large intestine to a similar level of BaSO4. However, no additional effect of glycerin enema to BaSO4 was observed. These results suggest that use of BaSO4 would be effective to reduce 223Ra accumulation in the large intestine during 223RaCl2 therapy and glycerin enema could help to clear BaSO4 from the body without lessening the effect of BaSO4. Conclusion: We demonstrated that our strategy with BaSO4 was effective to reduce radiation exposure to the large intestine during 223RaCl2 therapy. This method could be useful to reduce adverse events on 223RaCl2 therapy.

Database: EMBASE

26. Safety and efficacy of radium-223 dichloride in Japanese patients with castration-resistant prostate cancer and bone metastases

Author(s): Uemura H.; Matsubara N.; Kinuya S.; Hosono M.; Yajima Y.; Doi T.

Source: International Journal of Clinical Oncology; May 2017 ; p. 1-10

Publication Date: May 2017

Publication Type(s): Article In Press

Abstract: Background: Radiation therapy with radium-223 dichloride improves overall survival, reduces symptomatic skeletal events in Caucasian patients with castration-resistant prostate cancer

(CRPC) and bone metastases, and is well tolerated. We report here the results of the first efficacy and safety study of radium-223 dichloride in a Japanese population. Methods: In this open-label, uncontrolled, non-randomized, phase I trial, radium-223 dichloride was given to Japanese patients with CRPC and >=2 bone metastases in 4-week cycles. The patients were divided into three cohorts, with cohort 1 and the expansion cohort receiving injections of radium-223 dichloride [55 kBq/kg body weight (BW)] every 4 weeks (Q4W) for up to six injections, and cohort 2 receiving an initial single radium-223 dichloride injection of 110 kBq/kg BW followed by up to five injections of 55 kBq/kg BW Q4W. Safety was determined via adverse event (AE) reporting, and biochemical bone markers were assessed for treatment efficacy. Results: In total 19 patients received at least one dose of radium-223 dichloride and 18 patients experienced at least one treatment-emergent AE (TEAE) of which the most common were anemia, thrombocytopenia, and lymphocytopenia. Serious AEs were reported in three patients but none were drug-related. In the patients of cohort 1 + expansion cohort (55 kBq/kg BW Q4W treatment; n = 16), prostate-specific antigen levels remained stable or slightly increased while the bone alkaline phosphatase (ALP) level significantly decreased. The response rates of bone ALP (>=30 and >=50% reductions) were 81.8 and 36.4% at week 12, and 81.3 and 50.0% at the end of treatment. Conclusions: Radium-223 dichloride was well tolerated in these Japanese patients and, at a dose of 55 kBq/kg BW, efficacy on biomarkers was as expected. The outcomes in Japanese patients were consistent with those reported in other non-Japanese populations. Trial registration: ClinicalTrials.gov record NCT01565746.

Database: EMBASE

27. Radium-223 Use in Clinical Practice and Variables Associated With Completion of Therapy.

Author(s): McKay, Rana R; Jacobus, Susanna; Fiorillo, Matthew; Ledet, Elisa M; Cotogna, Patrick M; Steinberger, Allie E; Jacene, Heather A; Sartor, Oliver; Taplin, Mary-Ellen

Source: Clinical genitourinary cancer; Apr 2017; vol. 15 (no. 2); p. e289

Publication Date: Apr 2017

Publication Type(s): Journal Article

PubMedID: 27651103

Abstract:BACKGROUNDRadium-223 has shown clinical efficacy in metastatic castration-resistant prostate cancer. Despite improvement in quality of life and survival, practice patterns and utility of this agent outside the context of clinical trials have not been fully characterized. The primary objective in this study was to evaluate variables associated with completion of 5 to 6 radium-223 doses.PATIENTS AND METHODSWe conducted retrospective analyses of patients who received radium-223 (n = 135). Patients were classified into 3 cohorts: 1 to 2, 3 to 4, or 5 to 6 radium-223 doses. We evaluated the association of clinical and laboratory variables with the number of cycles administered (5-6 vs. 1-4 doses).RESULTSTwenty-five patients (18.5%) received 1 to 2 radium-223 doses, 27 (20.0%) received 3 to 4, and 83 (61.5%) received 5 to 6. The most common reasons for treatment discontinuation included disease progression (61.5%, n = 40), patient preference (15.4%, n = 10), and toxicity (10.8%, n = 7). Factors associated with therapy completion in univariate analysis included previous sipuleucel-T treatment (P = .068), no previous abiraterone or enzalutamide treatment (P = .007), hemoglobin ≥ lower limit of normal (LLN; P = .006), white blood cell count ≥ LLN (P = .045), absolute neutrophil count (ANC) ≥ LLN (P = .049), lower alkaline phosphatase (P = .029), and lower lactate dehydrogenase levels (P = .014). Factors associated with therapy completion in multivariable analysis included previous sipuleucel-T treatment (P = .009), hemoglobin ≥ LLN (P = .037), and ANC ≥ LLN (P = .029).CONCLUSIONSeveral clinical parameters are associated with radium-223 therapy completion. In general, these parameters reflect earlier disease stage. These data are

hypothesis-generating and prospective testing of the optimal number of radium-223 doses is warranted.

Database: Medline

28. Clinical Correlates of Benefit From Radium-223 Therapy in Metastatic Castration Resistant Prostate Cancer.

Author(s): Alva, Ajjai; Nordquist, Luke; Daignault, Stephanie; George, Saby; Ramos, Jorge; Albany, Costantine; Isharwal, Sudhir; McDonald, Matthew; Campbell, Gregory; Danchaivijitr, Pongwut; Yentz, Sarah; Anand, Aseem; Yu, Evan Y

Source: The Prostate; Apr 2017; vol. 77 (no. 5); p. 479-488

Publication Date: Apr 2017

Publication Type(s): Multicenter Study Journal Article

PubMedID: 27990667

Abstract:BACKGROUNDWe sought to identify potential clinical variables associated with outcomes after radium-223 therapy in routine practice.METHODSConsecutive non-trial mCRPC patients who received ≥1 dose of radium dichloride-223 at four academic and one community urology-specific cancer centers from May 2013 to June 2014 were retrospectively identified. Association of baseline and on-therapy clinical variables with number of radium doses received and clinical outcomes including overall survival were analyzed using chi-square statistics, cox proportional hazards, and Kaplan-Meier methods. Bone Scan Index (BSI) was derived from available bone scans using EXINI software.RESULTSOne hundred and forty-five patients were included. Radium-223 was administered for six cycles in 74 patients (51%). One-year survival in this heavily pre-treated population was 64% (95%CI: 54-73%). In univariate and multivariate analysis, survival was highly associated with receiving all six doses of Radium-223. Receipt of six doses was associated with ECOG PS of 0-1, lower baseline PSA & pain level, no prior abiraterone/enzalutamide, <5 BSI value, and normal alkaline phosphatase. In patients who reported baseline pain (n = 72), pain declined in 51% after one dose and increased in 7%. PSA declined ≥50% in 16% (18/110). Alkaline phosphatase declined ≥25% in 48% (33/69) and ≥50% in 16/69 patients. BSI declined in 17 (68%) of the 25 patients who had bone scan available at treatment follow-up. Grade ≥3 neutropenia, anemia, and thrombocytopenia occurred in 4% (n = 114), 4% (n = 125), and 5% (n = 123), respectively.CONCLUSIONSPatients earlier in their disease course with <5 BSI, low pain score, and good ECOG performance status are optimal candidates for radium-223. Radium-223 therapy is well tolerated with most patients reporting declines in pain scores and BSI. Prostate 77:479-488, 2017. © 2016 Wiley Periodicals, Inc.

Database: Medline

29. Factors Associated With Survival Following Radium-223 Treatment for Metastatic Castration-resistant Prostate Cancer.

Author(s): Wong, William W; Anderson, Eric M; Mohammadi, Homan; Daniels, Thomas B; Schild, Steve E; Keole, Sameer R; Choo, C Richard; Tzou, Katherine S; Bryce, Alan H; Ho, Thai H; Quevedo, Fernando J; Vora, Sujay A

Source: Clinical genitourinary cancer; Apr 2017

Publication Date: Apr 2017

Publication Type(s): Journal Article

PubMedID: 28545997

Abstract:BACKGROUNDRadium-223 (223Ra) improves survival in patients with metastatic castration-resistant prostate cancer (mCRPC). This retrospective analysis was performed to better understand its efficacy in routine clinical practice and identify factors associated with survival.MATERIALS AND METHODSSixty-four patients with mCRPC who received 223Ra between 2013 and 2015 were the basis of this retrospective study. Clinical outcomes and patient characteristics were obtained. Potential prognostic factors for survival were evaluated by univariate analysis using the log-rank test and multivariate analysis using the Cox proportional hazard method.RESULTSThe median survival was 12.9 months. Twenty-one patients (33%) developed a skeletal event, and the median time to the first skeletal event was 4.4 months. In univariate analysis, factors significantly associated with survival included: no prior chemotherapy, ≤ 5 bone metastases, baseline prostate-specific antigen (PSA) ≤ 36 ng/mL, baseline alkaline phosphatase (ALP) 12 g/dL, ALP response after 223Ra treatment, PSA decrease during 223Ra treatment, and absence of > 25% PSA increase during 223Ra treatment. In multivariate analysis, 4 factors remained significant: no prior chemotherapy, ≤ 5 bone metastases, baseline ALP < 115 U/L, and ALP response after 223Ra treatment.CONCLUSIONWhen 223Ra is administered in routine clinical practice, clinical outcomes can be more variable than those reported in the randomized study owing to patient heterogeneity. Four factors were identified to be significantly associated with survival after 223Ra treatment. These pretreatment factors may be used as stratification factors in future studies to investigate whether 223Ra would be more effective for patients with newly diagnosed metastatic disease that is sensitive to androgen deprivation therapy.

Database: Medline

30. Radium-223-dichloride in metastatic prostate cancer: Preliminary results of therapy response using 11Ccholine PET/CT and bone scan

Author(s): Ghedini P.; Graziani T.; Lodi Rizzini E.; Lima G.M.; Matti A.; Montini G.C.; Nanni C.; Castellucci P.; Fanti S.; Pettinato C.; Civollani S.; Marengo M.; Monari F.; Morganti A.G.

Source: Clinical and Translational Imaging; Apr 2017; vol. 5

Publication Date: Apr 2017

Publication Type(s): Conference Abstract

Abstract: Background-aim: The purpose of our study was to evaluate the response to Radium-223 therapy using Choline PET/CT and Bone Scan in castration-resistant prostate cancer (mCRPC) patients. Methods: 14 patients were retrospectively enrolled (age mean/range = 72.3/58-86 years-old). Our inclusion criteria were (1) symptomatic bone metastasis in mCRPC (2) 6 cycles of Ra-223 treatment; (c) Bone scan and Choline-PET/CT were performed before (BS1; PET1) and 2 months after the end of treatment (BS2; PET2). Alkaline phosphatase (ALP), PSA, HB and LDH values were measured before and after the end of treatment. BS2 and PET2 were reported as complete (CR) or partial response (PR). The appearance of a new bone lesion at PET2 or BS2 was considered as (PD) progression disease. Radiological and clinical follow up ranged from 3 to 6 months. Results: 78.5% (10/14) of patients showed PR at PET2; 14.2% (2/14) showed a CR of bone metastasis at PET2. 14.2% (2/14) patients showed PD at PET2. Considering the 10 patients with PR at PET2, 8/10 showed increasing PSA-trend while considering the 2 patients with CR at PET2, both showed increasing PSA-trend. 100% of patients of three groups showed a significant decrease of ALP (mean reduction of 46.1%). 85.7% (12/14) of patients showed PR at BS2; 14.2% of patients showed PD at BS2. 2 PET2 in PR were instead in PD at BS2; 1 PET2 in CR was in PR at BS2. Conclusions: Preliminary results showed a good response in term of palliative treatment of painful bone metastases. To better evaluate the disease reponse in discordant patients (PET vs BS) a longer follow up and larger number of patients are warranted. PSA, ALP, HB and LDH trends don't seem able to predict PET or Bone SCAN results,

but could be correlated with overall survival. Delta-SUVmax could represent an additional evaluation parameter to predict the treatment response, but visual interpretation is still necessary.

Database: EMBASE

31. Radium-223: Are there predictors of response to therapy?

Author(s): Buttigliero C.; Vignani F.; Tucci M.; Parente A.; Manfredi M.; Podio V.; Angusti T.

Source: Clinical and Translational Imaging; Apr 2017; vol. 5

Publication Date: Apr 2017

Publication Type(s): Conference Abstract

Abstract: Background-aim: Radium-223 dichloride (Ra-223) is an alphaemitter approved by regulatory agencies for the treatment of castration-resistant prostate cancer (CRPC) with symptomatic bone metastases and no known visceral metastatic disease. Yet, predictors of response to Ra-223 and their cut-off values still remain to be clarified. The aim of this study was to evaluate the efficacy and feasibility of Ra-223, and the potential association selected biomarkers in mCRPC patients. Methods: In our center, since September 2015, 22 patients with highburden mCRPC (i.e. 19 with[20 bone metastases, 2 between 6 and 20, and 1 with a "superscan") received Ra-223. All of them were previous treated with systemic anticancer therapy, bone-targeted agents or bone radiotherapy. All patients were monitored for performance status (ECOG-PS), pain [by Numerical Rating Scale (NRS)], and safety (using the Common Terminology Criteria for Adverse Events, version-4.03). Disease progression was evaluated by Computed Tomography (CT) at the third cycle of Ra-223 and by CT and Bone Scan (BS) 8 weeks and 4 months after the last cycle. Time to total-PSA progression, total-ALP response, total-ALP normalization and the variation of ALP and PSA levels were also assessed. Results: Of 22 patients, 16 completed Ra-223 therapy (12 completed 6 cycles, one 5 cycles, two 4 cycles, and one 3 cycles) whereas 6 are still ongoing. Patients discontinued Ra-223 for progression of visceral disease (2/16), adverse events (AEs, grade [G] 3-4, hematological or non-hematological; 2/16) or for a marked increase of ECOG-PS (1/16). During treatment all of them had good ECOG-PS (0-2), good pain control (NRS 1-3), and few AEs (diarrhea, nausea, asthenia, hyporexia, weight loss and dysgeusia) which were all mild (G1-2). Hematologic toxicity was acceptable, being G2-transient leukopenia (2/16) and G2-transient anemia (3/16). Of the 16 patients, 5 experienced progression of extra-skeletal disease: 3 after 6 cycles and 2 in early restaging CT. One patient died due to cardiovascular disease. At the end of therapy, 14/16 patients were re-staged, being classified into two groups according to scintigraphy: patients with progression of skeletal disease (PD) and patients without skeletal progression (NPD: partial response or stable skeletal disease). The median time to increase of PSA levels was 4 months (4.5 months in NPD and 3.4 months in PD patients), and the rate of patients with total-ALP response was 43% (6/14) (66% in the NPD and 0% in the PD group), similar to the ALSYMPCA trial. The rate of total ALP normalization was 43%. A significant difference was observed between NPD and PD patients in terms of variation of both ALP (41% reduction vs. 47% increase, respectively; $p = 0.001$) and PSA (average increase of 154.6 ng/ml sd 268.6 vs. 1017.1 sd 1165.4, respectively, $p<0.001$). Conclusions: Despite the small sample size, results from the present study confirm the feasibility of Ra-223 in mCRPC, with manageable toxicity, even in high-risk patients. Anemia appears to be the only factor that may limit the number of cycles administered. It would be useful to establish cut-off values of disease predictors, such as total-ALP response and variations of ALP or PSA levels, to guide treatment decision during the course of Ra-223 therapy; but we need more patients and longer follow-up.

Database: EMBASE

32. Radium-223 in the treatment of metastatic castrationresistant prostate cancer (MCRPC)

Author(s): Vazzana C.; Grana C.; Chinol M.; Morano S.

Source: Clinical and Translational Imaging; Apr 2017; vol. 5

Publication Date: Apr 2017

Publication Type(s): Conference Abstract

Abstract: Background-aim: In the past years, the only drugs approved to relieve bone pain originating from metastatic prostate and breast cancers were R-emitting radiopharmaceuticals. These drugs did not prove to prolong survival when used as single agent and resulted associated with important adverse events. This situation has changed with the advent of radium-223 due to the good safety profile and evidence of improved survival. Cooperation between nuclear medicine physicians and other specialists involved in cancer management involved the combination of radium-223 with recently approved drugs in mCRPC patients. Methods: Two recently approved drugs for the treatment of advanced prostate cancer-radium-223 (Xofigo) and abiraterone acetate (Zytiga)-will be studied in combination in a phase III clinical trial. The trial of abiraterone with or without radium-223 has begun enrolling patients with castration-resistant prostate cancer that has spread to bone, not yet been treated with chemotherapy, and is causing no or mild symptoms. The endpoint of the randomized, double-blind, placebo-controlled study will be symptomatic, skeletal, event-free survival at 3 years, or, more specifically, whether the addition of radium-223 to standard abiraterone will prolong life and delay the time to skeletal-related events such as painful fractures or bone pain. Secondary endpoints include overall survival, time to opiate use for cancer pain, time to pain progression, time to cytotoxic chemotherapy, radiological progression-free survival, and number of participants experiencing adverse events. Results: Previous studies showed that all main secondary efficacy end points were achieved in radium-233 treated patients compared with placebo. Moreover, radium-223 was associated with low myelosuppression rates and fewer adverse events. Conclusions: Radium-223 has been shown to delay the time to a patient's first skeletal-related event, as well as to prolong survival, in patients with mCRPC, symptomatic bone metastases, and no known visceral metastatic disease. These ongoing trials may help the oncologists to understand the best way to combine new therapies for advanced prostate cancer with radium-223.

Database: EMBASE

33. Optimization of acquisition protocol by gamma camera imaging of patients undergoing radium-223 dichloride treatment

Author(s): Maruzzo M.; Basso U.; Zagonel V.; Zorz A.; Scaggion A.; Paiusco M.; Evangelista L.; Massaro M.; Saladini G.

Source: Clinical and Translational Imaging; Apr 2017; vol. 5

Publication Date: Apr 2017

Publication Type(s): Conference Abstract

Abstract: Background-aim: Radium-223 dichloride (223Ra) is a novel boneseeking alpha-emitter tracer used for the treatment of bone-dominant castrate-resistant prostate cancer (CRPC) patients. 223Ra decays by emitting a 1.1% gamma or X-rays, with relevant energy peaks at 81, 84, 95, 154 and 270 keV. Despite this low percentage of gamma emission, imaging after 223Ra injection by using gamma camera is possible. The aim of this study was to optimize the acquisition protocol by gamma camera imaging of patients undergoing 223Ra treatment in order to make the exam tolerable. Methods: From March 2016 to today, 8 CRPC patients underwent 223Ra treatment (6 administrations every 28 days 55 kBq/kg). Thirtyeight images were acquired on the dual head gamma camera 3/800 ECAM Signature (Siemens). Every patients performed scintigraphic acquisition

at 24 h and/or 48 or 72 or 120 h, after the injection. Only 2 out 8 patients had post-223Ra images for 5 out of 6 administrations. Patient energy spectrum was acquired to optimize the energy window setting. Low Energy High Resolution (LEHR) or Medium Energy General Purpose (MEGP) collimator were tested. Being the emission count rate insufficient to acquire tomographic imaging, whole body (WB) scans or static planar images were performed. Planar acquisition time ranged between 20 and 30 min. WB scan speed varied from 3 to 5 cm/min. Results: The MEGP was selected because the quality of images was higher than LEHR and also the ratio of tumor/background resulted better. After the spectrum analysis, two energy windows were set to 82 +/- 20% keV (that includes the 81, 84, 95 keV peaks) and 154 +/- 20% keV, excluding the 270 keV peak. The selected imaging protocol for static planar images was 256 9 256 matrix, zoom 1, acquisition time equal to 30 min. However, some static scans were acquired for 25 min reporting a good image quality. WB scan acquisition time varies from 15 to 42 min. The selected imaging protocol for whole body scan was 256 9 1024 matrix and scan speed of 4 cm/min. Larger lesions were detected in both the scans and also the quantification was performable. Conclusions: All the acquisitions were well-tolerable by the majority of the patients, although their critical condition. However, the choice to perform a WB scan rather than a static acquisition should be considered in accordance with the patient health condition. Less tolerable patients can be studied by a static acquisition of almost 20 min.

Database: EMBASE

34. Radium-223(RAD) in men with symptomatic castration-resistant prostate cancer: Guideline versus clinical reality

Author(s): Heidegger I.; Kanzelmeyer S.; Pfister D.; Porres D.; Paffenholz P.; Heidenreich A.

Source: Journal of Urology; Apr 2017; vol. 197 (no. 4)

Publication Date: Apr 2017

Publication Type(s): Conference Abstract

Available in full text at Journal of Urology - from Ovid

Abstract:INTRODUCTION AND OBJECTIVES: RAD is one of the new life prolonging therapeutic aproaches in symptomatic mCRPC prior to or after docetaxel treatment. According to guidelines RAD should be initiated early in the progression of mCRPC and it is not to be used as palliative therapy. We analysed the data of RAD therapy in a large single centre cohort of mCRPC patients with the purpose to explore the guideline compliance. METHODS: A total of 94 patients with symptomatic mCRPC were retrospectively analyzed. All patients had skeletal metastases and no evidence of visceral metastases. The following data were analyzed: proper pretherapeutic work-up including PSA, Hb, platelets, alk. Phos., VAS, creatinine, ECOG performance status, in-house versus external referals, number of cycles, type of pre-treatment. Oncologic outcome parameters such as cancer specific & overall survival as well as biochemical and clinical-free survival were evaluated using descriptive statistical analysis. RESULTS: Mean patient age was 72.9 (52-84) years. 46 (48.9%) pts received prior DOC; 34 (36.2%) were DOC-naive and in 14 (14.9%) pts the status was unknown. Mean PSA was 267,69 (2.5-4710) ng/ml, mean alk. Phosp. was 177,4 (54.5-594) U/l and mean HB was 12.01 (9.8-15.1) g/dl. Required lab values were missing in 22.3% of pts. ECOG performance status was 0,1 and 2 in 45 (47.9%), 14 (14.9%) and 8 (8.5%), resp.; in the remainder no ECOG was documented. Pts received a mean number of 4 (1-6) cycles; 43 (47.8%) pts received 6 cycles whereas 17 (18.9%), 5 (5.6%) and 25 (27.8%) pts received 4, 5, and 3 cycles, resp. Reason for early discontinuation was: disease progression in 12, poor performance status in 10 and bone marrow suppression in 4. All in-house referals but only 21.5% of outside referals received 6 cycles Rad223. After a mean follow-up of 23.2 (3-30) months, 25 (26.6%) are DOD, 63 (67%) pts are alive and in 6 (6.4%) pts the status is unknown. There was a significant difference in survival rates between 3 and 6

cycles with 62.5% vs 81.1% (p < 0.02) as well as between outside and in-house referals (p < 0.02). CONCLUSIONS: Although RAD is guideline recommended therapy, clinical reality demonstrates that there the treatment is still inappropriately in 50% of the patients with a significant difference between tertiary referal centres and the community. Observed survival differences are most probably due to the low number of cycles which reflect the terminal stage of disease. More information has to be distributed in the community.

Database: EMBASE

35. Efficacy and safety of radium-223 by radical local therapy at initial diagnosis: A retrospective subgroup analysis of alsympca trial

Author(s): Klotz L.; Sweeney C.; Dicker A.; Vogelzang N.; Morris M.; Verholen F.; Wagner V.; Lu C.; Parker C.; Sartor O.

Source: Journal of Urology; Apr 2017; vol. 197 (no. 4)

Publication Date: Apr 2017

Publication Type(s): Conference Abstract

Available in full text at Journal of Urology - from Ovid

Abstract:INTRODUCTION AND OBJECTIVES: Radium-223 (Ra-223), a targeted alpha therapy, significantly improved overall survival (OS) versus (vs) placebo (pbo) for patients (pts) with metastatic castration resistant prostate cancer (mCRPC) in ALSYMPCA trial (HR = 0.70; 95% CI, 0.58-0.83; P =2 bone lesions and no known visceral metastases. Pts were randomized 2:1 to 6 injections of Ra-223 (55 kBq/kg IV; q4 wk) plus best standard of care (BSoC) or matching pbo plus BSoC. Exploratory subgroup analyses were performed to evaluate outcome of Ra-223 vs pbo by RLT (defined as radical prostatectomy or radiation to prostate) and according to metastatic status at initial diagnosis. RESULTS: 921 pts were treated (Ra-223, n = 614; pbo, n = 307). 392 (43%) received RLT at initial diagnosis and 529 (57%) did not. Median OS was longer with Ra-223 vs pbo regardless of whether pts received RLT or not [(with RLT: 15.3 vs 11.8 mo, HR: 0.704 (0.523- 0.948); without RLT: 14.7 vs 10.8 mo; HR: 0.684 (0.543-0.862)] (table). Metastatic status at diagnosis was documented for 576 pts (63%); 306 were documented as non-metastatic (M0) and 270 as metastatic (M1). Median OS was longer with Ra-223 vs pbo regardless of metastatic status at diagnosis [M0: 14.1 vs 9.6 mo, HR: 0.674 (0.491-0.925); M1: 15.6 vs 11.5 mo, HR: 0.638 (0.454-0.895)] (table). Therapies received prior to ALSYMPCA trial initiation were mainly RLT (mostly M0), bilateral orchiectomy, LHRH agonist, anti-androgens, chemotherapy and external radiotherapy to bone. These prior therapies were generally balanced between Ra-223 and pbo groups. Safety and pts demographics for the subgroups will be presented. CONCLUSIONS: Compared with pbo, Ra-223 improved OS in mCRPC patients. A subgroup analysis indicates that OS is consistent regardless of whether pts had received RLT or not at initial diagnosis. Similarly, OS is consistent regardless of metastatic status at initial diagnosis. (Table presented).

Database: EMBASE

36. A comparison of toxicities and clinical benefit of radium 223 between different age groups

Author(s): Song Y.P.; Walshaw R.; Choudhury A.; Ellis T.; Parikh O.; Logue J.

Source: Clinical Oncology; Mar 2017; vol. 29 (no. 3)

Publication Date: Mar 2017

Publication Type(s): Conference Abstract

Abstract: Aims: Radium 223 is an effective treatment for patients with metastatic castrate resistant prostate cancer. It has been shown to improve symptoms and increase overall survival (OS). We hypothesised that there would be no difference in toxicities and clinical benefits between older and younger patients. Methods: This retrospective study included patients treated with radium 223 in two cancer centres from December 2013 to February 2016. The median age in the ALSYMPCA1 trial was 71 years. Hence, patients were divided into those below 72 years and those 72 years and above. Toxicities were graded with CTCAE version 4. Statistical analysis was carried out with SPSS. Results: 129 patients were treated during this period. The median age was 71 years (55-89). All were treated with 50 kBq/kg with a median of 5 cycles (1- 6). 50.4% were below 72 years, 49.6% were 72 years and above. 63% of the younger group were previously treated with docetaxel compared to 38% of the older group (P =0.004). 63% of the younger group and 59% of the older group had previous abiraterone while 31% and 23%, respectively, had previous enzalutamide. 51% of those below 72 years and 59% of those above reported symptomatic improvement (P =0.326). Median OS was 8.2 months in the younger group and 8.6 in the older group. 13/129 patients had grade 3 anaemia. This included 17% of the younger group and 3% of the older group (P =0.009). There was one patient in each group with grade 3 neutropenia, but no neutropenic sepsis or grade 3 thrombocytopaenia. 9% of patients developed a skeletal-related event. This included 5% of the older and 12% of the younger group. Conclusion: Radium 223 is well tolerated but a larger percentage of the younger group developed toxicities, with a significantly higher incidence of grade 3 anaemia. This may be associated with a higher proportion of younger patients receiving docetaxel. Clinical benefits were similar in both groups.

Database: EMBASE

37. Hematologic Safety of Radium-223 Dichloride: Baseline Prognostic Factors Associated With Myelosuppression in the ALSYMPCA Trial.

Author(s): Vogelzang, Nicholas J; Coleman, Robert E; Michalski, Jeff M; Nilsson, Sten; O'Sullivan, Joe M; Parker, Christopher; Widmark, Anders; Thuresson, Marcus; Xu, Lei; Germino, Joseph; Sartor, Oliver

Source: Clinical genitourinary cancer; Feb 2017; vol. 15 (no. 1); p. 42

Publication Date: Feb 2017

Publication Type(s): Journal Article

PubMedID: 27613490

Abstract:BACKGROUNDMyelosuppression is common in patients with progressive castration-resistant prostate cancer and bone metastases. Radium-223 prolongs overall survival in these patients but may cause myelosuppression; understanding risk factors will improve clinical decision making. We describe hematologic safety of radium-223 in ALSYMPCA and post hoc analyses identifying patients at increased risk for hematologic toxicity.PATIENTS AND METHODSHematologic parameters and adverse events were analyzed. Multivariate analyses assessing baseline risk factors for hematologic toxicities were performed separately for radium-223 and placebo patients.RESULTSNine hundred one patients received radium-223 (n = 600) or placebo (n = 301); 65% of radium-223 and 48% of placebo patients had the full 6 cycles. Grade 3/4 thrombocytopenia was more common in radium-223 versus placebo patients (6% vs. 2%). Logistic regression analyses identified significant baseline predictors for grade 2-4 hematologic toxicities related to radium-223 treatment: extent of disease (6-20 vs. < 6 bone metastases; odds ratio [OR] = 2.76; P = .022) and elevated prostate-specific antigen (OR = 1.65; P = .006) for anemia; prior docetaxel (OR = 2.16; P = .035), decreased hemoglobin (OR = 1.35; P = .008), and decreased platelets (OR = 1.44; P = .030) for thrombocytopenia. Neutropenia events were too few in placebo patients for a comparative analysis.

There were no significant associations between hematologic toxicities and number of radium-223 injections received (4-6 vs. 1-3).CONCLUSIONRadium-223 has a favorable safety profile with a low myelosuppression incidence. Understanding baseline factors associated with myelosuppression may assist clinicians in avoiding severe myelosuppression events with radium-223.

Database: Medline

38. A phase 2 randomized, doubleblind, placebocontrolled trial of radium-223 dichloride with exemestane and everolimus in patients with HER2-negative, hormone receptor-positive breast cancer and bone metastases

Author(s): Rugo H.S.; Drumea K.C.; Campone M.; Barnadas A.; Petrenciuc O.; Zhang A.; Li R.; Coleman R.E.

Source: Cancer Research; Feb 2017; vol. 77 (no. 4)

Publication Date: Feb 2017

Publication Type(s): Conference Abstract

Available in full text at Cancer Research - from Highwire Press

Abstract: Background: Treatment options for bonedominant metastatic breast cancer (MBC) are limited. Radium-223, a firstinclass alpha emitter with a targeted antitumor effect on bone metastases (mets), was well tolerated and reduced bone biomarker levels in a phase 2 study in patients with bonedominant MBC (Coleman et al. Breast Cancer Res Treat. 2014). In patients with HER2 estrogen receptor (ER) bonedominant MBC, everolimus + exemestane (EVE+EXE) improved progressionfree survival (PFS) versus EXE alone. Radium-223 combined with EVE+EXE may improve outcomes in patients with HER2 ER bonedominant MBC; this trial will evaluate efficacy and safety of radium-223 versus placebo in these patients (NCT02258451). Trial design: Patients are randomized to receive (1:1) radium-223 (50 kBq/kg [55 kBq/kg after National Institute of Standards and Technology update] IV) or placebo x 6 cycles q 4 wk + EXE (25 mg PO q d) + EVE (10 mg PO q d) plus best supportive care. EXE+EVE continues until disease progression or unacceptable toxicity. Stratification is by geographic region (EU/N America vs Asia), prior hormone therapy (1 vs >= 2), and presence of visceral disease (yes vs no). Eligibility criteria: Eligible patients are preor postmenopausal with HER2 ER MBC and have >= 2 bone mets or have soft tissue and/or visceral mets. Patients must have measurable disease per RECIST v1.1, >= 1 prior line of hormone therapy for MBC, and 12 prior skeletalrelated events; be on bisphosphonates or denosumab; and have an ECOG score of 0-1. Patients must have had no past or current need for chemotherapy for MBC, no unresolved spinal cord compression, and no prior EVE treatment. Specific aims: The primary end point is symptomatic skeletal event-free survival (SSEFS). Secondary end points are overall survival; times to opiate use, pain progression, and cytotoxic chemotherapy; radiologic PFS; and safety. Safety and efficacy are assessed every 4 weeks. Longterm safety is assessed until study termination. Statistical methods: Assuming a 1sided alpha of 0.1, 90% power, ~ 160 SSEFS events will be required for the analysis. Efficacy will be analyzed by a stratified logrank test. Safety analysis will be descriptive. Present and target accrual: Estimated enrollment is ~ 311 patients. Currently, 74 patients are randomized. .

Database: EMBASE

39. A phase 2 randomized, double-blind, placebo-controlled trial of endocrine therapy +/- radium-223 dichloride in HER2-negative, hormone receptor-positive breast cancer patients with bone metastases

Author(s): Coleman R.E.; Fried G.; Petrenciuc O.; Sawhney A.; Li R.; Rugo H.S.

Source: Cancer Research; Feb 2017; vol. 77 (no. 4)

Publication Date: Feb 2017

Publication Type(s): Conference Abstract

Available in full text at Cancer Research - from Highwire Press

Abstract: Background: Bonemetastatic breast cancer (MBC) treatment is limited. In a phase 2a study of bone-dominant MBC patients, radium-223, a first-in-class alpha emitter with targeted cytotoxic effect on bone metastases (mets), reduced bone biomarker levels with favorable safety (Coleman et al. Breast Cancer Res Treat. 2014). Trial design: This study evaluates efficacy and safety of radium-223 versus placebo (pbo), each + endocrine treatment (ET), in patients with HER2 estrogen receptor (ER)bonedominant MBC (NCT02258464). Patients receive (1:1) radium-223 50 kBq/kg IV or pbo q 4 wk (6 cycles) + ET + denosumab or bisphosphonates + best supportive care. Stratification is by geographic region (EU/N America vs Asia), number of prior ET lines (1 vs >= 2) for MBC, and number of prior skeletalrelated events (SREs) (1 vs 2). Eligibility criteria: Eligible patients are preor postmenopausal with HER2 ER bonedominant MBC and >= 2 bone mets or with soft tissue and/or visceral mets, and 12 prior SREs (external beam radiotherapy, pathologic bone fracture, spinal cord compression, orthopedic surgery); they have received >= 1 line of ET for MBC and are considered appropriate for further ET. Patients must have evaluable disease (RECIST 1.1), be taking bisphosphonates or denosumab for >= 1 month before study treatment, have an ECOG score 01, and have adequate hematologic, renal, and liver function. Patients must not have had visceral or brain mets or leptomeningeal disease, or need chemotherapy for MBC, and must not be suitable for everolimus for MBC. Patients are not eligible if they had prior radium-223 treatment or have untreated spinal cord compression. Specific aims: The primary end point is SSEfree survival (SSEFS). Secondary end points are radiologic progressionfree survival; overall survival; times to opioid use, pain progression, and cytotoxic chemotherapy; pain improvement rate; and safety. Patients are assessed for efficacy and safety and are followed to SSE, radiologic progression, death, or withdrawal. Statistical methods: Assuming 1sided alpha 0.1, power 90%, ~ 119 SSEFS events are needed for analysis. Timetoevent analysis will use a logrank test, accounting for stratification. KaplanMeier estimates and survival curves will be given for each treatment group. Safety analyses will be descriptive. Present and target accrual: Target accrual is ~ 227. Currently, 40 patients are randomized. .

Database: EMBASE

Exercise: Relative Risk

The relative risk is the ratio of probability of an event (a specified outcome) occurring in one group (i.e. those exposed to a particular intervention) compared to those in another group (i.e. those not exposed – a control group).

The relative risk can be interpreted using the following chart. First, you must determine whether the event (the outcome measure) is adverse or beneficial.

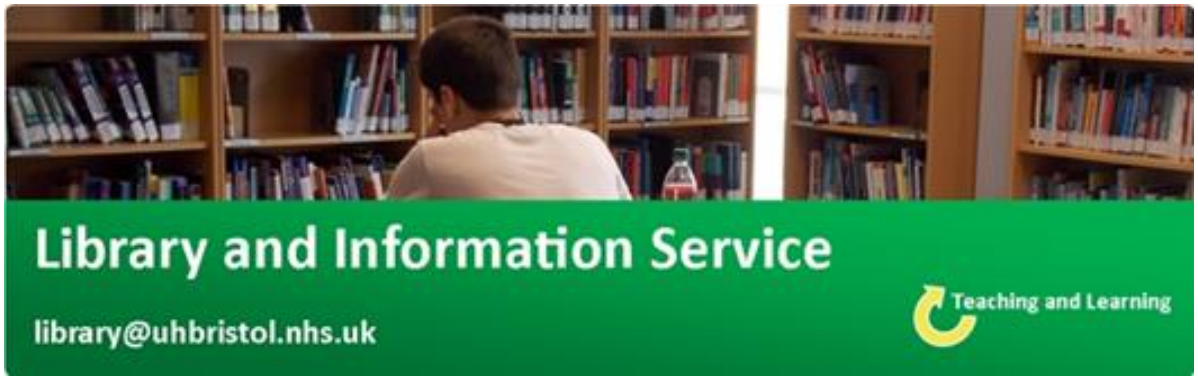
Relative Risk	Adverse outcome (e.g. death)	Beneficial outcome (e.g. recovery of limb function)
<1	Intervention better than control	Intervention worse than control
1	Intervention no better or worse than control	Intervention no better or worse than control
>1	Intervention worse than control	Intervention better than control

Have a go at interpreting the relative risks for these three studies using the chart above. Is the intervention better or worse than the control?

	Intervention	Population	Outcome measure (think: adverse or beneficial?)	Relative Risk
Study 1	Drug X	Adults at risk of a heart attack	Heart attack	1.2
Study 2	Therapy programme Y	Smokers	Smoking cessation	0.8
Study 3	Probiotic Z	Children on antibiotics	Diarrhoea	0.3

*Find out more about relative risk in one of our **Statistics** training sessions.*
For more details, email library@uhbristol.nhs.uk.

Answers: Study 1: worse; Study 2: worse; Study 3: better



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