Chapter 10

Radium-223 chloride: extending life in prostate cancer patients by treating bone metastases

Michel D. Wissing, Fijs W.B. van Leeuwen, Gabri van der Pluijm, Hans Gelderblom

Clin Cancer Res. 2013 Nov 1;19(21):5822-7

Abstract

The treatment scope for patients with metastatic castrate-resistant prostate cancer (mCRPC) is rapidly expanding. On May 15th, 2013, the US Food and Drug Administration (FDA) approved radium-223 chloride ($^{223}RaCl_2$) for the treatment of mCRPC patients whose metastases are limited to the bones. Radium-223 is an α-emitting alkaline earth metal ion, which, similar to calcium ions, accumulates in the bone. In a phase III study (ALSYMPCA), mCRPC patients with bone metastases received best standard-of-care treatment with placebo or $^{223}RaCl_2$. At a prespecified interim analysis, the primary endpoint of median overall survival was significantly extended by 3.6 months in patients treated with radium-223 compared with placebo ($p < 0.001$). The radioisotope was well tolerated and gave limited bone marrow suppression. $^{223}RaCl_2$ is the first bone-targeting antitumor therapy that received FDA approval based on a significantly extended median overall survival. Further studies are required to optimize its dosing and to confirm its efficacy and safety in cancer patients.

Introduction

Prostate cancer is the most prevalent and second deadliest cancer in men in the United States and Europe.[1] Most morbidity and virtually all mortality from prostate cancer occur once the tumor has become metastatic and castrate-resistant (mCRPC).[2] Therefore, research aimed at the development of novel therapies for prostate cancer has primarily focused on this patient group. Although a decade ago no therapy existed with a proven significant benefit on the median overall survival of mCRPC patients, patients now have the options to be treated with multiple life-extending therapies. These therapies consist of agents that selectively target the androgen pathway (abiraterone acetate, enzalutamide) and taxanes (docetaxel, cabazitaxel), which target microtubules.[3-8] Furthermore, the immunotherapy sipuleucel-T has been approved for its use in asymptomatic or minimally symptomatic mCRPC patients.[9, 10]

Prostate cancer primarily metastasizes to the bone.[11] Bone metastases may lead to severe morbidity, such as bone marrow failure, pathological fractures, and spinal cord compression, reducing quality of life and potentially resulting in death.[12, 13] Hence, specific treatment of bone metastases may significantly lower the burden of prostate cancer disease.[14, 15] Multiple agents have been approved by the United States Food and Drug Administration (US FDA) for the palliative treatment of bone metastases in mCRPC patients, such as external beam radiotherapy and the β-emitting radiopharmaceuticals strontium-89 (1.5-2.2 MBq/kg) and samarium-153 (37 MBq/kg) (Table 1). Such therapies result in symptomatic relief in more than half of patients.[16, 17] However, the duration of response is limited; the effect of these treatments on overall survival has not been studied. Moreover, as surrounding tissue, including the bone marrow, is damaged as well, significant adverse events such as bone marrow failure may occur in treated patients.

Table 1. Characteristics of radiopharmaceutical agents regularly used in clinic for the treatment of prostate cancer related bone metastases.

Therapeutic isotope	**Rhenium-186**	**Samarium-153**	**Strontium-89**	**Radium-223**
Half-life (days)	3.8	1.9	50.5	11.4
Administered agent	^{186}Re-HEDP	^{153}Sm-EDTMP	$^{89}SrCl_2$	$^{223}RaCl_2$
Binding inducing factor	Bisphosphonate ligand	Lexidronam ligand	Ca^{2+} similarity of Sr^{2+}	Ca^{2+} similarity of Ra^{2+}
Therapeutic irradiation	1 β-particle	1 β-particle	1 β-particle	4 α-particles, 2 β-particles
Stable decay product	^{186}Os	^{153}Eu	^{89}Y	^{207}Pb
Standard dose	1295 MBq	37 MBq/kg	1.5-2.2 MBq/kg	50 kBq/kg
FDA approval based on	not approved	relief of bone pain	relief of bone pain	improved median overall survival
Targeted prostate cancer population	patients with painful skeletal metastases	patients with confirmed osteoblastic metastatic bone lesions	patients with painful skeletal metastases	CRPC patients with symptomatic bone metastases and no known visceral metastatic disease

On May 15th, 2013, the FDA approved radium-223 chloride ($^{223}RaCl_2$; Xofigo; previously named alpharadin) for the treatment of bone metastases in mCRPC patients based on interim results from a phase III randomized clinical trial, the ALSYMPCA study (Alpharadin in the treatment of patients with symptomatic bone metastases in castration-resistant prostate cancer). This marks the first FDA-approved radionuclide that has been shown to extend overall survival in mCRPC patients in a phase III study. In this review, we will discuss the (pre)clinical development of $^{223}RaCl_2$, focusing primarily on the most recent results from the ALSYMPCA study. Subsequently, we discuss the FDA approval and future implications this approval may have in clinical practice.

Radium-223 chloride

$^{223}RaCl_2$ is a water-soluble radium salt. In ionic form, radium accumulates in bones at areas with increased bone turnover because of chemical similarity to calcium ions; both are alkaline earth metals.[18, 19] Radium-223 is an α-emitting radioisotope that decays via seven daughter nuclides before it stabilizes as lead-207 (Fig. 1). During the decay of each radium-223 isotope, four α-particles and two electrons (β-particles) are emitted (Table 1). Both α- and β-irradiation can induce local therapy by inducing damage in the surrounding tissue. Because of the size and high energy of α-particles, these particles are highly effective in inducing double-strand breaks in DNA within 100 μm. The half-life of radium-223 is 11.4 days; the half-lives of its daughter nuclides range from seconds to minutes. These daughter nuclides do not have a chemical similarity to calcium ions. Therefore, the half-lives of radon-219 (4.0 s), bismuth-211 (2.1 min) and thallium-207 (4.8 min) seem to be long enough to allow diffusion from the primary accumulation site.

Early preclinical and clinical studies

In a preclinical study, nude rats with MT-1 human breast cancer xenografts were treated with pamidronate, a bisphosphonate used against skeletal complications of cancer, with or without radium-223.[18] Although all rats treated with pamidronate only had to be sacrificed within 21 days, 40% of rats treated with pamidronate and radium-223 at 10 or 30 kBq survived beyond 50 days. Compared with β-emitting particles such as strontium-89, rodents treated with radium-223 showed no signs of bone marrow suppression or other toxicities.[20] In a phase I study, $^{223}RaCl_2$ was administered to 15 prostate and 10 breast cancer patients with bone metastases.[21] Patients received a single i.v. injection of radium-223 with activities up to 250 kBq/kg. More than 50% of patients reported pain relief, while toxicity was low. Grade 3 leukopenia occurred in three patients; the maximum-tolerated dose (MTD) was not established. Radium-223 accumulated in the skeleton, particularly in sites with metastases. In the blood, radioactivity levels diminished quickly: to 6% after 1 hour and to <1% 24 hours

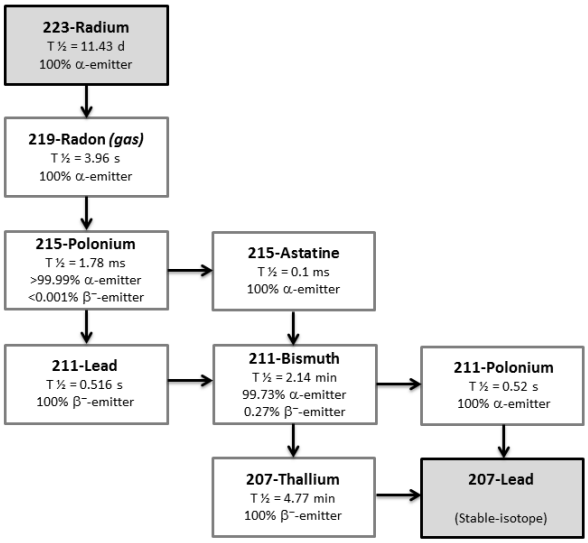

Figure 1. Radioactive decay of radium-223. Radium-223 decays via seven daughter nuclides to lead-207, resulting in the emission of both α-particles (vertical step in diagram) and β-particles (horizontal step in diagram).
T½, half-life.

after injection. Recently, similar findings were presented from another phase I study.[22] In this study, ten mCRPC patients received radium-223 up to 200 kBq/kg, among which six patients received a second dose of 50 kBq/kg. The MTD was again not established, and radium-223 was rapidly cleared from the blood, primarily into the small bowel.

A subsequent phase II study compared treatment of 50 kBq/kg radium-223 with placebo treatment in 64 CRPC patients with painful bone metastases.[23, 24] Median time to skeletal-related event (SRE) was 14 weeks in the radium-223-treated group versus 11 weeks in patients treated with placebo (p = 0.257).[23] Low toxicity of radium-223 was confirmed in this phase II study. None of the 33 $^{223}RaCl_2$-treated patients discontinued treatment because of adverse events. Grades 3 and 4 hematological adverse events occurred in 3 (9.1%) and 0 (0%) radium-223-treated patients and in 1 (3.3%) and 1 (3.3%) placebo-treated patients, respectively. Severe non-hematological adverse events occurred in 3 (9.1%) $^{223}RaCl_2$-treated patients and in 5 (16.7%) placebo-treated patients. In a follow-up report 24 months after the first injection of study medication, no long-term treatment-related toxicity was noted.[24] Median overall survival was 65 weeks in the $^{223}RaCl_2$-treated group, and 46 weeks in the placebo-treated group (p = 0.056).

ALSYMPCA

The ALSYMPCA phase III study was initiated in 2008, comparing the efficacy and safety of

$^{223}RaCl_2$ with that of placebo (a saline injection) in patients with symptomatic CRPC with bone metastases.[25] Patients needed to have at least two bone metastases, diagnosed by bone scintigraphy. Patients were eligible if they had previously received docetaxel, if they were unfit for docetaxel, if they declined therapy with docetaxel, or if docetaxel was not available. Patients were excluded if they had visceral metastases. Patients received an i.v. injection (50 kBq/kg) once every 4 weeks for a maximum of 6 cycles.

In total, 921 patients were included at 135 study locations worldwide, primarily in North America, Australia and Europe.[26] Six hundred fourteen patients received radium-223, of whom 352 had received docetaxel before $^{223}RaCl_2$ treatment (57.3%). In the placebo group, a similar percentage had received prior docetaxel (56.7% (174 patients)). Other baseline characteristics, such as age, disease stage, and baseline opioid use, were similar between the two treatment groups as well.[25]

The primary endpoint of the ALSYMPCA study was overall survival. In general, the median overall survival in patients treated with radium-223 was extended by 3.6 months compared with placebo-treated patients ($p < 0.001$). For patients who had received docetaxel before participation in the ALSYMPCA trial, median overall survival was 14.4 months in $^{223}RaCl_2$-treated patients versus 11.3 months in placebo-treated patients (hazard ratio (HR) = 0.71; 95% confidence interval (CI) 0.56-0.89); for patients who had not received prior docetaxel, the median overall survival durations were 16.1 months and 11.5 months, respectively (HR = 0.74; 95% CI 0.56-0.99).[25]

The key secondary endpoint in the ALSYMPCA trial was time to symptomatic skeletal event (SSE), defined as the time to first use of external-beam radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fractures, spinal cord compression, or tumor-related orthopedic surgery. Imaging to assess for skeletal events was only performed when clinically indicated to avoid registration of asymptomatic fractures. Time to SSE was 15.6 months in $^{223}RaCl_2$-treated patients versus 9.8 months in the placebo-treated group ($p < 0.001$; HR = 0.66; 95% CI 0.52-0.83).[25] Time to initial opioid use and time to external beam radiotherapy were both increased in patients treated with radium-223 (HR = 0.670 and HR = 0.621, respectively).[27] Sixteen and 24 weeks after initiation of radium-223 treatment, patients had significantly less pain compared with baseline ($p < 0.001$ and $p = 0.001$, respectively).

Further analysis revealed that an increase in the levels of total alkaline phosphatase was associated with an increased risk for death in the patient population studied in the ALSYMPCA trial ($p < 0.0001$).[28] In patients treated with radium-223, a ≥30% reduction in total alkaline phosphatase levels compared with the baseline was seen in 47% of patients versus 3% of placebo-treated patients.[25]

In general, radium-223 was well tolerated by patients, with grade 3 or 4 adverse events occurring more frequently in the placebo-treated group (62%) than in patients treated with radium-223 (56%). The only reported non-hematologic grade ≥3 adverse events that occurred more frequently in the $^{223}RaCl_2$-treated patient group were anorexia (2% versus 1%) and a

decreased appetite (2 patients versus 0 patients). Comparing grade ≥3 hematologic adverse events in the $^{223}RaCl_2$-treated group with the placebo group, anemia occurred in 13% and 13%, neutropenia in 3% and 1%, and thrombocytopenia in 6% and 2%, respectively.[25] Analysis of these hematologic adverse events revealed that a baseline total alkaline phosphatase of ≥220 U/L strongly predicted anemia.[29] Apart from the use of radium-223 instead of placebo, other baseline predictors for neutropenia and thrombocytopenia were prior docetaxel use and more than six bone metastases. However, prior external beam radiotherapy to the bone was associated with a decrease in anemia and neutropenia.

FDA approval

Interim results from the ALSYMPCA phase III clinical trial led to approval of radium-223 by the FDA for the treatment of mCRPC patients who have symptomatic bone metastases and no visceral metastases. It was recommended to be administered at 50 kBq/kg every 4 weeks with a maximum of 6 doses, which is equal to the treatment regimen in the ALSYMPCA trial. This approval makes radium-223 the first agent available for CRPC patients that significantly increases overall survival by exclusively treating bone metastases.

Despite its decision to approve radium-223, the FDA required four additional studies, besides final analysis of ALSYMPCA study results.[30] Non-compliance with this decision, or negative results could result in the FDA revoking the approval.

As mentioned previously, no MTD for radium-223 has been established.[21, 22] Results from phase I studies suggested concentrations higher than 50 kBq/kg could be administered to patients with relatively few changes in the toxicity profile of the agent. Two recent phase II studies confirm that treatment up to 100 kBq/kg has similar toxicities compared with radium-223 at 50 kBq/kg, while the efficacy of radium-223 is increased.[31, 32] Therefore, the FDA required a randomized phase II study to further assess the efficacy and safety of radium-223 in CRPC patients with bone metastases at concentrations higher than 50 kBq/kg. If these results suggest a beneficial risk-benefit profile for higher doses, an additional phase III study will be required to confirm the optimal activity level.

The FDA required the company to perform three studies to further assess the safety of radium-223: an observational study in 1200 CRPC patients with bone metastases, evaluating the long-term safety of radium-223 administered at the recommended dose; a randomized clinical trial in CRPC patients with bone metastases and no visceral metastases to further assess the safety of radium-223, particularly for enhanced assessment of the effect of radium-223 on healthy bone marrow and secondary malignancies, such as acute myeloid lymphoma (AML) and myelodysplastic syndrome (MDS);[33] finally, an assessment of the short- and long-term safety of a radium-223 rechallenge, for which the company was required to perform a study in which CRPC patients with bone metastases were re-treated with radium-223.

Discussion

With the FDA approval of $^{223}RaCl_2$ for CRPC patients with symptomatic bone metastases regardless of prior chemotherapy, the treatment scope for mCRPC patients has further expanded. By excluding patients with visceral metastases, the most rational step for oncologists would be to use radium-223 primarily as a first-line therapy in mCRPC patients. That said, a subpopulation may also be eligible for radium-223 treatment as second-line therapy or later.

Considering the results of radium-223 treatment in the robustly designed and well-conducted ALSYMPCA trial, it is expected that the approval and consequently clinical use of radium-223 will expand beyond the United States in the near future. In addition, radium-223 may improve the quality of life and survival for patients with other tumor types who suffer from bone metastases. However, such expansions require additional clinical investigations. Finally, the FDA approval of radium-223 as the first metastasis-targeting agent based on an improved median overall survival confirms that selectively treating metastases may be an effective strategy in patients with advanced solid tumors for whom palliative treatment is the only option, strengthening the development of such agents.

A major limitation of the ALSYMPCA phase III study is that the group of patients selected for this study may not correspond to the patient population in clinical practice that will receive radium-223 treatment. Patients with visceral metastases were excluded from participation in the trial. Considering that β-emitting radionuclides, such as samarium-153, have been shown to induce pain relief in patients with advanced prostate cancer, further research is required to address whether radium-223 provides clinical benefit for patients with visceral metastases.[16, 17] Based on the approval of radium-223, physicians may decide to administer this agent to this group of patients as well, although its efficacy has not been proven. Furthermore, patients were excluded from the ALSYMPCA study when docetaxel was available, patients were fit for (and willing to receive) docetaxel treatment and had not received docetaxel before. Nevertheless, the FDA does not exclude this group of patients for radium-223 treatment in its approval letter. Until the required post-marketing studies have been conducted that will indicate whether mCRPC patients eligible for docetaxel treatment will also benefit from radium-223, its clinical benefit in this patient group remains uncertain. Currently, no long-term follow-up is known for patients in the ALSYMPCA trial, limiting the toxicity profile of the drug. Although the high number of therapeutic emissions in the decay process of radium-223 may yield a strong therapeutic effect, the daughter nuclides, which do not have affinity to the bone, may diffuse throughout the body and cause damage in healthy tissue. Although no bone marrow suppression was seen in the short term, it will be important to follow patients over time to ensure that there are no long-term harmful effects from radium-223 treatment. Most of the FDA's post-marketing requirements therefore focus on drug safety, particularly on the long-term effects of radium-223 treatment and safety of radium-223 rechallenge at a later stage.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63(1):11-30
2. American Cancer Society [Internet]. Dublin, OH; c2013 [updated 2013 May 15; cited 2013 Aug 1]. Survival rates for prostate cancer. Available from: http://www.cancer.org/cancer/prostatecancer/detailedguide/prostate-cancer-survival-rates.
3. Tannock IF, de Wit R, Berry WR et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15):1502-1512.
4. de Bono JS, Oudard S, Ozguroglu M et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376(9747):1147-1154.
5. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364(21):1995-2005.
6. Fizazi K, Scher HI, Molina A et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13(10):983-992.
7. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187-1197.
8. Ryan CJ, Smith MR, de Bono JS et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368(2):138-148.
9. Small EJ, Schellhammer PF, Higano CS et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. J Clin Oncol 2006;24(19):3089-3094.
10. Kantoff PW, Higano CS, Shore ND et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363(5):411-422.
11. Lange PH, Vessella RL. Mechanisms, hypotheses and questions regarding prostate cancer micrometastases to bone. Cancer Metastasis Rev 1998;17(4):331-336.
12. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12(20 Pt 2):6243s-6249s.
13. Nieder C, Haukland E, Pawinski A, Dalhaug A. Anaemia and thrombocytopenia in patients with prostate cancer and bone metastases. BMC Cancer 2010;10:284.
14. Goyal J, Antonarakis ES. Bone-targeting radiopharmaceuticals for the treatment of prostate cancer with bone metastases. Cancer Lett 2012;323(2):135-146.
15. Saylor PJ, Armstrong AJ, Fizazi K et al. New and emerging therapies for bone metastases in genitourinary cancers. Eur Urol 2013;63(2):309-320.
16. Sartor O, Reid RH, Hoskin PJ et al. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. Urology 2004;63(5):940-945.
17. Serafini AN. Samarium Sm-153 lexidronam for the palliation of bone pain associated with metastases. Cancer 2000;88(12 Suppl):2934-2939.
18. Henriksen G, Breistol K, Bruland OS, Fodstad O, Larsen RH. Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. Cancer Res 2002;62(11):3120-3125.
19. van Leeuwen FW, Verboom W, Reinhoudt DN. Selective extraction of naturally occurring

radioactive Ra2+. Chem Soc Rev 2005;34(9):753-761.
20. Henriksen G, Fisher DR, Roeske JC, Bruland OS, Larsen RH. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter 89Sr in mice. J Nucl Med 2003;44(2):252-259.
21. Nilsson S, Larsen RH, Fossa SD et al. First clinical experience with alpha-emitting radium-223 in the treatment of skeletal metastases. Clin Cancer Res 2005;11(12):4451-4459.
22. Carrasquillo JA, O'Donoghue JA, Pandit-Taskar N et al. Phase I pharmacokinetic and biodistribution study with escalating doses of (223)Ra-dichloride in men with castration-resistant metastatic prostate cancer. Eur J Nucl Med Mol Imaging 2013;40(9):1384-1393.
23. Nilsson S, Franzen L, Parker C et al. Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. Lancet Oncol 2007;8(7):587-594.
24. Nilsson S, Franzen L, Parker C et al. Two-year survival follow-up of the randomized, double-blind, placebo-controlled phase II study of radium-223 chloride in patients with castration-resistant prostate cancer and bone metastases. Clin Genitourin Cancer 2013;11(1):20-26.
25. Parker C, Nilsson S, Heinrich D et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369(3):213-223.
26. clinicaltrials.gov [Internet]. Bethesda, MD: National Institutes of Health, c1993-2013 [updated 2013 July 30; cited 2013 Aug 1]. A Phase III Study of Radium-223 Dichloride in Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases (ALSYMPCA). Available from http://clinicaltrials.gov/ct2/show/study/NCT00699751.
27. Nilsson S, Sartor AO, Bruland OS, Fang F, Aksnes AK, Parker C. Pain analyses from the phase III randomized ALSYMPCA study with radium-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients with bone metastases. J Clin Oncol 2013;31(suppl):Abstract 5038.
28. Sartor AO, Amariglio R, Wilhelm S et al. Correlation between baseline variables and survival in the radium-223 dichloride (Ra-223) phase III ALSYMPCA trial with attention to total ALP changes. J Clin Oncol 2013;31(suppl):Abstract 5080.
29. Parker C, Garcia-Vargas JE, O'Bryan-Tear CG, Fang F, Vogelzang NJ. Hematologic safety of Ra-223 dichloride (Ra-223) in castration-resistant prostate cancer (CRPC) patients with bone metastases from the phase III ALSYMPCA trial. J Clin Oncol 2013;31(suppl):Abstract 5060.
30. United States Food and Drug Administration [Internet]. Silver Spring, MD; c2013 [updated 2013 May 14; cited 2013 Aug 1].Summary review of Xofigo, application number: 203971Orig1s000. Available from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203971Orig1s000SumR.pdf.
31. Parker CC, Pascoe S, Chodacki A et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. Eur Urol 2013;63(2):189-197.
32. Nilsson S, Strang P, Aksnes AK et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. Eur J Cancer 2012;48(5):678-686.
33. Leone G, Fianchi L, Voso MT. Therapy-related myeloid neoplasms. Curr Opin Oncol 2011;23(6):672-680.