COUNTERPOINTS

Current Controversies in Hematology and Oncology

Which Should Be Used First in Symptomatic Metastatic Castration-Resistant Prostate Cancer, Docetaxel or Radium?

It is not unusual for metastatic prostate cancer to progress despite treatment with abiraterone acetate, enzalutamide, or both. What should the next step be for men with metastatic castration-resistant prostate cancer? According to Dr Robert Dreicer, the answer is docetaxel, whereas Drs Jing Li and Andrew Armstrong maintain that radium-223 should be used prior to docetaxel.

Docetaxel Still the Optimal First Choice for Symptomatic Metastatic Castration-Resistant Prostate Cancer

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The management of metastatic castration-resistant prostate cancer (mCRPC) has evolved rapidly over the past several years, with the unprecedented approval of 5 new therapeutic agents.[1]

Given the rapid introduction of novel agents into the therapeutic armamentarium, our current inability to define the optimal therapeutic paradigm for patients with mCRPC is understandable. One of the key decision points in the management of patients with mCRPC is the presence or absence of disease-related symptoms, the most common of which are pain, progressive fatigue, and anorexia.

Physicians managing advanced prostate cancer are well aware of the significant bone tropism of the disease, and the long history of effective symptomatic management of metastatic bone pain with external beam radiotherapy. In this context, clinicians who are managing patients who have mCRPC with symptomatic progression while taking abiraterone acetate (Zytiga, Janssen Biotech) and/or enzalutamide (Xtandi, Astellas/Medivation) are increasingly challenged to decide between radium-223 (Xofigo, Bayer/Algeta) and docetaxel as the next systemic therapy,

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Radium-223 Is the Preferred Therapy in Bone-Predominant Symptomatic Metastatic Castration-Resistant Prostate Cancer

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Despite much progress in mCRPC treatment in recent years, optimal treatment sequences are still unclear, particularly in the post-abiraterone or post-enzalutamide treatment space. For men with bone-predominant disease (ie, no visceral or bulky nodal metastases) and symptomatic progression, current off-protocol options include crossover therapy to another oral novel hormonal agent (enzalutamide to abiraterone, or abiraterone to enzalutamide), docetaxel, or radium-223. Given the limited efficacy to support enzalutamide after abiraterone or abiraterone after enzalutamide[1,2,3] owing to cross-resistance mechanisms, this position piece will explore the therapeutic choice between docetaxel and radium-223 and will advocate for radium-223.

More than 90% of patients with mCRPC have radiologic evidence of bone metastasis,[4] which is the major

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assuming that the patients have bone metastases and other disease findings appropriate for radium-223. In 2015, my choice remains docetaxel.

Docetaxel: Impact on Pain and Quality of Life

More than a decade has passed since the US Food and Drug Administration's (FDA's) approval of docetaxel following the published results of the TAX 327 study, which compared weekly and every-3-week docetaxel regimens with standard mitoxantrone; all patients also received prednisone. In that trial, median overall survival was 18.9 months for patients treated with docetaxel administered every 21 days vs 16.5 months for patients treated with mitoxantrone. This translated into a 24% relative reduction in death with docetaxel (*P*=.009).[2] For several years following docetaxel's approval, there remained a palpable degree of therapeutic nihilism regarding the risk/benefit ratio of docetaxel among many urologists who, as the gatekeepers of a large segment of men with evolving castration-resistant disease, significantly influenced when patients with mCRPC were referred to medical oncologists.

Recent evidence suggests that the bulk of the diffusion of docetaxel use in the management of advanced prostate cancer by medical oncologists predates the availability of level 1 evidence in 2004. Despite this, recognition of the clinically meaningful impact of docetaxel's administration to men with pain and other symptoms from mCRPC is at least partially responsible for broad acceptance of this therapy today.[3]

Given more than a decade of wide-ranging clinical experience with docetaxel in the management of advanced prostate cancer, there is universal recognition that despite the modest survival benefit seen in randomized trials, this agent has a very high level of overt antitumor activity. It is not uncommon for patients with symptomatic mCRPC to begin to improve following a single dose of therapy.

The most prominent disease-related symptoms in mCRPC are pain, progressive fatigue, and anorexia. In contrast to the paucity of evidence supporting the impact of radium-223 on pain, evidence from both randomized trials and phase 2 studies with pain endpoints for docetaxel are widely available.[4-6] Among the earliest studies, Beer and colleagues treated 25 patients using a weekly docetaxel schedule and evaluated the palliative response, which was defined as a 2-point reduction on the 6-point Present Pain Intensity scale (from the McGill-Melzack Pain Questionnaire) without an increase in analgesic consumption, or as a 50% decrease in analgesic use without an increase in pain. The investigators noted that 12 patients (48%) achieved a palliative benefit.[6]

In TAX 327, reduction in pain assessed by means of the Present Pain Intensity scale was a prespecified secondary endpoint. Of the 1006 patients enrolled, 45% had significant pain at study entry. A reduction in pain was more frequent among patients receiving docetaxel every 3 weeks than among those treated with mitoxantrone (35% vs 22%, *P*=.01).[2]

> Docetaxel remains my preferred therapeutic option given the existing data and long experience.

Prospective assessment of quality of life (QOL) in TAX 327 was assessed by the self-administered Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire.[7] Of 815 men who completed the FACT-P at baseline, 374 (46%) had substantial pain and of these, 345 (92%) also had substantial impairment in QOL. Men treated with docetaxel/prednisone every 3 weeks were more likely to have an improvement in QOL compared with those receiving mitoxantrone (22% vs 13%; *P*=.009).[2] Similarly, a randomized phase 2 trial comparing docetaxel/prednisolone with prednisolone alone demonstrated a significant benefit of docetaxel/corticosteroid on the QOL of mCRPC patients.[8]

Radium-223: Impact on Pain and Quality of Life

In the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) phase 3 trial that led to the regulatory approval of radium-223, a total of 927 patients were randomly assigned 2:1 to receive radium-223 or placebo. Of the patients enrolled, 43% had not received prior docetaxel. The primary endpoint of this well-conducted study was overall survival, with secondary endpoints including time to the first symptomatic skeletal event and various biochemical endpoints.[9] There was no prospective assessment of pain in this study. QOL was assessed using the FACT-P, and the mean change in the FACT-P total

score from baseline to week 16 significantly favored the radium-223 group (*P*=.006).

To date, the only available data that provide insight into the impact of radium-223 on pain come from a phase 2 trial that assessed pain relief from a range of single doses of radium-223 measured at 8 weeks after administration using a pain index comprised of a visual analogue scale and patient-recorded analgesic use.[10]

Therapy-Related Toxicity

Toxicity data from the ALSYMPCA phase 3 trial demonstrated a very favorable toxicity profile of radium-223, with minimal hematologic toxicity and a low rate of grade 3 or 4 gastrointestinal toxicity. In this trial, 28% of patients randomly assigned to radium-223 were more than 75 years of age. In a post hoc analysis of TAX 327, 20% of men randomized to the every-21-day docetaxel/prednisone arm were older than 75 years.[11] Grade 3 or 4 events were uncommon in this analysis, although there was a trend toward increasing frequency with increasing age. Nonhematologic toxicities were more common, with grade 3 or 4 fatigue in 10% of men aged 75 years or older.

Bone Targeting vs Systemic Therapy

Although historically, the incidence of soft tissue metastases in advanced prostate cancer was felt to be in the 20% to 25% range, more recent data suggest that this percentage is higher and growing.[12,13] In both the pre- and post-docetaxel enzalutamide phase 3 trials, 59% to 71% of patients had a component of soft tissue/visceral disease.[14,15] One of the emerging challenges to managing patients with radium-223 as a single agent, given the 6-month treatment course, is the potential for soft tissue/visceral disease progression, even in the setting of overall control of bone metastases. Although studies of combinations of radium-223 and next-generation androgen receptor–targeted agents are ongoing, this approach remains undefined.

Conclusion

Over the past several years, the next-generation androgen receptor–targeting agents abiraterone and enzalutamide have become the preferred frontline therapy for mCRPC. Unfortunately, the vast majority of patients managed with these agents will develop overt disease progression requiring subsequent therapy. For patients with significant disease-related symptoms, the ability to offer a rapid, therapeutic intervention with a high likelihood of therapeutic benefit is critical. Although radium-223 is a reasonable option in this setting for a subset of patients, docetaxel remains my preferred therapeutic option given the existing data and the long clinical experience with it in this clinical setting.

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cause of disability, decreased QOL, death, and increased treatment cost.[5] Symptomatic skeletal events include spinal cord compression, pathologic fracture, and the need for palliative bone surgery or external beam radiotherapy,[6] and result in the major morbidities from bone metastases; however, progressive pain and bone marrow failure also contribute in major ways to adverse outcomes. Previously approved bone-targeting treatments—eg, zoledronic acid and denosumab—delay the onset of skeletal events in patients with bone metastasis. However, these are not associated with improved survival in mCRPC.[6,7] The majority of men with mCRPC likewise do not have visceral metastases, and thus the care of men with bone-predominant disease is a common therapeutic dilemma.

Efficacy of Radium-223

Radium-223 acts as a calcium mimetic and bone-seeking α particle emitter. It selectively binds to areas with increased bone turnover, leading to new bone growth in and around osteoblastic bone metastases.[8] With radium, 95.3% of radium-223 decay energy is emitted as high-energy α particles, which induce double-stranded DNA breaks and therefore result in a localized cytotoxic effect at selective areas.[9]

Radium-223 significantly improves overall survival (OS) regardless of previous exposure to docetaxel. In the updated ALSYMPCA data analysis, radium-223 improved median OS to 14.9 months, compared with 11.3 months with placebo.[10] Radium-223 also demonstrated beneficial effects in all main secondary efficacy endpoints, including median time to first symptomatic bone event, median time to increase in serum bone alkaline phosphatase (BAP) or prostate-specific antigen (PSA), and BAP level reduction.[10,11] In a further subgroup analysis in this trial, stratified data demonstrated OS benefit in the radium-223 group regardless of prior docetaxel exposure.[10,12] Of note, this benefit was seen in men who were taking concurrent anti-bone resorptive agents such as zoledronic acid.

In addition to prolonging OS, radium-223 has been associated with improvements in pain, fatigue, and health-related QOL, without major adverse events/toxicity.[10,11,13-18] Fewer patients in the radium-223 group reported pain as an adverse event (50% vs 62%); and fewer patients in the radium-223 group required opiate medication for pain relief (36% vs 50%).[16] The radium-223 group had significantly prolonged median time to external beam radiation therapy for bone pain (hazard ratio [HR], 0.67; 95% CI, 0.53-0.85).[16] Morris and colleagues[13] reported at the 2015 American Society of Clinical Oncology Genitourinary Cancers Symposium that radium-223 was associated with meaningful pain relief in 42% of mCRPC patients not requiring opiates who received radium-223. Further data on men with more severe pain are anticipated in future studies, and the timing of onset, as well as known pain flares with radium-223, needs to be better clarified. Radium-223 also prolonged median time to first symptomatic skeletal event to 12.2 months, compared with 6.7 months in the placebo arm,[10] and is the only agent shown to significantly decrease the risk of spinal cord compression in men with mCRPC (HR, 0.52; 95% CI, 0.29-0.93).[11]

In addition to these benefits, radium-223 has been associated with a beneficial effect on health care resource utilization and hospitalization by leading to fewer days of hospitalization in both the post-docetaxel and docetaxel-naive groups.[17] In addition to these benefits, a significantly higher percentage of radium-223–treated patients had a favorable mean improvement in QOL, measured by the FACT-P score, from baseline to week 16 compared with the placebo group (-2.7 vs -6.8, *P*=.006).[10]

> We believe that the majority of men would choose the lower-risk and equally efficacious option.

These data combined compare favorably with those on docetaxel chemotherapy, which in the pivotal TAX 327 study was associated with a pain response in only 35% of evaluable patients with significant baseline pain[4] but at the cost of significant chemotherapy toxicity including alopecia, peripheral neuropathy, nausea and vomiting, fatigue, and neutropenic fever with infections.

Safety of Radium-223

The short path of the α particles from radium-223 (3 to 4 cell diameters) minimizes its toxic effect on adjacent healthy bone marrow and makes it a highly targeted agent with minimized side effects on normal tissue.[19] Although prior β emitters, such as strontium-89 and samarium-153, led to significant myelosuppression and transfusion-dependent anemia, radium-223 has not been

associated with a significant degree of bone marrow suppression, thus permitting repeat dosing.

Radium-223 was generally well tolerated in both post-docetaxel and docetaxel-naive patients, with fewer overall adverse events occurring in patients treated with radium-223 compared with placebo (all adverse events, 93% vs 96%; grade 3 or 4 adverse events, 56% vs 62%).[10] In fact, the higher rate of more severe adverse events observed in men treated with placebo is likely due to disease progression, which was slowed and reduced in the radium-223–treated men. Radium-223 was not associated with significant myelosuppression in the ALSYMPCA data analysis; grade 3 or 4 neutropenia affected 3% of patients in the radium-223 group and 1% of patients in placebo group.[10] Patients in the post-docetaxel subgroup had a higher incidence of grade 3 or 4 thrombocytopenia with radium-223 than with placebo (9% vs 3%), whereas the incidence was similar between treatment groups among patients with no previous docetaxel use (3% vs 1%). The incidence of grade 3 or 4 anemia was similar between the radium-223 and placebo groups within both docetaxel subgroups (8% vs 9%).[10-12] There also were no clinically significant nonhematologic adverse events related to radium-223. Diarrhea was more commonly observed in the radium-223 group (25% in radium-223 group vs 15% in the placebo group)[10] owing to radium excretion in the bowel. However, diarrhea was generally low grade, manageable, and reversible.

The long-term safety of radium-223 also was investigated. In the prospective US Expanded Access Program (EAP), the tolerability of radium-223 in heavily pretreated patients with CRPC and bone metastases was confirmed.[20] Follow-up data from the ALSYMPCA study at 1.5 years reported no increased incidence of second primary cancers, aplastic anemia, or myelodysplasia associated with radium-223 therapy.[21] Finally, a 3-year safety follow-up of ALSYMPCA identified no major safety issues.[22] In addition, there were no adverse safety risks seen with the concurrent use of enzalutamide or abiraterone acetate with radium-223 in this EAP,[23] and the concurrent use of palliative external beam radiotherapy, antiandrogens, corticosteroids, and androgen synthesis inhibitors was permitted and safely given in the pivotal phase 3 ALSYMPCA trial. These data affirm the long-term safety of radium-223, alone or in combination with other systemic hormonal therapies.

One important feature of radium-223 is that docetaxel can be given safely after radium-223. In ALSYMPCA, the men who received chemotherapy following radium-223 demonstrated a similar safety profile and outcome as the group that received chemotherapy following placebo.[24] Although these data are limited and based on selected patients with limited follow-up, and further prospective data are needed, the existing data support the ability to give docetaxel chemotherapy at full dose and schedule after radium-223 in the majority of men. Radium-223 was well tolerated in the prespecified docetaxel subgroup analysis of ALSYMPCA, with a low incidence of myelosuppression in both post-docetaxel patients and docetaxel-naive patients with mCRPC.[12] Patients in the post-docetaxel subgroup had a higher incidence of grade 3 or 4 thrombocytopenia with the radium-223 arm compared with the placebo arm, though incidences of grade 3 or 4 anemia and neutropenia were similar between radium-223 and placebo regardless of previous docetaxel use.[12] These data suggest that radium-223 is safe and effective when given prior to docetaxel and does not limit subsequent therapy.

The Case for Radium-223 Prior to Docetaxel

OS was improved with docetaxel in men with mCRPC (21% relative improvement in the hazard ratio for death over time; 2.4-month absolute improvement), which was associated with improved radiographic response rates and pain/QOL outcomes.[4,25] However, docetaxel is associated with multiple significant side effects. In TAX 327, 15% of docetaxel-treated patients had low-grade adverse events, including fatigue, nausea/vomiting, alopecia, diarrhea, nail changes, sensory neuropathy, anorexia, changes in taste, stomatitis, dyspnea, tearing, peripheral edema, and epistaxis.[4] In addition, 26% of the patients in the every-3-weeks docetaxel group and 20% of those in the weekly docetaxel group had at lease 1 serious adverse event.[4] Although effective, these undesirable toxicities lead many men with mCRPC to decline chemotherapy and providers to not offer chemotherapy to eligible men. For this reason, the utilization of docetaxel chemotherapy is less than 30% to 50% in US men with mCRPC.[26]

The improvement in OS with radium-223 is substantial and similar in magnitude to chemotherapy in eligible patients. In men treated with radium-223 prior to docetaxel, radium-223 improved survival by 31% (HR, 0.69; P=.01), with a median improvement in survival of 4.6 months over placebo.[12] Cross-trial comparisons of these agents are not possible given the differences in patient populations and the different methods for assessing endpoints, but these data suggest that radium-223 is both highly efficacious and safe in eligible men with mCRPC, and is a real option in men who prefer to defer docetaxel chemotherapy. When faced with the therapeutic dilemma and the above data, we believe that the majority of eligible men would choose the lower-risk and equally efficacious option (radium-223), reserving the higher risk but also efficacious docetaxel for subsequent therapy. Finally, we wish to state clearly that this argument does not apply to

men with visceral disease and/or bulky (>3-4 cm) nodal disease, for which docetaxel clearly would be preferred to improve survival and control disease.

Conclusion

In conclusion, radium-223 provides a substantial survival benefit, provides pain palliation, and delays symptomatic bone-related events; it also improves and maintains QOL without severe toxicities. Therefore, we favor the use of radium-223 prior to docetaxel in patients with bone metastatic CRPC without visceral or bulky nodal disease and offer this as a routine option to eligible men. Although docetaxel is also reasonable, docetaxel can be safely administered after radium without any major detriment to bone marrow function or risk of infection. Prospective studies are needed to clarify the optimal sequencing and combinations of these systemic therapies with other effective systemic agents, but until that time, the present evidence supports radium-223 as an effective frontline option after abiraterone acetate or enzalutamide in men with bone-metastatic symptomatic CRPC.

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