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Challenging Cases

Should the Denosumab Metastasis Prevention Trial Change Practice for Men with Nonmetastatic Prostate Cancer?

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Presentation of the Case

A 68-year-old man presents for management of prostate-specific antigen (PSA)-recurrent prostate cancer. His PSA level had become undetectable after prostatectomy for a high-risk localized tumor but began to rise 8 months later. This later led to the initiation of androgen deprivation therapy (ADT), which he has received for the last 3.5 years. After initially falling in response to ADT, his PSA level again trended steadily upward and is now 13.2. Restaging with an abdominal and pelvic computed tomography scan and a bone scan reveals no evidence of metastases. Is this man likely to benefit from denosumab?

Bone is the most common site of metastasis for advanced prostate cancer. Bone metastases can cause considerable morbidity in the form of pain, pathologic fractures, and even spinal cord compression. Two bone-targeted therapies (zoledronic acid and denosumab) have been shown to reduce the risk for skeletal events (SREs) among men with bone metastases and a rising PSA level despite a testosterone level <50 ng/dL (castration-resistant prostate cancer [CRPC]). Until recently, no therapy had been shown to reduce the risk for developing bone metastases for the first time. Denosumab 147 was a randomized, placebo-controlled, phase III trial that enrolled 1,432 men with CRPC, no bone metastases, and at least one feature consistent with a high risk for the development of bone metastases (PSA ≥8 ng/mL or PSA doubling time ≤10 months). Participants were treated every 4 weeks with s.c. denosumab (120 mg) or placebo.

The trial was positive because denosumab led to a 4.2-month significantly longer bone-metastasis-free survival time relative to placebo (median, 29.5 months versus 25.2 months; hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.73–0.98; $p = .028$) [1]. The time to first bone metastasis and risk for symptomatic bone metastasis were also significantly better with denosumab treatment. Dror Michaelson and Philip Saylor discuss the potential implications of this trial.

Pro

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The pivotal trial of denosumab in men with nonmetastatic CRPC reported a significant benefit in preventing the development of metastasis [1]. Bone-targeted therapy in prostate cancer has a well established role, because the majority of morbidity and mortality attributable to prostate cancer is a function of the skeletal metastases that characterize this disease. In contrast to hormone therapy and cytotoxic chemotherapy, which focus on antineoplastic effects, bone-targeted therapies such as denosumab and zoledronic acid focus on impacting the bone milieu to produce benefit [2].

A randomized, phase III study of zoledronic acid in men with metastatic CRPC demonstrated a significant benefit in preventing SREs, a composite outcome that combines symptomatic and asymptomatic pathologic fractures, the need for radiation therapy or surgery to treat bone metastases, spinal

Con

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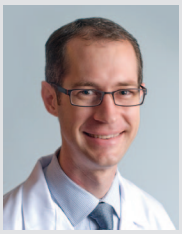

Philip J. Saylor

Denosumab 147 is the first ever trial to demonstrate a significant delay in time to the development of prostate cancer bone metastases [1]. This is a major accomplishment, particularly given that previous clinical trials with bisphosphonates (clodronate [2] and zoledronic acid [3]) were negative. Though this result adds to an impressive and growing body of clinical trial evidence in support of denosumab for patients with advanced cancers [4–6], there are several reasons that these results must be interpreted carefully.

First, the enrollment criteria selected a specific subset from within the larger overall population of men with nonmetastatic CRPC. All men met at least one of two PSA criteria associated with a high risk for the development of bone metastases (PSA ≥8 ng/mL or a PSA doubling time ≤10 months). A similar trial designed to examine zoledronic acid did not include either

Challenging Cases Editor: David Ryan, M.D., MGH Cancer Center, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114, USA. Received December 6, 2011; accepted for publication December 8, 2011; first published online in *The Oncologist Express* on January 20, 2012. ©AlphaMed Press 1083-7159/2012/$40.00/0 http://dx.doi.org/10.1634/theoncologist.2011-0433

cord compression, and change in antineoplastic therapy to treat bone pain [3]. On the basis of this study, zoledronic acid became the accepted standard of care for bone-targeted therapy in men with metastatic CRPC.

More recently, a double-blind, multicenter trial treated 734 men receiving androgen ablative therapy for nonmetastatic prostate cancer with either denosumab or placebo [4]. Significant improvements in bone mineral density were seen in the denosumab-treated men, along with a lower incidence of vertebral fractures (1.5% at 36 months, versus 3.9% in the placebo group; relative risk, 0.38; $p = .006$). Another important trial, published in 2011, compared denosumab with zoledronic acid among 1,900 men with metastatic CRPC [5]. The investigators found that the time to first SRE was 3.6 months longer in men treated with denosumab than in those treated with zoledronic acid (HR, 0.82; $p = .008$.). There was greater suppression of bone turnover markers in men treated with denosumab, whereas the overall adverse event rates were comparable in the two treatment arms. These studies further established a role for bone-targeted therapy, and in particular for denosumab, in men with advanced prostate cancer.

The current landmark trial in men with nonmetastatic CRPC extended these findings by demonstrating that bone metastases can be prevented or delayed with bone-targeted therapy. In men with high-risk features for the development of bone metastases, the median time to initial metastasis was 25.2 months in the placebo group and 29.5 months in the denosumab group. Considering the clinical impact of bone metastases on men with prostate cancer, a median delay of 4.2 months in their development is a meaningful observation with immediate treatment implications. Moreover, treatment with bone-targeted therapy should continue for men with advanced prostate cancer even after the development of bone metastases, because both zoledronic acid and denosumab have shown benefit in preventing SREs after the development of metastases.

Though the majority of bone metastases detected in the Denosumab 147 study were not symptomatic, the study design required that men be immediately withdrawn from the investigational study drug upon detection of initial metastasis. One implication of this design was that the ability to establish when metastases became symptomatic was limited. A second implication was that bone-targeted treatment was discontinued sooner than would be done in standard practice. The impact of denosumab on the development of symptomatic metastases is therefore not yet established, and conceivably the true benefit of ongoing bone-targeted therapy would be greater than represented in this study.

In balancing the risk–benefit ratio of treatment, the main toxicity to consider is the development of osteonecrosis of the jaw (ONJ), a difficult but fortunately rare complication with denosumab [5–7]. The incidence of ONJ was 5% in this study and it resolved in 39% of observed cases with conservative management. It is important to emphasize to all practitioners the critical role for universal dental examinations as bone-targeted therapies are used in more patients and for longer durations. The more widespread recognition of ONJ risk, and of these PSA criteria and was closed early for futility because of a low rate of new metastases. Clinicians who consider metastasis prevention as directed by the Denosumab 147 trial must do so with a keen eye to the specific high-risk enrollment criteria.

Second, the clinical impact of this strategy may be more modest than it appears to be at first glance. Prevention of bone metastases is an important goal because that they can cause pain, immobility, and other morbidity. The trial was designed to assess the metastasis-free survival time, an endpoint that includes both symptomatic and asymptomatic lesions. Men underwent scheduled bone scans every 4 months throughout the trial. In the event-driven analysis, 440 of the 605 new metastases were asymptomatic. Although the difference in the incidence of symptomatic metastasis was significant (69 with denosumab versus 96 with placebo; HR, 0.67; 95% CI, 0.19–0.92; $p = .01$), 716 men had to be treated every 4 weeks for a median of 19 months in order to prevent 27 cases of symptomatic metastasis.

Third, men managed as directed by this trial will undergo long durations of potent monthly osteoclast inhibition. A typical man in the treatment arm received close to 2 years of high-intensity therapy prior to detection of his first metastasis. Trial-directed therapy was then stopped. But with the development of that first metastasis, he had then arrived at the point of most clearly demonstrated benefit with monthly osteoclast inhibition. In men with CRPC metastatic to bone, zoledronic acid reduces the risk for SREs by 35% relative to placebo [7, 8]. When denosumab was later compared with zoledronic acid, it further lengthened the time to first SRE (20.7 months versus 17.1 months; $p = .008$). So after close to 2 years of metastasis prevention with denosumab, treatment should likely be continued indefinitely. What duration of such therapy is safe? That question is not addressed within the published literature because trials using monthly zoledronic acid or denosumab have generally featured ≤2 years of therapy.

ONJ is a prominent concern with prolonged therapy and can lead to substantial morbidity. The incidence of ONJ in the treatment group rose with prolonged treatment (1% at 1 year, 3% at 2 years, and 4% at 3 years) and was 5% overall. Those men are poor candidates for further osteoclast inhibition even as their disease is at risk for progression. It is also important to note that the incidence of ONJ may be >5% with further treatment and follow-up. Finally, the risk for ONJ may be higher in a nontrial population if baseline and ongoing dental exams are not universally carried out. Treatment-related ONJ with this strategy clearly deserves further study.

Finally, this treatment strategy must be assessed in the context of the rapidly expanding arsenal of systemic therapies for advanced prostate cancer. The Denosumab 147 trial tells us that early institution of denosumab delays by 4 months the appearance of scan-detectable metastases and lengthens the time to symptomatic metastases. The overall survival time was not changed and we do not yet know what effect this strategy has on the longer-term risk for skeletal events. Docetaxel, sipuleucel-T, cabazitaxel, and abiraterone acetate all improve survival in men with advanced prostate cancer [9–13]. Alpharadin and MDV3100 have also preliminarily been reported to improve survival outcomes. It is not clear how best to optimize the use of these agents to promote the length and quality of our patients' lives.

adoption of preventative measures, will hopefully result in a diminished incidence in the future.

At the current time, because skeletal-related complications are the main source of morbidity in men with prostate cancer, the significantly longer time before the appearance of skeletal metastases is an important benefit that establishes denosumab as the standard of care for men with CRPC and a high risk for development of bone metastases.

DISCLOSURES

M. Dror Michaelson: None.

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Osteoclast inhibition is one of the cornerstones of the management of advanced prostate cancer. Denosumab has been shown to be tolerable and effective for men with CRPC metastatic to bone. Now the metastasis prevention trial has revealed an enticing improvement in the metastasis-free survival time. This result must be received with caution because the true clinical benefits and the long-term risks of this strategy remain to be better defined.

DISCLOSURES

Philip J. Saylor: None.

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