Bone-Targeted Therapy in Prostate Cancer in 2017: Lost Opportunities, Confusion, and Controversy

Fred Saad, Centre Hospitalier de l’Université de Montréal, Université de Montréal, Montreal, Quebec, Canada

See accompanying article doi:10.1200/JCO.2016.69.0677

Since 2004, the number of management options for patients with metastatic prostate cancer has increased dramatically, with six agents showing improvements in overall survival (OS). In 2002, zoledronic acid (ZA) demonstrated efficacy in reducing the risk of skeletal-related events (SREs) as well as in delaying their appearance. Until then, no agent had shown any improvement in survival in metastatic castration-resistant prostate cancer (mCRPC), but this underpowered study did show an unexpected trend in improving OS. Around the same time, the Medical Research Council from the United Kingdom (MRC-PR05) reported results from the use of oral clodronate. Initially, the investigators reported no survival advantage in hormone-sensitive metastatic prostate cancer, but with longer follow-up, the study did show an improvement in OS. Of note, clodronate was continued from the hormone-sensitive state and throughout the castration-resistant prostate cancer (CRPC) state. Given the positive results with ZA in the latest stage of the disease, it made sense to investigate whether it would be even more effective in an earlier disease state, such as in metastatic hormone-sensitive prostate cancer. Also of interest was whether it would add to the effectiveness of docetaxel, which had been the first agent to demonstrate a survival advantage in men with mCRPC. The Cancer and Leukemia Group B/National Cancer Institute of Canada conducted a randomized study in newly diagnosed metastatic prostate cancer that compared administering ZA upfront at the time of initiating hormone deprivation therapy for the first few years of the study, or to discontinue therapies at the first sign of PSA progression on the basis of PSA. Recent studies have shown improvements in OS excluded PSA progression as a reason for drug discontinuation. One can only wonder if radium-223, docetaxel, cabazitaxel, or even abiraterone or enzalutamide would have resulted in positive survival outcomes if patients had discontinued therapies at the first sign of PSA progression in the CRPC state. In those studies, treatment was continued until radiographic progression, so evidently, therapies that have no effect on PSA would be doubly harmed by early stoppage if one wants to determine usefulness.

Mason et al.5 present the results of the SOC plus celecoxib arms (1 year) with and without ZA (2 years). The authors describe the history behind the celecoxib arms that were discontinued early given the lack of perceived efficacy at interim analysis. Fortunately, follow-up was maintained, which allowed the data to mature. The results demonstrate that overall, there was no survival advantage to celecoxib with or without ZA. However, even with a severely underpowered study, the combination of celecoxib and ZA (the M1 arm) did show a survival advantage that was in the range of that observed with docetaxel. Also of importance is that >60% of patients did not complete the planned 2 years of ZA, as a result of defining progression on the basis of PSA. Recent studies that have shown improvements in OS excluded PSA progression as a reason for drug discontinuation. One can only wonder if radium-223, docetaxel, cabazitaxel, or even abiraterone or enzalutamide would have resulted in positive survival outcomes if patients had discontinued therapies at the first sign of PSA progression in the CRPC state.

Corresponding author: Fred Saad, MD, Centre Hospitalier de l’Université de Montréal, 900 rue St-Denis, Montreal, QC, Canada; e-mail: fred.saad@umontreal.ca

© 2017 by American Society of Clinical Oncology.

Downloaded from ascpubs.org by 94.160.5.213 on March 31, 2017 from 094.160.005.213
Copyright © 2017 American Society of Clinical Oncology. All rights reserved.
In STAMPEDE, in which patients are hormone sensitive when they enroll in the study, PSA progression indicates that that patients had entered the CRPC state. When one considers that drugs such as ZA are likely to be most useful when patients become castration resistant, it becomes challenging to demonstrate benefit in terms of FFS and OS if the drug is discontinued when CRPC begins. In retrospect, it now seems evident that PSA progression was not an appropriate reason to discontinue celecoxib and ZA.

Do bone-targeting therapies add anything to the treatments we now have for mCRPC? The first evidence that targeting the bone could prolong survival as well as reduce symptomatic bone complications came from the Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) radium-223 study. Unfortunately, the value of maximizing control of the bone microenvironment with supportive bone-targeted therapy (ie, ZA and denosumab) in an era of life-prolonging therapies remains difficult to estimate given the lack of well-designed, adequately powered studies with long-term follow-up. For now, we are obliged to look at post hoc analyses of randomized studies such as the abiraterone 302 study that allowed asymptomatic or minimally symptomatic patients with or without a bisphosphonate to enroll in the study. A preplanned analysis demonstrated that patients receiving a bisphosphonate had better survival, delayed appearance of pain, and delayed time to a decline of performance status compared with those not receiving a bisphosphonate. An improvement in OS was also observed in a phase 3b study of radium-223 in which patients receiving radium and denosumab had statistically significantly better survival than those receiving radium alone. When examining symptomatic bone complications, two prospective studies demonstrated an advantage of a combined approach. The Taxane, Radioisotope, Zoledronic Acid (TRAPEZE) study showed a significant delay in SREs when docetaxel was combined with ZA than when docetaxel was used alone. Interestingly, the benefit in terms of delayed SREs was in the same range as that seen in the pivotal ZA study when chemotherapy was not in use. Even in the ALSYMPCA trial, Sartor et al found that radium-223 in combination with a bisphosphonate led to a significant reduction in SREs when compared with placebo, whereas radium alone did not show a significant reduction in SREs when compared with placebo.

Although it is unclear why a bone-targeted therapy in combination with a cox inhibitor would improve survival in patients with metastatic hormone-sensitive prostate cancer, these results should at least make us pause and reflect on whether we have adequately studied the impact of bone-targeted therapies in prostate cancer. Although most would agree that it is unlikely that a bone-targeted therapy in hormone-sensitive prostate cancer significantly improves OS, messages get confused regarding the setting of mCRPC when one cites results from trials in patients with hormone-sensitive and nonmetastatic prostate cancer. Physicians and patients may end up with the impression that there is no role for the use of bone-targeted therapy in the management of prostate cancer throughout the whole disease spectrum. I believe this may be detrimental and a step backward in the optimal management of patients with bone metastatic prostate cancer.

Although we may never fully appreciate whether bone-supportive therapies contribute to improving survival in patients with prostate cancer, they continue to play an important role in patients with mCRPC. I believe this should be part of a treatment strategy that combines maximizing survival and minimizing morbidity in patients destined to die as a result of prostate cancer.

REFERENCES


AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Bone-Targeted Therapy in Prostate Cancer in 2017: Lost Opportunities, Confusion, and Controversy

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Fred Saad
Honoraria: Astellas Pharma, Amgen, Janssen Oncology, Bayer AG, Sanofi
Consulting or Advisory Role: Astellas Pharma, Amgen, Bayer AG,
Janssen Oncology, Sanofi
Research Funding: Astellas Medivation (Inst), Amgen (Inst),
Bayer AG (Inst), Janssen Oncology (Inst), Sanofi (Inst)