PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

PSMA-Targeted Radiotherapy in Metastatic Castration-Resistant Prostate Cancer

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H&O Could you describe the design of the VISION study that was recently published?

OS The phase 3 VISION trial, which was recently published in the *New England Journal of Medicine*, was designed to look at standard-of-care treatment plus or minus the investigational radioligand therapy lutetium 177 prostate-specific membrane antigen-617 (^{177}Lu-PSMA-617) in men with metastatic castration-resistant prostate cancer (CRPC). The design was based on that of the ALSYMPCA trial, which examined standard-of-care treatment plus or minus radium-223 dichloride (Xofigo, Bayer) for patients with metastatic CRPC. The results of ALSYMPCA led the US Food and Drug Administration (FDA) to approve the use of radium-223 in 2013 for men with metastatic CRPC.

A major difference between ALSYMPCA and VISION is that the patients in VISION were much more heavily pretreated; the landscape has changed so much in recent years. All of the patients in VISION had disease that had failed to respond to abiraterone, enzalutamide (Xtandi, Astellas), or both, and to at least one taxane chemotherapy. Many of the men had disease that had failed to respond to 2 taxane chemotherapies; these were incredibly heavily pretreated patients.

The patients in VISION were selected through the use of gallium 68 PSMA-11 positron emission tomography (PET). Eligibility criteria included the presence of a metastatic lesion on PSMA PET, and patients with lymph nodes of 2.5 cm or larger or with visceral lesions of 1 cm or larger that were PSMA-negative were excluded. We enrolled 813 patients after evaluating more than 1000 with scans and randomly assigned them in a 2:1 ratio to ^{177}Lu-PSMA-617 or control treatment. The median follow-up was 20.9 months.

H&O What did the trial find?

OS In the intent-to-treat analysis, median overall survival (OS) was significantly longer in the ^{177}Lu-PSMA-617 group than in the control group, at 15.3 vs 11.3 months, respectively (hazard ratio [HR], 0.62; P <.001). That is a strikingly positive finding in patients who were pretreated with virtually all the standard approaches. Median radiographic progression-free survival (PFS) also was significantly longer in the ^{177}Lu-PSMA-617 group than in the control group, at 8.7 vs 3.4 months, respectively (HR, 0.40; P<.001).

In addition, all key secondary endpoints favored ^{177}Lu-PSMA-617 over the control treatment, including rates of decline in prostate-specific antigen (PSA), objective response rate, and median time to first symptomatic skeletal event.

Although high-grade treatment-emergent adverse events, such as high-grade bone marrow suppression, high-grade anemia, and low platelet count, were more common with ^{177}Lu-PSMA-617 than with control treatment (52.7% vs 38.0%, respectively), that finding was quite reasonable in this heavily treated population. Dry mouth was observed in approximately one-third of the isotope-treated patients.

H&O Did the pandemic have any effect on the study?

OS The trial began to enroll patients in June of 2018, and it accrued patients quickly enough that any effects of the pandemic on accrual were minimal. Some of the follow-up care was affected, such as assessments of radiographic PFS, because patients were reluctant to visit the clinic during the pandemic.

H&O What was the effect of the early withdrawal of patients in the control arm on the conduct and interpretation of the study?

OS During the early phases of this open-label study, we found that certain sites were not providing adequate follow-up to the patients who had been randomly assigned to the control arm. We shut down the study at those sites where inadequate follow-up was the greatest problem and sent strongly worded messages to the remaining investigators in an effort to ensure adherence to proper follow-up of patients in the control arm going forward. When we reported this problem to the FDA, it agreed that although OS would be assessed within the intent-to-treat group, radiographic PFS would be evaluated in a subset of patients to be accrued on a go-forward basis. These changes did not really matter much in the end because radiographic PFS was positive in the intent-to-treat subset, and OS was positive in the radiographic PFS subset. Still, the significant changes that occurred because of control group dropout were mitigated by the adjusted analysis that took place, as well as by exclusion of the sites that were causing the most problems.

H&O What would you say are the implications of the study findings?

OS On the basis of the strong OS benefit in heavily pretreated patients, I anticipate that the FDA, the European Medicines Agency, and other regulatory agencies around the world will recognize this as a pivotal study and grant approval to ^{177}Lu-PSMA-617 therapy. That is a big statement, but I think the results are convincing. The intent-to-treat OS analysis should convince even skeptics that ^{177}Lu-PSMA-617 is a highly active therapy, and this analysis is bolstered by radiographic PFS data, image-based response, response according to Response Evaluation Criteria in Solid Tumors (RECIST), and PSA data.

H&O What are the benefits and advantages of PSMA-targeted radiotherapy?

OS The most important benefit of this treatment is its unequivocal efficacy in a patient population with disease that is difficult to treat. These are patients whose disease failed to respond to abiraterone, enzalutamide, and docetaxel. In more than 40% of cases, disease failed to respond to cabazitaxel (Jevtana, Sanofi-Aventis) as well. Some patients may be eligible for precision therapy approaches, such poly(ADP-ribose) polymerase (PARP) inhibition in those with mutations in homologous recombination repair genes, and pembrolizumab (Keytruda, Merck) in those with microsatellite instability–high or mismatch repair–deficient cancer. Precision therapeutic approaches apply to only a small percentage of patients, however—probably less than 15%.

Another important advantage of ^{177}Lu-PSMA-617 is relatively low toxicity. Previous studies that have compared ^{177}Lu-PSMA-617 with chemotherapy have found less toxicity with radioligand therapy.

H&O Are certain patients more or less suitable for PSMA-targeted radiotherapy?

OS We need further studies to define suitability in more detail. Factors such as various pretreatments, genetic alterations, findings on circulating tumor DNA, distribution of metastases, and standardized uptake value on PSMA PET all need to be examined.

> Once enough people have been trained, it should be relatively easy to expand the use of ^{177}Lu-PSMA-617.

H&O Could you talk more about the risks of ^{177}Lu-PSMA-617?

OS We saw a little bit of myelosuppression with ^{177}Lu-PSMA-617, although we do not know how much of this was related to patients already having some degree of myelosuppression. We saw a slight increase in renal adverse events, but I am not convinced that this difference was meaningful because of the variations in duration of follow-up. We also saw dry eye and dry mouth, both of which can be problematic. But overall, the treatment was very well tolerated.

H&O What, if any, are the barriers to delivery and treatment?

OS Providers, who can be nuclear medicine technologists or radiation oncologists, must be licensed to provide this

treatment. The treatment also needs to be administered in a multidisciplinary setting, which is not available at all centers. However, once enough people have been trained, it should be relatively easy to expand the use of ^{177}Lu-PSMA-617.

H&O How does this treatment compare with the other treatment options that are available for metastatic CRPC?

OS Pembrolizumab is FDA-approved for a subset of patients with microsatellite instability–high or mismatch repair–deficient cancer; sipuleucel-T (Provenge, Dendreon) is approved for use in early-stage disease; and the chemotherapeutic agents docetaxel and cabazitaxel are used in selected patients. The studies of abiraterone and enzalutamide show a clear benefit of these agents either before or after docetaxel. The CARD study, by de Wit and colleagues, examined the use of cabazitaxel in patients with metastatic CRPC who had been pretreated and whose disease progressed after both docetaxel and either abiraterone or enzalutamide.

H&O What are the next steps in adopting PSMA-targeted radiotherapy?

OS The next step is to evaluate ^{177}Lu-PSMA-617, which has been shown to be effective in heavily pretreated patients, in earlier-stage disease. In addition to looking at beta emitters, such as ^{177}Lu, we also need to be looking at alpha emitters. I believe that actinium-225 in particular needs to be looked at carefully. We also need to look at combinations of PSMA-targeted radiotherapy with agents such as PARP inhibitors, to determine whether they have a synergistic effect. This is a brand new therapy, so we have much more work to do to answer all the questions we have.

H&O What are the potential mechanisms of resistance?

OS Lack of PSMA expression is certainly a mechanism of resistance. We also expect tumor cells to be able to learn how to repair their DNA. Another issue is tumor heterogeneity; some cells will make more PSMA than others. Logic tells us that cells with high-level expression of PSMA are going to be more susceptible to PSMA-targeted radiotherapy. Overall, we need to learn a lot more about resistance patterns, drivers of resistance, and differences between primary and secondary resistance, just as we have for platinum and other chemotherapeutic agents. This field is ripe for harvest.

H&O What other studies are looking at PSMA-targeted radiotherapy?

OS Ongoing phase 3 trials looking at the use of PSMA-targeted radiotherapy are PSMAfore, which is now accruing patients (NCT04689828), and a logical extension to the VISION study, PSMAddition (NCT04720157). PSMAfore, which is comparing optimal hormone therapy plus or minus ^{177}Lu-PSMA-617, is studying patients with metastatic CRPC who have been treated with novel hormones but have yet to receive chemotherapy. In contrast, all patients in the VISION study were required to have had chemotherapy before treatment. PSMAddition is bringing ^{177}Lu treatment into the upfront space in castration-sensitive disease.

POINT Biopharma has announced a phase 3 trial (NCT04647526) to evaluate a treatment in which its compound, called PSMA I & T or PNT2002, is bound to ^{177}Lu (^{177}Lu-PNT2002 PSMA therapy). The design of this trial will be similar to that of PSMAfore.

Disclosures

Dr Sartor has done consulting for Advanced Accelerator Applications, Astellas, AstraZeneca, Bayer, Blue Earth Diagnostics, Bavarian Nordic, Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis Pharmaceuticals, Constellation Pharmaceuticals, Dendreon, EMD Serono, Fusion Pharmaceuticals, ITM Isotopen Technologien Muenchen, Janssen, Myovant Sciences, Myriad Genetics, Noria Therapeutics, Novartis, Noxopharm, Progenics Pharmaceuticals, POINT Biopharma, Pfizer, Sanofi, TeneoBio, Telix Pharmaceuticals, and Theragnostics; and has received grants or research support from Advanced Accelerator Applications, AstraZeneca, Bayer, Constellation, Endocyte, Invitae, Janssen, Merck, and Progenics Pharmaceuticals.

Suggested Readings

de Wit R, de Bono J, Sternberg CN, et al; CARD Investigators. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med.* 2019;381(26):2506-2518.

Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.

Sartor O, de Bono J, Chi KN, et al; VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer [published online June 23, 2021]. *N Engl J Med.* doi:10.1056/NEJMoa2107322.