PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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The Clinical Implications of the PROTEUS Trial

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H&O What was the impetus for the PROTEUS trial?[1]

MET The standard treatment for many patients with solid tumors is a combination of surgery to remove macroscopic localized disease and systemic therapy to address microscopic systemic disease. Trials conducted in the 1990s and early 2000s found no benefit from androgen deprivation therapy (ADT) combined with prostatectomy for prostate cancer, but many of the patients in those trials were at low risk for recurrence, so clinically meaningful endpoints were not achieved. I was part of a research group whose work showed that prostate cancers that relapse contain high levels of intratumoral androgens, which are a source of growth for prostate cancer cells. When androgen receptor pathway inhibitors (ARPIs) came along, we designed phase 2 studies that combined ARPIs with surgery to try to improve the outcomes of patients who were at high risk for relapse. Beginning in 2009, we conducted a series of 4 phase 2 trials over approximately 10 years that enrolled between 35 and 118 patients, with each trial looking at different combinations of ARPIs after surgery.[2-5] The positive results of these trials provided supportive data for the PROTEUS study.

H&O What was the design of PROTEUS?

MET PROTEUS was a double-blind, placebo-controlled phase 3 trial for patients with newly diagnosed high-risk localized or locally advanced prostate cancer. A total of 2109 patients were randomly assigned in a 1:1 ratio to receive ADT plus the ARPI apalutamide (Erleada, Janssen) at 240 mg/d or ADT plus placebo for 6 cycles (28 days each) before and after radical prostatectomy with pelvic lymph node dissection. Our hypothesis was that the addition of systemic therapy to surgery would improve both short-term endpoints (measured with pathologic complete response or minimal residual disease) and long-term outcomes (measured with metastasis-free survival by conventional imaging or prostate-specific membrane antigen positron emission tomography). Secondary endpoints included event-free survival, time to first subsequent treatment, time to distant metastasis, and safety.

H&O Could you describe the results?

MET At a median follow-up of 61.7 months, the percentage of patients with a pathologic complete response or minimal residual disease was significantly higher in the apalutamide group than in the placebo group, at 9% vs 1%. In addition, the percentage of patients with metastasis-free survival was significantly higher in the apalutamide group than in the placebo group, at 78% vs 74%, with a 20% reduction in the risk of metastasis or death by blinded independent central review. I consider the 20% reduction in the risk of metastasis or death to be a challenging endpoint because the median age of patients in this study was 66 years, so we would expect deaths from a variety of causes over long-term follow-up. The improvement in investigator-assessed metastasis-free survival was even more pronounced, with a 26% reduction in the apalutamide group vs the placebo group.

Event-free survival, time to first subsequent treatment, and time to distant metastasis all significantly favored apalutamide over placebo. Grade 3 or 4 adverse events (AEs) occurred in 40% of the patients in the apalutamide group

and 31% of those in the placebo group.

The bottom line is that PROTEUS was a rigorously designed prospective, randomized, blinded trial that was the largest trial ever done in patients with newly diagnosed high-risk localized or locally advanced prostate cancer. Both the primary endpoints were positive, 4 of the secondary endpoints were positive, and the exploratory endpoints were positive. All endpoints were positive except metastasis-free survival by conventional imaging; this analysis lost power owing to the small number of events.

H&O Could you describe the AEs in more detail?

MET In both cohorts, most of the treatment-related AEs were related to ADT and included such predictable symptoms as fatigue and hot flashes. The main symptom that was more likely to occur in the apalutamide group than in the placebo group was rash, which is a known side effect of apalutamide. The rash is not like the rash that occurs with penicillin, which might lead to hives on first exposure and possibly anaphylaxis on second exposure. When someone experiences a rash with apalutamide, the drug can be held for a short time and then reintroduced at a lower dose, or the dose can simply be reduced if the rash is less extensive.

Treatment-related AEs occurred in 27% of patients in the apalutamide cohort and 19% of those in the placebo cohort, with treatment-related AEs leading to a dose reduction or interruption in 12% of those in the apalutamide group and 2% to 4% of those in the placebo group. All-grade AEs leading to death occurred in fewer than 1% of patients in both groups, but the rate was higher in the apalutamide group, at 0.7%. After approximately half of the patients were enrolled, we observed that cardiovascular deaths were more common in the apalutamide group than in the placebo group—in part because eligibility standards for surgery were not the same for every country in this international study. In response, we added a requirement that all patients undergo a cardiovascular assessment at baseline and before prostatectomy. After that amendment, no more cardiovascular deaths occurred.

H&O How have the results of PROTEUS affected the treatment of patients with high-risk localized or locally advanced prostate cancer?

MET The results have not had any effect so far because apalutamide does not have US Food and Drug Administration (FDA) approval at this point for use in patients with high-risk localized or locally advanced prostate cancer. The PROTEUS data will be presented to the FDA for approval. Nobody on the PROTEUS team is saying that this regimen is better than the existing standards of care; we did not compare the PROTEUS regimen with radiation plus ADT or with radiation plus ADT and abiraterone.

Oncologists in other countries may see the data and decide to recommend this approach, but I would caution them against using it in patients who are older than 75 years, for whom radiotherapy may be a safer choice. I would also emphasize the importance of conducting a thorough cardiovascular assessment with the cardiovascular risk assessment forms that we employed in PROTEUS. Anyone who receives a score higher than 1 should be seen by a cardiologist to mitigate the possible risks of ADT/apalutamide and surgery. This advice will apply to US patients as well if PROTEUS leads to FDA approval, even if the FDA does not specify all these parameters.

> We need to produce far more data regarding quality of life with perioperative apalutamide.

H&O How should clinicians and patients decide between ADT/ARPI therapy with radiation, as in STAMPEDE,[6] and ADT/ARPI with surgery?

MET This is a key question in the care of patients with localized high-risk prostate cancer. I look at treatment as having 3 possible components: surgery, radiation, and ADT. The ADT may be given for 6 months in the salvage setting, for 1 year in the PROTEUS setting, and for 2 years in the primary radiation setting. In addition, it may be given with or without an ARPI. When I meet with a patient, I go through the possible side effects of all 3 of these modalities and we discuss the pros and cons of each, including incontinence rates, impotence rates, side effects of systemic therapy, and the options that are available after relapse. The incontinence rates are highest in patients who experience relapse after surgery and require salvage radiation, which I refer to as double local therapy. Patients come in with various preferences; one patient will favor surgery over radiation for personal preference reasons, whereas another will ask why someone would choose surgery when radiation is an option. It is important for us as clinical experts to ensure that each patient is appropriately educated and making decisions based on data because a lot of false information appears on the Internet.

H&O PROTEUS also included a substudy comparing the regimen directly with radical prostatectomy alone. What will that analysis add, and when might we see it?

MET In the substudy, which enrolled 400 patients, we compared the PROTEUS regimen with surgery alone, using a primary endpoint of 3-year event-free survival that includes prostate-specific antigen (PSA) failure. The European Medicines Agency requested this sub-study, which is why the endpoint is different from metastasis-free survival, which is required by the FDA. I have not seen the data yet, but we expect that positive results will be presented at the European Society for Medical Oncology Congress in October 2026.

H&O When should postoperative radiation be used in patients like those in PROTEUS, and how should providers decide on this, given the PSA suppression in this setting?

MET We left postoperative radiation up to the treating physician in PROTEUS because the data have shown that adjuvant radiation is not better than early salvage. To my mind, there is little reason to administer radiation to someone who has an undetectable PSA level. The only case in which radiation might make sense right after surgery is a patient who had unresectable or T4 disease after 6 months of ADT/apalutamide followed by surgery. The long-term toxicity of radiation after surgery can be high, especially regarding urinary continence. At our center, we provide salvage radiation at early signs of recurrence. We do not wait until the PSA level has reached 0.2 ng/mL; we begin when the level is approximately 0.1 ng/mL.

H&O How should clinicians define high risk for the purposes of applying this regimen? And does the benefit hold consistently across risk subgroups?

MET All the patients in this study had high-risk and high-volume disease. If patients had a highest Gleason score of 8, at least 6 positive core biopsy results were required (unless the PSA level was >20 ng/mL, in which case 3 positive cores were required). If patients had a Gleason score of 9 or 10, they required just one positive core biopsy result. The study also allowed patients with lymph node positivity up to stage N1.

H&O What further studies should be conducted regarding the addition of apalutamide to treatment?

MET We need to produce far more data regarding quality of life with perioperative apalutamide. We also need more studies that involve analysis of tumor tissue to differentiate patients who are likely to experience an optimal response from those who are likely to experience a relapse. A subset of patients are likely to benefit from combination therapy with other agents, such as chemotherapy or poly(ADP-ribose) polymerase (PARP) inhibitors, for example, or compounds currently in development. Patients deserve to have detailed conversations with their providers about all the components of their treatment options, and as providers, we would like to have as many data as possible to help them make the best decisions.

Disclosures

Dr Taplin, who is the primary investigator of PROTEUS, serves on the advisory board of Johnson & Johnson.

References

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