ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Drug Approvals for Prostate Cancer

Ian F. Tannock, MD, PhD
Emeritus Professor of Medicine and Medical Biophysics
Princess Margaret Cancer Centre
University of Toronto
Toronto, Canada

H&O What are the most recent drug approvals for prostate cancer?

IT The most recent drug approvals for men with prostate cancer primarily consist of "me-too" drugs. The first-in-class drugs abiraterone and enzalutamide (Xtandi, Astellas) have made a large impact by improving survival across all stages. Although they work differently, they achieve essentially the same result by reducing androgen stimulation of prostatic tissue. Two other utamide drugs, apalutamide (Erleada, Janssen) and darolutamide (Nubeqa, Bayer HealthCare), have also been approved.[1,2] Companies claim that these newer drugs offer slight improvements over abiraterone and enzalutamide, but the supporting evidence is minimal. Unless patients have attributes making them more likely to have side effects from enzalutamide or abiraterone, there is no advantage to using them.

Another approval is lutetium-177 (^{177}Lu)-PSMA-617 (Pluvicto, Novartis), a radioisotope attached to a linker molecule that recognizes prostate-specific membrane antigen (PSMA).[3] This is an example of a theranostic, where a positron emission tomography (PET) scan is performed to see the expression of PSMA, and if positive, the hybrid lutetium molecule is applied, and lutetium radioactivity kills the cancer cells.

The poly(ADP-ribose) polymerase (PARP) inhibitors olaparib (Lynparza, AstraZeneca), niraparib (Zejula, GSK), talazoparib (Talzenna, Pfizer), and rucaparib (Rubraca, Clovis Oncology) are active against cancers with preexisting defects or mutations in DNA repair pathways.[4-8] They have been approved for prostate cancer with DNA repair defects.

Historically, the standard treatment of androgen deprivation involved orchiectomy, but this has been largely replaced by the injection of gonadotropin-releasing hormone (GnRH) agonists, which require an antiandrogen (such as bicalutamide) to be administered initially to prevent disease flare from the temporary increase in serum testosterone levels that these agents cause. GnRH antagonists that do not cause this temporary increase in serum testosterone, such as degarelix (Firmagon, Ferring) and relugolix (Orgovyx, Sumitomo Pharma/Pfizer), have been developed and approved. However, these alternatives do not offer a significant advantage and are more expensive.

H&O How has the approval of these newer drugs affected the use of older agents?

IT Most oncologists still rely on the older drugs, which are becoming generic and hence more affordable. The DNA repair inhibitors are likely used in a small group of patients with DNA repair deficiencies. However, it is not clear if they are used optimally; for example, after patients have been through standard treatments like hormone therapy, docetaxel, and cabazitaxel.

H&O Are the existing studies adequate to determine which drug in a particular class is the best choice for a particular patient?

IT No. The trials of olaparib and other PARP inhibitors,

and of ^{177}Lu-PSMA-617, have been poorly designed.[3,4] The fundamental principle of a phase 3 trial is to compare the new treatment with the best available treatment. The companies and the investigators supporting these trials are, in my opinion, displaying questionable judgment. For example, in the PROFOUND trial that established olaparib for DNA repair–deficient prostate cancer, around 30% of the participants had never received docetaxel, which is the standard first-line drug for castrate-resistant prostate cancer, and 80% had not received cabazitaxel, despite the fact that both agents have been shown to improve survival.[4] Instead, the investigators compared men who received the PARP inhibitors with control patients who received abiraterone if they had received enzalutamide, or enzalutamide if they had received abiraterone. We already know that abiraterone and enzalutamide are effective drugs, but responses to one of these drugs after the other has been used are short-lived and rare. The investigators manipulated the results by using an inadequate control, and the same approach was taken with the trial of ^{177}Lu-PSMA-617. Strangely, journals like *The New England Journal of Medicine* have accepted these papers. It is disheartening that they have been allowed to use these substandard control groups.

H&O Can you discuss the doses of these newer drugs? Do any of them have similar issues as abiraterone or enzalutamide?

IT We have proposed a trial, which we hope will proceed in the United Kingdom, in which we would compare full and half doses of utamide drugs, with enzalutamide being the main focus. In earlier-phase studies of all these drugs, the dose that was sufficient to maximally inhibit the target and to cause maximum response rate—indicating the drug's effectiveness—was about one-third of the registered dose. The trials kept the dose high, which was possible because these are not very toxic drugs compared with chemotherapy.

There is good evidence that any of these drugs can be used at half the current dose, cutting the cost in half. Additionally, other studies have shown that when abiraterone is given with food, it enhances absorption.[9] You can use one-quarter of the dose of abiraterone with food and achieve similar drug levels as a full dose when fasting. Consequently, all these drugs, including the older ones and the "me-too" drugs, could potentially be used at lower doses. Radioactivity causes the killing of cancer cells by ^{177}Lu-PSMA, so a higher dose might yield more killing. However, there are off-label effects in the kidney and other areas.

H&O How does the cost of newer agents compare with the cost of older agents?

IT Newer agents are always more expensive and usually fall within the range of $10,000 to $20,000 per month—a ridiculous, obscene price. This cost is independent of the drug's production expenses and its value in the clinical spectrum. Patients with prostate cancer who have undergone standard therapies and are still relatively well might benefit from ^{177}Lu-PSMA-617 if they are PSMA-positive on a PET scan, or they might benefit from a PARP inhibitor such as olaparib or niraparib if they have DNA-repair defects. I currently see no justification for using these agents in earlier stages of the disease. They are excessively expensive and irrelevant for many people worldwide. If you live in a low- or middle-income country, these drugs are impractical and too costly. Fortunately, abiraterone, enzalutamide, docetaxel, and cabazitaxel are all available in generic form in India and elsewhere, making these drugs more accessible in many countries.

Disclosures

Dr Tannock has no disclosures.

Suggested Readings

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