Innovations Lead to More Targeted Prostate Cancer Treatments

The main treatment for prostate cancer—the third leading cause of cancer death in American men—often is "watchful waiting." But what happens before, during, and after that waiting period has changed tremendously in recent years. Innovative and improved methods and drugs allow for a more precise diagnosis, better risk stratification, targeted treatment options, and longer survival.

Innovations in diagnosis include a revised histologic grading system, which was incorporated into the 2016 World Health Organization classification of tumors. The new grading system ranks prostate cancer on a 1-to-5 scale, making it more discriminating, as validated in a study of more than 25,000 men.

The use of new prognostic biomarkers has advanced risk stratification. According to a recent review, biopsy guided by ultrasound misses between 21% and 28% of prostate cancers and undergrades between 14% and 17%.[1] But new serum-, tissue-, and image-based biomarkers may help identify potential false negatives. The prostate cancer antigen 3 test, for example, has an 88% negative predictive value for subsequent biopsy. Molecular biomarkers also can predict clinical progression, risk of adverse pathology, and metastatic risk.

Fortunately, biopsy guided by ultrasound is getting more precise. Advances in magnetic resonance imaging (MRI) now allow for "targeted biopsies." The enhanced MRI has 89% sensitivity and 73% specificity for identifying prostate cancer. According to one study of 1,003 men, targeted prostate biopsy using MRI-ultrasound fusion identified 30% more cases of Gleason score ≥ 4 + 3 than did systematic prostate biopsy.[1] Updates in positron emission tomography are garnering interest for improved staging because this technology allows for better detection of local recurrence, regional lymph node metastases, and distant metastases.

Once a prostate cancer diagnosis has been confirmed, the decision of what to do next may be watchful waiting (treating symptoms palliatively), but recent research suggests that active surveillance that includes regular prostate-specific antigen testing, physical examinations, and prostate biopsies may be a better choice, particularly for men with less aggressive cancer. One study of 1,298 men with mostly very low-risk disease followed for up to 60 months found metastasis in only 5; only 2 died. The Prostate Testing for Cancer and Treatment (ProtecT) trial found that the number of deaths in the active monitoring group did not differ significantly from those in the surgery or radiation groups.

What should be the contemporary standard of care? Androgen deprivation therapy (ADT) is still the go-to treatment for men with metastatic prostate cancer. Although ADT has been associated with toxicity, a meta-analysis found continuous ADT was better than intermittent in terms of disease progression and survival.[1]

Other research has focused on which types of prostate cancer respond best to specific therapies. Molecular subtyping (already available in bladder and breast cancer) is gaining popularity. Prostate cancer was thought to derive from glandular luminal cells, but recent evidence supports the idea that basal cells play a role as well. Researchers who analyzed nearly 4,000 samples suggest that luminal B tumors respond better to postoperative ADT than do nonluminal B cancers. These findings suggest that "personalized" ADT treatment may be possible.[2]

Several drugs have been shown to improve survival: Among them, docetaxel, abiraterone acetate, enzalutamide, and cabazitaxel. In the STAMPEDE trial, men with locally advanced or metastatic prostate cancer who received ADT plus abiraterone and prednisolone had significantly higher rates of overall and failure-free survival.[3]

Docetaxel, which can extend survival by 10 to 13 months compared with standard ADT, is taking on a bigger role for its ability to delay progression and recurrence while being well tolerated. Options for men whose cancer does not respond to ADT include abiraterone and enzalutamide. Both act on the androgen axis to slow progression and improve survival.

More than 30% of patients treated with radical

prostatectomy will have recurrent cancer as will 50% of those treated with salvage radiation therapy. Bicalutamide has shown extremely promising action against recurrent cancer. In one study, the cumulative incidence of metastatic prostate cancer at 12 years was 14.5% in the bicalutamide group, compared with 23.0% in the placebo group.[4]

But while that study was going on, it was superseded by injectable gonadotropin-releasing hormone agonists as first-choice hormonal therapy with radiation. However, the researchers say that does not negate their findings on high-dose bicalutamide, which present "proof of principle" that adding hormone-based therapy to salvage radiation therapy is associated with significant and clinically important lower rates of metastases and death.

Multimodal therapy and precision medicine are becoming bywords in prostate cancer treatment. Drugs on the horizon likely will be tailored to tumor molecular biology, with genetic information used to specifically guide diagnosis and treatment. Prostate cancer may still be a slow killer, but immunotherapies (like sipuleucel-T, the first FDA-approved cancer vaccine), hormonal therapies, and bone-targeting agents enable men with prostate cancer to not only live longer but also with a better quality of life.

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