CLINICAL UPDATE

Novel Approaches to Disease Management

Selecting Early Therapy in Prostate Cancer

Daniel Petrylak, MD
Director, Genitourinary Oncology Research Program
Codirector, Signal Transduction Program
Yale Comprehensive Cancer Center
Yale School of Medicine
New Haven, Connecticut

H&O What are the unmet needs in the treatment of prostate cancer?

DP At this time, there are no curative treatments for metastatic disease. Thus, unmet medical needs for prostate cancer include the development of new targets and treatments for refractory patients. Additionally, tumor markers are needed to determine the correct sequence of drugs for castration-resistant prostate cancer (CRPC). Currently, clinical parameters are used to select treatments such as hormones (abiraterone acetate [Zytiga, Janssen Biotech], enzalutamide [Xtandi, Astellas/Medivation]), chemotherapeutic agents (docetaxel, cabazitaxel [Jevtana, sanofi-aventis]), DNA-damaging agents (radium-223 [Xofigo, Bayer/Algeta]), and immunotherapeutic agents (sipuleucel-T [Provenge, Dendreon]). Markers of resistance and response could help to determine the optimal sequencing of these therapies.

H&O Which patients benefit from treatment with early docetaxel?

DP At the current time, a significant survival benefit has been seen with early docetaxel combined with androgen blockade among patients with liver metastases or more than 4 bone metastases. Further follow-up may also show survival benefits for those patients with low-volume disease.

H&O Which patients benefit from early immunotherapy?

DP The patients to benefit the most from immunotherapy are those with CRPC prostate-specific antigen (PSA) levels of 22 ng/mL or less. In a pooled analysis, a 13-month difference in survival in favor of sipuleucel-T over placebo was observed in these patients. This survival benefit declined to 7.1 months in patients with a PSA between 22.1 and 50 ng/mL, to 5.4 months in patients with a PSA of 50.1 to 134 ng/mL, and to 2.8 months in patients with a PSA of greater than 134 ng/mL. Thus, it would seem that earlier treatment with immunotherapy results in a greater benefit to patients with CRPC.

H&O Do patients with metastases but not castration-resistant disease benefit from a particular type of treatment approach?

DP Currently, there is no standard treatment for those CRPC patients who have an asymptomatic PSA rise and no evidence of metastatic disease. Trials are under way evaluating agents such as enzalutamide, abiraterone, and ARN-509 in this patient population.

H&O Do symptoms influence treatment selection?

DP In early hormone-sensitive disease, symptoms do not influence whether patients receive chemotherapy. However, it would be unusual for solitary metastases to engender significant bone pain. Among CRPC patients with symptomatic disease, immunotherapy with sipuleucel-T is not indicated. Chemotherapy, hormonal therapy, and radioisotope therapy are all appropriate treatments for patients with symptomatic bone pain that requires narcotic analgesics.

H&O What studies support the use of early chemotherapy?

DP The CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial by Dr Chris Sweeney and colleagues from the Eastern Cooperative Oncology Group (ECOG) randomized 790 prostate cancer patients with metastatic disease that was not castration-resistant to either static continuous hormone therapy or hormone therapy plus 6 cycles of docetaxel without prednisone. The trial showed a significant improvement in survival with docetaxel, particularly in those patients who had poor-risk parameters, namely visceral metastases or more than 4 lesions on bone scan. The median overall survival was 57.6 months with docetaxel plus androgen-deprivation therapy (ADT) vs 44 months with ADT alone (hazard ratio, 0.61; *P*=.0003). Approximately 64% of the patients had high-risk disease; among these patients, the median improvement was 17 months. The hazard ratio was 0.6 (*P*=.0006), which clearly showed a benefit for early chemotherapy in these patients.

These patients subsequently went on to receive other therapies. Among the patients who received cytotoxic therapy in the control arm, approximately 50% progressed. The adverse events were typical of chemotherapy: fatigue, drop in blood counts, alopecia, and weight gain from fluid. The results of this trial suggest that the use of early chemotherapy should be adopted as the standard of care for those patients with 4 or more bone metastases or visceral disease. A trend toward improved survival was seen in those patients with lower volume disease, and this difference may become significant with further follow-up.

A trial by Dr Gwenaelle Gravis and coworkers in Europe had a similar design. Patients received 10 cycles of docetaxel plus hormones or hormones alone. This trial enrolled 385 patients, less than half the number of patients in the ECOG trial, and it therefore could have been underpowered. There was a 4-month, nonsignificant difference in survival in favor of the early chemotherapy. The median overall survival was 58.9 months (95% CI, 50.8-69.1) in patients who received ADT plus docetaxel and 54.2 months (42.2 months-not reached) in patients who received ADT alone (hazard ratio, 1.01; 95% CI, 0.75-1.36). However, a problem with this trial is that many of the patients were in an early stage of disease and/or had a better prognosis as compared with the ECOG trial, so any difference might not have been as clear. There were other parameters, including declines in PSA and time to PSA progression, that were superior in the combined treatment arm.

In conclusion, early chemotherapy should be considered for those patients with high-volume metastatic disease as defined in the ECOG trial. The benefit for patients with fewer than 4 lesions on bone scan is yet to be determined. Although confirmation of these observations was not reported in the trial performed in Europe, differences in statistics and design can account for the disparate findings.

Disclosure

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Suggested Readings

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