Chemotherapy in Prostate Cancer Beyond Metastatic CRPC

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Although great therapeutic advances have been made in metastatic castration-resistant prostate cancer, the role of systemic approaches in the management of patients outside of metastatic castration-resistant prostate cancer remains largely undefined.

During the past decade there has been substantial progress in the treatment of prostate cancer, resulting in the US Food and Drug Administration (FDA) approval of a number of life-prolonging therapeutics for patients with metastatic castration-resistant disease.[1] These accomplishments resulted from our enhanced understanding of the biological mechanisms of androgen receptor (AR) pathway activation, complex tumor microenvironment interaction of bone metastasis, antitumor immunology, and new oncogenic pathways. Taxanes represent the most active class of traditional chemotherapeutic agents for prostate cancer. Docetaxel is the first therapy that demonstrated survival benefit in the pivotal TAX 327 trial[2] and remains the first-line nonhormonal treatment of metastatic castration-resistant prostate cancer (mCRPC). Cabazitaxel is another chemotherapeutic agent that showed survival benefit in patients who were previously treated with docetaxel,[3] and is currently approved for use in the second-line setting. Although great therapeutic advances have been made in mCRPC, the role of systemic approaches in the management of patients outside of mCRPC remains largely undefined.

In the article that accompanies this commentary, Drs. Lam and Flaig provide an excellent review on the role of chemotherapy in various stages of prostate cancer, with special emphasis on metastatic hormone-sensitive prostate cancer (mHSPC).[4] The authors conclude that current data support the use of upfront combined chemotherapy and androgen deprivation therapy (ADT) in properly selected patients with metastatic disease but not nonmetastatic/high-risk disease. The authors provide a thorough discussion of three randomized phase III trials—CHAARTED, STAMPEDE, and GETUG-AFU 15, which evaluated the role of combined ADT/docetaxel in patients with mHSPC.[5-7] A significant prolongation of overall survival in favor of the combined approach was seen in the CHAARTED and STAMPEDE trials, with absolute benefits of 10 months or longer. Interestingly, a significant survival benefit was not observed in the GETUG-AFU 15 study. While the differences in outcomes between these trials remain unexplained, it is likely reflective of differences in patient populations. It is noteworthy that the survival in the ADT-alone control group of the GETUG-AFU 15 study is 54.2 months compared with 44 months on the CHAARTED study and 43 months on the STAMPEDE study, which suggests a difference in the distribution of elements of prognostic significance between the two positive studies and the GETUG-AFU 15 study populations (especially in terms of extent of disease). In addition, GETUG-AFU 15 is a smaller study, hence more follow-up time and number of events may be needed before final conclusions can be drawn.

Although it appears clear, in our opinion, that all patients with newly diagnosed mHSPC should be offered a combined docetaxel/ADT treatment, there are a few questions that remain unclear. Perhaps the most important question is whether all patients, regardless of the extent of disease (high- vs low-volume), should be routinely offered the combined approach. This is particularly important in view of the stage migration affecting virtually all stages of prostate cancer. Most men with newly diagnosed prostate cancer at the present time are asymptomatic and have relatively low clinical disease burden, whereas the proportion of men presenting with higher-volume disease as defined on these studies is relatively small.[8] Evaluation of all mHSPC studies conducted over the past 3 decades indicates that overall survival figures have extended from 2.5 to almost 5 years with virtually the same ADT treatments employed. The main difference is a progressive increase in the proportion of patients with low disease burden in the most recent studies. The CHAARTED trial was initially designed to enroll patients with more than four bone and/or visceral lesions (high-volume disease). To increase enrollment, the study eligibility was later revised to include patients with any metastatic disease not meeting the original inclusion criteria (low-volume disease).[5] A post-hoc subgroup analysis of GETUG-AFU 15 that attempted to retrospectively classify the patients according to the CHAARTED criteria showed no significant difference in survival between high-volume and
low-volume subgroups.[6] It is important to recognize that all extent-of-disease classifications employed in clinical trials conducted over the past 3 decades in mHSPC are primarily prognostic, to a great extent intuitive, and have not been adequately validated in terms of their relationship with treatment outcomes. Furthermore, none of these randomized trials were designed to specifically address the question of high- vs low-volume disease; therefore, specific therapeutic recommendations according to extent of disease cannot be made at this time. We feel the current data are sufficiently strong to allow physicians and patients to make sensible therapeutic choices. It is also important to recognize that other life-prolonging therapies, such as the novel AR-targeted drugs abiraterone and enzalutamide, are currently being evaluated in prospective randomized trials and may become part of the standard approach for patients with mHSPC.

The role of chemotherapy for patients with nonmetastatic relapsed (biochemically) disease and clinically high-risk localized disease remains undefined. Preliminary data on the patients with high-risk localized disease in the STAMPEDE trial showed a significant relapse-free survival (RFS) benefit with the addition of docetaxel, but no overall survival benefit. Similarly, the recently published GETUG 12 trial demonstrated RFS improvement with the addition of docetaxel and estramustine to ADT in patients with high-risk localized disease, but the survival analysis has not yet been reported.[9] Preliminary reports of the Radiation Therapy Oncology Group (RTOG) 0521 study showed that the addition of docetaxel to adjuvant ADT/radiation resulted in an absolute benefit of 4% in 4-year overall survival compared with ADT/radiation alone.[10] However, the survival improvement in this study did not meet its prestated survival criteria; in addition, the study is criticized for its design, which used a one-sided statistical analysis. At this time, there is no definitive data to support the use of chemotherapy in patients with M0 disease.

Historically, clinical trials of biochemically relapsed and locally advanced disease have faced significant challenges. Lack of consensus on study design, patient and treatment selection, lack of validated study endpoints, evolving competitive standard and research approaches, long follow-up time required, and need for substantial research support are among the obstacles that the research community has faced in conducting trials in this paradigm. The results in mHSPC would strongly argue in favor of vigorous exploration of the role of taxane-based chemotherapy outside the metastatic paradigm.

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