Commentary (Oh/Kantoff): The Role of Cytotoxic Chemotherapy in Prostate Cancer

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In this review, we describe how clinical investigators addressed some of the challenges in prostate cancer chemotherapy trials 20 years ago, and we indicate what has evolved in the field since that time. We consider the impact that prostate-specific antigen measurement had in this setting, evolving clinical paradigms, multidisciplinary programs, and the current armamentarium of cancer treatment, including targeted molecular therapy, for patients with hormone-refractory disease.

Chemotherapy for prostate cancer has evolved over the past 20 years, but many daunting challenges remain. In 1985, Dr. Eisenberger and his colleagues published a landmark review of chemotherapy that critically evaluated the accrued experience of this class of agents in prostate cancer and concluded that there was no routine role for cytotoxic chemotherapy in the treatment of advanced prostate cancer.[1] More importantly, however, they created a blueprint for clinical trials that continues to serve as an important guide for moving forward in the 21st century. In the current thoughtful review, Eisenberger and Sinibaldi highlight our significant progress in prostate cancer management over the past 20 years and look into the future. Importantly, they address new issues that have developed as a result of the use of the prostate-specific antigen (PSA) test, which has completely changed the landscape of prostate cancer diagnosis, presentation, natural history, progression and response assessment in the past 2 decades, for better or, perhaps at times, for worse.

Looking Back to Move Forward
While rereading the 1985 review by Eisenberger et al, we were struck by the strength of its underlying principles and how they continue to apply today. Twenty years ago, prostate cancer clinical research methodology was in the midst of a transformation from descriptive phenomenology to well-designed systematic clinical trials.
Remarkably, 17 randomized trials including 1,464 patients with hormone-refractory prostate cancer (HRPC) were analyzed in this review, and yet the overall complete and partial response rate was only 4.5%. Eisenberger et al appropriately suggested that the National Prostate Cancer Project (NPCP) category of stable disease for 12 weeks was not a clear measure of drug efficacy. In analyzing each of these randomized trials for a survival endpoint and placing them all on a single curve, the authors highlighted the dismal prognosis of HRPC, the lack of a clear therapeutic strategy that appeared to improve survival and the need to use an objective endpoint such as survival in measuring drug benefit. Even today, with earlier recognition of HRPC because of PSA use, an emphasis on quality of life with improved supportive care, and a host of new drugs in phase II and III testing, it is important to remember that prostate cancer remains a leading cause of cancer death and suffering in the United States.
Regarding phase II trials, Eisenberger et al made several important points that warrant comment. They suggested that use of objective response rates of greater than 20% could be a useful threshold for testing the efficacy of a new drug. As in 1985, most patients with HRPC today have bone metastases, although approximately 30% to 40% have soft-tissue disease, usually in lymph nodes.[2,3] Measurable responses, though they represent a specific subgroup of HRPC patients, continue to be an important measure of drug activity, and screening of agents in this group using objective response continues to be useful. Unfortunately, most patients do not have measurable disease and, in the past 20 years, we have not established and standardized an objective approach to measuring response to therapy in bone.
Finally, the suggestion was made in this article—well before serum PSA testing became routinely available—that a study design of new agents should include a lead-in period without treatment, followed by randomization to treatment A vs B. If one treatment arm were superior with regard to survival, correlation of survival with a biomarker response (such as normalization of acid phosphatase) would strengthen the argument that a treatment effect was responsible for the
improvement in survival. This proposed study design was certainly ahead of its time, and the value of several of these concepts—lead-in periods in diseases with heterogeneous clinical course, randomized designs, biomarker correlation—have particular relevance today as we consider new agents.

PSA as an Endpoint
PSA has represented both an important advance and a problematic one, as we seek to understand how to interpret declines after therapeutic intervention. Dozens of phase II trials of HRPC patients have used maximum PSA declines of greater than 50% as a primary endpoint for efficacy of chemotherapy and new agents.[4] Recently, however, a phase III trial (TAX 327) demonstrating a survival benefit with docetaxel (Taxotere)-based chemotherapy has not shown that such a decline is a surrogate for survival. On the other hand, the Southwest Oncology Group [SWOG] 9916 trial did demonstrate that a 30% or greater decline in PSA at 3 months was potentially a surrogate for survival.[5]

Despite the value of PSA as a potential marker of antitumor activity in HRPC, there continues to be concern that its utility could be drug-dependent. A recent presentation at the annual meeting of the American Society of Clinical Oncology showed that some patients with HRPC treated with the multitargeted kinase inhibitor sorafenib (Nexavar) had dramatic rises in PSA associated with improvements in radionuclide bone scan.[6] Particularly as newer agents are evaluated either alone or in combination with cytotoxic chemotherapy, relying too heavily on PSA endpoints may lead us to pursue agents of limited value, or perhaps more likely, discard drugs with greater value than is reflected in a decline in PSA after treatment.

Moving forward, we remain dependent on PSA to help us screen new drugs and combinations for efficacy in phase II trials. However, we should combine PSA declines with novel imaging techniques and other pharmacodynamic endpoints, which may enhance detection of antitumor activity. We will also need to consider PSA kinetics to better stratify patients for clinical trials, since it is clear that even in HRPC, rapid PSA doubling time is associated with a more aggressive cancer phenotype and may suggest a different therapeutic susceptibility to certain drugs.[7]

New States of Disease
As nicely outlined by Eisenberger and Sinibaldi, the advent of PSA testing has completely changed the landscape of prostate cancer. In the current era, relapsing patients are diagnosed much earlier because of PSA testing and, as a result, usually undergo salvage hormonal therapy in the absence of metastatic disease. This has created two new major groups of patients for whom optimal management is unknown: those who are hormone-naive with rising PSA levels, and those who are hormone-refractory but nonmetastatic. The hormone-naive, rising-PSA patient has become well characterized in recent years. Some patients in this category will do quite well without therapy, but some will progress rapidly and die of disease within several years. This latter group represents an important focus of clinical research, since we recognize that they are most likely to die of their cancer. Efforts to incorporate effective cytotoxic chemotherapy as well as novel drugs in such populations are ongoing, since hormonal therapy is unlikely to permanently control their disease. Hormone-refractory but nonmetastatic prostate cancer patients also represent an important area for future research, since we expect that this population will only grow in the future. Drugs that may delay progression to bone or other metastatic sites and that have novel mechanisms of action will be particularly suited to treating these patients. However, the heterogeneity in this group and the continued reliance on PSA by patients and clinicians will be an important hurdle to overcome as we design appropriate studies. Randomized trials using progression-free and overall survival are keys to successful drug development in this group.

Finally, neoadjuvant and adjuvant use of cytotoxic chemotherapy and new agents represents the "final frontier" of therapeutic intervention in diagnosed prostate cancer.[8] Short of preventing cancer altogether, the paradigm of treating high-risk patients with chemotherapy after surgery and/or radiation therapy is well established in many solid tumors but not prostate cancer. The logical stepwise development of cytotoxic chemotherapy over the past 20 years suggests that docetaxel—having been shown to produce a survival benefit in HRPC patients—may sustain or enhance that benefit if administered prior to the development of hormone-refractory metastatic disease. Several large randomized trials are evaluating the use of docetaxel or mitoxantrone (Novantrone) given before or after definitive local treatment and hopefully will demonstrate a survival benefit to the early use of chemotherapy in properly selected patients.
Conclusions
The world has changed since Eisenberger et al reviewed the status of cytotoxic chemotherapy 20 years ago. Prostate cancer is now considered a "chemosensitive" disease, and many ongoing phase II and III trials are building on effective chemotherapy by combining this modality with newer agents, using chemotherapy earlier in the course of disease, and finding and developing drugs aimed at novel targets.

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Disclosures:
The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

References:


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