Management of High Risk Metastatic Prostate Cancer: The Case for Novel Therapies

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Purpose: We reviewed the results of preliminary studies of select novel agents for metastatic prostate cancer and discuss the potential benefit of these agents for earlier stage disease, eg biochemically recurrent prostate cancer with high risk features.
Materials and Methods: Available data on select investigational immunotherapies as well as endothelin-A receptor antagonists and survivin inhibitors were obtained and reviewed through PubMed searches, conference proceedings and unpublished proprietary information, when available.
Results: A large number of promising agents are in varying stages of development. Phase III results have been reported for the endothelin-A receptor antagonist atrasentan. Several immunotherapies are currently in phase II/III trials, namely the *GM-CSF* transduced tumor cell vaccine GVAX®, the prostatic acid phosphatase loaded dendritic cell vaccine Provenge® and the prostate specific antigen expressing poxvirus vaccine PROSTVAC®-VF. Another immunotherapy, the prostate specific membrane antigen immunoconjugate MLN2704 (Millennium Pharmaceuticals, Cambridge, Massachusetts), is in phase I/II study. The first clinical inhibitors of survivin are in early phase I studies. Several of these agents, including atrasentan, have shown statistically significant but modest effects in the advanced disease setting in which they have been studied.
Conclusions: Clinical trial design with these novel therapies presents particular challenges since most of these agents may induce disease stabilization rather than disease regression. There is a risk of false-negative results and failure to recognize a potentially efficacious agent if these cytostatic agents are studied only in men with advanced, heavily pretreated disease in whom life expectancy is measured in months. We advocate the early referral and enrollment of men with high risk prostate cancer in clinical trials.

Key Words: prostate, prostatic neoplasms, antineoplastic protocols, immunotherapy, drug therapy

Until recently chemotherapy did not have a major role in the management of metastatic prostate cancer. Reports of mitoxantrone and prednisone inducing responses in advanced prostate cancer but not altering survival began to be published in the late 1990s.[1,2] In 2004, 2 large, randomized trials demonstrated a survival advantage for docetaxel based chemotherapy over that of mitoxantrone/prednisone.[3,4] By demonstrating a survival benefit for chemotherapy for advanced hormone refractory disease these trials changed prostate cancer management. More recently 2 large, randomized trials designed to examine the role of earlier systemic therapy at biochemical relapse, that is Radiation Therapy Oncology Group 0014 and Eastern Cooperative Oncology Group 1899, closed due to failure to accrue. However, it is clear that many clinicians are in fact extrapolating the results of the 2 chemotherapy trials to treatment for less advanced disease, beginning docetaxel based chemotherapy at biochemical progression. While this may be a rational treatment decision for the individual patient and physician, it creates obstacles for investigating new treatment strategies, including novel therapies that may offer benefit earlier in the disease course.

A clinical vignette of a patient referred for clinical trial participation illustrates why timely referral and enrollment into early clinical trials of investigational agents may be important for these patients and for research. A 67-year-old patient on androgen ablation therapy was found to have increasing serum PSA and evidence of bone metastases. After an initial response to 6 courses of docetaxel PSA again began to increase. Carboplatin was then added to docetaxel for an additional 6 courses with at best stable PSA, followed by a progressive PSA increase. At the point that he was referred for clinical trial participation this patient had grade 2/3 sensory neuropathy and an Eastern Cooperative Oncology Group performance status of 3. Because he was ineligible for any study, an opportunity to participate in a clinical study was lost and benefit to the patient as well as to clinical science was also lost. Although the specific choice of carboplatin was unusual in this case and it added toxicity without proven benefit, treating clinicians frequently add agents to docetaxel or paclitaxel, such as platinum agents or estramustine, before offering the patient the option of clinical trial participation.

Such heavily pretreated patients are generally not eligible for the Intergroup trials now underway even when their performance status has not been impaired by multiple chemotherapy courses. Important trials currently open and ac-

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cruing slowly include the Cancer and Leukemia Group B 90203 study of neoadjuvant docetaxel before prostatectomy in patients at high risk and the Southwest Oncology Group 9921 phase III study of adjuvant chemotherapy for high risk prostate cancer. While these and other studies ask crucial questions about the value of early systemic therapy, some of the best contenders for future therapy for high risk metastatic disease may be the novel agents that are now showing promise in phase I to III trials for androgen independent prostate cancer. These agents generally are not cytotoxic and they have been borne out in studies of molecular targets identified in experimental and histopathological evaluation of prostate cancer carcinogenesis and progression, making early intervention studies rational and worthy of rapid accrual.

A number of promising new agents targeting tumor growth pathways are now in various stages of development for treating prostate cancer. They include the epothilone B analogue BMS-247550, the PSMA antibody MDX-070, the PSMA immunoconjugate MLN2704, the oral platinum satraplatin, the vitamin D analogue DN101, the oral mammalian target of rapamycin inhibitor AP23573, survivin inhibitors and a large array of angiogenesis inhibitors. There has also been a high level of research activity in immunotherapies for prostate cancer, taking advantage of the fact that antigens specific to the prostate gland can be targeted with relative safety following localized therapy to ablate the prostate.

GM-CSF TUMOR CELL VACCINE

Background and Mechanism of Action

GM-CSF is secreted endogenously in response to immune and inflammatory stimuli. It is a growth and activation factor for neutrophils, monocytes, eosinophils and dendritic cells. As a vaccine component, it serves to recruit dendritic cells to the vaccine site. The *GM-CSF* transduced tumor cell vaccine GVAX® has been tested for hormone refractory prostate cancer. This cellular vaccine is generated from the 2 allogeneic cell lines LNCaP and PC-3, which have been genetically modified to secrete GM-CSF and then irradiated to prevent further cell division.[5,6]

Clinical Trials

G-9803. This phase II trial enrolled 96 patients with metastatic prostate cancer, including 55 with hormone refractory disease and 41 who were hormone naive. The most common adverse event was injection site reaction. By the criteria of the National Cancer Institute Consensus PSA Panel 1 hormone naïve patient had a partial PSA response and 1 with metastatic hormone refractory prostate cancer had a complete response, including PSA normalization and lesion regression on bone scan. In hormone refractory patients with metastatic bone disease at baseline there was a trend toward longer median time to disease progression, as measured by bone scan in those who received the higher dose of vaccine compared to comparable patients who received the lower dose (140 vs 85 days, $p = 0.095$).[7]

G-0010. In this phase II study 80 patients with metastatic hormone refractory prostate cancer were treated for 24 weeks in a dose escalation trial. Vaccine specific antigenic protein antibodies were measured by Western blot of vaccine lysates against patient serum collected at baseline, and weeks 12 and 24. Type I carboxyterminal telopeptide, a biological marker useful for monitoring osteoclast activity in metastatic prostate cancer, was assayed at the same time points. PSA was collected at each treatment visit. Overall 80 patients enrolled, completed treatment and were followed a median of 5.4 months with no dose limiting toxicities observed. In the high dose group 6 of 19 patients (32%) showed PSA decreases following repeat vaccinations. In addition, stable or decreasing type I carboxyterminal telopeptide levels occurred in 34 of the 55 patients (62%) tested, including those in all dose groups.[8,9]

VITAL-1. The first phase III study of GVAX®, VITAL-1, which was initiated in July 2004, is enrolling chemotherapy naïve, asymptomatic patients. It is comparing the vaccine to docetaxel chemotherapy plus prednisone. The trial is expected to enroll 600 patients and it is designed to monitor survival duration in the vaccine treatment arm. More than 70 clinical trial sites in the United States are now open and patient accrual is ongoing.

VITAL-2. The second phase III trial, which is now under way, is enrolling symptomatic patients with cancer related pain. It is comparing the vaccine plus docetaxel/prednisone to chemotherapy alone. This trial is also designed to monitor survival duration in the vaccine plus docetaxel treatment arm.

SIPULEUCEL-T

Background and Mechanism of Action

Sipuleucel-T (Provenge®) is an immunotherapy cellular product consisting of autologous peripheral blood mononuclear cells, including antigen presenting cells, that have been cultured in vitro with a recombinant fusion protein composed of prostatic acid phosphatase and GM-CSF.[10]

Clinical Trials

P-16. This phase II study of sipuleucel-T with bevacizumab enrolled 22 patients with androgen dependent prostate cancer.[11] Sipuleucel-T was given intravenously on weeks 0, 2 and 4. Patients received 10 mg/kg bevacizumab intravenously immediately following sipuleucel-T, which was continued every 2 weeks thereafter until disease progression or toxicity was observed. Disease progression was defined as a doubling of baseline or nadir PSA, or the development of metastases. PSA measurements were recorded and PSADT was calculated. Median pretreatment PSADT in the 21 evaluable patients was 6.7 months and median PSADT on treatment was 12.7 months, representing an approximate 90% increase in PSADT ($p = 0.004$). Eight patients showed at least a 200% increase (range 212% to 758%) in PSADT while on study compared with their pretreatment rate of change. In addition, 41% of patients showed a decrease in absolute PSA from baseline (range 6% to 72%). No patient on study had objective disease progression. Four patients were removed from study due to toxicity.

D9901. This randomized, phase III trial enrolled 127 patients with asymptomatic androgen independent prostate cancer.[12,13] On intent to treat analysis median overall survival was 25.9 months in patients randomized to sipuleu-