The Case for Early Chemotherapy for the Treatment of Metastatic Disease

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Purpose: Several important questions are raised by the data from Southwest Oncology Group 99-16 and TAX 327. What is the optimal timing of chemotherapy for metastatic hormone refractory prostate cancer? Should asymptomatic patients be treated? Is there a theoretical survival advantage for treatment for hormone sensitive prostate cancer? We reviewed arguments for the early use of docetaxel in the hormone sensitive and hormone naïve disease states.

Materials and Methods: Androgen independent prostate cancer was traditionally viewed as a chemoresistant disease. At best palliation of bone pain but not improved survival could be achieved with the combination of mitoxantrone and prednisone. Median survival rates for chemotherapy in this disease state were reported to be between 10 and 12 months. Phase II studies administering docetaxel weekly or every 3 weeks as a single agent or in combination with estramustine demonstrated median survival rates of 14 to 23 months, which appeared to be an improvement over standard therapy. Consequently the 2 randomized trials, Southwest Oncology Group 99-16 and TAX 327, were designed to confirm the preliminary observations of improved survival with docetaxel based therapy.

Results: TAX 327 and Southwest Oncology Group 99-16 treated asymptomatic as well as symptomatic patients. Thus, in contrast with mitoxantrone/prednisone, which was approved in symptomatic men with hormone refractory prostate cancer, the exact timing of the initiation of chemotherapy in docetaxel treated patients is still the subject of debate.

Conclusions: Studies should be performed to investigate the optimal timing of chemotherapy as well as sequencing with androgen ablation in patients at high risk for progression and death from metastatic prostate cancer. Prognostic factors for death that have been identified in patients with androgen independent prostate cancer are hemoglobin, alkaline phosphatase, visceral disease and performance status.

Key Words: prostate, prostatic cancer, neoplasm metastasis, docetaxel, drug therapy

Approximately 70% to 80% of men who undergo androgen ablative therapy for metastatic prostate cancer respond rapidly, as demonstrated by a decrease in prostate cancer related symptoms and decreases in serum PSA. Unfortunately androgen ablation for metastatic prostate cancer rarely results in long-term survival and, thus, it is palliative with a median response duration of between 18 and 24 months. Although the merits of combined androgen blockade vs medical castration with luteinizing hormone-releasing hormone agonists or bilateral orchiectomy continue to be debated,[1] further refinement of hormonal blockade will probably not result in significant survival gains. Eventually after approximately 18 to 24 months of androgen blockade most patients progress to HRPC. Historically the duration of survival in the hormone refractory state is between 10 and 12 months.

Treatment in patients with hormone refractory disease has been problematic. Secondary hormonal therapies produce PSA decreases but to our knowledge they have never been demonstrated to improve survival. Prednisone alone has been demonstrated to provide palliation in patients with HRPC.[2] Chemotherapy had been viewed as toxic and ineffective. Previously the recommended therapy for this androgen independent state has been a combination of mitoxantrone and low dose prednisone.[3,4] This combination therapy improved bone pain symptoms but it did not prolong survival compared to prednisone alone.

More recently 2 trials in more than 1,700 patients demonstrated a significant survival benefit for the combination of docetaxel and prednisone.[5,6] Median survival with every 3 week dosing of docetaxel was 17.5 months in the SWOG 99-16 trial and 18.9 months in the TAX 327 trial compared with 15.6 and 16.5 months in the mitoxantrone groups ($p = 0.02$ and 0.009, respectively). In the 2 studies significantly higher rates of PSA decrease were observed in docetaxel treated than in mitoxantrone treated patients. However, this PSA decrease did not fully account for the survival benefit in the docetaxel groups. These studies were the first demonstrating survival benefit in HRPC and treatment with docetaxel has supplanted mitoxantrone as the standard of care for initial treatment in patients with HRPC.

Several important questions are raised by the data from SWOG 99-16 and TAX 327. What is the optimal timing of chemotherapy in metastatic HRPC? Should asymptomatic patients be treated? Is there a theoretical survival advantage for treatment in hormone sensitive prostate cancer? We

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† Financial interest and/or other relationship with Aventis, Novartis, Abbott, GPL Biotech, Cell Genysis, Celgri and Centrion.

DOI:10.1016/j.juro.2006.06.077

reviewed the arguments for the early use of docetaxel in the hormone sensitive and hormone naïve states of disease.

THE CASE FOR EARLIER CHEMOTHERAPY FOR ANDROGEN SENSITIVE PROSTATE CANCER

Hormone refractory clones may be present in the initial population of prostate cancer cells before castration and this population could be enriched through clonal selection after androgen blockade. Alternatively hormone resistant cells could develop through aberrant activation of the androgen receptor by other signal transduction pathways. Preclinical models support the use of early chemotherapy to eliminate androgen independent clones, leaving only clones sensitive to androgen blockade. Some preclinical models suggest that, while androgen blockade is effective treatment for androgen sensitive prostate cancer, there may be a subset of androgen resistant cells that emerges within days following castration. Apoptosis in prostate cancer cell lines is regulated by the ratio of the pro-apoptotic protein bax to the anti-apoptotic protein bcl-2. A high bax-to-bcl-2 ratio promotes the formation of pro-apoptotic bax/bax homodimers.[7] Lower bax-to-bcl-2 ratios favor bcl-2/bcl-2 homodimerization and bax/bcl-2 heterodimerization with the 2 complexes inhibiting apoptosis.[7] Initially following rat castration the bax-to-bcl-2 ratio in the rat prostate is increased.[8] However, within the next few days the bax-to-bcl-2 ratio decreases precipitously, indicating that bcl-2 expressing cells may be selected for by castration. Early treatment with chemotherapy may eliminate this androgen independent clonal population earlier, allowing a potentially improved therapeutic effect of androgen therapy.

Determining the optimal sequencing of chemotherapy and hormonal therapy for prostate cancer is made crucial by the observation that there appears to be antagonism between chemotherapy and hormonal therapy for breast cancer. Contradictory evidence for the optimal sequencing of chemotherapy and hormonal therapy for prostate cancer has been found in preclinical trials. Eigl et al noted that mice with Shionogi or LNCaP xenografts that were given concomitant therapy with paclitaxel and castration demonstrated significant improvement in median time to disease progression compared to mice receiving sequential therapy.[9] However, mice initially treated with paclitaxel showed an attenuated response to castration following chemotherapy. A study by Tang et al evaluated different sequences of docetaxel and androgen ablation in severe combined immunodeficient mice inoculated with the LNCaP prostate cell line.[10] Tumor volume was at least 50% smaller in all docetaxel groups compared to castration alone. The smallest tumors at week 4 and the greatest growth delay were found in mice treated with docetaxel for 2 weeks, followed by castration. Apoptosis assays also indicated a greater degree of apoptosis in the docetaxel followed by castration group. As in other studies, the bax-to-bcl-2 ratio decreased following castration. However, the bax-to-bcl-2 ratio remained increased following docetaxel, indicating increased apoptosis.

There is clinical evidence to support an evaluation of these sequences. Neoadjuvant chemotherapy using docetaxel without androgen blockade can result in a PSA decrease of greater than 50%. The small study by Hussain et al in 39 men suggested that treatment with docetaxel followed by androgen blockade may improve the outcome, as demonstrated by the PSA response.[11] Patients received premedication with 8 mg dexamethasone, followed by 70 mg/m^2 docetaxel every 3 weeks for up to 6 cycles. They then received 30 mg leuprolide acetate intramuscularly or 10.8 mg goserelin acetate subcutaneously 3 weeks after the last docetaxel administration. A PSA decrease of 50% or greater was seen in 48.5% of those who received docetaxel. This rate of PSA response was similar to that seen in HRPC.[5,6] They also found that 20% of their patients demonstrated a 75% or greater decrease in serum PSA. None of the patients had a change in testosterone despite premedication with dexamethasone. Furthermore, these cancers retained their responsiveness to androgen therapy, as demonstrated by a decrease in PSA following total androgen suppression. Median PSA following 4 months of total androgen suppression decreased from 5.7 ng/ml after docetaxel to 0.1 ng/ml after total androgen suppression. Interestingly the men with a shortened PSA doubling time before study entry actually had more prolonged disease control following docetaxel and androgen suppression compared with that in the longer doubling time group (3.5 vs 6.6 months), suggesting that a subset of patients at high risk may demonstrate an enhanced benefit from early chemotherapy.

Several clinical trials could be designed based on these clinical and preclinical observations. To potentially prevent the emergence of bcl-2 enriched clones, chemotherapy could be administered in patients with metastatic disease before androgen blockade. An appropriate point for starting androgen blockade would need to be selected. This could be at a predefined number of cycles or at PSA nadir. Conversely PSA nadir following androgen blockade may be used as a trigger point for early chemotherapy since this may select patients at high risk for metastatic disease for aggressive treatment. It has been demonstrated that patients in whom PSA does not normalize after androgen blockade have poorer overall survival. On the other hand, chemotherapy could be administered at the time of androgen blockade in patients at high risk. One must keep in mind that accrual in these types of trials may be difficult due to the decreasing number of patients who have metastatic disease and have not undergone previous androgen blockade.

THE CASE FOR EARLY CHEMOTHERAPY FOR HRPC

In contrast to the androgen dependent state, there are sparse preclinical data to support the use of chemotherapy early in the course of metastatic HRPC. There is also a dearth of randomized data supporting the use of early chemotherapy for HRPC. Thus, the proper timing of chemotherapeutic treatment in the course of hormone refractory metastatic disease is unclear. Decision points for beginning cytotoxic therapy for HRPC are 1) the first PSA increase, 2) changes on imaging, such as abdominal and pelvic computerized tomography, and bone scans, and 3) symptoms of bone pain.

Studies evaluating the combination of mitoxantrone with a corticosteroid led to its approval for use in symptomatic patients with HRPC. Tannock et al randomized 161 patients with symptomatic HRPC to mitoxantrone with prednisone or prednisone alone.[4] As indicated by a 2-point decrease in pain on the McGill-Melzack pain questionnaire, palliation was achieved in 29% of patients with mitoxantrone and prednisone but only in 12% of those with prednisone