

Systemic Therapy for Prostate Cancer

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Systemic therapy plays an important role in the management of prostate cancer. Since the pioneering work of Dr. Charles Huggins in the 1930s, medical science has known that prostate cancer cells were, to some extent, dependent on the presence of androgens (steroid hormones) for their growth and survival.¹ Hormonal therapy, with various forms of androgen manipulation and androgen receptor interaction, has been the primary form of systemic therapy for prostate cancer since that time. In recent years, a role has been proven for systemic chemotherapy as well. Clinical research trials are now investigating the role of new biologic agents and immunotherapy. This commentary will review the current status of the systemic therapy for prostate cancer.

Hormonal Therapy: General Principles

The androgen receptor is the primary driver of cell growth for prostate cancer.² Stimulation of the androgen receptor can be reduced by depletion of circulating androgens, blocking the binding of androgens to the androgen receptor, or a combination of the two methods.

Depletion of androgens can be accomplished directly by bilateral orchiectomy (castration) or indirectly by administration of estrogens or luteinizing hormone releasing hormone (LHRH) analogues.³ Both of these classes of drugs exert their effect indirectly via reduction of the production of luteinizing hormone by the pituitary, with subsequent loss of luteinizing hormone signal to the testicles to produce testosterone. Both classes of drugs are capable of reducing serum testosterone levels to levels equivalent to orchiectomy.

Blocking the binding of androgens to the androgen receptor can be accomplished with anti-androgens. Anti-androgens accomplish inhibition of prostate cancer cell growth by competitive binding to the androgen receptor versus androgens.

Anti-androgens administered to a patient with functional testes do not decrease testosterone levels, but actually cause some increase.

A third means of manipulation of the androgen and androgen receptor interaction could have a role in the management of prostate cancer, but has not been well studied. Medications approved only for the treatment of benign prostatic hypertrophy, such as 5-alpha reductase inhibitors, block the conversion of testosterone to dihydrotestosterone (DHT).³ DHT binds more strongly to the androgen receptor than testosterone, and theoretically, blocking the conversion of testosterone to DHT could diminish prostate cancer cell growth.

Roles of Hormonal Therapy

Hormonal therapy has been used to treat various states of prostate cancer, including metastatic disease, disease manifest only by a rising prostate-specific antigen (PSA) after primary therapy, as adjuvant therapy^a post primary therapy, as neoadjuvant therapy^b prior to and/or with primary therapy, and as a primary therapy for localized disease.

Metastatic Disease

The role of hormonal therapy in metastatic disease is well accepted as first-line therapy. All of the three methods of testosterone depletion, (e.g., orchiectomy estrogens, or LHRH analogues) are equally effective.³ LHRH analogues, although expensive, are the primary therapy used in most patients. Many patients prefer injections to orchiectomy, and estrogens can be associated with significant thrombo-embolic cardiovascular risk. Between 70-90% of patients will respond initially with a decrease in PSA and clinical improvement in symptoms. Median duration of response to this therapy is about 18

a Adjuvant therapy is treatment, such as chemotherapy, radiation therapy or hormone therapy, given to a patient after the primary treatment to increase the chances for a cure.

b Neoadjuvant therapies are similar to adjuvant therapies except they are given prior to the primary treatment.

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months. There is controversy over whether treatment should begin when metastatic disease is diagnosed or only at the onset of symptoms. A review of the randomized clinical trials suggests that there is a benefit with higher rates of one- and five-year disease-free progression and ten-year survival among those who receive immediate versus deferred therapy.⁴

Anti-androgens in standard doses as monotherapy have been demonstrated to be inferior to testosterone depletion.⁵ Their use as single agents in general should be restricted to patients who refuse testosterone depletion because of concern over loss of sexual function.

Combined androgen blockade (CAB), the addition of anti-androgen to testosterone depletion, is also controversial. Randomized trials have produced mixed results. Three meta-analyses of the data have all suggested a small improvement in five-year survival as opposed to simple testosterone depletion

intermittent therapy is to have periods of time away from the side effects (hot flashes, fatigue, etc.) and toxicities (deterioration of bone density, loss of muscle mass, etc.) of testosterone depletion, but also there is speculation that the onset of hormone refractory prostate cancer could be delayed.¹³ This method is not yet supported by data from a large randomized clinical trial, but is attractive to many patients and physicians.

Adjuvant Hormone Therapy

There are minimal data on the use of hormone therapy after prostatectomy. In a trial reported by the Eastern Cooperative Oncology Group (ECOG), men who were discovered to have positive lymph nodes when their pathology was reviewed after surgery were given continuous LHRH analogue therapy either immediately post surgery or at the time of recurrence.¹⁴ At ten years there was a dramatic survival benefit (72% versus 49%) for those men who received immediate versus deferred treatment, respectively. This trial has been criticized because there were only 98 men accrued. However, the data are so compelling that one would be hard pressed not to recommend immediate adjuvant hormonal therapy to all men who have positive nodes at the time of prostatectomy.

Neoadjuvant Hormonal Therapy

Neoadjuvant hormonal therapy has been tested in clinical trials prior to surgery and also prior to (as well as concurrent to and after) primary radiation therapy. The neoadjuvant surgical studies have consistently failed to demonstrate any disease-free or overall sur-

vival benefit for neoadjuvant hormonal therapy given for anywhere from three-to-eight months pre-surgery.

On the other hand, several large clinical trials have shown a disease-free and, in some, a survival benefit for hormonal therapy administered prior to and continued concurrent with radiation therapy for patients with high-risk prostate cancer. Three of these important trials include RTOG 86-10, the Bolla study from EORTC, and the D'Amico trial.^{15,16,17} There are preclinical data to suggest that androgen depletion does make prostate cancer cells more sensitive to radiation, and this phenomenon could explain why neoadjuvant hormonal therapy is beneficial with radiation and not surgery.¹⁸

Hormonal Therapy as Primary Therapy

Some physicians advocate hormonal therapy as primary therapy for prostate cancer.¹⁹ There are no data to suggest that primary hormonal therapy can be done with curative intent. For that reason, the use of primary hormonal therapy should probably be reserved for those who need treatment, but are unwilling or unable due to co-morbidities or age to pursue a curative primary treatment, such as surgery or radiation.

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with orchiectomy or LHRH analogues.^{6,7,8,9} There are some minor side effects with anti-androgens (e.g., diarrhea, gynecomastia, etc.), but the biggest objection to the addition of anti-androgens is the significant monetary cost of these drugs as compared to marginal survival benefit. It should be determined by each patient and his physician whether the potential benefit of CAB is worth the cost.

PSA Recurrence as the Only Sign of Disease

It has become common clinical practice in the PSA era to treat patients who have a PSA level that begins to rise but have no evidence of metastases, at some point after primary surgery or radiation therapy. The rationale is to prevent or delay the onset of overt metastatic disease. Not all patients who have a PSA recurrence die of prostate cancer. Recent studies have demonstrated that several factors, including time to PSA recurrence, Gleason score at diagnosis, and PSA doubling time, are all important in determining a patient's risk of dying of prostate cancer when he does have a rising PSA.^{10,11,12}

There has also been a trend toward the use of intermittent hormonal therapy in patients with a rising PSA. The rationale for

Hormonal Resistance

As noted previously, the median duration of response to hormonal therapy in patients with metastatic prostate cancer is about 18 months. Virtually all patients develop disease that progresses in spite of this first-line hormonal treatment. This condition has variably been termed androgen-independent prostate cancer or hormone-refractory prostate cancer (HRprostate cancer). Regardless of the terminology, there is evidence to suggest that the androgen receptor is still the predominant driver of prostate cancer cell growth, even in this state of the disease.²⁰ Therefore, LHRH analogues are usually continued.

Secondary hormonal manipulations may be effective in some patients with HRprostate cancer, with reported response rates of 20-60%.²¹ These secondary therapies include the addition of anti-androgen, anti-androgen withdrawal, estrogens, corticosteroids, and suppression of adrenal androgen production with drugs like ketoconazole. There are no clinical trials to suggest a survival benefit from any of these second-line therapies, but in general, they are not especially toxic and are, therefore, useful in selected patients.

Systemic Cytotoxic Chemotherapy

As in other metastatic cancers, clinical trials using chemotherapeutic agents have been undertaken in an attempt to find effective therapy for HRprostate cancer. Early trials were limited by the lack of conspicuously effective agents and the lack of significant numbers of patients with measurable disease. After the discovery of PSA, declines in this serum protein could be used as a marker of disease response to therapy in phase II trials. The PSA Working Group recommended a sustained decline in PSA of 50% or more from baseline as an indicator of response in phase II trials.²²

In the 1990s, two phase III trials compared mitoxantrone and a corticosteroid to the steroid alone in patients with HRprostate cancer.^{23,24} Both of these trials showed a significant benefit in terms of palliation of pain, although there was no survival benefit. Based on this palliative benefit, the combination of mitoxantrone and prednisone was the first chemotherapy regimen to be approved by the Food and Drug Administration (FDA) for the treatment of HRprostate cancer.

The results of these trials led to renewed interest in the use of chemotherapy in HRprostate cancer and a more rigorous preclinical and clinical search for new active agents. Drugs that affected intracellular microtubules, including vinca alkaloids, taxanes, and the combination of either of these classes with estramustine, had enough activity to generate a large number of phase II trials. Docetaxel was the most active of these agents.

The documentation of 50% PSA decline rates in 30-65% of the phase II trials with docetaxel led to the initiation of two large phase III trials using docetaxel in combination with another agent versus the then standard mitoxantrone and prednisone.^{25,26} Both of these trials, SWOG 9916 and TAX 327, demonstrated an improvement in overall survival for docetaxel given every three weeks in combination (with estramustine or prednisone,

respectively) versus mitoxantrone and prednisone. In addition, patients on docetaxel did better in terms of pain relief and quality of life than those receiving mitoxantrone. These were truly historic studies, which were the first phase III trials to demonstrate that chemotherapy can prolong survival in patients with HRprostate cancer (hazard ratios 0.80 and 0.76). There were increased adverse thromboembolic events in the SWOG 9916 trial, which used estramustine with docetaxel. For that reason, docetaxel every three weeks with daily oral prednisone is now FDA-approved and the standard of care for chemotherapy in HRprostate cancer.

The Next Steps

Now that we have a regimen that can prolong survival in HRprostate cancer, the next steps will be to improve on the first-line therapy of docetaxel and prednisone, develop new agents or regimens for patients who have progressed on docetaxel, explore the role of chemotherapy in the earlier states of prostate cancer, and develop effective biologic and immunotherapy for prostate cancer.

Agents that have been combined with docetaxel include carboplatin;²⁷ high-dose calcitriol;²⁸ thalidomide;²⁹ various small molecule growth factor tyrosine-kinase inhibitors, such as gefitinib and imatinib;^{30,31} large molecule antibody-to-cell-surface receptors, such as vascular endothelial growth factor;³² the endolthelin A receptor antagonist atrasentan;³³ proteasome inhibitors, such as bortezomib;³⁴ and even vaccines for prostate cancer.³⁵

Currently no agents are approved for second-line treatment of HRprostate cancer after failure of initial chemotherapy. A phase III trial of the oral agent satraplatin has recently been completed, and the results are awaited with anticipation.³⁶

Systemic chemotherapy, which is effective in an advanced cancer, is often more effective in early states of disease. Two large clinical trials of chemotherapy in combination with androgen depletion in earlier states of prostate cancer are underway as adjuvant therapy post-prostatectomy in patients with high risk for recurrence. An Intergroup United States trial is comparing mitoxantrone and hormone therapy to hormonal adjuvant therapy alone. A large international pharmaceutical company-sponsored trial will test the addition of docetaxel to hormonal therapy in the adjuvant setting. In addition neoadjuvant chemotherapy with docetaxel will be tested in combination with hormonal therapy prior to and concurrent with radiation in patients with high-risk disease. The results of these trials will determine the effectiveness of these chemotherapy strategies in early stage prostate cancer.

Finally, as we learn more about the cancer genome and the immune system, new biologic agents that can be directed at specific targets and new ways to stimulate the host immune system to recognize and destroy prostate cancer cells are being developed and nearing routine use in patients. The progress being made should greatly enhance our ability to alter the course of prostate cancer with systemic therapy. **NCMedJ**

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