Management of Advanced/Metastatic Prostate Cancer: 2000 Update

Over the past several years, the clinical presentation of prostate cancer has evolved so that more patients than ever before are presenting with clinically localized disease. However, a significant number of men continue to present with advanced disease, which often includes metastatic disease to the bone.

Drs. Hussain and Dawson provide a scholarly review of the management of advanced and hormone-refractory prostate cancer. Their review focuses on the new rather than the old, providing us with an in-depth discussion of the molecular biology of the disease and describing some promising discoveries.

Hormonal therapy, as currently administered, produces a dramatic response followed by a disappointing progression. Can we alter the grim prognosis of advanced prostate cancer by using novel agents, by delivering hormonal therapy earlier in the course of the disease, or by using innovative means such as intermittent therapy? Most likely we will, but not imminently. Meanwhile we need to ask, what is the status of management for advanced prostate cancer, and what do we know about current treatments?

Biochemical Failure

The two major challenges faced by clinicians treating patients with prostate cancer are biochemical failure and refractory disease. Widespread screening has markedly reduced the number of newly diagnosed cases of advanced prostate cancer. We are now treating more patients with "curable" lesions. In fact, nearly two-thirds of all newly diagnosed patients undergo either radiation or surgery. Unfortunately, a significant percentage of these patients will fail, as manifested by a rising prostate-specific antigen (PSA) level. This stage (which I call D1.5) is the most common presentation of advanced prostate cancer,[1] and it represents a unique opportunity in human oncology in that the patient has minimal tumor burden and there is a marker—PSA—to ascertain progression and response. Opinions on how best to treat these patients vary. Options include local radiation for prostatectomy failures, salvage prostatectomy for radiation failures, cryotherapy, observation, and various types of hormonal therapy.

Most clinicians agree that once the PSA begins rising, if the patient has a reasonable life expectancy, death from prostate cancer is inevitable. What usually occurs is that the patient is offered one of the above-described treatments and then eventually fails with a second rising PSA. This then presents a second challenge to the clinician, or what I describe as D2.5—a rising PSA in the face of hormonal therapy. The patient may have a negative bone scan and manifest no symptoms, yet he has progressive hormone-refractory disease.

Therefore, the treatment challenges facing clinicians in this disease are biochemical failure after a local therapy and biochemical failure after hormonal therapy in asymptomatic patients. The authors describe many promising methods to deal with these situations. I believe future treatment will combine agents that interfere with signal transduction, angiogenesis, receptor binding, and cell migration. Progress is being made in the development of antisense therapy, promoters of apoptosis, and various types of gene therapy.

Exisulind Therapy

Most clinical trials are focusing on single-agent approaches rather than combinations of the above, despite the fact that testis cancer, for example, cannot be cured with single-agent platinum therapy. One monotherapeutic agent being investigated in clinical trials is exisulind (Aptosyn), a selective apoptotic antineoplastic drug. It has been found to be beneficial in patients with adenomatous polyposis coli (APC), a genetic syndrome associated with familial adenomatous polyposis (FAP) and Gardner's syndrome. Exisulind impedes progression of the disease by chemoprevention of new polyps and regression of existing polyps. It is also effective in inducing apoptosis in prostate cancer.
A recent multicenter study confirmed the promise of this agent in decreasing and retarding rises in PSA after biochemical failure. Although exisulind delays the need for hormonal therapy, the ability to delay progression does not qualify the agent for approval by the Food and Drug Administration. First, it must demonstrate a survival benefit, and that could be a decade away. Studies now being developed will combine this drug with other agents, including traditional forms of chemotherapy, to see if a benefit ensues.

While most patients with hormone-refractory disease live only 9 to 13 months, patients with biochemical failure may live 10 to 13 years. Therefore, an agent like exisulind may prolong survival, but it will be decades before we can confirm that it actually does so. Considering the current climate for drug approval, it will be many years before we see some of the agents that the authors discuss available for clinical use, unless activity is present in advanced refractory disease or untreated metastatic disease. In this reviewer’s opinion, the promise of many of the agents described will not be in advanced refractory disease but rather in the treatment of patients with a lesser tumor burden and a rising PSA after failed local therapy.

**Hormonal Therapy**

Thus, the real threat of prostate cancer is biochemical failure (D1.5) and its natural progression to the hormone-refractory state (D2.5). We know that hormonal therapy can produce dramatic but short-lived responses in metastatic hormonally sensitive disease. Chemotherapy has also demonstrated the ability to induce significant responses in refractory disease.

However, is there any evidence that aggressive intervention such as hormonal therapy, with or without chemotherapy, can improve the outcome of patients with biochemical failure? The honest answer is no, although in certain stages of disease with a similar tumor burden, it has had some impact. The germane question then becomes, can we obtain any meaningful information from current trials that will aid in deciding how to treat biochemical failure? Moreover, can hormonal therapy not only prolong time to progression but also extend life?

If we analyze stage D2 (metastatic) disease, two studies suggest that early therapy does indeed prolong life. These are the Veterans Administration studies and the recently completed Medical Research Council (MRC) study.[2,3] In men with locally advanced and metastatic disease, 1 mg of diethylstilbestrol was slightly superior to a toxic dose of 5 mg, an ineffective dose of 0.2 mg, or a placebo. The MRC study revealed a survival advantage to early therapy in asymptomatic patients with locally advanced disease.

**Early vs Delayed Therapy**

What do we know about the treatment of lymph node-positive disease? A recently reported intergroup trial in men with node-positive prostate cancer demonstrated a marked improvement in survival with immediate vs delayed hormonal therapy.[4] In addition, Bolla and colleagues have provided documentation that the combination of hormonal therapy and radiation therapy is superior to radiation alone in the management of T3 prostate cancer.[5]

The above trials all support a survival advantage when hormonal therapy is administered early. The advantage, however, is more pronounced in patients with a lesser tumor burden. Therefore, it would seem that hormonal therapy administered to patients with a rising PSA after failed local therapy would provide the same benefit. The questions to be answered include: How long and with what agents? Would intermittent therapy result in a survival benefit? Should chemotherapy be considered in conjunction with hormonal therapy?

**Conclusions**

Many questions about advanced and hormone-refractory prostate cancer remain unanswered. Where clinical trials are available, patients should be encouraged to participate. Until the answers become apparent, I believe that hormonal therapy, with or without chemotherapy, should be offered to most patients with biochemical failure. Predicated on the exciting activity of newer forms of chemotherapy on hormone-refractory prostate cancer, I believe that patients with stage D2.5 disease should be offered these therapies. Again, the authors are to be congratulated for an informative review of a complex disease state.

**References:**


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