Advances in Oncology
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Current Developments in the Management of Solid Tumor Malignancies

Current Management of Hormone-Refractory Prostate Cancer

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How does a tumor become hormone-refractory?

Both clinical and laboratory studies show that there are cells in the tumor at the time of diagnosis that resist and survive the androgen ablative therapies that are used to treat prostate cancer. The term "hormone refractory" has been used to describe tumors that, over time, adapt to a castrate environment and learn how to grow despite low levels of testosterone in the blood. My opinion is that classifying a tumor as "hormone refractory" is misleading. We know, for example, that the tumors that are progressing do so with rising levels of prostate-specific antigen (PSA), which is an androgen-responsive gene; we know that androgen receptors are not only present in tumors that are considered "hormone refractory" but that receptor levels are increased relative to those at the time of diagnosis. Tumors with high levels of receptor can be activated by the residual low levels of androgen that remain despite castration.

In addition, a proportion of the receptors are mutated, making them respond to other ligands besides testosterone. We also know that many of these so-called "refractory" tumors respond to second- and third-line hormonal therapies. There may be a tumor that would ultimately resist every hormone, but it is not entirely clear when that would actually happen.

Do you recommend an alternate way of classifying these tumors?

We prefer to consider tumors that are progressing despite castrate levels of testosterone to be castration resistant, and classify them on the basis of the changes in the androgen receptor that lead to continued signaling, including those receptors that become activated independent of ligand, by receptor tyrosine kinases such as HER2.

Is a hormone-refractory tumor necessarily an advanced one?

No. If you treat patients who have localized prostate cancer with hormonal therapy alone for 3–8 months and surgically remove the prostate, fewer than 5% are tumor-free. This is further evidence that cells that resist and survive castration are present at the time of diagnosis.

What is the prognosis for patients with hormone-refractory prostate cancer?

An additional concern I have with the "hormone-refractory" label is that it assumes a patient will not respond to hormonal manipulations, and may deprive him of potentially beneficial therapies that are minimally toxic. That said, the prognosis of a patient who is progressing following castration is highly variable, particularly as we are using androgen ablative therapies earlier and earlier in the course of the disease. Consider 2 patients: the first received androgen ablation with a rising PSA after radical prostatectomy with no other signs of cancer; the second received androgen ablation when he was noted to have painful bone metastases from prostate cancer. While the first sign of progression may be a rising PSA in both cases, clearly the prognosis of the patient with a rising PSA alone will be different than one with a rising PSA and bone metastases. We and others have developed predictive models called nomograms to help counsel patients on their prognosis. In these cases, factors such as performance status, level of alkaline phosphatase (which indicates bone metastasis), anemia, and lactic dehydrogenase level, among others, can be used to assess prognosis.

One additional example of the shift toward early diagnosis and treatment is the improved survival of the control groups of patients treated on randomized comparative trials. In chemotherapy trials for prostate cancer in the 1980s, the median survivals were consistently around 10 months; in contemporary trials, survival is in the range of 16–20 months or more. Some of that improvement is a result of improved treatment, but a great deal is due to identifying and treating patients earlier.

Is there an accepted standard of care for treating patients with hormone-refractory prostate cancer?

The standard of care in terms of chemotherapy is now docetaxel (Taxotere, Aventis), based on 2 randomized trials

showing a survival benefit that were recently published in the *New England Journal of Medicine*.

A critical question is at what point chemotherapy should be used for the patient who is progressing on hormonal therapy. To address this, Dr. Michael Carducci at Johns Hopkins is conducting a trial through the Eastern Cooperative Oncology Group that seeks to determine whether it is better to try different hormones after a patient becomes resistant to treatment with one hormone, or if it is better to move directly to chemotherapy. This study involves patients who failed first-line hormones who had not had chemotherapy, and they are randomized to docetaxel or ketoconazole and hydrocortisone.

Unfortunately, docetaxel is not curative, and the median duration of response time is approximately 6 months. If a patient has a median predicted survival of 2 years and the addition of docetaxel delays progression by 6–8 months, it is unclear whether this is best added early or late. Dr. Carducci's trial will help address this question.

Are combinations of docetaxel and radiotherapy in use?

The results of randomized trials looking at this issue have been anticipated for a long time, and there are a number of groups studying combinations of docetaxel, androgen deprivation, and radiation therapy in high-risk patients. The results of phase II noncomparative trials have established the safety of the approach, which has enabled the phase III trials to proceed.

How has evidence that docetaxel extends survival in patients with hormone-refractory prostate cancer affected the treatment of this disease?

These 2 studies showed for first time that chemotherapy could prolong life. This is extremely important for patient counseling. What is somewhat disturbing is that there was evidence pointing in this direction as long as 10 years ago, but the trials were only completed this year. The findings provide the justification to evaluate chemotherapy earlier in the illness, where it is likely to provide even greater benefit. This paradigm of using chemotherapy with modest efficacy earlier in the course has had a significant impact on the survival of patients with lung, colon, breast, and other tumors where the available chemotherapy is arguably less effective than what is available for prostate cancer. In the past, physicians treating castration-resistant (hormone-refractory) prostate cancer were hesitant to use chemotherapy at an early stage.

What is considered second-line therapy?

There is no standard second-line therapy right now, although there are randomized trials that are ongoing or under development in this setting.

Can agents that are used in androgen-ablation therapy to treat patients with prostate cancer be used to prevent prostate cancer?

Androgen deprivation is likely to have some role in preventing cancer, or at least delaying its development. However, the question is whether patients will accept the side effects. Castration prevents prostate cancer, but most people will not trade immediate castration for possible prostate cancer prevention.

Do you believe that it will be possible in the future to use such therapy to prevent prostate cancer without the side effect of chemical castration?

There are several current trials that will provide important data in this area. The finasteride (Proscar, Merck) study that was just completed showed a lower frequency of cancer overall but a higher frequency of high-grade cancers in those patients who developed them. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is looking at a comparison of placebo, vitamin E alone, selenium alone, and the combination of vitamin E and selenium. That trial has already reached its accrual, with approximately 32,000 men.

Have targeted agents been used to treat hormone-refractory prostate cancer?

Targeted agents are just coming to the forefront. There are 2 general categories: targets that are present on cancer cells that can be used to deliver radioactive or chemical payloads, and those that contribute to growth. A new paradigm being explored by many groups is how best to profile a tumor, independent of its site of origin, based on the molecular alterations that are contributing to growth. Prostate-specific membrane antigen (PSMA) is a protein on prostate cancer cells that is being targeted in a number of different ways, including directed radioactive antibodies and antibody drug conjugates. This is possible because antibodies that bind PSMA are rapidly internalized, selectively delivering therapy to the cancer cell. Various immunization strategies are also under study. A number of groups are developing novel ways to target the androgen receptor directly, recognizing its role in continued growth, while others are exploring varies tyrosine kinase inhibitors based on molecular profiling data from castration-resistant tumors.

Most of the agents directed at these targets—including trastuzumab (Herceptin, Genentech), imatinib mesylate (Gleevec, Novartis), gefitinib (Iressa, AstraZeneca) and bevacizumab (Avastin, Genentech)—have shown limited activity as single agents in prostate cancer. Based on laboratory studies showing synergy, a number are being studied in combination, especially in combination with docetaxel. At this point, however, it is unknown whether these combinations will be better than docetaxel alone. An important consideration for these studies is that the molecular profile of the tumor that is removed surgically may be distinctly different from a tumor that has metastasized, even in the same patient.

Are there new agents that have shown promise in the treatment of this disease?

At this year's meeting of the American Society of Clinical Oncology, there were reports of results with the epothilones. Satraplatin is a third-generation platinum being tested

now in phase III clinical trials. Researchers at the University of Texas M. D. Anderson Cancer Center are looking at docetaxel in combination with imatinib in a national randomized trial. Several studies with various biologics are going forward.

Has the quality of life of patients with hormone-refractory prostate cancer improved in recent years?

Yes. In fact, the first chemotherapy regimen approved for the treatment of prostate cancer, mitoxantrone and prednisone, was approved on the basis of an improvement in quality of life even though there was no survival benefit shown. In the more recent trials, palliation rates were higher with docetaxel compared to mitoxantrone and prednisone, the previous standard. But we also have other therapies available for symptom control and symptom prevention, including zoledronic acid (Zometa, Novartis), which reduces skeletal events, and SM-153 lexidronam (Quadramet, Cytogen) and strontium chloride (Metastron, GE Healthcare), which reduce progression of bone metastasis. These have not been shown to prolong life, but they have certainly improved quality of life. Agents like erythropoietin to treat anemia have also had a significant impact.

Is there anything that needs to be done to improve clinical trials of patients with hormone-refractory prostate cancer?

A major problem is that the overall participation of men in prostate cancer trials is about one quarter of that of women. Physicians, patients, and third-party payers need to be convinced that participation in clinical trials is important. Sponsors also need to support trials that are large enough to show differences among treatment arms.

Will the survival benefit shown with docetaxel encourage more people participate in clinical trials?

In the past, there was a sense of nihilism surrounding treatments for hormone-refractory prostate cancer. Now that we have data showing a survival benefit, participation will likely improve. This development has changed the entire tone of the discussion. As we start building on docetaxel, we can now look for treatment that is superior to the current therapy, rather than one simply that works at all. The data that we now have will allow us to give patients a great deal of important information about their treatment: what it can do, what it cannot do, and what the side effects will be.

What are some exciting directions for future research?

Our group is focused on targeted therapies, including androgen-receptor targeting and PSMA. I believe that we will also see significant advances in medical imaging, which will help us ascertain more about the biology of a patient's tumor without doing biopsies. Medical imaging will also help us to assess treatment effects more quickly.

Suggested Reading

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