Management Protocols for Advanced Prostate Cancer

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I. Castrate Resistant Disease

Castrate resistant disease is not really hormone refractory. The androgen receptor remains a relevant target for therapy even in patients who are "castrate resistant". There are also other potential targets including the immune system. People have talked about a class of chemotherapy; I like to think about chemotherapy as DNA or DNA repair targeted therapy. There are a number of mechanisms for castrate resistance, in other words, when the cancer continues to grow after standard castration, and these include amplification of the androgen receptor, mutation of the androgen receptor, modification of the androgen receptor, modification of androgens or the ligands that bind and activate the receptor and modifications in the co-stimulators that the androgen receptor continues to need in order to stimulate growth and proliferation.

II. AR Activation in Castrate Patients

An important issue is that we don't often know which mechanism is relevant in an individual patient when it comes to androgen receptor activation in castrate patients, and in fact it is difficult to impossible to detect which mechanism is important in an individual patient. Current data suggests that the most important mechanism is increased availability of androgens within the tumor environment whether that be androgens from the adrenal gland or androgens from within the tumor that are manufactured by the tumor itself that then bind to the androgen receptor and stimulate the growth of the cancer.

III. What we know…

Prostate cancer requires androgen receptor signaling for development and sustenance, and androgen receptor activation is required throughout the natural history of prostate cancer. Androgen activation in castrate-resistant prostate cancer occurs via many different mechanisms, and successful blockade of the receptor pathways will confer greater therapeutic control on metastatic prostate cancer. We know that not only in the laboratory but also in patients.

IV. Abiraterone

The first approved drug that makes use of these concepts is Abiraterone. Abiraterone blocks the synthesis of a number of different androgens, and as a result it impacts the concentration of androgens within the tumor. There is also a feedback loop that leads to

increase in aldosterone, which is responsible for some of the side effects of the drug and is the reason that we also give the drug with low-dose prednisone, which is a requirement to prevent some of the side effects and what turns out to be up regulation of the steroids.

The COU-AA-301 study led to the demonstration and approval of Abiraterone. The study looked at about 1,200 patients with metastatic, progressive, castrate-resistant prostate cancer that had already failed chemotherapy. They were randomized to receive either Abiraterone plus prednisone or prednisone by itself, and the primary endpoint was overall survival. This was conducted in the U.S., Europe, Australia, and Canada at 147 sites in 115 different countries.

The study was a 2:1 randomization. There were 800 patients in the Abiraterone group, and about 400 patients received placebo and prednisone. The study was done in a typical castrate-resistant prostate cancer population. The median age was 70. Most were White, and most had a good performance status with minimal symptoms. About 40% of them did have some pain and 30% of the patients had at least two prior chemotherapies. Almost all of the patients had bone metastases and about half had lymph node metastases. Importantly, about 10% of the patients had liver or lung metastases. It was an advanced group of patients.

Clearly the patients who received Abiraterone survived longer than those who received the placebo, and the median or the average was in the order of 15 months while the other patients were in the order of 11 months. This was highly statistically significant and led to the approval of Abiraterone. The survival benefit was equivalent across all the different sub-types of cancers. There was also an improvement in time to progression and an improvement in progression-free survival as well as in the fraction of patients who had a PSA decrease. About 40% of patients had a decrease with Abiraterone and 10% with placebo only.

Some of the side effects included 30% of the patients in the Abiraterone group having some signs of fluid retention as opposed to 22% who had only steroid, which can also cause fluid retention. Seventeen percent of the patients in the Abiraterone group had low potassium, which is a direct impact of the other steroid pathway. There were some mild liver abnormalities that need to be monitored, and increased blood pressure is a direct impact once again of the pathway and needs to be monitored. There is also a low but slightly increased risk of cardiac events possibly due to the increased blood pressure.

V. Other Agents

The other agent that is in active development and for which the phase III trial has been completed but the results are not yet known is MDV3100. This agent was studied in essentially the same trial design as the Abiraterone trial. There is also one other agent, ARN-509, that is also an androgen receptor blocker.

VI. Castrate-Resistant Disease Non-Hormonal Treatment Options

We begin to thing about patients as being those with a good prognosis and those with a poor prognosis. Patients with a good prognosis are asymptomatic or “low volume.” We could use the standard docetaxel chemotherapy, and we have the option for immunotherapy with sipuleucel-T or Provenge, and we have an option for investigational

therapy. For the patients with a poor prognosis, those who are symptomatic, standard docetaxel chemotherapy is available as well as cabazitaxel. There are also investigational chemotherapy options.

VII. Sipuleucel-T: Autologous APCs Cultured with Antigen Fusion Protein

Sipuleucel-T is a new therapy in the sense that recombinant protein, which is a protein that is made in the laboratory, is mixed with white cell. The white cells then process the androgen and theoretically become activated white cells. The activate white cells are then infused back into the patient and theoretically attack the cancer cells. In terms of the logistics of therapy, the patients go to an apheresis center for leukapheresis. The white cells are shipped off to a company who does the processing. The product is then sent back to the physician's office who infuses the white cell preparation, and the process is repeated a total of three times.

The phase III data was from a study of patients who were minimally symptomatic. Patients with metastatic, castrate-resistant prostate cancer were randomized on a 2:1 basis to either Sipuleucel-T or placebo. At the time of progression, the patients were treated however the physician desired, and the primary endpoint was overall survival. There was an improvement in survival in the patients who were treated with Sipuleucel-T, and the median survival was 26 months versus 22 months in the placebo arm, a value that was statistically significant. The drug is generally well tolerated with some chills, fever, headache, influenza-like illness, myalgia, hypertension, hyperhidrosis and some groin pain.

Importantly, there is no impact on time to disease progression. Our ability as physicians to measure disease progression is really bad, and there is a possibility that something "bad" happened in the control group though it's hard to imagine what that might be. It may be that something "good" happened to the treated group that is unrelated to the cancer. Importantly, there is no effect on symptoms or PSA with the use of this therapy.

Sipuleucel-T is an expensive regimen at $93,000 for the treatment, which does not include the apheresis and infusion costs, and there are logistical issues with regard to where the apheresis will be done and the ability to process the cells. The company is rapidly correcting the logistics issues, but these are the issues that have led to discussions in the public as well as the medical media regarding the utility of the therapy.

VIII. Other Immune Therapy Approaches

In terms of other immune therapy approaches, there is a drug called Ipilimumab, which is a drug that targets a protein called CTLA4, which essentially turns off the brake on the immune system allowing it to react against the cancer. There is a potential for severe autoimmune disease including autoimmune diarrhea, but there have been effects against prostate cancer in phase II trials. There are a number of trials ongoing.

We are also participating in a trial of a true vaccine, which is a PSA-TRICOM vaccine. It is based on the "prime" and "boost" concept that was utilized in a lot of childhood anti-infective vaccines. It's a trial being conducted in castrate-resistant patients who have also

receive chemotherapy once again utilizing the concept of radiation enhancing the immune response.

IX. How do we measure "immune activation"?

We have a challenge in terms of measuring the immune activation, and there are some efforts ongoing at our institution to try to develop markers to do that.

X. Cabazitaxel Phase III

Cabazitaxel is a drug that was approved by the FDA for treatment of castrate-resistant prostate cancer. The phase III trial was performed in patients with metastatic disease who had received docetaxel therapy previously. They were randomized to receive cabazitaxel of mitoxantrone, which is another chemotherapy drug that has been shown to improve symptoms in prostate cancer patients but has never been shown to improve survival. The primary endpoint was survival. The patients that were enrolled were the typical group that we might see with about 90% of the patients having bone metastases, half of the patients having lymph node metastases and about 25% of the patients having some kind of lung, liver or other organ involvement from their cancer.

There was an improvement in survival from 13 to 15 months with cabazitaxel, which was a surprise to many of us. Unfortunately, it is a drug that has a number of side effects most important of which is a fever in the face of a low white count and diarrhea, which can occasionally be quite severe.

Although survival was improved in the cabazitaxel group, about 5% of the patients who died did so as a direct result of toxicity of the drug as opposed to only 2% in the mitoxantrone group. This number would be unacceptable to most oncologists and patients, and as a result the FDA asked the company to do a trial of a lower dose of the agent as well as a trial comparing it directly to docetaxel.

XI. Cabozantinib

Another drug that a lot of us in the field got kind of excited about is a drug called Cabozantinib. A trial was done mostly at Michigan, and it was an interesting trial design that we first helped popularize a number of years ago in which patients get the drug for a lead-in or run-in period of about 12 weeks. If their cancer is stable, they then go on to either discontinuing or continuing the agent in a randomized manner whereas if there has been evidence of a response or benefit the patient is continued. Surprisingly, there were a lot of responses in this trial. There were actually changes in the bone scan, and that was not something that we expected. In the randomized setting there was clear inhibition and slowing of disease progression, but the thing that got people excited is there were a number of patients who had extensive bone metastases and 12 weeks later the bone scans had normalized.

Interestingly, the PSA responses lagged behind the bone scan responses, and so most of us believe that the responses are some kind of impact on the bone itself that then later on leads to an effect on the cancer because the bone is actually supporting the growth of the cancer. This is being evaluated in some additional ongoing trials, and we are a little bit confused by the results. Cabozantinib has been advertised to be both a VEGFR inhibitor

as well as an inhibitor of Met, but all of the VEGFR inhibitors that have been tested in this disease have been negative. There have been no similar dramatic reports of bone scan improvement with other Met pathway inhibitors that are being studied. Whether it is due to the combined effects on both Met and VEGFR or if it is due to some unknown effect of the drug remains to be determined. There is currently ongoing a large phase III trial in which one of the primary endpoints is pain, and there a number of imaging and biopsy trials that are either ongoing or planned trying to understand the effects of this drug on the bone stroma versus on the tumor itself.

XII. Alpharadin

Alpharadin is a radioactive nucleotide, Ra-223, and the data regarding it has not yet been fully presented at any scientific meeting. In the *Wall Street Journal*, however, and in other financial papers we have gotten the following quote: "Alpharadin's Phase III ALSYMPCA trial met its primary endpoint by considerably improving overall survival of patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases. An Independent Data Monitoring Committee recommended that the study be stopped and that the patients on placebo be offered Alpharadin therapy. Bayer wrote that the *"overall survival result was statistically significant (two-sided p-value = 0.0022, HR = 0.699, the median overall survival was 14.0 months for Alpharadin and 11.2 months for placebo).* Alpharadin's safety and tolerability in the Phase III trial was similar with those in Phases I and II." Many of us are interested in seeing the actual data so that we can evaluate it in more detail.

XIII. Prostate Cancer 2011

Advanced prostate cancer has become increasingly a chronic disease in which we have to conduct chronic disease management. There is an opportunity for multiple therapies in patients with advanced prostate cancer, which therefore means that issues of toxicity and quality of life become increasingly important. We have to also begin to take into account many of the issues of co-morbid disease and aging in this population.

In regard to the issue of chronic disease management, the androgen receptor pathway remains key even in patients with castrate-resistant disease. The standard chemotherapy or what I call DNA targeted therapy clearly plays a role in the disease and has been shown to improve with two different agents. Immunotherapy probably plays a role, and we have at least one approved immunotherapy agent, Sipuleucel-T. Bone stromal targeting also plays a role.

XIV. What do we need to know?

We are left with a large number of questions that span the natural history and the various disease states.

- When do we start androgen ablation in patients whose PSA rises?
- How early do we start more potent androgen receptor targeting agents such as Abiraterone and MDV-3100?
- When do we introduce non-androgen receptor targeting therapies?

- Can we afford “personalized” long-term therapy?