

## **Emerging Treatment Protocols**

### **New Treatments**

**Tia Higano, MD**

#### **I. Overview**

When you start with clinically localized cancer that can progress to the situation that we've been talking about where the PSA is rising but there is no evidence of metastatic disease that can progress to when there is evidence of metastatic disease in the bones but it's still hormone sensitive. In either of these cases, if hormonal treatment is given, the PSA can start rising even though there are very low levels of testosterone. That can be in the non-metastatic setting or in metastatic settings, most of which we are going to be talking about in terms of these new treatments.

#### **II. Immunotherapy**

##### **1. Provenge**

I find that a lot of patients and doctors are interested in immunotherapy, and the immunotherapy that is closest to becoming potentially FDA approved is Provenge, which is a cellular vaccine. This form of vaccine has been studied in two smaller trials and more recently a large phase III trial that was reported this spring at the urology meetings in which men who had minimally symptomatic prostate cancer that had spread to the bone who had never received chemotherapy before were randomized to receive either the vaccine or placebo. The actual vaccine is given over a one-month period, one infusion every two weeks three times, and then patients were followed for survival.

What was shown in this randomized trial was that the patients who were treated with the vaccine actually had improved survival over those who had received the placebo. The median improvement in survival was 4.1 months. It is very good news that we saw the survival benefit, and it is important that it was pretty much the same as what we saw in two other much smaller trials of Provenge. Some of you may recall that it did not get approved a couple of years ago, and it's nice to see that the survival improvement is consistent.

This is not a toxic regimen and is really very well tolerated with some infusion kinds of things that go away after 48 hours. Some of the cons are that this is something we have trouble with in cancer—what kind of treatment can you give somebody that improves survival but doesn't change what we call time to progression? Second of all, because the patients didn't have pain when they walked into the study, we didn't show that patients got a lot better from pain. It didn't have an effect on PSA. We think this is the next interesting drug that will be approved by the FDA based on these very promising phase III data, but you never know.

## **2. Ipilimumab**

The next drug that is far in its development is a drug that blocks the CTLA4 activity in the immune system. In essence, ordinarily T cell activation, which is a special kind of immune cell, is very important in causing reactions in our bodies, especially reacting to foreign substances. The CTLA4 is a break on that, and so there is this balance between activation and inactivation. What we would like, however, is for our immune system to react against the cancer. The CTLA4 antibody is Ipilimumab, and there have been some studies looking at Ipilimumab alone and subsequently with radiation therapy because we believe based on some laboratory studies that if you radiate the tumor cells some of these important antigens that make it foreign will be released and allow the immune system to better react.

We know that this is a very potent type of immunotherapy because of the side effects. We also saw that there are drops in PSA, and there are signs of improvement on the scans. The findings of the study looked good enough that this immunotherapy is now being brought to a phase III trial in which patients have to have failed prior chemotherapy but can't have had more than two chemotherapy regimens. They also have to have at least one bone lesion that has not been irradiated. That can be included, and if you have something like autoimmune disease, rheumatoid arthritis, for example, you can't go on because we don't want to make that worse with the immune treatment. Systemic radiation is not allowed either. All patients will get radiation to at least one bone site, and then they will either get the Ipilimumab or placebo.

## **III. Summary of Immunotherapy**

In terms of immunotherapy in prostate cancer, it looks like Provenge will be approved by the FDA in the spring. Studies have shown that the survival benefit is in people who have metastatic disease who are hormone resistant or castrate resistant and don't have a lot of symptoms. G-VAX, another vaccine, is no longer being manufactured, and the clinical trials have been closed, but interestingly in one of the trials it actually looked like very late the survival was better, so our group in Seattle is going to complete the survival data. The Ipilimumab is just starting phase III.

## **IV. ZD4054**

ZD4054 is an endothelin antagonist, and it theoretically would block a lot of bad things from going on without affecting some of the normal things that you want the substance to do. We looked at two doses of the drug, 10 or 15 milligrams, versus placebo. Both doses resulted in improved survival over placebo, and based on this study, Astra Zeneca, which makes ZD4054, started the ENTHUSE program of phase III trials looking at ZD4054 in different stages of prostate cancer.

## **V. Treatments in Studies**

There are numerous other trials that are in progress looking at combinations of chemo and other agents, and I won't belabor these except to say the most completed trial to date is the one combining docetaxel and bevacizumab. We are expecting those results to come out next spring in our cancer meetings. There are more active drugs available than I have ever seen in my career as a prostate cancer medical oncologist, and there are many ongoing and planned registration trials. There's a tremendous amount of potential, but we really need to get these trials completed.