# Understanding New Drug Protocols: Managing Hormone Sensitive, Non-Metastatic Relapse/Castrate-Resistant Metastatic Prostate Cancer

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Moving from prostate cancer awareness to the question of what do we do when the disease reoccurs or progresses, we will hear from Dr. Daniel Petrylak, who is the Principle Investigator in the development of Taxotere, which is the first drug approved for advanced stage prostate cancer, and one that many people can owe their lives to.

## I. New Agents and Chemotherapy Advances

**Daniel Petrylak, MD**

I will talk about the role of the medical oncologist and some of the newer drugs that are out there. When should a patient see an oncologist? There are four situations where I think it is appropriate: high risk localized disease; rising PSA after local therapy; hormone sensitive disease; and endocrine resistant disease. This slide shows the natural history of metastatic prostate cancer: the initial rapid decline in serum tumor markers like PSA following initiation of hormone therapy unfortunately lasts only 18-24 months, as the treatment is not curative; eventually, all patients begin to progress. The earlier belief of not using hormone therapy after hormone failure is no longer true. Hormone refractory or endocrine resistant prostate cancer remains a big problem, as the androgen receptor is still active, so it is not truly hormone refractory. Prostate cancer in some way is becoming independent of the testicles or independent of the adrenal glands.

Other ways to activate the androgen receptor include having large amounts of the receptor forming through the message being increased, or having atypical activation as through the oncogene p10 pathway, important to angiogenesis and cell metabolism. Prostate cancer is thus sometimes difficult since, unfortunately, there is currently no good marker to indicate when treatments should be changed.

A new drug now being evaluated by FDA which hopefully will be approved in the next year is abiraterone, a hormone treatment with activity both before and after chemotherapy. A randomized trial now underway, comparing abiraterone plus prednisone versus placebo plus prednisone in patients who previously failed docetaxel, is showing a survival benefit. The hormone axis remains active. Another trial is treating patients with abiraterone prior to treatment with docetaxel. MDV3100 is a drug which prevents testosterone from hitting its target and interacting with DNA; trial results are similar to abiraterone. AFFIRM is the phase 3 registration trial in patients who fail prior docetaxel treatment.

Controversy remains as to when chemotherapy should be initiated. Chemo can be initiated when PSA rises in the nonmetastatic patient, in the asymptomatic patient with metastases (more controversial of a situation), in the patient whose bone scan is worsening, and in a patient with symptomatic bone pain. The question is whether this is too late to start chemotherapy. For many years, chemotherapy had been thought to be toxic and ineffective for this state of disease, which is not the prevailing wisdom now. Since the 1990s, taxanes have been studied; these agents interfere with cellular structure or scaffolding of cancer cells, thus preventing cells from dividing, and may lead to inactivation of androgen receptor.

The TAX327 and SWOG9916 trials compared the use docetaxel against mitoxantrone and prednisone. Both trials were designed to looked at a survival benefit. Trials showed a stage migration where patients appeared to do a little bit better with docetaxel, with 20-24% improvement in survival. Long-term survival was slightly better than what was seen prior.

Angiogenesis is overexpressed in cancer, particularly in high grade prostate cancer. There is evidence for angiogenesis as a target for prostate cancer treatments. The CALGB trial showed improvement in median survival with treatment of docetaxel and bevacizumab versus docetaxel without bevacizumab. Other drugs which inhibit angiogenesis include thalidomide and Revlimid, a thalidomide derivative. Studies using Revlimid combined with docetaxel, in patients with and without prior chemotherapy, show responses even in patients who just failed Taxotere and were put on this particular regimen. The randomized trial MAINSAIL is accruing, and comparing docetaxel-Revlimid to docetaxel-prednisone.

The TROPIC study in Europeans looked at the use of another taxane, carbazitaxel, versus mitoxantrone in patients with fairly high PSAs and prior chemotherapy. Results showed a three-month improvement in overall survival with carbazitaxel, which was significant. Blood count drops were seen as a side effect; patients should receive growth factors to prevent these particular side effects.

Finally, bone health is important in prostate cancer, where fractures and bone pain can develop. A study with Zometa looked at skeletal related events as its primary outcome; Zometa showed a significant reduction in SREs, as well as a reduction to first time SREs. A survival was seen on initial analysis. Another drug which will probably get approved by FDA is denosumab, which affects a different portion of bone metabolism called RANK ligand; the agent shows a trend towards an improved SRE rate and lower events.

In sum, the standard care for prostate cancer in first line still remains docetaxel and prednisone; novel phase 3 clinical trials are combining docetaxel with novel targeted agents; carbazitaxel is approved as second line therapy for castration resistant prostate cancer; and new biological approaches are being evaluated in second line disease.

**Male Participant**

Can you speak about the effects on the immune system that are caused by chemotherapy?

**Dr. Petrylak**

This has always been an issue which Susan will address in more detail. Generally, between seven and 14 days, the patient's white blood cell counts drop. This is when a patient is most susceptible to getting an infection and should be monitored carefully, then treated with antibiotics appropriately. The effect on the immune system is very complex. There are immune stimulatory effects which we do not know how to quantitate; this brings up the issue of when to start chemotherapy now with Provenge onboard.

**Male Participant**

I had my prostate removed and have had radiation. I am suffering from extreme fatigue.

**Dr. Petrylak**

Without reviewing your case and lab values, it is very difficult for me to say what the source of your fatigue is; it could be an endocrine or hormone problem. You need to review this with your physician.