



Clinical Trials



Metastatic Castration Resistant Prostate Cancer (CRPC)

Are There Any Options After Docetaxel Fails?

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One of the most challenging problems in the management of prostate cancer is the treatment of a patient who no longer responds to androgen ablation therapy and has failed chemotherapy with docetaxel. Fortunately there is a surge of research with a spectrum of newer therapies for this subset of patients which hopefully will translate into survival benefit in the very near future. In this brief review I will highlight a sampling of newer drugs in clinical trail, their mechanism of action and what early data is available concerning their efficacy.(1)

NEW HORMONE THERAPIES

Contrary to what one might assume, hormone resistant prostate cancer cells actually have an increased number of androgen receptors on their membrane surface and still are sensitive to stimulation and growth by androgenic hormones.(2) In addition there is evidence that prostate cancer cells themselves have the capacity to synthesize androgen and stimulate their own growth. There are two exciting new hormonal therapies in phase 3 clinical trials at the present time.

The first is abiraterone which blocks a very early enzyme in the sequence of testosterone synthesis. The drug virtually eliminates adrenal gland androgen production and the synthesis of androgen by prostate cancer cells. Early trials have shown significant activity in hormone insensitive patients whether they had received prior docetaxel or not. Combined partial response and stable disease occurs in more than 60% of patients with PSA decline of more than 30% in 50% of patients. The medium time to progression is more than a year in patients who have not been treated with docetaxel and 250 days in those who received prior chemotherapy.(3)

A second hormonal agent is MDV-3100 which is a powerful androgen receptor blocker and inhibitor of proliferative signaling to the nucleus of the prostate cancer cell. This leads to increased apoptosis (programmed cell death) of the prostate cancer cell and a clinical response. Early data in hormone insensitive and docetaxel resistant prostate cancer has shown PSA decline of >50% in 55% of patients with a median duration of control of 200 days. This drug has no major toxicities and is now entering phase III trials.(4)

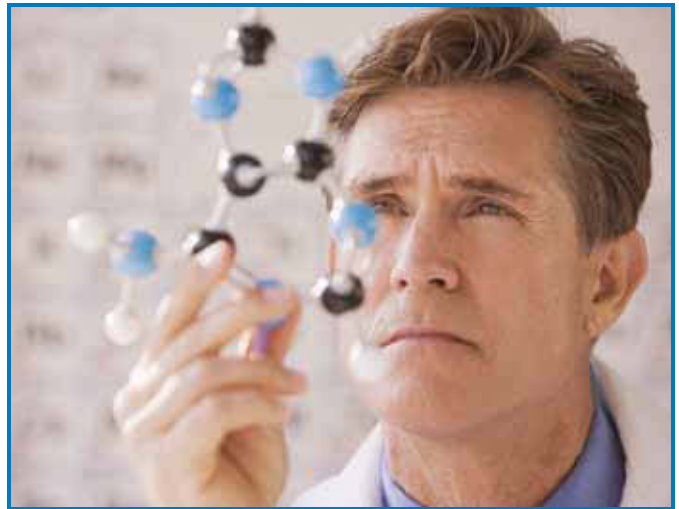
1. New Chemotherapy

The development of second line chemotherapy after failure of docetaxel has been disappointing. Although sartraplatin, an oral platinum compound, showed improvement in progression free survival (11.1 vs. 9.7 weeks) compared to prednisone alone there was no overall survival benefit and this drug was not approved by the FDA.

In June 2010, the FDA quickly approved a new taxane, cabazitaxel after a phase III trial reported survival advantage in patients who failed prior docetaxel therapy. Cabazitaxel was compared to mitoxantrone (a drug approved by the FDA for treatment of prostate cancer) in docetaxel refractory patients. In this trial there was a statistically significant improvement in median overall survival in the group of patients receiving cabazitaxel (15.1 months vs. 12.7 months) with modest toxicity. Response rate, progression free survival and PSA decline all favored the group receiving cabazitaxel. (5)

2. Immune Based Therapy

Our immune system is of great importance in protecting us from the development and growth of malignant cells. If a cancer does develop, the immune system has failed to adequately recognize abnormal cells with cancer generating mutations. The immune system is still important in slowing and controlling malignant growth. Treatment with high dose interleukin-2 can program natural killer cells and



T-lymphocytes to recognize tumor antigens and cure a small percentage of patient with metastatic renal cell cancer or malignant melanoma.

In prostate cancer there are a number of strategies to use immune based therapies to interfere with prostate cancer growth. Sipuleucel-T (Provenge®) has recently been approved by the FDA for patients with metastatic disease and minimal symptoms. The drug is a unique vaccine in which antigen presenting cells (dendritic cells) are removed from the patient and mixed in the laboratory with a broad spectrum of prostate cancer antigens and immune stimulating molecules. The “programmed” dendritic cells are then injected back into the patient. Although there is little drop in the PSA or objective evidence of tumor shrinkage the overall survival of treated patients is improved from 21 to 26 months.(6) *(Continued on page 14)*



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Prostvac is a different type of vaccine that also may extend survival. A poxvirus encoding genes for prostate cancer proteins and 3 immuno- stimulating molecules has been tested in CRPC patients with asymptomatic or mildly symptomatic metastatic prostate cancer. In a placebo controlled trial of 122 patients the 3 year survival was 30% in vaccine patients and 17% in the control group. Median overall survival was 24.5 months versus 16 months favoring the vaccine.(7)

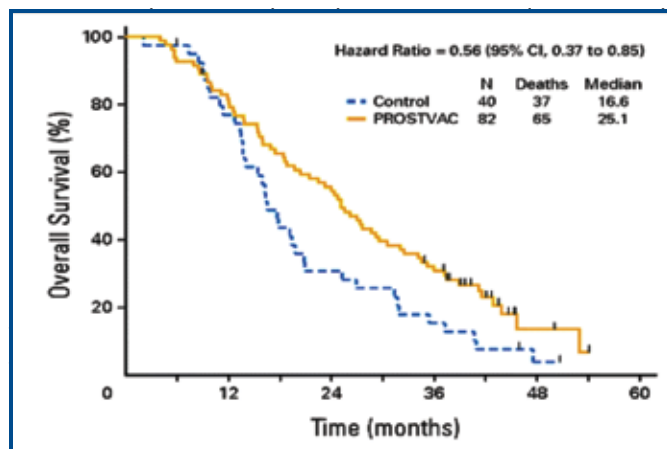


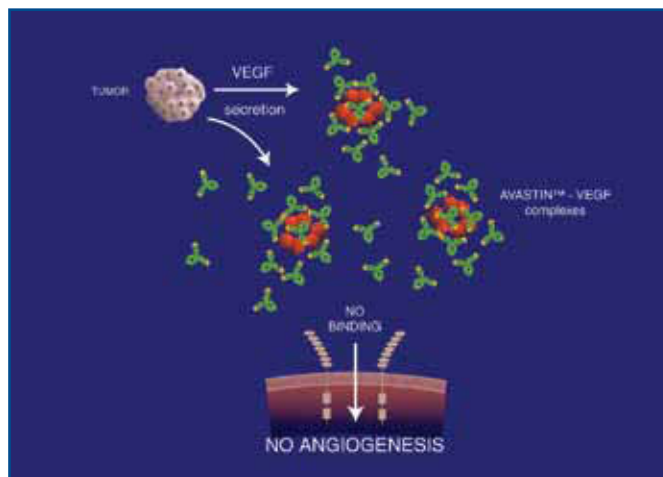
Figure 1: Prostvac Improves Survival

A third ingenious immune based therapy is the use of a toxin conjugated monoclonal antibody to prostate surface membrane antigen. A complex of the antibody with maytansine a powerful microtubule poison attaches to the surface of the prostate cancer cell and is then internalized. The toxic compound is then released within the malignant cell leading to cell death with minimal systemic toxicity. This agent appears promising in early trials.(9)

3. Antiangiogenesis

All cancers need to develop their own vascular system to grow beyond 2mm in size. Anti-angiogenesis, long a theoretical strategy to disrupt cancer growth became a reality with the development of bevacizumab (trade name Avastin®), a monoclonal antibody to vascular endothelial growth factor (VEGF) a ligand to more than 10 cellular receptors involved in neo-angiogenesis. This drug has been approved in combination with chemotherapy for treatment of colon, breast, lung, kidney and brain tumors. Initial small studies combining bevacizumab with docetaxel in prostate cancer were promising but a larger trial recently presented showed progression free survival improvement but no overall survival benefit.(10)

AVASTIN BLOCKS ANGIOGENESIS



Two other oral drugs with antiangiogenic properties have reported positive results in small trials. Cediranib was tested in 24 CRPC patients who had failed docetaxel and had measurable soft tissue lesions. Thirteen of the twenty-four patients showed evidence of tumor regression and four met criteria for a partial response.(11) Lenalidomide, an immune modulating agent with antiangiogenic activity has been studied in relapsed CRPC patients with a short PSA doubling time (<3 months). PSA response rates were 40% with a lengthening of the PSA doubling time from 3 to greater than 6 months. This drug is also being studied in combination with docetaxel.(12) There are other multi-targeted tyrosine kinase inhibitors (block angiogenesis receptors as well as epithelial growth factor pathways) that are in trials in CRPC patients. Sunitinib and sorafenib are approved for use in renal cell cancer and both have activity in prostate cancer but have significant toxicities that may limit their effectiveness in elderly men with co-morbidities and prostate cancer.

4. Bone Directed Therapy

Endothelin peptides are molecules found on the cell surface of prostate cells that modulates vasomotor tone, cell proliferation, invasion and osteoblastic stimulation. In prostate cancer, endothelin I levels are significantly elevated and bind to the endothelin-A receptor triggering cancer growth and osteoblastic activity in metastatic disease to bone. Atrasentan is an oral selective endothelin-A receptor antagonist and has demonstrated in clinical trials delay in time to PSA progression and improvement in skeletal events related to metastasis. Because there was no overall survival

TABLE 1: CASTRATION RESISTANT PROSTATE CANCER – POTENTIAL NEW OPTIONS

Hormone Therapy

- Abiraterone
- MDV3100
- TAK-700

New Chemotherapy

- Cabazitaxel
- Epothilones

Immune Modulation

- Vaccines (Sipuleucel-T) prostrvac, GVAC
- Ipilimumab
- Immunotoxins (MLN2704)

Antiangiogenic

- Bevacizumab
- Cediranib
- Lenalidomide
- Sunitinib

Bone Targeted Therapies

- ZD4054 (endothelin A) inhibitor
- Alpharadin (radium 223)
- Denosumab (osteoclast inhibition)

benefit in these studies atrasentin was not approved by the FDA. A more potent inhibitor of endothelinA, ZD4054, has shown survival benefit in a phase II trial and a large phase III trial is now underway.(13)

Skeletal related events (bone fractures, need for radiation therapy and spinal cord compression) is a major clinical problem facing men with metastatic prostate cancer to bone. A recent trial compares denosumab, a monoclonal antibody inhibiting osteoclast activity, with zoledronic acid, an IV bisphosphate also inhibiting osteoclast activity. Although there was no survival difference between the two arms, denosumab was clearly more effective than zoledronic acid in preventing skeletal related events. There was no evidence of renal toxicity with denosumab but the incidence of osteonecrosis of the jaw was similar.(14)

RADIOPHARMACEUTICALS

Metastatic bone disease is characterized by continuing bone remodeling and both osteoclast and osteoblast activity. Radiolabeled elements are taken up into the bone matrix as bone repair occurs and

the delivery of radioactivity to these areas of active cancer is therapeutic with reduction in bone pain in 70-75% of patients treated with either strontium 89 or samarium-153. Alpharadin (radium-223) is a novel bone seeking, radioactive alpha particle emitting pharmaceutical that targets osteoblastic metastatic sites. The advantage of the new compound is minimal bone marrow suppression and activity (pain relief and PSA decline) that is ongoing.(15)

It took decades to finally show that systemic therapy aside from hormone ablation could be of survival benefit in men with CRPC. The docetaxel data has seemed to unlock a tidal wave of investigation into multiple targeted, immune based and even new hormonal therapy that will likely add to our armamentarium of treatments for prostate cancer and prolong survival for our patients with this difficult disease.

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