



Foundation
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Research

Newsletter

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Provenge

By: Paul F. Schellhammer, M.D.

Provenge is an immunotherapy that has been found in a large, randomized, control trial (the highest level of evidence, often termed level I evidence) to provide a survival benefit for patients with advanced prostate cancer. Advanced cancer is defined as men with spread of cancer to bone and/or lymph nodes who have received hormone therapy and whose cancer is progressing. The mantra of medicine over the last decade has emphasized treatment according to levels of evidence or evidence-based therapy. Evidence-based treatment emphasizes that the therapy delivered has been rigorously tested in clinical trials to produce the intended result and to provide an advantage over prior therapies. When a pharmaceutical company brings its product to the FDA for approval, this evidence-based, randomized clinical control data is carefully scrutinized and based on this data, the FDA provides approval for new pharmaceutical agents or biologic products. Provenge met this rigorous scrutiny and was approved by the FDA on April 29, 2010.

The year 2010 has been groundbreaking for new therapies for patients with prostate cancer! In 2004, the FDA approved Taxotere chemotherapy for the treatment of men with advanced prostate cancer. This was a singular landmark event since it was the first agent to prolong survival since the introduction of hormone therapy in 1941 – a 65 year draught, almost unprecedented in the field of oncology. Now in 2010 the FDA has approved two additional therapies – Provenge, as noted above, and Carbitaxel, a new chemotherapy, and based on reports of a recently analyzed clinical trial, will almost certainly approve Abiraterone, an extraordinarily potent form of androgen deprivation. Of importance, each of these agents attacks the cancer through different mechanisms - Provenge, through immunotherapy, Carbitaxel through chemotherapy, and Abiraterone through hormonal suppression.

So the challenge now will not so much be whether there is an agent available to treat men with advanced and metastatic prostate cancer, but what is the best combination or sequence of these newly available treatment possibilities. The expectation is that the treatments will be additive; the hope is that they will be synergistic.

However, there is a cloud on the horizon. And like most issues in recent years, it is centered on the economy – will the cost of these agents pose an obstacle to their delivery? In the United States, pharmaceutical and biologic agents are brought to market only after FDA approval which focuses on safety and efficacy. Once the governmental agency, the FDA, gives its approval, the federal agency responsible for re-imbusement, CMS (Centers for Medicare and Medicaid Services) has routinely covered the cost of treatment for patients who have the same characteristics as those treated in the clinical trial – so-called “on label” drug delivery. The cost of Provenge, \$93,000, has produced “sticker shock”. On close examination, this cost is not very different from the cost of other chemotherapies and biologics, since it is not spread over a prolonged period of time. Provenge comes to market at a time of great economic turmoil and since it may be a harbinger of an additional round of equally and even more expensive drugs, it raised the red flag to CMS. Arguments on the side of the biotech company, Dendreon, which produces Provenge, include the significant survival benefit, the short duration of therapy (4-6 weeks), and importantly, virtually negligible side effects. It is unique in that the survival advantage is not largely consumed by the time required to deliver therapy and manage side effects from therapy. Development has been a time and resource intensive exercise having been in the process of evolution for over 15 years at the cost of greater than one billion dollars. Furthermore it may serve as a platform for the treatment of other malignancies.

I believe there is the need for thoughtful arbitration to establish reasonable pricing for a fair return on investment. This cannot be directed at one product but requires an overview of all therapies for cancer. To

arbitrarily make decisions about payment or denial of payment for one product, is unfair for industry and even much more so unfair for patients with prostate cancer. A rational and measured assessment of fair return as opposed to what the market may bear when it comes to treatment of patients with malignancies is appropriate and justified.

As a physician involved in the Provenge trial from the onset, as a prostate cancer patient, and as a past member of the Executive Committee of the American Urological Association, I was asked to present, along with a number of other physicians, at the recent CMS MedCac conference in Baltimore, MD November 17. Excerpts of that presentation follow:

Good morning. I am a urologic oncologist whose primary focus has been and continues to be the care of the patient with prostate cancer. I have been in practice for 35

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Provenge

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years with Urology of Virginia and Eastern Virginia Medical School in Norfolk Virginia.

The public health burden of urological disease in the United States is large and growing. Urologists are the specialists who most often diagnose and treat prostate cancer, the second leading cause of cancer deaths among men in the U.S. Prostate cancer will affect nearly 227,000 men in the U.S. this year and result in over 32,000 deaths. It is estimated that seventy-five percent of prostate cancer patients are Medicare beneficiaries.

I was diagnosed with prostate cancer in 2000 and currently have castration resistant disease without evidence of metastases. Therefore I am not eligible to receive Provenge. I make this statement now to emphasize, as I will again in the following discussion, that I am advocating only for "on label" use of Provenge as approved by the FDA based on randomized controlled trial data.

I am a strong advocate for evidence-based medicine and the importance of well-designed randomized clinical trials to develop clinical evidence of the effectiveness of drugs, devices, and procedures. Personally I have participated in a number of NCI Cooperative Group and industry-sponsored trials over the past two decades. In 1999, the Urology Department at Eastern Virginia Medical School began enrolling patients in the clinical trials studying Provenge. Our Department at EVMS has enrolled 75 patients in trials of autologous cellular immunotherapy, specifically of Provenge. I have become very familiar with the product.

Androgen ablation, or hormone therapy, is the accepted treatment for PSA failure with or without metastases after definitive therapy for localized prostate cancer. Patients may eventually develop metastases after androgen ablation. This progression usually detected by imaging or PSA rise and is often identified in the absence of symptoms. Chemotherapy, specifically docetaxel (Taxotere), has been demonstrated, through two randomized clinical trials, to provide a survival advantage at this stage of disease, conferring a 2.5-3 month increase in survival compared to standard therapy. However, chemotherapy can cause serious acute and chronic toxicity; predominantly fatigue, and is associated with a 15-20 percent rate of discontinuation of therapy secondary to adverse events. Therefore many patients with castration resistant disease who are without symptoms will defer docetaxel all together until cancer recurrence creates symptoms, and up to 50 percent of men with castrate-resistant prostate cancer will

avoid docetaxel treatment because of their concern and fear about the impact of the treatment on their quality of life. It should be noted that docetaxel is not administered alone, but in conjunction with prednisone or other corticosteroids, which have their own set of side effects including immune suppression, weight gain and development or worsening of diabetes.

There is a period between detection of castration-resistant disease and the development of symptoms during which patients may choose to defer chemotherapy. Trials of Sipuleucel-T cell immunotherapy were developed to determine if it would favorably stimulate immune response and delay progression of disease in this disease state. Two randomized controlled trials have now been completed that yield consistent findings of a statistically significant survival benefit for Provenge immunotherapy among men with castration-resistant metastatic prostate cancer. In the pivotal IMPACT trial which enrolled 512 men, Provenge provided a survival prolongation of 4.1 months. Provenge was administered over one month – sometimes a little longer --however the survival benefit was not consumed by the time required to administer treatment or manage toxicity. Most adverse events were mild and resolved within 48 hours. Remarkably only three patients (<1%) in the Provenge arm of the IMPACT trial were unable to receive all three infusions because of adverse events. So we have the following situation -- one month of therapy confers a 4.1 month survival benefit. In contrast, six months of docetaxel chemotherapy is required to provide a 2.8 month survival benefit. This benefit to burden ratio overwhelmingly favors Provenge. Add to this the time (sometimes associated with hospitalizations) required to manage the toxicity of chemotherapy and the benefit to burden ratio is further amplified. Provenge is unique as a treatment for far advanced disease where the survival advantage is not consumed by the time required for delivery of treatment and management of treatment toxicity.

As approximately 50 percent of patients in both arms of the IMPACT trial received docetaxel after the study treatment, treatment with Provenge did not preclude subsequent therapies. At this time, it is not known if docetaxel will increase survival if administered after Provenge and the optimal sequence of treatments must be determined through further clinical trials. Provenge is the first active cellular immunotherapy agent that has been demonstrated to be effective against malignant disease. It can be legitimately termed a breakthrough. Provenge represents a new treatment class and a fourth modality that can be brought to bear against prostate cancer. Urologists hope it promises to be the foundation for a kinder, gentler, more effective therapy than is now available for

metastatic castrate-resistant disease. In addition, it may also provide a platform for the treatment of other malignancies.

Greenlight Laser Therapy; Advances in the Treatment of the Enlarged Prostate

By: Gregg R. Eure, M.D., FACS

GreenLight Laser Therapy is a minimally invasive treatment option for an enlarged prostate that combines the effectiveness of the traditional surgical procedure known as transurethral resection of the prostate (TURP) with fewer side effects and a quicker recovery. Enlarged prostate, also known as Benign Prostatic Hyperplasia (BPH), is a common condition in men that is present in nearly half of all men beyond the age of 50 with half of those affected suffering from the symptoms. These include frequent urination, especially at night, sudden urgency to void, weak stream and the feeling of incomplete emptying. The diagnosis can usually be made from the patient's history and a few simple office based tests. It is also important to rule out prostate cancer; this can usually be done with a blood test to measure prostate specific antigen (PSA) and a digital rectal exam (DRE).

Symptoms from the enlarged prostate come from an overgrowth of the middle or interior portion of the gland. This causes restriction of the flow of urine from the bladder. Although medications can be effective, in most men the disease process continues to progress. This can create other medical problems including bladder damage and even erectile dysfunction. The symptoms can also affect quality of life. It is often this change in lifestyle that will cause a patient to seek treatment.

Urology of Virginia, the department of urology at Eastern Virginia Medical School, and members of Sentara Medical Group, began performing the GreenLight Laser Treatment over 7 years ago. The number of treatments have continued to grow both in our group of urologists and globally. I have performed nearly 1000 cases and over 500,000 GreenLight procedures have been done worldwide. I have been fortunate to have had the opportunity to train doctors both in the United States and internationally. We have initiated and published several clinical trials involving the GreenLight Laser. We are also part of a registry where we share and compare

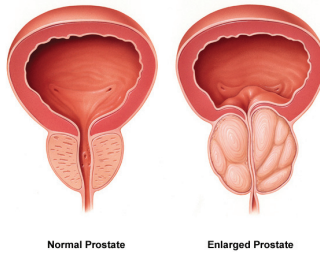
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Greenlight Laser Therapy, Advances in the Treatment of the Enlarged Prostate

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our results with other Centers of Excellence worldwide.

The GreenLight Laser is a very advanced technology. We have been consultants with American Medical Systems, the company that manufactures the laser, and have participated in studies to further improve the technology. The laser generates heat in the prostatic tissue

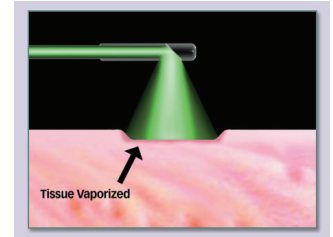


that causes the overgrown tissue to vaporize or melt away. There is no incision, cutting or use of electrical current as was the case with the traditional transurethral resection. The technique is termed Photo Vaporization or PVP. The latest device is the

XPS laser with a MoXy fiber. This laser fiber will allow the urologist to perform the outpatient procedure on larger, more difficult prostates in a shorter amount of time yet maintain the same excellent



safety profile. The first case in the United States using the



XPS laser was performed in our department. This technology is now available for appropriate cases and provides safe and durable treatment option for the enlarged prostate or BPH.

Kidney Cancer and Beyond

By: Steven B. Riggs, M.D.

Kidney cancers continue to be a lethal disease accounting for approximately 209,000 new cancer cases and 102,000 deaths per year worldwide. It is the 7th most common cancer in men and 9th in women. In 2008, over 600 surgeries for this disease were performed in Virginia alone. Treatment options for localized disease include surgical removal, termed normal nephrectomy, or destruction of the tumor by energy sources such as freezing (known as cryoablation) or heating (known as radio frequency ablation (RFA)). These approaches, in general, are highly effective in treating tumors that are confined to the kidney and since the remainder of the kidney is left in place, renal function is minimally impaired. Radical nephrectomy (total removal of kidney) may be the necessary treatment for some patients but every effort is made to use a kidney sparing approach so as to preserve renal function. However, for tumors that have spread locally and or beyond the kidney (known as metastasis) surgical treatment alone is less effective. Under these circumstances, many patients are offered treatment with

a combined approach of surgery and antitumor medications. Fortunately, since 2005, a number of new and improved medical therapies for renal cell carcinoma have emerged. There are currently three FDA approved agents (e.g. Sorafenib, Sunitinib and Temeolimus) and many others in clinical trials or awaiting FDA approval. All of the current and emerging therapies have one common goal; improve cancer control while hopefully decreasing side effects (toxicities). These medications come in different names and formulations (i.e. pill and intravenous forms) and all essentially try to slow down or block the growth of the cancer. Kidney cancer appears to progress and spread by creating new blood vessels to supply nutrients which sustain the cancer and allow it to spread. A way of imagining how these medications work is as follows: think of a key and lock mechanism. The medications for kidney cancer either do not allow the promoting agent, the key, to be formed accurately enough to work, or prevents its insertion into the lock. As in the case with most cancers rising from one organ (i.e., prostate, breast, colon), there are a number

of sub-types of kidney cancer and certain medications appear to be more or less effective depending on the specific type of kidney cancer the patient has.

Our department has assumed a leadership role in delivering therapy for renal cell carcinoma. We offer laparoscopic, robotic, and open surgery depending upon the tumor characteristics and the patient's condition. We perform cryoablation and RFA in conjunction with the interventional radiologist. As already noted, most of our treatments for disease that is confined to the kidney are focused on curing cancer without compromising renal function.

Our goal is to achieve "personalized medicine" in the treatment and cure of kidney cancer. In order to achieve this goal we have constructed a large clinical database and tissue repository. We at Urology of Virginia / EVMS will continue to make further improvements and contributions to the field of kidney cancer and bring these benefits to patients living in South-east Virginia.

From the Research Lab

By: Liz Smith, M.S.

Medical pathologists, specialized in the study and diagnosis of disease, determine whether cancer is present in tissue specimens obtained from a biopsy of an organ, or from the entire organ removed by surgery. The histologist a highly trained individual in specimen processing, prepares the specimens for the pathologist to examine under the microscope to accurately diagnose cancer, and provide valuable information (histology), i.e. Gleason scores, pathologic staging and classification, to the urologist that will help determine the course of action in treatment. Cancer research uses

these same tissues/techniques to gain information beyond cancer diagnosis.

Conventional histology involves the thin sectioning of paraffin embedded/fresh tissue obtained from a biopsy or an organ. Each of these sections is placed on a glass slide and stained for the pathologist to review. This process is not only time consuming and consumes a significant amount of tissue. The tissue microarray (TMA) is a newly popularized technique (~10 years) in research that allows the pathologist or researcher to test a number of tissues in parallel using much smaller sample amounts. TMAs are paraffin blocks that may contain up to 1000 tissue

cores. The TMA can then be sectioned, stained and reviewed to gain information from each of the cores and an overview of all of the cores for interrelationships.

Construction of a tissue microarray is a very precise process. Conventional donor blocks/slides are reviewed for areas of interest based on Gleason score, staging, or classification. Areas of interest are then cored, with core size ranging from 0.6mm to 2.0mm; the cores are placed in a recipient paraffin block. Precise recording of donor core locations within the block is required to produce a useful TMA.

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From the Research Lab

By: Liz Smith, M.S.

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There are a number of advantages to TMA use in cancer research. Molecular analyses is faster by almost 100-fold, a large number of molecular targets can be analyzed and valuable tissue is not wasted. The primary disadvantage to TMAs is that due to the small surface area, the cored sample may not be representative of the tumor: however careful array design and construction can circumvent this problem.

The Urology of Virginia and EVMS biorepository provides recently consented tissue and archival specimens for high-throughput TMA analysis. We are using this tissue to study new biomarkers, which can add to the accuracy of categorization of disease severity and ultimately lead to personalized and more successful therapy for patients with prostate, kidney, and bladder cancer.

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