SUMMER 2013, VOL. 2, NO. 2

Pathways in Cancer

Clinical insight and analysis in advanced cancer care

Minimally Invasive Treatment Options for Prostate Cancer

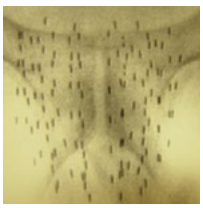
John Stevenson, MD

Radiotherapeutic treatments fall under the broad classifications of noninvasive and minimally invasive. Examples of noninvasive radiation therapy modalities include teletherapy (commonly referred to as external beam therapy), typically delivered with a linear accelerator, and contact therapy, which includes treatments such as radioactive isotope contact therapy in the suppression of pterygium formation or in the treatment of ocular melanomas. External beam therapy is the most common type of radiotherapeutic treatment in the United States and is widely applied in the management of prostate cancer. As the focus of this newsletter will be minimally invasive treatments, we will save noninvasive external beam therapy for a future article. Brachytherapy (commonly referred to as implant therapy) is a minimally invasive treatment and places a radioactive source in close proximity to the area of treatment utilizing needles or catheters inserted into the target area. There are two distinct options for the minimally invasive management of prostate cancer with brachytherapy: permanent interstitial low-dose rate (LDR) seed implantation and high-dose rate (HDR) interstitial brachytherapy.

Interstitial brachytherapy has been around for quite some time, the earliest work having been done with the implantation of hollow needles filled with the naturally occurring radioactive isotope radium. Modern brachytherapy in the management of adenocarcinoma of the prostate involves the use of either low-dose rate permanent radioactive seed implantation or the temporary implantation of a high-dose rate radioactive source.

LDR procedures utilize a variety of radioactive isotopes including Iodine-125, Palladium-103 or Cesium-131. Palladium-103 seeds are shown here, each seed about the size of an uncooked grain of rice. A typical implant will place 80 to 120 seeds into the prostate and periprostatic tissues. These isotopes differ in their physical characteristics, most importantly the half-life and energy of radioactive emission. As more research is being done to examine the biological response of prostate cancer cells to ionizing radiation, it is becoming clear that the overall time required to deliver the treatment plays an important role in the effectiveness of a given dose of radiation. Cesium-131, the newest of the isotopes, has the shortest half-life at 9.7 days. Compared to the half-life of Iodine-125 of 60 days, this shorter half-life will result in a greater biological impact of the dose delivered with a Cesium-131 prostate implant. In this instance the radiation dose is deposited six times faster with Cesium as compared to Iodine. The typical dose delivered with LDR brachytherapy for the primary treatment of prostate cancer ranges from 100 Gy for a Cesium-131 implant to 145 Gy for an Iodine-125 implant. The procedure is performed as an outpatient surgery and takes about an hour to complete.

Another improvement in LDR brachytherapy is the use of stranding of the radioactive seeds. This process involves the mechanical linking of adjacent seeds to prevent migration and movement which results in a more homogeneous dose distribution. As shown in the photograph below, the seeds are held in a linear configuration by an outer sheath. The impact of this process is clearly evident in the two radiographs below. The radiograph on the left is a non-stranded implant, the one on the right was performed with stranded seeds. Stranding allows the placement of seeds outside of the prostate parenchyma to deliver dose beyond the capsule which may be beneficial in certain clinical situations. Stranding has also been shown to dramatically reduce the risk of seed embolization to the lungs and other parts of the body.



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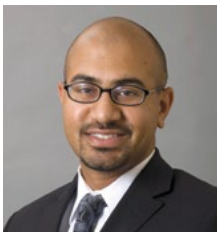
Advances in the Therapy of Castrate-Resistant Prostate Cancer



Shahzad Siddique, MD

Prostate cancer is the most common cancer in men, and the second leading cause of death. One in six men born today in the United States will be diagnosed with prostate cancer at some point in their lives. Advanced prostate cancer is typically treated with androgen deprivation therapy. Despite a high initial response rate, resistant disease develops in all men in one to three years. Chemotherapy is the mainstay for the treatment of castrate-resistant prostate cancer (CRPC). Historically the survival rate in this population has ranged from nine to 13 months. Advances in this therapeutic arena include newer cytotoxic agents, immunotherapy and treatments that target the androgen pathway. There are also new agents that target bony metastasis in prostate cancer.

The combination of docetaxel and prednisone is the standard first line therapy for CRPC. Based on the TAX-327 trial in chemotherapy-naïve patients with metastatic CRPC, this combination was associated with a three-month improvement in survival. Carbazitaxel is a taxane derivative that was approved by the FDA in June 2010 for second line therapy for CRPC. The TROPIC trial included 755 men and evaluated the combination of prednisone and carbazitaxel versus mitoxantrone in a patient population with progression after docetaxel. The experimental arm had an improvement of survival of 2.4 months. The most significant high-grade toxicities include neutropenia and diarrhea.

Sipuleucel-T is a therapeutic cancer vaccine approved by the FDA April 2010 for asymptomatic or minimally symptomatic CRPC. Peripheral blood mononuclear cells were obtained from patients through leukapheresis and cultured ex vivo with a recombinant fusion protein (PA2024). PA2024 consisted of a prostate antigen (prostatic acid phosphatase) fused to an immune activator (granulocyte-macrophage-colony-stimulating-factor). The vaccine was re-infused back into the patient, thereby inducing an immune response to prostatic acid phosphatase expressing prostate cancer cells. The IMPACT trial randomized 512 asymptomatic or minimally symptomatic patients with CRPC and no visceral metastasis to sipuleucel-T versus placebo. Most of the patients were chemotherapy naïve. The study met its primary endpoint of overall survival with an improvement of 4.1 months in the treatment arm. Adverse effects were mild to moderate in nature and resolved 1 to 2 days after the infusion. Common adverse events include chills, fatigue, fever, nausea and headaches. There were no significant differences in time to objective disease progression, and minimal PSA responses.

> "Chemotherapy is the mainstay for the treatment of castrate-resistant prostate cancer (CRPC)."

Abiraterone acetate (AA) is a novel inhibitor of steroid biosynthesis. It was approved in April 2011 for use in CRPC after docetaxel failure based on the COU-AA-301 trial. This trial randomized 1,195 patients with CRPC after docetaxel failure to AA and prednisone versus placebo. There was a 3.9 month improvement in overall survival in the treatment group. The main adverse events were low grade and include fatigue, back pain, nausea, bone pain, arthralgias, fluid retention and hypokalemia.

Enzalutamide is an androgen-receptor-signaling-inhibitor that was approved by the FDA in August 2012 based on the AFFIRM trial. This trial randomized 1,199 patients with CRPC treated with prior docetaxel to Enzalutamide versus placebo. There was a 4.8 month improvement in overall survival in the treatment group. The most common adverse events were fatigue, diarrhea and hot flashes.

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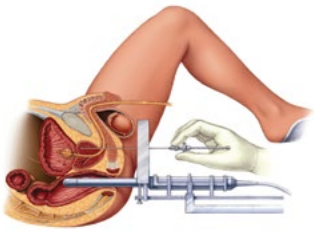
Minimally Invasive Treatment Options for Prostate Cancer, continued from page 1

HDR brachytherapy is the temporary placement of a high activity radiation source into the prostate, using the isotope Iridium-192. Iridium has a half-life of 74 days and an average energy of gamma emission of 380 keV. Needles (catheters) are inserted into the prostate in a minimally invasive procedure similar to permanent seed brachytherapy. The needles are placed through the perineal skin into the prostate under ultrasound guidance as shown in the illustration. A CT scan of the prostate with the catheters in place is obtained and three-dimensional computer planning is performed prior to placement of the radioactive source. This pre-planning approach affords considerable flexibility in the shaping of dose delivery to the prostate, as well as sparing of critical normal structures. The patient is then brought to the treatment facility and the catheters are connected to the high dose rate machine for delivery of treatment. The HDR machine, under robotic control, places the single Iridium-192 source into each catheter for a dwell time of a few seconds to a few minutes, shaping the dose distribution as defined by the computer plan. The only time the patient is radioactive is during the source placement, after completion of treatment the radioactive source and catheters are removed. The dose delivered to the prostate with this technique as monotherapy is approximately 35 to 40 Gy. Despite the lower absolute dose as compared to LDR brachytherapy, the radiobiological impact is considerable as the treatment time is reduced to only a few days.



Side effects are similar with both modalities and related to dose delivered to the adjacent urethra, bladder and rectum. Most patients will experience temporary irritative uropathy which typically will last for a few weeks to a few months. Minor rectal irritation can occur and is manifest as discomfort with the passage of bowel movements and intermittent rectal bleeding. Most patients will retain potency. Incontinence and other complications are fortunately uncommon. Local control of disease with brachytherapy is excellent; there is currently no known advantage with respect to control of cancer when comparing LDR and HDR brachytherapy in the primary management of prostate cancer in comparably staged patients.

Advances in the Therapy of Castrate-Resistant Prostate Cancer, continued from page 2

Prostate cancer is a disorder with a penchant to spread to the bone. Bony metastasis can be asymptomatic, but may also cause significant pain and functional impairment. Therapy is palliative with the goals of controlling pain and limiting complications. Zoledronic acid is a bisphosphonate that is proven to reduce skeletal related events (SRE) in CRPC. SRE is a composite end point that includes pathologic fractures, cord compression, surgery to the bone and radiation therapy to the bone. Denosumab is a monoclonal antibody that binds to the RANK ligand and affects osteoclast formation and activation. Denosumab was compared to zoledronic acid in a study of 1,901 men with CRPC and at least one bony metastasis. The time to first skeletal-related metastasis was significantly delayed in the experimental arm. There was no significant difference in overall survival or time to disease progression. There was also a higher rate of osteonecrosis of the jaw in the denosumab arm. Radium 223 is a radiopharmaceutical agent that was approved in May 2013 for patients with CRPC, symptomatic bony metastasis and no visceral metastasis. The ALSYMPCA trial randomized 921 patients with CRPC, and bony metastasis to radium 223 or placebo. A majority of the patients had prior docetaxel therapy. There was a 3.6 month improvement in survival, decreased pain, decreased incidence of SRE and prolonged time to first SRE. Toxicities were mild and include myelosuppression.

There have been several exciting new agents recently approved in the treatment of CRPC. These agents work through different pathways and generally have milder toxicities. Two of these agents are oral (AA and Enzalutamide). There are also new agents that target bony metastasis and prevent SRE in prostate cancer. The ideal sequence for the use of these therapies is unknown, and there is no data concerning combination therapy. We now have multiple new drugs that extend life and improve quality of life in CRPC.

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TUMOR BOARDS

Mercy Cancer Institute of Greater Sacramento's multidisciplinary approach to cancer care includes regularly scheduled Tumor Boards held throughout Sacramento, offering clinical review of patient cases for optimal treatment results. For each of our Tumor Boards, physicians are eligible for 1 CME credit. Lunch is also provided.

To present a case at an upcoming Tumor Board, please email or call contacts noted below. To present a case, please provide the patient's name, date of birth, disease site and where path and imaging can be found.

Mercy Cancer Center: Breast-focus

3rd Friday of each month at 12:30 p.m.
Location: 3301 C Street, Suite 550, Conference Room
Available via WebEx

Contact: Dawn Lenakakis, CTR
dawn.lenakakis@dignityhealth.org
916.537.5262 for access information

Mercy General Hospital

Wednesdays at 12:15 p.m.
Location: Greenhouse Conference Room
Available via WebEx

Contact: Dawn Lenakakis, CTR
dawn.lenakakis@dignityhealth.org
916.537.5262 for access information

Mercy Hospital of Folsom

4th Wednesday of every other month at Noon (September, November, January, March, May, July)
Location: CC1 and 2 or PCU conference room

Contact: Mansoor Javeed, MD
mansoor.javeed@dignityhealth.org
916.984.6230

Mercy San Juan Medical Center

Thursdays at 12:30 p.m.
Location: Conference Room 2
Available via WebEx

Contact: Dawn Lenakakis, CTR
dawn.lenakakis@dignityhealth.org
916.537.5262 for access information

Methodist Hospital of Sacramento

3rd Friday of each month at Noon
Location: Bistro Conference Room

Contact: Monica Zunker
monica.zunker@dignityhealth.org
916.683.9616

Sierra Nevada Memorial Hospital

Thursdays at 12:30 p.m.
Location: OPC 110-120

Contact: Debby Kirk,
debby.kirk@dignityhealth.org
530.274.6600

St. Joseph's Medical Center

Thursdays at Noon
Location: St. Joseph's Medical Center Auditorium

Contact: Cora Rios
cora.rios@dignityhealth.org
209.461.5104

Woodland Healthcare

Tuesdays at 12:15 p.m.
Location: DCR 5

Contact: Michelle Ing, PA
michelle.ing@dignityhealth.org
530.662.3961

Mark Twain Medical Center

4th Wednesday of each month at 12:30 p.m.
Location: Classroom 2

Contact: Deborah Peterson
deborah.peterson2@dignityhealth.org
209.754.9132