LHRH Agonists in the Treatment of Advanced Carcinoma of the Prostate

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The 9th most common cancer in the world, prostate cancer is the number 1 non-skin cancer in US men and thus a primary concern in managed care. Prostate cancer effected 18% of American men and caused death in 3% in 2005; in 2006, an estimated 234,460 new cases are expected to be diagnosed along with 27,350 reported deaths. Early detection, achieved through screening via digital rectal examination (DRE) or prostate-specific antigen (PSA) testing, is key to improving long-term prognosis and survival, as is the use of the luteinizing hormone-releasing hormone (LHRH) agonists and chemotherapy when appropriate. By monitoring the use and encouraging the implementation of these tools, professionals in managed care oncology can improve outcomes, preserve quality of life, and control costs in their patients with prostate cancer. The need for executives within managed care organizations to improve the identification and care of these men has increased substantially as managed care organizations have re-entered managed Medicare markets.

Screening, Diagnosis, and Staging

Prostate cancer is most commonly diagnosed in older men (>50 years of age), with the only other well-established risk factors being ethnicity and family history of disease. Other screening systems, such as the I to IV staging system and the Whitmore-Jewett staging system are similar in distinction and carry 4 primary levels. Classification of prostate cancer using the aforementioned staging systems is typically

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based on results of DRE, PSA testing, and needle biopsy in the earlier stages and computed tomography, bone scans, and endorectal coil magnetic resonance imaging (MRI) in the later stages. Those prostate cells identified as being cancerous are further classified according to tumor grade, typically using the Gleason grading system. The Gleason grading system assigns a grade to each of the 2 largest areas of cancerous cells in the tissue samples. Grades range from 1 to 5, with 1 being the least aggressive and 5 being the most aggressive. The 2 grades are then added together to produce a Gleason score. A score of 2 to 4 is considered low grade; 5 through 7, intermediate grade; and 8 through 10, high grade. Grading offers a good indication of the cancer’s behavior and is useful as a predictor of outcome, with lower grade tumors characterized by slower growth and better prognosis and higher grade tumors characterized by aggressive growth, metastasization, and poorer prognosis.

Treatment
Age, cancer stage, and comorbid conditions are all considerations when choosing the appropriate treatment for a patient diagnosed with prostate cancer. Early-stage disease can typically be treated with surgery (prostatectomy) and brachytherapy or external-beam radiation. Orchietomy, hormonal therapy, chemotherapy, and radiation can be used alone or in combination for advanced or metastatic disease, or these therapies may be used as supplementation in early-stage disease. This review will focus on the pharmacotherapeutic treatment options, namely: hormonal therapy (LHRH agonists) and chemotherapy. The place of LHRH agonists in the treatment of prostate cancer is shown in Figure 1.

Hormonal Therapy
The goal of hormonal therapy in the treatment of prostate cancer is to suppress the level of testosterone produced by the testes and ultimately lead to apoptosis, or programmed cell death, in cancerous prostatic cells. Originally, surgical removal of the testes, or orchietomy, was the only means by which this reduced production of testosterone could be achieved. This procedure still remains the most reliable means of suppressing testosterone production in the body; however, orchietomy is an invasive and permanent procedure and is associated with side effects such as impotence, hot flashes, and gynecomastia. Estrogen therapy, including the use of diethylstilbestrol (DES), offers a less permanent means of testosterone suppression and was used commonly as an alternative to orchietomy 20+ years ago; however, this means of therapy is associated with significant cardiovascular adverse events that often outweigh the advantages it has over surgery.

LHRH Agonists. In use for more than 20 years, the LHRH agonists offer a third option by which testosterone production can be suppressed in the treatment of prostate cancer. Although these agents carry many of the same antiandrogen-specific side effects as orchietomy or estrogens (ie, impotence, hot flashes, gynecomastia), LHRH agonists offer testosterone suppression that is not invasive or permanent and without serious cardiovascular adverse events. LHRH agonists are synthetic analogs of...
LHRH agonists exert their therapeutic effect by stimulating the production of luteinizing hormone (LH), which subsequently stimulates the production of testosterone. Since the endocrine system registers elevated levels of LHRH, the body ceases production of new normal LHRH as well as LH and testosterone. This initially leads to a rise in the patients’ level of testosterone, lasting 7 to 10 days, followed by a rapid decline in testosterone to approximately 90%–95% of the normal level (“castration level”). This suppression of testosterone production has the same deleterious effect on prostate cells as orchiectomy and estrogen therapy with the specific advantages mentioned previously.

However, the initial 7- to 10-day rise in testosterone associated with LHRH therapy can potentially lead to a temporary increase in the growth of prostate cells with such associated symptoms as bone pain in those patients who already have metastases to the bone. This “flare response” is only temporary, as mentioned previously, and is typically treated with antiandrogens such as bicalutamide (CASODEX) or flutamide (EULEXIN).³

Four LHRH agonists are currently approved for use in the palliative treatment of advanced carcinoma of the prostate: leuprolide (ELIGARD, LUPRON, VIADUR), triptorelin (TRELSTAR), histrelin (VANTAS), and goserelin (ZOLADEX) (Table 1).³ All of the LHRH agonists demonstrate similar efficacy and differ only in formulation or dosing regimen. Typically, these agents are used for patients with advanced disease (T2–T4), disease that is metastatic to the bone, or in elderly patients a PSA doubling time of <6 months. The LHRH agonists are available as injections at 3-, 4-, or 6-month intervals or as subcutaneous implants.³ Currently, the most common dosing regimens seen in the managed care setting for the LHRH agonists is the 3-month injection, coupled with initial antiandrogen therapy to compensate for the flare response. Therapy with the LHRH agonists can be administered continuously in cases of particularly aggressive disease or intermittently to control less aggressive disease and minimize drug-related adverse events. The most common adverse events reported with LHRH agonists are impotence, hot flashes, gynecomastia, hip fracture, osteoporosis, increased risk of hip fracture, and decline in cognitive function.

The LHRH agonists are also used by some clinicians prior to radical prostatectomy, but there is no definitively proven value for this technique. Likewise, LHRH agonists are also used in conjunction with radiation therapy, but debate exists over how long after radiation should therapy with the agents be initiated.

Chemotherapy

Some patients with advanced or metastatic carcinoma of the prostate do not respond to hormonal therapy and even experience disease progression while receiving hormonal therapy. These patients are considered to have hormone-refractory prostate cancer (HRPC). Although several different clinical distinctions exist for the HRPC, it can be functionally defined as prostate cancer that is characterized by three consecutive increases in PSA while a patient is receiving hormonal therapy. In these patients in whom hormonal therapy is not effective, chemotherapy is the next viable pharmacotherapeutic option and has been since the approval of mitoxantrone for HRPC roughly 5 years ago.

Although mitoxantrone was the first chemotherapeutic agent approved for use in the treatment of HRPC, the most commonly used chemotherapy regimen this indication combines docetaxel (TAXOTERE) with a corticosteroid such as prednisone. This is the result of 2 head-to-head studies published in 2004 comparing docetaxel with mitoxantrone in which docetaxel-treated patients demonstrated improved median survival and overall survival (18.2 months vs. 16.4 months and 18.9 months vs. 16.0 months for docetaxel vs. mitoxantrone in the 2 studies, respectively).⁴ ⁵ Previously, mitoxantrone had been approved for use in HRPC with no demonstration of a survival benefit; instead the agent was approved because approximately 33% of symptomatic patients experienced an improvement in pain when administered the therapy.⁶ ⁷

As with other chemotherapy agents, mitoxantrone and docetaxel are
associated with adverse events such as fatigue, nausea and vomiting, hair loss, and low blood cell and platelet counts. Some of these adverse events can be managed with other agents, such as antiemetics for chemotherapy-induced nausea and vomiting (CINV).

Cost Considerations
Much debate exists in the field of managed care over the initiation of pharmacotherapy for prostate cancer and the benefits derived from early intervention in light of the costs incurred. Although early pharmacotherapy may improve outcomes in the treatment of prostate cancer after surgery and radiation, there is no definitive evidence to support that notion and doing so leads to dramatically increased costs. Instead, waiting for specific clinical markers indicating more aggressive disease before initiating drug therapy will help to control costs without adversely effecting outcomes.

For example, if a patient diagnosed with prostate cancer has no aggressive or metastatic disease on biopsy, there is likely little to no benefit derived but much cost incurred by initiating hormonal therapy or chemotherapy at this stage in the disease. However, when PSA levels reach the 25 to 30 range or when PSA doubling time is <6 months, there is an obvious and urgent need to initiate pharmacotherapy in order to improve the overall prognosis of the patient. By way of reference, the normal range for PSA is approximately 2 to 3 ng/mL for men aged between 40 and 50 years, 3 to 4 ng/mL for men aged between 50 and 60 years, and 4 to 5 ng/mL for men aged between 60 and 70 years. For men over the age of 70, the normal range for PSA is approximately 6 to 7 ng/mL.

Intermittent therapy is another way by which costs can be controlled without sacrificing outcomes. Rather than administering hormonal therapy or chemotherapy continuously after a patient’s disease has been diagnosed, clinical markers can again be used as indicators for the discontinuation and re-initiation of therapy. PSA levels and doubling time are again the primary outcomes to be monitored in using this treatment methodology, with discontinuation of therapy signaled by PSA levels below the target initiation range. Not only does intermittent therapy control costs by saving on the amount of drug product used and administration costs, but this method of treatment also reduces the incidence of adverse events and the costs associated with those events (eg, CINV drugs, medical care for hip fractures, etc). The reduced incidence of adverse events associated with intermittent therapy also stands to improve patient quality of life and increase medication adherence as well.

Table 1. Dosing of LHRH agonists for the treatment of advanced carcinoma of the prostate.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Formulation</th>
<th>Dosage Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEUPROLIDE</td>
<td>1 mg</td>
<td>SC Injection</td>
<td>Daily</td>
</tr>
<tr>
<td>ELIGARD</td>
<td>7.5 mg</td>
<td>SC Depot</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td>22.5 mg</td>
<td>SC Depot</td>
<td>Quarterly</td>
</tr>
<tr>
<td></td>
<td>30 mg</td>
<td>SC Depot</td>
<td>Q4 Month</td>
</tr>
<tr>
<td></td>
<td>45 mg</td>
<td>SC Depot</td>
<td>Q6 Month</td>
</tr>
<tr>
<td>LUPRON</td>
<td>7.5 mg</td>
<td>IM Injection</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td>22.5 mg</td>
<td>IM Injection</td>
<td>Quarterly</td>
</tr>
<tr>
<td>ZOLADEX</td>
<td>3.6 mg</td>
<td>IM Injection</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td>10.8 mg</td>
<td>Implant</td>
<td>Monthly</td>
</tr>
<tr>
<td>TRELSTAR</td>
<td>3.75 mg</td>
<td>IM Injection</td>
<td>Monthly</td>
</tr>
<tr>
<td></td>
<td>11.25 mg</td>
<td>IM Injection</td>
<td>Quarterly</td>
</tr>
<tr>
<td>VANTAS</td>
<td>50 mg</td>
<td>Implant</td>
<td>Annually</td>
</tr>
<tr>
<td>VIADUR (65mg LEUPROLIDE Freebase)</td>
<td>72 mg</td>
<td>Implant</td>
<td>Annually</td>
</tr>
</tbody>
</table>

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Conclusions
Prostate cancer represents a significant concern in the managed care setting, with advanced metastatic disease demonstrating a median survival of 18–24 months. Screening and diagnosis, along with the choice of appropriate therapy based on the staging of the disease, are crucial to the administration of effective care. Well established in the treatment of advanced disease for over 20 years, the LHRH agonists present an ideal first-line option that is favorable to orchietomy or estrogen therapy because of the less invasive and permanent nature of the treatment as well as the lack of serious cardiovascular adverse events.
• For quite some time, oncology has performed “just in time” mixing to avoid wastage. What this means is that the patient’s lab results are assessed just prior to administration, and dosing is titrated at that time. This may mean that the original order placed 48 hours in advance is modified or canceled altogether. Like practices under the current system, vendors may only charge the program for wasted single-dose vials.

• As mentioned previously, patient collection is rife with conflict. Moreover, a CAP vendor may be more anxious to collect patient payment, as they have to wait at least 14 days to bill them.

• The ability to forecast who will use what may create constant turmoil. Doctors who use too much “emergency drug” may upset vendor inventory models. Oncologists are worried about CAP drug sources and contamination along with the 48-hour ordering window.

• Both parties can be fired as the result of a dispute. This year, if there was a choice (which there is not), physicians could fire their vendor and choose another one for 2007. While this is a long process, vendors can file a grievance with CMS and get the physician removed from the CAP program.

Could there have been a solution that would have attracted cancer practices and a better variety of Oncology-savvy vendors?

Here are some possible and simple solutions that might have attracted cancer practices and a better variety of Oncology-savvy vendors?

1. Ensure that CAP treatment guidelines are established based on clinically supported guidelines for all common cancers and supportive therapies. This way the vendor can better predict utilization and physicians will be more likely to avoid denials for medical necessity. The physician clinic should be paid an incentive for consistently utilizing guidelines so that CAP is more profitable for them.

2. Allow a formulary for multi-source cancer and supportive therapies. This will provide incentives for manufacturers to lower costs to CAP vendors and allow vendors to make a profit on the program.

3. Have a replacement program where automatic ordering is done through automated drug cabinets, as it is now. The CAP vendor will replace the drug rather than supplying it in 24 to 48 hours. This will minimize the wastage issue. It would also mean that vendors and cancer practices could use current ordering channels.

4. Allow the practice to bill for the drug rather than having the vendor wait. This would mean that the practice would receive payment for the administration. The vendor would receive payment for the drug in the case of “clean” claims within 14 days. Practices that consistently violate the 14-day window would have to relinquish billing duties to the CAP vendor, including drug administration.

5. CMS (or any other payor that attempts a CAP program) should take on the task of explaining CAP and CAP vendor relationships to patients. After all, CMS is the ultimate beneficiary if this program works.

When hormonal therapy fails and a patient’s cancer is classified as being hormone-refractory, chemotherapeutic options are available for the palliative treatment of the advanced disease. Docetaxel remains the new gold standard in this drug class, with clinical trials demonstrating improvements in survival with the agent over mitoxantrone.

Well timed and judicious administration of both hormonal therapy and chemotherapy allows for controlled costs in the managed care setting without sacrificing outcomes. Using clinical markers such as specific PSA levels or PSA doubling times allows the vigilant clinician the freedom to control the course of therapy and in turn control costs and reduce adverse events. In the long run, this leads to virtually identical outcomes to continuous therapy with improved quality of life for the patient and lower direct and indirect medical expenditures for all parties involved.

References


