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Atrasentan for Metastatic Hormone Refractory Prostate Cancer

Summary

- ✓ **Atrasentan (Xinlay®) is an anti-cancer drug from a new class of agents called selective endothelin-A receptor antagonists. The orally administered drug is being studied in a subset of patients with advanced prostate cancer.**
- ✓ **Phase II and III studies evaluating time to clinical and radiographic progression failed to demonstrate a significant benefit with atrasentan versus placebo.**
- ✓ **The adverse effects, observed more frequently in those treated with atrasentan than in placebo-treated patients, were peripheral edema, rhinitis, headache, infection, dyspnea, and heart failure.**
- ✓ **Atrasentan's role in the various stages of advanced prostate cancer, and relative to the chemotherapeutic agent docetaxel, has not been determined.**

The Technology

Atrasentan (Xinlay®) is an oral anti-cancer drug belonging to a new class of agents known as selective endothelin-A receptor antagonists (SERA). The drug binds to endothelin receptors and prevents naturally produced endothelin from exerting its effects.^{1,2}

Endothelin is a protein produced by normal and malignant cells. It has a potent ability to constrict blood vessels, and it influences the growth, proliferation, and survival of normal and malignant cells. Endothelin is thought to play a role in prostate, ovarian, colon, breast, endometrial, and cervical cancers; melanoma;

and Kaposi's sarcoma. It also affects osteoblasts (bone building cells) and is thought to contribute to bone metastases in advanced prostate cancer.^{1,2}

Regulatory Status

Atrasentan has not been approved for use in Canada, Europe, or the US. The manufacturer (Abbott Laboratories) submitted a new drug application to the US Food and Drug Administration (FDA) for use in metastatic hormone refractory prostate cancer. In September 2005, the Oncologic Drugs Advisory Committee recommended against FDA approval of atrasentan, because it failed to delay progression of the disease by a statistically significant amount compared with placebo.^{3,4}

Patient Group

Prostate cancer is the most common cancer, and the third highest cause of cancer-related death in Canadian men. It is estimated that 20,500 men will be diagnosed with prostate cancer in 2005, and 4,300 will die of the disease.⁵

A portion of patients will progress to a more advanced cancer stage despite treatment of the localized disease and ongoing hormone therapy. These patients are considered to be hormone refractory. The likelihood of cancer recurrence after the treatment of localized disease is approximately 25% in 10 years.⁶ Metastases to the bone are common, and can cause pain, loss of mobility, decreased quality of life, and fractures.^{2,7} The median survival of men with hormone refractory prostate cancer is 12 months to 20 months.^{6,8}

Current Practice

The treatment of localized prostate cancer includes the surgical removal or irradiation of the prostate, or “watchful waiting.” Because the growth of prostate cancer tends to be slow, some patients may be monitored for evidence of progression or symptoms of the disease before more active treatment is initiated. Hormone therapy, which may also be used for patients with advanced disease, includes orchiectomy (castration) or drug therapy (luteinizing hormone-releasing hormone agonists). Anti-androgen therapy (drugs to block the effects of testosterone) may also be used.⁹

Prostate cancer patients who progress despite hormone therapy have few treatment options. Treatments focus on symptom control, and although they are not curative, they may offer life prolongation.⁶ In April 2005, docetaxel (Taxotere[®]), a chemotherapeutic agent used in breast, lung, and ovarian cancer treatment, was approved to treat patients with hormone refractory metastatic prostate cancer.¹⁰ Clinical trials show that docetaxel (with prednisone or estramustine) significantly improves survival versus active control. In one study, the median survival time was reported as 17.5 months versus 15.6 months with docetaxel compared to mitoxantrone ($p=0.02$).¹¹ Pain control was also improved with docetaxel. Adverse effects include neutropenia, fatigue, nausea and vomiting, hair loss, peripheral edema, cardiovascular events, and diarrhea.^{6,11}

Symptom control treatments include radiation of lesions, radioisotopes, chemotherapy, and narcotics for pain control. A bisphosphonate, zoledronic acid, has shown modest benefits in the control of bone pain and the reduction in skeletal complications.⁷

The Evidence

Atrasentan for advanced metastatic prostate cancer has been studied in two randomized trials (a phase II and a phase III study) where time to progression (TTP) was the primary end-

point.^{12,13} Data from the two trials were pooled in a meta-analysis.¹⁴ The phase II trial has been published.¹²

The types of patients who were enrolled were similar in both studies. They had documented metastatic prostate cancer showing signs of progression despite hormone therapy, minimal or no cancer related pain, and a life expectancy of more than six months. Disease progression, which was similar between trials, was defined as pain requiring narcotics or other symptom control therapies; new symptoms of tumor growth or a metastatic event requiring therapy; new bone lesions; or new or progressive soft tissue lesions.^{12,15}

In the phase III study, patients were randomized to receive atrasentan 10 mg daily (408 patients) or placebo (401 patients). The trial was terminated early, because it failed to meet its primary endpoint, and most patients had progressed within three months.^{16,17} No significant difference in TTP was detected between the treatment and placebo groups based on the intention-to-treat analysis.¹⁵ The median TTP was 91 and 86 days for the atrasentan and placebo groups respectively [hazard ratio 0.885, 95% confidence interval (CI) 0.755 to 1.037, log rank $p=0.123$].¹⁷

Radiographic progression (75%) and pain (20%) were the most common progression events. Unlike the phase II study, where bone scans were completed based on clinical need or at the end of the study, scans in the phase III study were scheduled every 12 weeks. The scheduling of scans may have had an impact on the ability to detect a difference between groups, because the time when the event occurred (i.e., metastases) and the time when it was detected (through a bone scan) may be different.¹⁷

The phase III study also failed to demonstrate a benefit of atrasentan on four of five secondary endpoints, including overall survival, progression-free survival, and other biochemical or radiographic events.¹⁷

The phase II study failed to detect a significant difference in TTP between atrasentan 2.5 mg (n=95), atrasentan 10 mg (n=89), and placebo (n=104) groups.¹² A statistically significant delay in TTP with atrasentan 10 mg versus placebo was detected when data from 1,002 patients were pooled in a meta-analysis (hazard ratio 0.863, 95% CI=0.747 to 0.997, median time to progression unspecified).¹⁴ Because of differences in the study design, treatment population, definition of disease progression, and bioequivalence of the active drug product administered, the validity of the pooled data has been questioned.¹⁷

Adverse Effects

In the phase III study, the adverse effects (AEs) reported more frequently for atrasentan versus placebo ($p \leq 0.05$) were peripheral edema (swelling) 40% versus 12%; rhinitis (nasal congestion) 36% versus 14%; headache 21% versus 14%; infection 13% versus 8%; dyspnea (difficulty breathing) 9% versus 4%; and heart failure 4% and 1%. The incidence of serious AEs was similar between groups. No significant difference was detected in the number of patients who discontinued therapy (18% and 16%) or died (6% and 5%) because of AEs in the atrasentan and placebo groups respectively.¹⁵

In an FDA review, cardiovascular toxicity was raised as a potential concern with atrasentan. Among patients receiving atrasentan, 42% had an event listed as heart failure, lung edema, or peripheral edema, compared with 13% of placebo patients. More cardiovascular events occurred in the atrasentan group versus the placebo group (i.e., myocardial infarction, nine versus two; and arrhythmias, 24 versus five). The number of cardiovascular deaths was reported as eight and two in the atrasentan and placebo groups respectively (statistical significance unreported).¹⁷

Administration and Cost

There is no cost information available. Atrasentan is administered by mouth, once daily, as a 10 mg capsule.¹⁸

Concurrent Developments

Atrasentan is being studied in combination with docetaxel, and with zoledronic acid, to determine dosing, safety, and efficacy in advanced prostate cancer.² Abbott is studying the effect of atrasentan in patients with earlier stages of prostate cancer, such as hormone naïve patients exhibiting signs of treatment failure, and in hormone refractory patients without metastases. Atrasentan is also being investigated in other malignancies, including kidney, ovarian, breast, brain, colorectal, and non-small cell lung cancers.¹⁶

Other agents, such as bevacizumab (Avastin[®]) and thalidomide, are in the early investigation stages for advanced prostate cancer.^{6,19} Preliminary studies with calcitriol (vitamin D) and docetaxel have shown promising response rates in metastatic prostate cancer. Further studies are planned.¹¹

Rate of Technology Diffusion

Docetaxel is the only agent shown to improve survival in metastatic, hormone refractory prostate cancer.^{6,11}

Additional clinical trials are needed to determine atrasentan's role in the subpopulations with advanced prostate cancer. Possible studies of interest could include active comparison with docetaxel; or atrasentan in combination with other treatments, such as radiotherapy or analgesics, in patients with significant cancer-related pain. Further surveillance may also be important to better evaluate the potentially serious adverse effects observed in clinical trials. The cost-effectiveness of atrasentan cannot be determined until its price is available.

Implementation Issues

Atrasentan's launch to market will likely be delayed because of the Oncologic Drugs Advisory Committee's recommendation.

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