Endothelin-A receptor antagonists in the treatment of hormone-refractory prostate cancer

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Abstract

Dysregulation of the endothelin axis has been implicated in the progression of prostate cancer; thus providing a potential therapeutic target. Atrasentan is a potent, selective, orally available endothelin-A (ET_A)-receptor antagonist that has been shown to block the mitogenic, anti-apoptotic, and bone-remodelling activity of endothelin-1 (ET-1) in pre-clinical studies. Orally bioavailable, with a half-life suitable for once-daily dosing, atrasentan provides optimal convenience for patients requiring long-term therapy. Phase I dose-escalation studies have shown the drug to be well tolerated at a recommended clinical dose of 10mg in patients with hormone-refractory prostate cancer (HRPC). This favourable tolerability profile has been confirmed in phase II studies, in which headache, rhinitis, asthenia and peripheral oedema have been identified as the most common adverse events. Recently, a large, multicentre phase II study has demonstrated that atrasentan delays disease progression and time to prostate serum antigen (PSA) progression in HRPC, and is associated with improvements in quality of life compared with placebo. Furthermore, evidence has emerged from this and other studies that atrasentan may attenuate tumour-induced bone remodelling, impeding the progression of skeletal disease in patients with HRPC.

Atrasentan is currently being investigated in phase III clinical studies in subjects with HRPC, with or without metastases. Data from 1,097 men pooled from phase II and one of the phase III (M00-211) have now been evaluated. Treatment with the selective endothelin-A receptor antagonist atrasentan produced a significant delay in time to disease progression (TTP)(median TTP: 115 days with atrasentan vs. 86 days with placebo; p=0.013 by log-rank) in the intent-to-treat cohort, defined as a composite of radiographic or clinical measures. Results of sensitivity analyses were consistent with the main treatment effect. Time to onset of bone pain was prolonged in the atrasentan arm (224 days vs. 124 days; p=0.003). Patients randomized to atrasentan experienced significantly less bone pain in an analysis of adverse events while on protocol (45% vs. 54% overall incidence; p=0.003; 9,7% vs. 14,4% grade ¾ bone pain; p=0.019, respectively).

Daily treatment with oral endothelin-A receptor antagonists like atrasentan produces a clinically meaningful and statistically significant improvement in time to disease progression and time to onset of bone pain in men with metastatic HRPC.