ALPHA PARTICLE THERAPY IN METASTATIC PROSTATE CANCER

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1. INTRODUCTION

Metastatic castrate resistant prostate cancer (CRPC) is a leading cause of cancer mortality among men in western countries. Although nearly 85% of patients present with localised disease, up to 40% will eventually develop metastatic disease during the course of illness. Of men dying from prostate cancer, more than 90% have bone metastases many with no other significant metastatic sites. Symptoms related to bone metastases and skeletal related events (SREs) account for the major cause of morbidity in these patients.

Bone-seeking radionuclides have been used in the treatment of prostate cancer bone metastases for many years. The first bone seeking radionuclide drug approved by the FDA was Strontium-89. Other agents have also been used including Samarium-153 EDTMP, Rhenium-186 (-188)-HEDP. These radionuclides are all emit short-range therapeutic beta radiation with bone marrow as the dose limiting toxicity. There is strong clinical trial evidence of benefit for these radionuclides in reducing pain in advanced prostate cancer; however, none of the drugs has been shown to improve survival, albeit none of the clinical trials were powered to detect differences in survival.

2. RADIUM-223

Over the past 10 years there has been increasing interest in bone-seeking radionuclides as disease modifying agents in metastatic prostate cancer when used in innovative ways. Recent data from a phase 3 RCT investigating Radium-223 (Xofigo) in advanced CRPC (ALSYMPCA Trial) has really opened the field to the prospect of significant benefits to patients. Radium -223 chloride (Xofigo) is natural bone-seeking calcium mimetic that emits high-energy alpha particles which delivers intense highly localised radiation within short area (2-10 cell diameter) resulting in irreparable double strand DNA breaks. These properties enable targeted delivery of radiation to sites of osteoblastic metastases with little effect on normal bone marrow. It has a half-life of 11.4 days and is excreted mainly through the intestine.

The ALSYMPCA trial was a phase 3 double blind placebo controlled RCT of Radium-223 in patients with progressive symptomatic CRPC who had previously received or were unfit for Docetaxel chemotherapy. Patients were randomised in 2:1 fashion to 6 × 4 weekly injections of radium-223 (50 kBq/kg IV) or placebo and were stratified according to prior Docetaxel use (yes or no), baseline alkaline phosphatase level (? > 100 versus < 100), and current bisphosphonate use. A total of 922 patients participated in the study and a planned interim analysis showed significant benefit from Radium-223 treatment, which lead to early termination of the trial. The results showed significant benefit in median survival with Xofigo treatment (median OS 14.0 vs. 11.2 months; P = 0.00185; HR = 0.695; 95% CI, 0.552-0.875). There was lower incidence of SREs in Radium-223 group including reduction in development of spinal cord compression (3% vs. 6%; p = 0.016) and time to first SRE was significantly delayed (13.6 vs. 8.4 months; P = .00046; HR = .610; 95% CI, .461-.807. Xofigo treatment was well tolerated with low incidence of grade 3 / 4 neutropaenia (1.8% vs. 0.8%) and thrombocytopaenia (4% vs. 2%). Radium-223 has recently been approved by the FDA and will most likely receive European approval by the end of 2013.

There are a number of challenges to the widespread use of this radionuclide including which type of clinician will prescribe and administer the drug in different countries as well as the crowded therapeutic landscape in CRPC.

3. CONCLUSION

Management of metastatic CRPC have become more exciting in the last decade with the approval of several new drugs including Abiraterone Acetate, Enzalutamide, Docetaxel, Cabazitaxel, and Provenge, but it has also raised issues regarding appropriate sequencing of these agents to get maximum benefit for the patient. Systemic radionuclides have an established role in palliation of bone metastases from prostate cancer and recent studies has demonstrated survival benefit in patients with metastatic prostate cancer for the alpha-emitting radionuclide, Radium-223 (Xofigo).

Future studies with Radium-223 will examine ways of improving outcome in advanced disease setting and also should explore the possible role in early stage prostate cancer by targeting bone micrometastases. Radium-223 is also being tested in breast cancer.