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in Hormone Refractory Prostate  
Cancer (HRPC)**

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# CHEMOTHERAPY AND TARGETED THERAPY IN HORMONE REFRACTORY PROSTATE CANCER (HRPC)

The TAX-327 study randomized 1006 men with metastatic hormone-refractory prostate cancer (HRPC) to receive 3-weekly docetaxel, weekly docetaxel or mitoxantrone, each with prednisone. An improvement in survival was seen both in this trial and in the SWOG group study of 3-weekly docetaxel and estramustine as compared to mitoxantrone and prednisone. Every 3 weekly docetaxel chemotherapy with prednisone has thus been approved for use in Europe. Several ongoing studies aim at improving upon the results with docetaxel and prednisone by adding newer targeted agents.

## ANGIOGENESIS

Vascular endothelial growth factor (VEGF) is a growth factor that is essential for neoplastic angiogenesis, tumor growth and metastasis. As prostate cancer is likely dependent on angiogenesis for its growth and progression, it would logically serve as a good target for this modality. Initially met with great enthusiasm, antiangiogenic agents such as bevacizumab are being used in combination with docetaxel and prednisone and a large ongoing cooperative group study is evaluating its benefits.

## ANTISENSE OLIGONUCLEOTIDES

One of the pathways that bypasses the androgen receptor (AR) involves deregulation of apoptotic genes. Bcl-2, which regulates apoptosis, mediates resistance to androgen ablation and chemotherapy in HRPC. Docetaxel and antisense oligonucleotide therapy targeting Bcl-2 (oblimersen sodium) has completed an EORTC phase II randomized trial. A phase I-II trial combining docetaxel +/- clusterin antisense oligonucleotide (OGX-011) that targets a cytoprotective gene is likewise in course in Canada.

## VITAMIN D

Calcitriol (1,25-dihydroxycholecalciferol, 1,25(OH)<sub>2</sub>D<sub>3</sub>) (DN-101) is the natural ligand for the vitamin D receptor. It modulates growth factor signalling, induces apoptosis through downregulation of the antiapoptotic protein Bcl-2 and is antiangiogenic. A phase II randomized trial revealed a 7 month improvement in survival with the combination of weekly docetaxel and DN-101, at a median of 18 months follow-up. A large phase III trial to further assess these findings is in course (ASCENT-2).

## BONE TARGETED THERAPY

HRPC is often associated with the development of painful bone metastases. Newer generation bisphosphonates may relieve pain caused by bone metastases, prevent treatment-related loss of bone mineral density, possibly slow the growth of metastases, and reduce skeletal complications. They are effective for the treatment of both osteolytic and osteoblastic metastases. Newer monoclonal antibodies such as denosumab are being evaluated in comparison to the well established bisphosphonates.

## ENDOTHELIN RECEPTOR

Endothelin A plays a role by inhibition of apoptosis, stimulation of proliferation, stimulation of osteoblasts and has pain nociceptive effects. In HRPC there are increased plasma concentrations of endothelin-1 (ET-1), decreased clearance of endothelin and increased endothelin-A expression. Atrasentan is an oral selective endothelin-A receptor antagonist. A meta-analysis of 2 randomized trials was characterized by a reduction in risk associated with disease progres-

sion, attenuation of rise in biomarkers, delay in time to biochemical progression, decrease in time and incidence of bone pain, and improvement in disease-specific QOL. A large randomized trial is evaluating the addition of atrasentan to docetaxel and prednisone.

## SATRAPLATIN

Second-line treatment in patients with HRPC is an unmet medical need. Satraplatin is a 3<sup>rd</sup>-generation oral platinum compound with in-vitro activity against taxane-resistant cell lines in a variety of tumor types. Activity in the EORTC trial led to the phase III SPARC (Satraplatin and Prednisone Against Refractory Cancer) of 950 patients treated with 1 prior cytotoxic chemotherapy. Treatment with satraplatin resulted in a 33 % reduction (per IRC) in the overall risk of disease progression ( $p < 0.001$ ; HR: 0.67; 95 % CI: 0.57–0.77). The effect of satraplatin on PFS increased over time. At median PFS, the improvement was 14 % (11.1 vs 9.7 weeks), reaching 81 % at the 75<sup>th</sup> PFS percentile (34.6 vs 19.1 weeks). Satraplatin was equally effective regardless of whether or not patients received prior docetaxel treatment and effective across all groups of patients evaluated. Overall survival results are eagerly awaited.

## CONCLUSIONS

The present and future has become clearer with an increased understanding of the patients and PSA kinetics in responding patients to chemotherapy. The future focus in HRPC will be based upon understanding of the molecular causes of castration resistance and therapeutic targeting. Satraplatin oral chemotherapy is well tolerated and offers promise in the second line therapy of HRPC.

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