

# Novel approaches for the treatment of prostate cancer



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'This issue of *Therapy* reviews several novel strategies for treating select populations of patients with newly diagnosed and advanced stages of prostate cancer.'

It is estimated that in 2007 over 27,000 men in the USA will die of prostate cancer, making this disease second only to lung cancer in terms of cancer-specific mortality [1]. The growing practice of screening for prostate-specific antigen has led to increasing numbers of patients being diagnosed with local disease and more patients undergoing treatment with either surgery or local radiation. However, a number of men with newly diagnosed prostate cancer have a more indolent form of disease, which raises questions about optimal treatment strategies. This issue of *Therapy* reviews several novel strategies for treating select populations of patients with newly diagnosed and advanced stages of prostate cancer.

Approximately 20–40% of prostate cancer patients who receive definitive local therapy will develop recurrent disease, manifested by rising serum prostate-specific antigen, and many will then undergo hormonal treatment. Patients with clinically localized prostate cancer who fail treatment with either radiotherapy or brachytherapy have limited treatment options. Among the novel approaches reviewed and discussed by Polascik in this issue are cryoablation, high-intensity focused ultrasound, photodynamic therapy and focal therapy [2]. Ismail *et al.* discuss two new concepts in adjuvant therapy – cryoimmunotherapy and cryochemotherapy. These experimental techniques can potentially be performed with minimal toxicity to patients and show promise for improving upon standard cryotherapy as a single modality [3].

A number of high-risk prostate cancer patients will develop either biochemical relapse or overt metastatic disease. While these patients can initially be treated with androgen-deprivation strategies, the vast majority will eventually develop androgen-independent

prostate cancer (AIPC). Cullig and Hobisch discuss recent basic scientific advances in our understanding of the nature and function of the androgen receptor (AR) [4]. They examine different ways to address AR hypersensitivity, critical coactivators and corepressors, the possibility of inducing expression of AR downstream genes in cells lacking AR expression, the relationship between hypoxia and AR activity and chemotherapy and androgen ablation. An important example of this is the recent discovery of fusion of the 5'-untranslated region of the *TMPRSS2* gene and either *ERG* or *ETV1* ETS transcription factor in the majority of prostate cancers [5]. This fusion may be an important factor in discriminating between aggressive and indolent disease.

Early clinical trials with chemotherapy in advanced prostate cancer have been disappointing. In the last decade, mitoxantrone with glucocorticoids was approved for treatment of prostate cancer, based on palliation of symptoms without improvement in survival [6,7]. More recently, two large Phase III trials demonstrated a survival advantage for docetaxel-based regimens compared with mitoxantrone with prednisone [8,9]. This helped to establish docetaxel-based therapies as the standard of care for patients with metastatic AIPC, and provided a platform for the translation of novel agents into new combination cancer therapies. Karakunnel and Dahut discuss novel targeting agents and their potential use in prostate cancer [10], including anti-angiogenic agents, growth factor inhibition, antisense agents and other molecular targets. A number of Phase II clinical studies employing a combination of these agents with traditional chemotherapy have produced early evidence of clinical benefit in patients with metastatic disease. Larger randomized studies are ongoing to determine the true clinical benefit of various combination approaches.

Bone metastases and skeletal complications are major causes of morbidity in men with prostate cancer. Lee and Smith discuss the use of bisphosphonates and data supporting the use of zoledronic acid to reduce skeletal complications in men with AIPC and bone

metastases [11]. In addition to studies utilizing bisphosphonates, they discuss the novel approach of using an antibody that inhibits the receptor activator of nuclear factor- $\kappa$ B-ligand signaling for prevention of bone metastasis and skeletal complications.

Novel experimental therapies involving tumor immunology have recently shown promise. The field of prostate cancer vaccines is currently in a state of active preclinical and clinical investigation. While no therapeutic cancer vaccine has been approved to date by the US FDA, recent preclinical and clinical findings have demonstrated that appropriate clinical trial design and end points, and the use of vaccines in new paradigms of combination therapies, may ultimately lead to the use of cancer vaccines for treatment of several types of cancer.

Several randomized studies have now shown improved overall survival of prostate cancer patients despite minimal tumor response as measured by traditional Response Evaluation Criteria in Solid Tumors criteria. In an editorial on the role of vaccines in prostate cancer, Gulley highlights the importance of the paradigm shifts in both protocol design and in evaluating the efficacy of cancer vaccines [12].

#### Financial & competing interests disclosure

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