New agents in metastatic prostate cancer

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Since the identification, in 1941, of the high antitumour activity of androgen deprivation therapy in patients with metastatic prostate cancer, only 3-weekly docetaxel was shown to improve survival, while zoledronic acid reduces the incidence of skeletal-related events in patients with castration-resistant prostate cancer (CRPC) [1,2]. The addition of estramustine to chemotherapy significantly improved overall survival in patients with CRPC in a meta-analysis of randomised trials [3]. Greater knowledge of prostate cancer biology has led to the isolation of many new and promising targets, and agents targeting these molecules are currently under development.

Several studies demonstrated that CRPC remains driven by the androgen receptor (AR) signalling pathway despite castrate androgen levels, indicating that "hormone-refractory prostate cancer" (HRPC) is not an appropriate designation. Abiraterone acetate is an oral and selective inhibitor of CYP17, a key enzyme in androgen synthesis. This agent is usually well-tolerated. In chemotherapy-naïve CRPC patients, abiraterone has shown impressive antitumour activity in phase I and phase II trials [4,5]. A large randomised phase III trial which enrolled more than 1000 CRPC patients recently completed its accrual, and is evaluating abiraterone in patients progressing after docetaxel. Other compounds that bind to the androgen receptor with a greater affinity than antiandrogens such as bicalutamide, inducing a strong inhibition of the AR signalling pathway, are in development [6]. For example, MDV3100 showed a promising activity in CRPC in a recent phase I/II trial [7] and a large phase III is starting to evaluate MDV3100 in patients with CRPC progressing after docetaxel.

With the demonstration of docetaxel activity in 2004, chemotherapy is still regarded as a potential area of research in prostate cancer: this includes the earlier assessment of docetaxel in hormone-naïve, metastatic prostate cancer, with a phase III trial (GETUG 15) having completed its planned accrual of 380 patients in 2008, and the development of newer chemotherapy agents including epothilones and cabazitaxel, a new-generation taxane, with a recently completed post-docetaxel phase IIII trial.

The skeleton is the primary site of metastases in patients with advanced prostate cancer, and virtually all patients who die from prostate cancer have bone metastases. Under normal conditions, bone undergoes continuous remodelling in a tightly coordinated and balanced process of bone resorption (mediated by osteoclasts) and bone formation (mediated by osteoblasts). In bone metastases, a perturbation between osteoblats and osteoclasts is induced by tumour cells, leading to a "vicious cycle" [8]. Besides bisphosphonates, the main and currently most advanced attempts to target osteoclast activation by cancer cells include denosumab, a fully human monoclonal antibody directed to RANK-L. Denosumab was shown to reduce uNTx levels significantly better than zoledronic acid does in patients with bone metastases and elevated levels while on intravenous bisphosphonate [9]. Denosumab is being investigated for its potential to help reduce or prevent skeletal complications due to bone metastases from prostate cancer in a large phase III trial ($n > 1700$) which completed its accrual in 2008. Dasatinib, a src inhibitor, was also demonstrated to result in decreased uNTx levels in patients with bone metastases and is currently being assessed in a phase III trial in CRPC in combination with docetaxel. Activation of the endothelin A (ET_A) receptor by endothelin-1 mediates a signalling cascade which promotes tumour cell growth and survival, angiogenesis, invasion, metastasis, and inhibition of apoptosis. ZD4054 is an oral, specific ET_A receptor antagonist with improved overall survival rates in a randomised phase II trial [10]. A large phase III programme (ENTHUSE) is ongoing to evaluate ZD4054 in advanced CRPC in different settings: in prevention of bone metastases, in patients with established bone metastases before chemotherapy, and in combination with docetaxel. Finally, phase I-II clinical data support the use of a bone-targeting strategy combining chemotherapy and bone-specific radiopharmaceuticals like samarium-153 [11].

Like other epithelial neoplasms, metastatic prostate cancer is characterised by an enhanced angiogenesis. Targeting the vascular endothelial growth factor (VEGF) pathway is being studied within two phase III programmes in CRPC using bevacizumab, a monoclonal antibody to VEGF, and VEGF-Trap, a fusion protein of domains of VEGFR2 and VEGFR1 trapping VEGF.

Finally, the long and never-ending story of immunotherapy for prostate cancer has recently provided two milestones including disappointing reported results with G-VAX and positive non-published results with APC8015.

Several limitations make drug development challenging in CRPC: its obvious biological heterogeneity, including or not, for example, aberrant ERG expression [12], the difficulty of having direct access to fresh tissue in a cancer where bone metastases are predominant, and the lack of surrogate endpoints for overall survival. The use of circulating tumour cells (CTCs) in the context of prospective trials may help resolve these issues: emerging data indicate that the quantitative assessment of CTCs may correlate with outcome and drug efficacy [13], while ongoing studies are seeking to use CTCs as an elegant technique to sample cancer cells in order to assess the expression of specific targets [14]. If fully established and made widely available, this technique may constitute a major progress in the attempt to individualise therapy in metastatic prostate cancer [15].

Conflict of interest statement

Participation to advisory boards for Astrazeneca, Sanofi-Aventis, Cougar, Novartis, Amgen, BMS, and Ipsen-Beaufour.

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