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EDITORIAL

Management of advanced prostate cancer – new drugs

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Androgen deprivation therapy by chemical or surgical castration remains the cornerstone in the management of advanced disease. Although initially effective, the effect of currently available androgen deprivation therapies is transient and most patients develop progressive disease despite low levels of testosterone. It is generally believed that tumour progression is associated with continued signalling via the androgen receptor pathway through mechanisms such as androgen receptor mutation, androgen receptor amplification, ligand-independent androgen receptor activation or enhanced local production of androgens. The recognition of the antiandrogen withdrawal response, which demonstrates the continuous importance of the androgen receptor signalling pathway in castrate resistant prostate cancer, has stimulated the development of new exciting androgen targeting therapies. MDV3100, which is a nonsteroidal compound and RD162, are examples of two new orally available interesting agents that target the androgen receptor with higher affinity than bicalutamide [1]. MDV3100 has shown promising phase I/II activity [2] and is currently evaluated in a placebo-controlled randomised phase III trial in patients progressive on docetaxel therapy. EPI-001 represents from a mechanistic point-of-view, a conceptually new and interesting compound. It binds to the N-terminal domain of the androgen receptor and has a new mode of action as it targets the transactivation of the androgen receptor, regardless of the presence of androgen [3,4]. Other efforts are made to further improve the blockage of testosterone production. Abiraterone acetate is an interesting, potent small molecule that irreversibly inhibits cytochrome p17 which catalyzes two key reactions in androgen biosynthesis [5]. This compound has been evaluated in a phase III trial in castrate-resistant patients previously treated with docetaxel (results are pending) and a second phase III trial is ongoing in patients who have not received prior ketoconazole or chemotherapy.

Since the data from the TAX 327 [6] and SWOG 9916 [7] trials were presented in 2004, every-three-week docetaxel has become a standard treatment for patients with castrate resistant prostate cancer. Indeed, these were the first trials demonstrating significant and principally important overall survival benefit using cytotoxic therapy for this patient category. Although significant, the survival benefits achieved by docetaxel-based therapy are rather small, improving the overall median survival compared to mitoxantrone with approximately three months, to less than 20 months [6,7]. Clearly, more effective regimens continue to be needed.

The last years, efforts have been made to improve the effects of docetaxel by either adding an agent to docetaxel/prednisone, develop more effective front line therapy or to find an effective second line therapy. Recently cabazitaxel, a novel taxane with a favourable low affinity to PGP (multidrug resistance P-glycoprotein) in combination with prednisone was approved by the FDA following a phase III trial demonstrating an overall survival benefit of 2.4 months as compared to mitoxantrone, in patients previously treated with docetaxel-containing chemotherapy [8]. If approved also by EMA, cabazitaxel is the reasonable second line option and furthermore the comparator for subsequent second line trials. The epothilone analogues are examples of other chemotherapeutics with promising phase I/II data under current evaluation [9,10].

Our understanding of the complex molecular pathogenesis of prostate cancer has continued to

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expand and several novel drugs that target specific molecules in pathways involved in cell signalling, proliferation, apoptosis, angiogenesis, and immune modulation are also under intensive investigation. Examples of candidate progression pathways include epidermal growth factor (EGFR) signalling, vascular endothelial growth factor (VEGF) signalling pathways, phosphatidylinositol 3-kinase (PI3K) / Akt mammalian target of rapamycin (mTOR) pathway as well as the insulin-like growth factor pathway.

Multiple tyrosine kinase inhibitors with a typical antiangiogenic profile, such as sunitinib and sorafenib are evaluated in prostate cancer but data are yet limited. So far, their efficacy appears to be modest or the toxicity significant [11–15]. Of note are the reported discordant radiological and PSA evaluations, indicating that PSA might not be valuable as a marker for response for these compounds and furthermore that the antitumoural effects caused by these substances in prostate cancer are not completely understood [11–15]. The anti-VEGF antibody bevacizumab has been evaluated in several phase II studies with promising results when given in combination with docetaxel regimens. An awaited large phase III frontline trial, CALGB 90401, was recently reported evaluating the addition of bevacizumab to standard docetaxel regimens. Unfortunately, this trial failed to meet the primary endpoint of demonstrating an overall survival benefit following the addition of bevacizumab [16] and the place for this compound in the treatment arsenal remains unclear.

Src and src-family kinases represent interesting target molecules since they are involved in multiple signalling pathways central to prostate cancer development and in the pathogenesis of bone metastases. For example is the value of adding the src-inhibitor dasatinib, which has also activity against bcr/abl, to standard docetaxel regimen, under evaluation in an ongoing phase III trial [17]. Other examples of novel targeted agents under investigation in advanced prostate cancer include the mTOR inhibitors everolimus and temsirolimus, various inhibitors of IGF-1R and custirsen (OGX-011), an innovative antisense oligonucleotide directed against the cytoprotective chaperone, clusterin [18].

Histone deacetylase inhibitors such as panobinostat (LBH589) are currently evaluated and represent principally interesting approaches to target tumour-induced epigenetic aberrations believed to be critical for androgen receptor mediated signalling [19].

In addition to targeted therapies, the slowly-growing nature and high expression of tumour-associated antigens of prostate cancer have stimulated the development of several immunotherapeutic approaches. Just some months ago, FDA approved the first therapeutic vaccine ever, sipuleucel-T, for asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer [20,21]. Sipuleucel-T consists of autologous dendritic cells derived from a patient's own peripheral blood mononuclear cells. The dendritic cells are collected through leukapheresis and exposed to a recombinant fusion protein composed of the tumour associated antigen PAP (prostatic acid antigen) linked to granulocyte-macrophage colony stimulating factor [20,21]. In the pivotal phase III trial, patients receiving sipuleucel-T had a median overall survival of 25.8 months compared to 21.7 for the patients receiving placebo, without any substantial side-effects related to the vaccine [21]. Other examples of vaccine approaches under evaluation are vector-based strategies (Prostvac) [22] or whole tumour cell vaccines (GVAX), the latter however with recently reported negative phase III trials [23,24]. Ipilipumab, an anti-CTLA4 monoclonal antibody, represents a principally different immunotherapeutic approach under evaluation since treatment with ipilipumab is supposed to enhance T-cell activation. Phase I and II data have indicated activity [25,26] and phase III studies are under way.

Several agents targeting the bone with different mechanisms of action are under intensive investigation. Denosumab, a fully human monoclonal antibody that specifically bind to the ligand of RANK has recently been approved by the EMA for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures [27]. Furthermore, denosumab recently was reported superiority over zoledronic acid in delaying or preventing SREs (skeletal related events) in patients with bone metastases from castrate resistant prostate cancer [28]. Radium-223 is a new promising alpha-emitting bone-seeking radiopharmaceutical which has proven well tolerated with demonstrated effects on bone-ALP concentrations and survival parameters in a randomised phase II study [29]. A subsequent phase III study is running and in late planning phase is a trial evaluating combined treatment with docetaxel. Finally, a number of endothelin A receptor (ETa) targeted agents are under evaluation, which rely on the importance of this receptor in the development of prostate cancer progression and formation of bone metastases. Atrasentan and ZD4054 are agents, proven to selectively inhibit ETa, with encouraging phase II data that are under extensive evaluation in several large, randomised phase III trials.

Considering the large number of compounds under evaluation, the next decade appears to be an exciting time for prostate cancer research and management of advanced disease. The emergence of therapies that rely on improved molecular understanding of biological processes behind prostate cancer progression

and therapeutic resistance is promising and stimulate to further research efforts.

How to best combine and evaluate significantly different treatments modalities such as radionuclides, vaccines, hormonal-, cytotoxic-, targeted- and other immunomodulatory treatments in terms of sequence, dosages, etc are examples of important issues that remain unclear and obviously will require significant work and multidisciplinary collaboration. Another important challenge is to strive for biomarker driven trials with the aim to clarify and define if certain populations, based on their tumour biological and/or clinical characteristics, are particularly sensitive to any of these treatment alternatives. By use of such strategies, we can better tailor and optimise the treatment of the individual patient while improving the cost/benefit for the society as a whole.

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