Challenges and Opportunities in Hormone-Resistant Prostate Cancer

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Article info

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Abstract

Context: The lack of options available for the treatment of hormone-resistant prostate cancer (HRPC) presents a significant challenge to clinicians. In the TAX 327 trial, treatment with docetaxel plus prednisone was demonstrated to improve survival compared with mitoxantrone plus prednisone but was associated with a higher incidence of adverse events, notably haematologic toxicities. Indeed, there is debate about the use of this cytotoxic regimen, particularly for patients with metastatic disease who are asymptomatic or only mildly symptomatic for pain.

Objective: There is a need to develop less toxic regimens suitable for such patients and to develop treatment options which offer better efficacy than the currently available agents.

Evidence acquisition: A nonsystematic review of the literature was performed in 2008. Databases browsed included PubMed, abstracts from congresses, and PR Newswire.

Evidence synthesis: A number of studies have been conducted or are underway to investigate the use of docetaxel in combination with a number of new agents, including high-dose calcitriol and the antiangiogenesis agents bevacizumab and aflibercept. Other treatments administered as monotherapy include abiraterone, denosumab, and satraplatin and the cancer vaccines G-VAX and Provenge.

One promising novel approach is antagonism of the endothelin A (ET_A) receptor, which plays a key role in tumour progression in HRPC. Atrasentan is an endothelin receptor antagonist with selectivity for the ET_A receptor and in a phase 2 study was associated with a significantly increased time to progression versus placebo. The atrasentan phase 3 study failed to meet its primary end point, although this may have been related to limitations inherent in the trial design. ZD4054 is a specific ET_A receptor antagonist that has shown a promising improvement in overall survival versus placebo in a phase 2 study and was generally well tolerated.

Conclusions: The ENDoTHelin A USE (ENTHUSE) programme, consisting of three large, multicentre phase 3 trials, is now ongoing to study ZD4054 as a monotherapy or in combination with docetaxel in patients with M0 and M1 HRPC.

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1. Introduction

The lack of treatment options currently available for advanced prostate cancer presents a significant challenge for both physicians and their patients. While hormone-based therapies are usually highly effective in the initial stages of prostate cancer, resistance to such therapy often develops, after which the prognosis is poor despite chemotherapy [1–3]. In the last few years, chemotherapy with docetaxel has been demonstrated to improve survival in patients with metastatic hormone-resistant prostate cancer (HRPC) [4,5]. However, this treatment option is associated with tolerability issues, and a need remains to develop more effective and less toxic regimens. This review will discuss a number of emerging opportunities that are being investigated in clinical trials to try and overcome these hurdles, including combination of docetaxel with novel therapeutic agents and antagonism of the endothelin A (ET\textsubscript{A}) receptor.

2. Evidence synthesis

2.1. Docetaxel monotherapy: the TAX 327 trial

The efficacy and tolerability of docetaxel for the treatment of HRPC was investigated in the TAX 327 study [4]. In this multinational trial, 1006 men with metastatic HRPC were randomised. Group 1 received docetaxel 75 mg/m\textsuperscript{2} every 3 wk (n = 335); group 2 received docetaxel 30 mg/m\textsuperscript{2} weekly for 5 wk out of every 6 wk (n = 334); and group 3 received mitoxantrone 12 mg/m\textsuperscript{2} every 3 wk (n = 337). All patients received prednisone 5 mg twice daily.

After a median follow-up of 20.8 mo in group 1 and 20.7 mo in groups 2 and 3, docetaxel administered every 3 wk was associated with a significantly reduced risk of death compared with mitoxantrone administered every 3 wk, with a hazard ratio of 0.76 (95% confidence interval [CI], 0.62–0.94; p = 0.009) [4]. The median survival times were 18.9 mo, 17.4 mo, and 16.5 mo for groups 1, 2, and 3, respectively.

Overall survival continued to be significantly higher in group 1 compared with group 3 (Fig. 1) in a 2008 data update, with median survival times of 19.2 mo, 17.8 mo, and 16.3 mo for groups 1, 2, and 3, respectively [5].

Despite the improved patient survival with docetaxel 75 mg/m\textsuperscript{2} administered every 3 wk, the overall incidence of adverse events was higher in group 1 and group 2 compared with group 3 (Table 1) [4].

Although the promising results from the TAX 327 trial as well as the Southwest Oncology Group (SWOG) 99-16 trial [2] led to the approval of docetaxel administered every 3 wk with prednisone for patients with metastatic HRPC in the United States and Europe, true consensus about the use of this regimen has yet to be reached. As shown in TAX 327, cytotoxic chemotherapy can be associated with severe adverse events, most notably haematologic toxicities including neutropenia, febrile neutropenia, anaemia, and thrombocytopenia. There is also controversy over when to initiate cytotoxic therapy and in which patient populations [1,6] because the age and general health status of many patients with HRPC often makes systemic chemotherapy unsuitable or inappropriate. For patients with metastatic disease who remain asymptomatic, the toxicities associated with docetaxel-based chemotherapy...
may be unacceptable, and even in symptomatic disease, the question remains as to whether, from the patient’s perspective, the improved survival of approximately 2 mo with docetaxel therapy is worth the toxicity risk.

Indeed, the TAX 327 trial data highlight the need to find new treatment options with greater efficacy and less toxicity than the currently available therapeutic approaches for HRPC. Several different approaches to address these challenges are now under investigation.

2.2. Docetaxel combinations in hormone-resistant prostate cancer

To improve both the efficacy and the tolerability of docetaxel monotherapy, investigators have focussed on alternative chemotherapeutic modalities which combine docetaxel with novel agents.

2.2.1. Docetaxel plus high-dose calcitriol

Calcitriol, a natural ligand for the vitamin D receptor, has been shown to have significant antitumour effects in various in vivo and in vitro cancer models, with additive or even synergistic activity observed when combined with cytotoxic chemotherapeutic agents, including docetaxel [7,8]. Promising results were observed in an earlier phase 2 trial investigating the combination of docetaxel and calcitriol, in which a ≥50% decline in prostate-specific antigen (PSA) level was seen in 81% of patients [9]. Subsequently, a new trial using docetaxel in combination with a high-concentration formulation of calcitriol, DN-101, was conducted [7,10]. The double-blind, phase 2, Androgen-independent prostate cancer Study of Calcitriol ENHancing Taxotere (ASCENT) trial randomised a total of 250 patients to receive weekly docetaxel 36 mg/m² for 3 wk of a 4-wk cycle, combined with DN-101 45 µg or placebo, taken orally 1 h prior to docetaxel administration. The primary end point of the ASCENT trial was the proportion of patients achieving a PSA response, defined as a ≥50% decline in PSA level, confirmed ≥4 wk later, with secondary end points including overall survival, tumour response, and progression-free survival.

After a median follow-up of 18.3 mo, a promising improvement in overall survival was observed in the docetaxel plus DN-101 group compared with doc-

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Table 1 – Overall incidence of haematologic and nonhaematologic adverse events in the TAX 327 trial adapted from Tannock et al [4].

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Docetaxel (3-weekly; n = 332)</th>
<th>Docetaxel (weekly; n = 330)</th>
<th>Mitoxantrone (n = 335)</th>
</tr>
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<tbody>
<tr>
<td><strong>Haematologic toxicities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>4.9</td>
<td>4.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>32.0</td>
<td>1.5</td>
<td>21.7</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>3.0</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2.7</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>Septic death</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Nonhaematologic toxicities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>65.0</td>
<td>50.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>53.0</td>
<td>49.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>4.5</td>
<td>5.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>41.0</td>
<td>36.0</td>
<td>36.0</td>
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<tr>
<td>Grade 3-4</td>
<td>2.7</td>
<td>2.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>32.0</td>
<td>34.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>2.1</td>
<td>4.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Sensory events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>30.0</td>
<td>24.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>1.8</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Nail changes</td>
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<td></td>
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<tr>
<td>All</td>
<td>30.0</td>
<td>37.0</td>
<td>7.0</td>
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<tr>
<td>Grade 3-4</td>
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<td>NA</td>
<td>NA</td>
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<tr>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>25.0</td>
<td>17.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>2.1</td>
<td>1.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

NA = not applicable.
etaxel plus placebo, with a hazard ratio of 0.67 (95% CI, 0.45–0.97; \( p = 0.04 \)) (Fig. 2). At the time of analysis, median survival in the docetaxel plus placebo group was 16.4 mo and had not been reached in the docetaxel plus DN-101 group but was estimated to be 24.5 mo.

More patients in the docetaxel plus DN-101 group achieved a PSA response (58%) compared with the docetaxel plus placebo group (49%), although the difference did not reach statistical significance (\( p = 0.16 \)). Measurable disease meeting Response Evaluation Criteria in Solid Tumors (RECIST) criteria was present in more docetaxel plus placebo patients compared with docetaxel plus DN-101 (47% vs 38%, respectively), and the tumour response was higher among DN-101 recipients compared with those receiving placebo (19% vs 24%, respectively). However, neither of these end points reached statistical significance.

Interestingly, there was no increase in the overall incidence of adverse events with docetaxel plus DN-101 combination chemotherapy compared with docetaxel plus placebo. Indeed, the addition of DN-101 was actually associated with a reduction in the incidence of serious adverse events and thromboembolic events (Table 2).

Fig. 2 – Overall survival and prostate-specific antigen (PSA) response in the Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT) phase 2 trial. Adapted from Beer et al [7]. Reprinted with permission from American Society of Clinical Oncology. © 2008 All rights reserved.

<table>
<thead>
<tr>
<th>Patients, %</th>
<th>Docetaxel + DN-101 (n = 125)</th>
<th>Docetaxel + placebo (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3–4 toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>6.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>27.0</td>
<td>41.0*</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.6</td>
<td>8.8b</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>1.6</td>
<td>8.0c</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>1.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Peripheral thromboembolism</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

\( a \ p = 0.023 \) versus docetaxel + calcitriol.
\( b \ p = 0.01 \) versus docetaxel + calcitriol.
\( c \ p = 0.02 \) versus calcitriol.
Despite these promising phase 2 data, the phase 3 ASCENT-2 trial, which compared the combination of DN-101 and weekly docetaxel to docetaxel administered every 3 wk as a standard of care, was terminated in early November 2007 after an unexpectedly higher number of deaths was observed by the trial’s Data Safety Monitoring Board among patients in the DN-101 group [11]. At the time of discontinuation, >900 patients of the planned total trial population of 1200 had been enrolled in the multinational study. Of note, the TAX 327 trial did not show any significant difference in efficacy between the weekly docetaxel and mitoxantrone treatment groups, suggesting that DN-101 may be better combined with docetaxel administered every 3 wk instead of docetaxel administered every week.

2.2.2. Other docetaxel combination therapies

Other approaches to docetaxel-based combination chemotherapy currently under investigation include administration of docetaxel with agents that inhibit tumour angiogenesis: bevacizumab and aflibercept.

Bevacizumab is a recombinant humanised monoclonal antibody which recognises all isoforms of the vascular endothelial growth factor (VEGF) and is approved as part of combination chemotherapy for use in metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic, non–small-cell lung cancer; and metastatic HER2-negative breast cancer [12]. VEGF levels in both urine and plasma are independent prognostic markers of survival in HRPC [13,14], and the phase 3 Cancer and Leukemia Group B (CALGB) 90401 trial will investigate the combination of docetaxel (75 mg/m² on day 1, every 3 wk) plus prednisone (10 mg/day) and bevacizumab (15 mg/kg on day 1, every 3 wk), compared with docetaxel plus prednisone alone [15]. Enrolment in the CALGB 90401 trial was completed in January 2008 with first results expected in 2009.

Aflibercept (VEGF Trap) is a unique, fully human fusion protein that inhibits angiogenesis by binding all isoforms of VEGF-A, as well as binding placental growth factor, which also has a role in tumour angiogenesis [16]. A phase 3 trial investigating docetaxel plus aflibercept versus docetaxel plus prednisone was initiated in August 2007 and will enrol 1200 patients [17]. The primary end point of this randomised, double-blind study is overall survival, with secondary end points of response in PSA level, pain response, time to occurrence of skeletal-related events, and progression-free survival.

2.3. The endothelin axis in hormone-resistant prostate cancer

A range of other potential HRPC therapies are currently in clinical development and use a variety of different approaches that do not include docetaxel-based regimens. As discussed by Joel Nelson in this issue [18], one promising therapeutic approach in HRPC is antagonism of the ETA receptor. Activation of this receptor by endothelin-1 initiates a signalling cascade which has many tumour-promoting actions, including stimulation of tumour cell growth, angiogenesis, invasion and metastasis, and inhibition of apoptosis [19]. Activation of the endothelin B (ETB) receptor has an opposing effect, including stimulation of cell death via apoptosis [20]. Therefore, the balance of ETA receptor and ETB receptor expression and activation is of importance, particularly in HRPC [19,21], where specific inhibition of the ETA receptor as a novel treatment strategy shows great promise.

2.3.1. Atrasentan

Atrasentan is a selective ETA receptor antagonist that has shown promising results in a phase 2 study [22]. In this randomised, double-blind trial, 288 patients with asymptomatic, metastatic HRPC were randomised to receive 2.5 mg or 10 mg of atrasentan once daily or placebo. The primary end point was time to progression, with secondary end points including PSA progression and changes in bone scans and in bone and tumour markers.

Atrasentan 10 mg was associated with a significantly increased time to progression versus placebo (196 d vs 129 d, respectively, among evaluable patients [p = 0.002]); in the intent-to-treat population, the improvement did not reach statistical significance (183 d vs 137 d, respectively; p = 0.13) but was associated with a 25% reduction in the risk of progression with atrasentan 10 mg and an almost 2-mo delay in median time to disease progression. However, in a phase 3 trial in patients with metastatic HRPC, atrasentan did not achieve the primary study end point, that of a reduction in the risk of disease progression relative to placebo [23]. Likewise, a phase 3 study in patients with nonmetastatic HRPC did not show a statistically significant difference between atrasentan and placebo groups for the primary end point, time to progression [24]. However, atrasentan was associated with significantly smaller increases in bone alkaline phosphatase and PSA compared with placebo in both phase 3 studies [23,24], suggesting that issues with trial design may be responsible for the poor survival outcome rather than the failure of
atrasentan itself [25]. The primary end point selected, progression-free survival, is difficult to define and measure accurately in HRPC, and in the atrasentan phase 3 trials it is unclear whether the asymptomatic progression, as measured by radiography, was of clinical significance. Patients were not followed for other signs of progression after initial radiologic progression was observed, and any determination of the potential long-term benefits of atrasentan therapy were obfuscated by early crossover of placebo-treated patients to open-label therapy. Thus, any delay in symptom development or effect on overall survival with atrasentan compared with placebo was unable to be measured.

2.3.2. ZD4054

ZD4054 is an oral, specific ETA receptor antagonist with no detectable activity at the ETB receptor [26]. In contrast, atrasentan is a selective, but not specific, antagonist and, as such, has low-level activity at receptor subtypes other than ETA receptor.

ZD4054 has demonstrated anticancer activity in preclinical studies, inhibiting tumour cell invasion, metastasis, and angiogenesis [27–29]. As discussed elsewhere in this supplement, ZD4054 showed a promising improvement in overall survival relative to placebo in a phase 2 clinical trial, which investigated once-daily oral ZD4054 (10 mg or 15 mg) in patients with HRPC and bone metastases who were pain free or mildly symptomatic for pain and had rising PSA levels despite medical or surgical castration [30].

In this trial, ZD4054 was associated with an overall survival time of 23.5 mo and 24.5 mo at the 15-mg and 10-mg dose levels, respectively, compared with 17.3 mo for placebo at the second analysis (Fig. 3). ZD4054 was also well tolerated at both dose levels, with the most common adverse events as expected from antagonism of the ETA receptor, including peripheral oedema, headache, and nasal congestion.

2.3.3. The ZD4054 ENTHUSE phase 3 clinical trials programme

The promising results from the phase 2 study of ZD4054 led to initiation of the ENdoTHelin A USE (ENTHUSE) phase 3 programme, consisting of three large randomised, double-blind trials to be conducted at >200 centres worldwide, which will enrol >3000 patients with HRPC (Fig. 4). Each trial in the ENTHUSE programme will use the ZD4054 10-mg/day dose because there was no evidence in the phase 2 trial that the higher dose of 15 mg was more effective.

The first trial will enrol patients with M0 HRPC, those with no evidence of metastatic spread and without symptoms, for whom there is currently no approved or proven therapy. This trial will have overall survival and progression-free survival as primary end points. A total of 1500 patients will be enrolled and followed for up to 3 yr after recruitment. Secondary end points include safety and tolerability, PSA level, and health-related quality of life.

The second trial will be conducted in patients with M1 HRPC in whom bone metastases are confirmed but who have no or only mild pain symptoms. This population is the same as the group...
that showed an improvement in overall survival in the ZD4054 phase 2 EPOC trial [30]. A total of 580 patients with bone metastases and rising serum PSA levels despite medical or surgical castration will be enrolled in this trial, which has a primary end point of overall survival. Secondary end points include progression-free survival, safety and tolerability, skeletal events and bone metastases, PSA level, and health-related quality of life. This trial includes a follow-up period of approximately 12 mo after the last patient is enrolled.

In the third trial, ZD4054 will be combined with docetaxel and compared with docetaxel treatment alone in 1044 patients with M1 HRPC with confirmed symptomatic metastases suitable for chemotherapy. The primary end point of this trial is overall survival, with secondary end points including progression-free survival, safety and tolerability, and the effect of treatment on skeletal events and PSA levels.

2.4. Other approaches for the treatment of hormone-resistant prostate cancer

2.4.1. New hormonal, targeted, and cytotoxic agents

Abiraterone is a new, oral, selective, irreversible inhibitor of 17 α-hydroxylase, C-lyase, and CYP450 c17 enzyme systems, which acts to inhibit androgen and oestrogen synthesis. Abiraterone has been investigated in both chemotherapy-naïve HRPC patients and in patients who have progressed on docetaxel therapy. A phase 1 trial of abiraterone 250–2000 mg/day in 21 chemotherapy-naïve men with HRPC found increased levels of adrenocorticotropic hormone and steroids upstream of CYP450 c17, and suppression of serum testosterone, downstream androgenic steroids, and estradiol were observed in all patients [31]. Declines in PSA levels of ≥30%, 50%, and 90% were observed in 14 patients (66%), 12 patients (57%), and 6 patients (29%), respectively, indicating that HRPC is still driven by hormone signalling at androgen receptors. In two parallel phase 2 trials, the null hypothesis was rejected, with a ≥50% decline in PSA level achieved by >60% of patients in the chemotherapy-naïve cohort (n = 44) and by >40% of patients in the docetaxel-treated cohort (n = 28) [32]. The median time to PSA-level progression was 252 d in the chemotherapy-naïve cohort and 167 d in the docetaxel-treated cohort. Abiraterone was also well tolerated, with no dose-limiting toxicities observed in the first study. Abiraterone plus prednisone was investigated in 38 patients with progressive HRPC who had failed prior docetaxel therapy [33]. Promising activity was observed; of the 35 evaluable patients, 11 (31%) progressed within 3 mo, 9 (26%) within 6 mo, and 2 (6%) after 6 mo. A decline in PSA level >50% from baseline occurred in 14 of 35 patients (40%) by 3 mo. Following these encouraging data, a phase 3 study was initiated in 2008 that will enrol 1158 patients with HRPC who had previously received docetaxel therapy [34]. The primary end point is overall survival, with a secondary end point of the proportion of patients showing a decline in PSA level ≥50%. The trial is scheduled to complete in 2011.

Another new hormonal therapy is MDV3100, a rationally designed small-molecule inhibitor of the androgen receptor which acts by blocking nuclear
translocation and DNA binding, overcoming resistance to conventional antiandrogens. Recent data from a phase 1/2 trial in patients with progressive HRPC showed that three out of three patients (100%) receiving MDV3100 30 mg/day had declines in PSA levels of 44–87% from baseline for ≥19 wk, while three out of three patients (100%) receiving 60 mg/day had declines in PSA levels of 74–96% for 14 wk [35]. MDV3100 was also well tolerated, with no significant adverse events reported.

Denosumab is a monoclonal antibody targeting RANKL, a mediator of osteoclast activity, which may have activity in bone metastases. Positive phase 3 results have been reported in breast cancer [36], and phase 3 studies in M0 and M1 prostate cancer are ongoing [37,38]. Together, the trials will enrol 3100 patients and will run until 2009–2010.

Results from the phase 3 registration trial of the third-generation oral platinum agent, satraplatin, were presented at the 2008 meeting of the American Society of Clinical Oncology (ASCO) [39]. In the Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial, 950 patients with HRPC received satraplatin plus prednisone or prednisone plus placebo. While the SPARC trial did demonstrate a significant improvement in progression-free survival—the secondary end point—with satraplatin therapy, the primary end point of overall survival was not reached, with a median overall survival time of 61.3 wk for the satraplatin arm and 61.4 wk for the placebo arm (hazard ratio: 0.98; 95% confidence interval, 0.84–1.15). Satraplatin was well tolerated, with myelosuppression the most common adverse event, occurring in 98.9% of patients in the satraplatin group. Haematologic toxicities observed with satraplatin therapy included grade 3–4 thrombocytopenia (22.6% of patients), leucopenia (14.5% of patients), neutropenia (22.3% of patients), and anaemia (11.9% of patients).

2.4.2. Immunotherapy

The dream of immunotherapy has been around for 30 yr; however, initial hopes for eliciting simple immune responses to tumour cells leading to effective treatment were soon tempered, as a much more complex picture of cancer immunology emerged. Cancer vaccine therapy is inherently well tolerated, however, and trials are currently underway with two such therapies in HRPC.

G-VAX, a cell line-based vaccine therapy, has shown promising activity versus docetaxel plus prednisone; additionally, a preplanned interim analysis of the VITAL-1 study, the first of two ongoing phase 3 trials investigating the use of G-VAX versus docetaxel plus prednisone in patients with HRPC, recommended that the study continue to completion [40]. A second phase 3 trial, VITAL-2, was initiated in 2005. Both phase 2 trials were terminated in 2008.

Vaccination therapy with autologous antigen-loaded dendritic cells (APC8015; Provenge) is being investigated in a randomised, double-blind, placebo-controlled phase 3 trial involving 500 patients with metastatic HRPC [41]. Results of an interim data analysis will be available in the second half of 2008.

3. Conclusions

Although there are treatments available for patients with HRPC, there are still many unmet needs and challenges to overcome, particularly in patients with metastatic disease who are asymptomatic or only mildly symptomatic for pain. While docetaxel-based chemotherapy is effective and has demonstrated a significant survival benefit compared with mitoxantrone, it is associated with significant adverse events, notably haematologic, which may make such treatment unsuitable or inappropriate for patients who are asymptomatic or only mildly symptomatic for pain.

Intense research efforts are underway identifying potentially more effective, better tolerated treatments such as docetaxel combination therapy. Several clinical trials investigating new treatment regimens are now underway.

One promising approach undergoing investigation is antagonism of the ETA receptor. In particular, the ETA receptor-specific antagonist ZD4054 has shown promise in clinical trials and continues to be investigated in a large phase 3 programme.

Conflicts of interest

Kurt Miller is a consultant for and has received honoraria from AstraZeneca.

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References


term=abiraterone&phase=2&rank=1.


