Novel and bone-targeted agents for CRPC

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Clearly, no neoplasm other than prostate cancer has benefited from so many breakthroughs since the beginning of this decade: the past two years can be considered exceptional due to the number of emerging agents against castration-resistant prostate cancer (CRPC), which have demonstrated positive outcomes in phase III trials. Until 2010, docetaxel (Taxotere) was the only agent capable of improving survival in patients with metastatic CRPC. Since then, positive results from phase III trials have been reported for sipuleucel-T, cabazitaxel, denosumab, abiraterone, radium-223, and enzalutamide, while other promising agents including notably orteronel, ipilimumab and cabozantinib are currently under study. Taken together, the incorporation of these agents in the routine management of patients with advanced prostate cancer (deemed as either with non-metastatic CRPC or asymptomatic metastatic disease) is proposed as either with endocrine therapies directly or indirectly targeting the androgen receptor (abiraterone, enzalutamide [formerly known as MDV3100]), chemotherapeutic agents (cabazitaxel), bone-targeting agents (denosumab), radiopharmaceuticals (radium-223) and immunotherapy (sipuleucel-T). Thus, their clinical benefits are likely to be, at least in part, incremental. An algorithm summarising the integration of novel agents for the management of patients with advanced prostate cancer (defined as either with metastases or castrate-resistant disease, or both) is proposed in Table 1. This report will not present the results of novel endocrine therapies in detail nor those concerning patients with non-metastatic CRPC or asymptomatic metastatic CRPC (like sipuleucel-T) which will be covered in presentations by Prof. Sternberg and Prof. Tombal during this ESMO meeting.

**patients progressing after docetaxel:** from nothing to being spoilt for choice

The most successful phase III trials recently conducted in CRPC focused on patients experiencing cancer progression after first-line docetaxel (Taxotere, Sanofi-Aventis, France) chemotherapy. Indeed, improving their outcome was the most unmet need and this stage also provided an opportunity to demonstrate an overall survival improvement more rapidly with an active drug over a shorter time frame. To date, four drugs have afforded an overall survival benefit on top of other clinical improvements in patients progressing after docetaxel: cabazitaxel [2], abiraterone [3, 4], alpharadin [5] and Enzalutamide (formerly known as MDV 3100) [6]. When available, their use should now be preferred over a rechallenge with docetaxel, which was regarded before 2010 as a reasonable option, without any proof of a gain in survival of patients who were experiencing progression several months after discontinuation of first-line docetaxel [7].

Cabazitaxel, a ‘second generation’ taxane with broader preclinical activity than docetaxel, was shown to improve overall survival when added to prednisone versus mitoxantrone plus prednisone in the TROPIC trial [hazard ratio (HR) 0.72; 95% CI 0.61–0.84]; median overall survival: 15.1 months versus. 12.7 months; P < 0.0001) in 745 patients with CRPC progressing after treatment with docetaxel [2]. Progression-free survival (PFS) was also improved with cabazitaxel–prednisone [HR 0.75 (95% CI: 0.65–0.87)]. The main side-effects included haematological toxicity and diarrhoea, consequently the use of prophylactic G-CSF with the currently recommended dose of...
Bisphosphonates, serum alkaline phosphatase, prior docetaxel, was found in various subgroups (according to the use of treatment) towards better overall survival in favour of the radium-223 arm (HR 0.695 (95% CI 0.552–0.875); P = 0.00046) with a median duration of 13.6 versus 8.4 months. Overall, tolerance was good with 22% experiencing diarrhoea versus 13% in the radium-223 arm (the drug is excreted by the small bowel), but there were no excess grade 3–4 events [5].

The Cou-301 [3, 4] and the Affirm [6] phase III trials that respectively established the role of abiraterone–prednisone and MDV 3100 in patients with CRPC progressing after docetaxel will be presented in detail by Prof. Sternberg.

**targeting the bone microenvironment in CRPC: now an established standard**

In the 2000s, zoledronic acid was the only drug to demonstrate an improvement in time to SRE over a placebo in patients with bone metastases from CRPC, with no demonstrated improvement in overall survival. Alpharadin was the first agent specifically designed to target cancer cells in the bone that was capable of achieving better overall survival in patients with CRPC, together with longer time to SRE (see the paragraph above). Of note, this benefit was obtained in patients with bone metastases from CRPC who had either experienced progression after docetaxel or who were considered unfit for docetaxel, and who were treated with and without a bisphosphonate [5].

Rank-L is a key protein secreted by osteoblasts, which promotes osteoclast differentiation and bone resorption. Evidence of increased Rank-L expression and decreased osteoprotegerin (a Rank-L natural inhibitor) was provided in preclinical models of bone metastases from CRPC [9]. Denosumab is a Rank-L inhibitor that was originally developed in a proof-of-concept randomised phase II trial in patients with bone metastases from CRPC with evidence of uncontrolled osteolysis (assessed on uNTx [10], a urine marker of ongoing bone resorption), while on IV bisphosphonate [11], substantially more patients achieved normalised urinary NTx levels, and further development of the agent was decided. The 103 phase III trial compared denosumab (injected subcutaneously) with IV zoledronic acid in 1901 patients with metastatic CRPC. Denosumab was superior to zoledronic acid in delaying/preventing SREs, as shown by the time to the first SRE (pathologic fracture, radiation or bone surgery, or spinal cord compression) of 20.7 versus 17.1 months, respectively (HR 0.82; P = 0.008). Denosumab also extended time to the first and subsequent on-study SRE (rate ratio 0.82; P = 0.008). Both uNTx and serum bone alkaline phosphatase were significantly suppressed in the denosumab arm compared with the zoledronic acid arm (P < 0.0001 for both). A similar tolerance pattern was observed, with both drugs associated with hypocalcemia and a rare (<2%) risk of osteonecrosis of the jaw, two events requiring prevention and monitoring [12].

**more to come?**

**more to come with bone targeting?**

Met is a tyrosine kinase expressed by osteoblasts and osteoclasts, and overexpressed by prostate cancer cells.

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**Table 1.** A proposed evidence-based treatment algorithm for patients with advanced prostate cancer (this table does not take into account whether drugs are approved, available and reimbursed)

<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>Standard treatment</th>
<th>Alternative options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-metastatic castration-resistant prostate cancer (CRPC)</td>
<td>None (continuing ADT)</td>
<td>Endocrine manipulations</td>
</tr>
<tr>
<td>Metastases, hormone naïve</td>
<td>ADT</td>
<td>Denosumab†</td>
</tr>
<tr>
<td>Metastatic CRPC</td>
<td>Denosumab†</td>
<td>Complete androgen blockade: ADT + AR inhibitor</td>
</tr>
<tr>
<td>Bone metastases from CRPC</td>
<td>Alpharadin†</td>
<td>Zoledronic acid</td>
</tr>
<tr>
<td>Asymptomatic CRPC</td>
<td>Sipuleucel-T† Abiraterone†</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Symptomatic CRPC</td>
<td>Docetaxel</td>
<td>Docetaxel + estramustine</td>
</tr>
<tr>
<td>CRPC progressing after docetaxel</td>
<td>Cabazitaxel Abiraterone† Alpharadin† MDV 3100†</td>
<td>Docetaxel rechallenge</td>
</tr>
<tr>
<td>CRPC progressing after docetaxel and novel drugs with an overall survival benefit</td>
<td>None (ADT)</td>
<td>Clinical trial</td>
</tr>
</tbody>
</table>

ADT, androgen deprivation therapy (=castration).

†Agents recently incorporated in the CRPC armamentarium based on positive phase III data.

25 mg/m² will be discussed on an individual basis in routine practice. Two ongoing phase III trials aim to optimise the use of cabazitaxel in patients with CRPC: a front-to-front comparison trial versus docetaxel in the first-line chemotherapy setting, and a trial aimed at defining the optimal dose (20 or 25 mg/m²) in the second-line setting.

Radium-223 (also called alpharadin) is a calcium-mimetic radiopharmaceutical with high bone affinity. As an alpha emitter, it has two major advantages: (i) only a few ‘hits’ are required to induce double-strand breaks in cancer cells and (ii) the first cell layer can stop its penetration into the bone marrow, thus preventing haematological toxicity. Radium-223 was first studied in a randomised, proof-of-concept phase II trial with favourable results versus a placebo in patients with bone metastases from CRPC [8]. The Alsympca phase III trial was then conducted in 922 patients (~60% of them had been pre-treated with docetaxel and 40% had been considered unfit for docetaxel), who were randomly assigned in a 2:1 fashion between radium-223 (50 kBq/kg/4 weeks × 6 cycles) and a placebo. The interim analysis showed improved overall survival [HR 0.695 (95% CI 0.552–0.875); P = 0.00046] with a median duration of 14 and 11.2 months, respectively. A similar trend towards better overall survival in favour of the radium-223 arm was found in various subgroups (according to the use of bisphosphonates, serum alkaline phosphatase, prior docetaxel, and the performance status). Time to the first skeletal-related event (SRE) was also improved [HR 0.610 (95% CI 0.461–0.807) P = 0.00046] with a median duration of 13.6 versus 8.4 months. Overall, tolerance was good with 22% experiencing diarrhoea versus 13% in the radium-223 arm (the drug is excreted by the small bowel), but there were no excess grade 3–4 events [5].

The Cou-301 [3, 4] and the Affirm [6] phase III trials that respectively established the role of abiraterone–prednisone and MDV 3100 in patients with CRPC progressing after docetaxel will be presented in detail by Prof. Sternberg.
Cabozantinib, a Met and VEGF-R2 inhibitor, was recently tested in patients with metastatic CRPC. Impressive preliminary results from a phase II study that enrolled 168 patients in 2011 were recently reported, including notably a partial or complete improvement in the bone scan in 85% and pain improvement in 60% of the patients [13]. Toxicity is as expected for a tyrosine kinase inhibitor, including fatigue, hypertension and palmar-plantar syndrome, and constitutes a challenge for the original 100 mg/day dose with respect to further development. A phase III trial was recently initiated with pain as the primary end-point and a global phase III trial with overall survival as the primary end-point in patients with metastatic CRPC failing docetaxel and abiraterone is also in the pipeline.

Another target for therapy is Src, which is expressed by osteoclasts and by some prostate cancer cells. Dasatinib, a Src inhibitor, was tested in patients with CRPC as a single agent and combined with chemotherapy [14]. The results from a large phase III trial testing docetaxel with and without dasatinib are awaited soon.

more to come with immunotherapy?

With sipuleucel-T, prostate cancer was the first example in oncology where immunotherapy was demonstrated to prolong overall survival [15]. Two other immune modulating treatments have proven effective in phase II trials and are currently under development in phase III: ipilimumab and prostvac. Ipilimumab is a CTLA-4 (cytotoxic T-lymphocyte antigen 4) inhibitor that was shown to be active [prostate-specific antigen (PSA) response and clinical improvement], with or without radiotherapy delivered to bone lesions in patients with metastatic CRPC [16]. Dramatic responses have been observed, although autoimmunity is a clear concern. Two phase III trials completed their accrual in 2012: a trial testing single agent ipilimumab in patients non-pretreated with docetaxel, and another trial testing ipilimumab in combination with radiotherapy in patients with post-docetaxel CRPC with bone metastases. Prostvac is a poxviral PSA-targeted vaccine that was suggested to improve overall survival (median 25.1 versus 16.6 months) in patients with metastatic CRPC in a randomised phase II trial, although the primary end-point of the trial, PFS, was not substantially improved [17]. Based on these data, a phase III trial is ongoing in patients with CRPC who did not previously receive docetaxel.

more to come: novel drugs with original targets?

Many potential targets have been identified in the recent past in CRPC and numerous trials are ongoing testing inhibitors which cannot all be presented in detail in this article. Among them, original technologies include antisense oligonucleotides like 0GX-011 (which targets clusterin, a chaperone protein) and OGX-427 (which targets heat-shock protein 27). OGX-011 was tested in a randomised phase II trial in combination with docetaxel. A better overall survival duration was reported in the combination arm (median 23.8 and 16.9 months, respectively) [18]. Two phase III trials are ongoing to confirm these results. Tasquinimod targets S100A9 and its anti-angiogenic and immune-modulation properties are still incompletely understood. This oral compound was tested in a randomised phase II trial in 201 asymptomatic patients with metastatic CRPC: the primary end-point, PFS, was substantially improved (7.6 months versus 3.3 months; P = 0.0042) [19]. A large phase III trial is ongoing in the same setting.

Finally, αv integrins may be a suitable target for therapy in CRPC patients, and the preliminary results with DI17E6, an integrin inhibitor, suggest anticancer activity [20]. A randomised phase II trial is ongoing.

disclosure

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references


