What are the expected developments in the medical treatment of bladder cancer

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To date, systemic chemotherapy is the only treatment that has been demonstrated to improve survival in patients with advanced bladder cancer. Before modern chemotherapy regimens, the median survival of these patients was six months [1]. The M-VAC regimen (cisplatin, methotrexate, doxorubicin and vinblastine), first reported in 1985, showed promising activity in urothelial carcinomas, but was limited by toxicity. High-dose M-VAC and the combination of gemcitabine and cisplatin (GC) were studied retrospectively, showing comparable activity with less toxicity for GC, which is currently considered the standard alternative to M-VAC.

In an effort to improve clinical outcomes, triplet chemotherapy regimens have been investigated. The combination of paclitaxel, gemcitabine and cisplatin (PCG) improved the overall response rate and showed a longer median survival in eligible patients. Recently, vinflunine has been approved as a second-line treatment in advanced bladder cancer after first-line platinum-based chemotherapy, based on the improvement obtained in overall survival in eligible patients and in response rates, disease control and progression-free survival in the overall patient population [2].

New chemotherapy drugs

After the taxanes and gemcitabine several other agents were tested in bladder cancer, aiming to improve both patients' outcome and treatment tolerance. Pemetrexed is a multitargeted antifolate (MTA) that inhibits multiple folate-dependent enzymes. This drug achieved a 33% response rate in chemo-naive patients, and 27% as second-line therapy [3]. This initially promising activity was not subsequently confirmed [4]. Piritrexim, an oral antimetabolite, demonstrated a 38% response rate when used as a single agent in chemotherapy-naive patients, whereas responses dropped to 23% in previously treated patients [5–7].

ABI-007 (Abraxane) is a novel albumin-bound nanoparticle formulation of paclitaxel. It is being tested in a phase II study as second-line chemotherapy after cisplatin failure. Preliminary results with a small patient number show 35% with a partial response and another 35% with stabilisation [8,9]. The results of this agent were updated at ASCO-GU 2011 with promising activity.

Pralatrexate is a novel antifolate with a unique activity profile. Mechanistic differences were established through enhanced cellular uptake and intracellular polyglutamylation of pralatrexate. The polyglutamylated metabolites have a prolonged intracellular half-life and this correlates with more antitumoral activity in xenograft models compared with methotrexate or pemetrexed [10]. Pralatrexate has been approved for treatment of relapsed or refractory peripheral T-cell lymphoma by FDA [11], and is a promising drug in solid tumours that are sensitive to other antifolates. A phase II clinical trial with pralatrexate as a second-line treatment in bladder cancer has completed accrual.

Eribulin is a non-taxane, structurally simplified, synthetic analog of the marine natural product halichondrin B, a large polyether macrolide derived from a marine sponge [12]. Eribulin inhibits microtubule dynamics, resulting in the suppression of microtubule polymerisation, without effects on depolymerisation [13]. In phase I studies, a small fraction of eribulin (<10%) was excreted by urine [14,15], and it can be administered at full doses in patients with renal dysfunction [16]. Eribulin shows activity as a monotherapy in urothelial tumours, showing a response rate of 38% in a phase II study [17].

In summary, modern combination chemotherapy regimens and new agents have produced modest survival benefits for patients with advanced transitional cell carcinoma (TCC) of the urothelial tract. Because the lack of chemotherapy response or drug resistance is the major cause of mortality in this disease, two main approaches are being developed to improve treatment outcome: the identification of effective targeted therapies and the optimisation of

chemotherapy through the use of molecular markers that predict chemosensitivity.

Development of biomarkers that predict positive or negative outcome is an essential first step toward individualised therapy, which is crucial to enable judicious patient selection, to avoid unnecessary toxicities, and to optimise the use of constrained financial resources. Thus, identification of biomarkers that can be confidently used for patient selection to produce optimal treatment benefits is a current and urgent challenge.

Molecular prognostic and predictive markers

Even though clinical and pathological variables provide certain prognostic and predictive information, they are not helpful at guiding the choice of the best therapeutic option for each individual patient. Active research is ongoing into several candidate biomarkers with the goal of facilitating the development of truly personalised medicine. In advanced bladder cancer, ERCC1 activity – related to resistance to cisplatin-based chemotherapy – emerged as an independent prognostic factor for survival in patients treated with cisplatin-based chemotherapy [18]. In the neoadjuvant setting, *BRCA1* has also emerged as a predictive marker for platinum-based therapy [19]. The level of expression of other genes, such as *p53*, *Rb*, *EGFR*, *VEGF*, and metalloproteinases, has also been studied [1].

However, prognostic models based on a single parameter are generally inadequate. To optimise treatment individualisation, molecular profiling should be extensively mapped. Complex genetic signatures obtained from gene expression microarray analysis have the potential to provide reliable prognostic and predictive value [20], but results must be confirmed in large cohorts before they are adopted into daily clinical practice.

Targeted therapies in bladder cancer

The better understanding of tumour biology and the complex cellular pathways that control cancer growth will improve the development of targeted therapies for the treatment of malignancies.

In bladder cancer, two tyrosine-kinase receptors – the epithelial growth factor receptor (EGFR) and HER-2 – are often overexpressed. Nonetheless, targeted agents against these kinases such as trastuzumab, lapatinib, and gefitinib [1] have demonstrated disappointing activity, and only erlotinib given in the neoadjuvant setting has shown relevant activity in a small fraction of patients [21]. We are in great need of discovery and validation of predictive molecular markers of response to define patient subgroups that can benefit from these therapies in the future.

Acknowledgement of the important role of angiogenesis in bladder cancer and the availability of new antiangiogenic drugs have prompted their use in metastatic bladder cancer. The vascular-endothelial growth factor (VEGF) is a key element in this process. Sunitinib and sorafenib are small molecule inhibitors of the VEGF tyrosine kinase receptor amongst other kinases, and these antiangiogenic agents have demonstrated activity in renal cell carcinomas, gastrointestinal stromal tumours (GIST; sunitinib), and hepatocellular carcinomas (sorafenib). Bevacizumab is an antibody against VEGF that is active in different types of cancer (breast, colorectal, lung, renal cell, glioblastoma, and ovarian).

In a preclinical model, sunitinib has demonstrated activity against urothelial carcinoma, both as a single agent and in combination with cisplatin [22]. Clinical activity of sunitinib as a second-line treatment has been reported in a phase II study from MSKCC. The study did not achieve the pre-planned response rate, but 29% stabilisations longer than three months were reported [23]. A phase II trial of sunitinib as first-line treatment in patients unsuitable for cisplatin has recently been reported [24]. These phase II, together with well-powered phase III studies, will define the role of sunitinib in the treatment of advanced bladder cancer.

Sorafenib has been tested as monotherapy in phase II trials, both as first- and second-line therapy, but no responses were observed [25,26].

Bevacizumab is under study in combination with chemotherapy as a first-line treatment. Preliminary results from a phase II trial combining cisplatin, gemcitabine, and bevacizumab have been communicated with promising results [27]. This scheme is now being tested in a randomised phase III trial compared with cisplatin, gemcitabine, and placebo in the CALG-B group. An ongoing phase II trial from MSKCC is evaluating the combination of gemcitabine, carboplatin, and bevacizumab in patients unfit to receive cisplatin.

The results from these trials will be available in the coming years to help us define whether there is a role for anti-angiogenic agents in the treatment of advanced bladder cancer.

The development of drugs that target genetic defects in selected patients with cancer has led to important treatment advances. However, there are still major

challenges that need to be optimised, and rapid improvement is being made in the field of genomic medicine in oncology. Recent findings on specific "druggable" targets found in urothelial tumours will be updated since the data presented at ASCO-GU 2011 [28].

Summary

It is plausible that in the immediate future, treatment will be customised for each individual based not only on tumour genetic or epigenetic expression, but also on different profiles (e.g., pharmacogenomic, immunological, and metabolomic). With an expanding list of potential biological targets and limited patient resources, definitive, prospective, and highly selective trials are needed to address the value of specific targeted agents. Prerequisites for the success of these trials include a clearly defined patient population, clearly defined endpoints, and rigorous statistical methods. Ultimately, well-powered phase III studies will determine if these targeted compounds can play a successful role in the treatment of advanced bladder cancer, and advances are only possible by a concerted international effort to enroll all patients with TCC in clinical trials.

Conflict of interest statement

Consultancy and lecture fees for Pierre Fabre.

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