New agents for bladder cancer

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Muscle-invasive bladder cancer is an aggressive disease with at least 50% of patients dying from metastases within 2 years of diagnosis. The 5-year survival rate for metastatic bladder cancer is <15%. Although modern combination chemotherapy regimens have improved median survival from 6 to 14 months compared with best supportive care, there is still a great opportunity for improvement. New therapies and strategies for better patient and treatment selection are now being investigated for advanced bladder cancer. These include agents that target several pathways involved in the pathogenesis of the disease—such as growth factor receptors, angiogenic pathways, p53, cell cycle checkpoints and apoptosis—as well as novel chemotherapeutic agents. Results from recent and ongoing trials suggest that some of these agents could soon emerge as useful players to overcome the limitations of our present therapies.

Key words: bladder cancer, urothelial tumors, transitional cell carcinoma, targeted therapies, chemotherapy

introduction

In 2009, ~71 000 new cases of urothelial cell carcinoma were diagnosed in the USA, and the disease accounted for ~14 000 deaths. The crude incidence in the European Union is 19.5/100 000/year, and mortality is 7.9/100 000/year. The most common form of the disease, which accounts for 70–80% of cases, is usually low grade, multifocal, superficial and papillary. The less common, muscle-invasive form of the disease accounts for ~20% of urothelial carcinomas. Muscle-invasive tumors are usually treated by radical cystectomy and chemotherapy. In spite of this, at least 50% of these patients die from metastases within 2 years of diagnosis, and the 5-year survival rate for metastatic bladder cancer is <15% [1]. The median survival with aggressive chemotherapy is 14 months. While this is superior to the estimated 6-month survival with metastatic disease prior to modern chemotherapy regimens, there is still a great opportunity for improvement. New therapies and strategies for better patient and treatment selection are now being investigated for advanced bladder cancer. Some of them are discussed and briefly reviewed here.

targeting growth factor receptors and signal transduction pathways

Inhibitors of the HER family of receptors, specially the epidermal growth factor receptors EGFR and HER2, have all entered clinical trials in bladder cancer patients. Gefitinib—a tyrosine kinase inhibitor of EGFR—in combination with chemotherapy in first-line metastatic bladder cancer did not appear to improve the response rate or survival compared with historical controls of gemcitabine and cisplatin alone [2]. Another clinical trial with the EGFR monoclonal antibody cetuximab in combination with cisplatin and gemcitabine chemotherapy in advanced or metastatic bladder cancer is currently recruiting (NCT00645593). Erlotinib is being evaluated in the neoadjuvant setting. Early results suggest that the treatment has beneficial effects on operative pathology and short-term outcomes (ASCO GU Symposium 2009, abstract 246).

Based on the efficacy of the combination of paclitaxel–gemcitabine–carboplatin and the synergy of trastuzumab with paclitaxel, a multicenter phase II study was performed in HER2 overexpressors but without striking signs of synergy. Lapatinib has been tested in a phase II study in pre-treated bladder cancer patients, showing a modest benefit in assessable patients. Additional studies in combination with chemotherapy (phase I EORTC study cisplatin–gemcitabine plus lapatinib) or as a maintenance therapy in patients responding to standard chemotherapy are being conducted [3].

A high proportion of bladder tumors overexpress FGFR3 (fibroblast growth factor receptor 3) [4], mutated forms of which have oncogenic properties, mediated predominantly by the Ras signaling pathway [5]. There is a strong rationale for FGFR inhibitors for treatment of bladder cancer. The drug TKI258 (Novartis) is a multikinase inhibitor of FGFR, VEGFR (vascular endothelial growth factor receptor) and PDGFR (platelet-derived growth factor receptor). This agent suppressed proliferation and xenograft growth in bladder cancer cell lines overexpressing FGFR3 (AACR 2008, abstract 4888) and is at present being evaluated in a phase II clinical trial in second-line advanced bladder cancer (NCT00790426).

The non-receptor tyrosine kinase Src is another potential therapeutic target in urothelial carcinoma. Src inhibitors have shown antimetastatic potential in a number of preclinical models, including bladder cancer, and, based on that, dasatinib is being tested in a phase II neoadjuvant trial (NCT00706641).
targeting angiogenesis

As is the case with many epithelial cancers, the VEGF, FGF and PDGF families of proangiogenic factors play an important role in urothelial cancers.

Bevacizumab, a monoclonal antibody against VEGF, showed promising efficacy in a phase II trial in combination with gemcitabine and cisplatin [six of 36 evaluable patients showing a complete response (CR), 18 a partial response (PR) and 10 stable disease (SD)] although at the expense of considerable toxicity (ASCO 2009, abstract 5018). It is now being tested in a phase III CALGB study (NCT00942331).

Several small-molecule inhibitors with mixed pharmacologies including sunitinib, which has VEGFR, PDGFR and Kit activity; sorafenib, which has VEGFR, Raf, PDGFR and Kit activity; vandetanib, which targets VEGFR, EGFR and RET; and pazopanib, which hits VEGFR, PDGFR and Kit, have also entered clinical investigations in bladder cancer.

Sunitinib showed modest activity in previously treated advanced urothelial carcinoma (two PR in 77 patients, and 43% SD) [6]. It has also been evaluated as first-line treatment in unfit bladder cancer patients who are not suitable for cisplatin-based chemotherapy, with 64% of patients obtaining significant clinical benefit from the drug. (ASCO GU Symposium 2008, abstract 291). Sorafenib showed no benefit in first-line treatment in advanced urothelial carcinoma (ASCO GU Symposium 2008, abstract 340). Phase II trials with vandetanib—in combination with docetaxel—(NCT00378794) and pazopanib (NCT01031875 and NCT00471536) in second-line, refractory metastatic urothelial carcinoma are ongoing.

targeting p53, cell cycle checkpoints and apoptosis pathways

Inactivating somatic mutations in p53 are very common (>50%) in muscle-invasive bladder tumors. p53 can also be functionally inactivated by MDM2, an E3 ligase responsible for ubiquitin-dependent degradation of p53. MDM2 overexpression occurs in ~30% of urothelial cell carcinomas. A number of agents are in developments that aim to restore p53 function in tumor cells. There are other, indirect ways in which to target p53-deficient tumor cells. Checkpoint kinase inhibitors may preferentially sensitize p53-deficient tumor cells to chemotherapy and radiotherapy. Several inhibitors of the Chk1 and Chk2 kinases are now in development, including AZD7762 (AstraZeneca), XL844 (Exelixis) and PF-00477736 (Pfizer).

Preclinical activity in bladder cancer has also been demonstrated with small-molecule inhibitors of mitotic proteins such as the kinesin spindle protein KSP/Eg5 (ASCO GU Symposium 2009, abstract 254). However, a phase II trial of the KSP inhibitor AZD4877 (NCT00661609) in second-line muscle-invasive bladder cancer did not meet pre-specified criteria for a response rate to enable future development in bladder cancer.

new chemotherapeutic agents

antifolates
Antifolates are known to be active in advanced bladder cancer, with a number of regimens incorporating methotrexate, including MVAC (methotrexate vinblastine, Adriamycin and cisplatin). The multitargeted antifolate pemetrexed has been tested in several trials. In a Hoosier Oncology Group study in 47 previously treated patients, objective responses were observed in 13 (28%), including CRs in three cases (6%) [7]. The median survival was 10 months. Pemetrexed was also evaluated in a phase II study in previously untreated patients in combination with gemcitabine, although the observed activity did not appear greater than with gemcitabine alone [8]. A subsequent trial conducted at the Memorial Sloan-Kettering Cancer Center (MSKCC) was closed due to insufficient activity. More modest activity in second line has been reported in a subsequent trial by Galsky et al. [9]. Pemetrexate, a pemetrexed analog, is now too in a phase II second line.

epothilones
Ixabepilone, an epothilone B analog, binds to and stabilizes the microtubules in a manner similar but not identical to that of paclitaxel. In an ECOG (Eastern Cooperative Oncology Group)-sponsored phase II study, five PRs were observed among 42 previously treated patients [10]. Responses were observed in visceral, nodal and soft tissue sites. The median survival was 8 months, and toxicity was moderate, consisting primarily of granulocytopenia, fatigue and sensory neuropathy.

microtubule dynamics inhibitors
Eribulin (E7389) is a synthetic analog of halichondrin B, a naturally derived compound that was first isolated from a marine sponge. While taxanes inhibit cell division by stabilizing microtubules, eribulin is a microtubule dynamics inhibitor that arrests the cell cycle through inhibition of the growth of microtubules without interfering with microtubule shortening. Eribulin produced one PR and two SD in three patients with heavily pre-treated bladder cancer in a phase I clinical trial and is being studied in a phase I/II study in patients with advanced urothelial carcinoma with renal insufficiency (NCT00365157).

Vinca alkaloids
Vinflunine, a novel Vinca alkaloid, showed evidence of activity as second-line therapy, as manifested by an objective response rate of ~15–18% [11, 12]. The phase III trial comparing vinflunine with best supportive care demonstrated a statistically significant improvement in survival in the eligible population.
Multivariate Cox analysis adjusting for prognostic factors showed a statistically significant effect of vinflunine on overall survival ($P = 0.036$), reducing the risk of death by 23%. This led to the approval in Europe of vinflunine as second-line therapy for advanced bladder cancer.

After several decades using chemotherapy without significant improvement in disease outcome, some new chemotherapeutic agents and targeted agents are now emerging as a potential ways to overcome present limitations of therapy.

disclosures
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references