Advanced bladder cancer: New agents and new approaches. A review

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Abstract

Objective: The aim of the present paper is to review findings from the most relevant studies and evaluate the potential of new drugs in treatment of metastatic urothelial cancer.

Methods: Studies were identified by searching MEDLINE and Pubmed databases up to 2009 using both medical subject heading (Mesh) and a free text strategy with the name of known individual chemotherapeutic drug and the following key words: ‘muscle-invasive bladder cancer’, ‘urothelial/transitional carcinoma’, ‘chemotherapeutics drugs and agents’. At the end of our research in literature we selected 63 articles and we have considered only studies in which almost 30 patients were enrolled.

Results: Radical cystectomy with pelvic lymph node dissection is the gold standard of treatment for clinically localized muscle-invasive bladder cancer. While more extensive lymph node dissection may have both prognostic and therapeutic significance, effective systemic therapies that eliminate micrometastases may improve outcome. Perioperative chemotherapy can be administered before (neoadjuvant) or after (adjuvant) cystectomy to eradicate subclinical disease and to improve survival.

Conclusion: The challenge remains as to how to integrate all of the relevant knowledge and data in a systematic manner so that researchers can gain the knowledge needed to devise the best therapeutic and diagnostic strategies. Future improvements in the treatment of advanced bladder cancer will rely not only on the optimization of currently available cytotoxic agents but also on the biologic profile of individual patient tumors and the appropriate therapies that target molecular aberrations unique to this malignancy. © 2013 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Chemotherapy; Targeted therapy

1. Introduction

Bladder cancer is the fourth most common genitourinary cancer among men and the seventh in women, with an incidence of more than 68,000 new cases and more than 14,000 certified deaths in the United States in 2008 [1]. The highest occurrence rates of bladder cancer are observed in Europe, North America, and Australia [2]. Muscle-invasive bladder cancer (clinical stage cT2-cT4a) is an aggressive epithelial tumor with a high rate of early systemic dissemination and 5-year survival depending principally on pathologic stage and nodal status [3]. Up to 50% of patients with infiltrating disease develop metastases and ultimately succumb to their disease [3]. Failure is usually due to occult metastatic disease present at the time of diagnosis. Radical cystectomy with pelvic lymph node dissection is the gold standard of treatment for clinically localized muscle-invasive bladder cancer. Survival after cystectomy is, at best, 65% (including patients with pT2) and varies from 36% to 48% at 5 years in major series [4–7]. Patients’ survival with pathologic stage T3-T4 and/or positive nodes is somewhere between 25% and 35%. This stage-dependent survival reduction is believed to be caused by the presence of micrometastases at the time of cystectomy. While more extensive
lymph node dissection may have both prognostic and therapeutic significance, effective systemic therapies that eliminate micrometastases may improve outcome. Perioperative chemotherapy can be administered before (neoadjuvant) or after (adjuvant) cystectomy to eradicate subclinical disease and to improve survival. Combination chemotherapy has been considered the standard care for patients with metastatic bladder cancer for decades because it has been found to be superior to the use of single agents [8]. Cisplatin-based combination chemotherapy regimens, such as methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) and cisplatin, methotrexate, and vinblastine, were standard treatment of patients with metastatic urothelial cancer [8–12]. The overall response rates (ORR) to ‘standard’ cisplatin-based combination regimen have varied between 39% and 65%, with complete response (CR) in 15%–25% and median survivals up to 16 months [12–16]. Nonetheless, almost all responding patients relapse within the first year with a median survival of 12 months [17]. The M-VAC combination continued to be the most common treatment regimen for advanced urothelial cancer until, in a study by von der Maase et al. [18], the cisplatin-gemcitabine (GC) combination was compared with classic M-VAC as first-line therapy in a multicenter randomized phase III trial. Subjects with T4b and/or node-positive and/or distant metastatic disease were randomized to 6 cycles of M-VAC or GC. At a median follow-up of 19 months, the regimens were not statistically different in terms of overall survival, time to disease progression, or response rate. The GC combination, however, was superior in terms of tolerability and effects on quality of life. In particular, GC resulted in a lower incidence of treatment-related mortality and fewer episodes of complicated myelosuppression, oral mucositis, and alopecia (resulting in fewer dose adjustments) and lesser effects on weight, performance status, and fatigue compared with the MVAC group. As a result, the GC combination is now widely considered to be a (second) standard of care, along with M-VAC, for patients with advanced bladder cancer, although there is some disagreement regarding the reported benefits [19]. To increase the percentage of patients who achieve disease stabilization and prolonged survival and improved quality of life during treatment, numerous novel agents, many of which are still in clinical trials, are being developed. A new generation of drugs might be applied orally on an outpatient basis with low toxicity. To date, however, the clinical trials with new anticancer agents are limited in their impact on long-term survival and safety. Unfortunately, it has become increasingly clear that bladder cancer is a tumor where reasonable and long-lasting treatment results will not be achieved soon. Especially patients with recurrent or progressive tumor have, to date, no defined second-line chemotherapy option. Both existing and new therapies need to be tailored to benefit a select group of patients whose risk of disease progression can be predicted on the basis of the molecular alterations, surrogate markers specific for their tumors. A profound understanding of the molecular biology of bladder cancer is crucial for the selection of new therapeutic modalities. Association of specific molecular alteration with chemoresponse can stratify patients on the basis of their individual ability to benefit from chemotherapy. The future goals of cancer therapy are to identify the molecular basis of bladder cancer genesis and progression to better define risk and response probabilities for the individual patient and to develop new therapeutic strategies aimed at the specific defects that characterize the specific bladder cancer. Accurate selection of a subgroup of patients most likely to benefit may become possible in a predictable manner in the near future.

2. New agents for treatment of advanced transitional cell carcinoma

2.1. Gallium nitrate

Although early clinical trials indicated that gallium nitrate, a ‘near metal’ compound, had activity against bladder cancer, its subsequent development centered primarily on its effect on bone metabolism and not on its antineoplastic activity. As a result, the drug was approved for the treatment of hypocalcaemia of malignancy. Pharmaceutical production of gallium nitrate, however, ceased during the late 1990s, stopping several gallium-based clinical trials. Gallium nitrate has recently awakened commercial interest and an oral formulation of gallium is in development. Gallium’s mechanisms of action include its targeting and binding transferrin and transferrin receptors and inhibiting ribonucleotide reductase. Recent investigations show that gallium activates caspases and induces apoptosis through the mitochondrial pathway [20], McCaffrey et al. [21] at the Memorial Sloan-Kettering Cancer Center, New York (MSKCC) conducted a randomized phase II trial of gallium nitrate (350 mg/m², days 1–5) plus fluorouracil (5-FU) (1000 mg/m², days 1–5) repeated every 28 days vs. M-VAC in 34 patients with advanced TCC. Although 5-FU has not been evaluated as a single agent in bladder cancer, it was combined with gallium nitrate on the basis of its clinical synergism with metal compounds in other cancer types. The response to gallium nitrate–5-FU was 12% (2 PR). Progression of disease was observed after 6 and 12 months. The M-VAC response was 94% (2 CR, 14 PR). At 17 months, however, the survival rates in both groups were equivalent. In summary, several studies of gallium nitrate as single agent [22–24] and in combination [25,26] have shown its activity in the treatment of advanced or refractory bladder cancer; however, some studies suggest significant toxicity. Evaluation in combination with new agents as gemcitabine and/or paclitaxel may also be warranted given its mechanism of action and nonoverlapping toxicity profiles.

2.2. Ifosfamide

Ifosfamide is an alkylating agent with modest activity in advanced TCC. The Eastern Cooperative Oncology Group
evaluated single-agent ifosfamide in a group of patients who had progressive disease after receiving systemic chemotherapy. Of the 56 eligible patients entered into the study, there were 5 CR and 5 PR with an ORR of 20%. Major toxic effects were gastrointestinal, hematologic, renal, and in the central nervous system (CNS). Concerns about significant renal and CNS toxicity led to a change of ifosfamide dosing halfway through this study. There were 4 early deaths to which the treatment probably contributed [27]. Nevertheless, ifosfamide has been evaluated as combination partner in other active regimens [28–32]. It, however, is too early to determine the activity of this agent in polychemotherapy regimen, but dosage is difficult and adds to toxicity.

2.3. Pemetrexed

Pemetrexed (Alimta; Eli Lilly, Indianapolis, IN) is a novel, multi-targeted antifolate agent. Early studies showed that concomitant supplementation of vitamin B12 and folate attenuated toxicity without compromising efficacy. Paz-Ares [33] investigated front-line single agent pemetrexed (with no folic acid and vitamin B12 supplementation) in patients with advanced UC. Pemetrexed yielded an objective RR of 30% and stable disease (SD) was achieved in 35% of patients. Toxicities included grade 4 neutropenia (35%), grade 3/4 anemia (17%), and grade 3/4 thrombocytopenia (9%); 22% of patients developed febrile neutropenia and 2 patients died. Forty-seven patients were enrolled in another phase II trial, with metastatic disease that had progressed at any time after initial therapy for metastatic disease or within 12 months of perioperative chemotherapy [34]. There were 3 (6%) CRs and 10 (21%) partial responses (PRs), for an overall RR of 28%, while 10 patients (21%) had SD. The median time to progressive disease was 2.9 months and the median OS was 9.6 months. Grade 3 or 4 hematologic events were thrombocytopenia (8.5%, 0%), neutropenia (4%, 4%), and anemia (2%, 2%). In another phase II trial of second-line pemetrexed from the Memorial Sloan Kettering Cancer Center, there was an objective response in 1 of 12 evaluable patients, for an overall RR of 8% (90% upper limit 29%) [35]. This level of activity did not meet the criteria for expansion, based on the predefined optimum 2-stage Simon design, and the trial was concluded after only 13 patients were enrolled. Combined front-line treatment with pemetrexed-gemcitabine was evaluated in 62 patients with advanced UC, 59% of whom had visceral metastases [36]. The RR was 26.5% and the median OS was 10.1 months. Grade 3/4 toxicities included anemia (13%), thrombocytopenia (10%), neutropenia (37%), febrile neutropenia (18%), and neutropenic sepsis (3%). These results were not much better than those achieved with gemcitabine alone as a single agent. Currently, a phase II trial is evaluating combined cisplatin and pemetrexed as front-line therapy for advanced UC.

2.4. Epothilones

The epothilones are novel non-taxane tubulin polymerization agents, and aza-epothilone B (BMS-247550; ixabepilone) is a semisynthetic analogue of the natural product epothilone B. Ixabepilone was evaluated for the second-line therapy of advanced UC in a phase II trial in 45 patients, of whom 40% had received a previous taxane [37]. Five patients had a PR among the 42 eligible patients, for a RR of 12%, and the median OS was 8 months. Toxicities were moderate, with neutropenia, fatigue, and sensory neuropathy being the most common. Further development is being considered.

2.5. Oxaliplatin

Oxaliplatin is a non-nephrotoxic third generation platinum analogue. Winquist et al. [38] evaluated oxaliplatin 130 mg/m$^2$ every 3 weeks in 18 evaluable patients with previously treated advanced UC, in a phase II trial. Patients were stratified as ‘cisplatin-sensitive’ or ‘cisplatin-resistant’ on the basis of previous cisplatin treatment. There was 1 PR in 10 cisplatin-sensitive patients, and no responses in 8 who were cisplatin-resistant. The combination of oxaliplatin and gemcitabine was evaluated in a front-line phase II trial of 30 patients, and a serum creatinine up to 1.5 times the upper limit of normal was allowed [39]. There were 3 CRs and 11 PRs, for an overall RR of 47%; the median survival was 15 months, and toxicities were manageable. Of interest, the combination of oxaliplatin and docetaxel is being evaluated in an ongoing front-line therapy trial, and patients with a serum creatinine level <1.8 mg/dL are eligible.

2.6. Nanoparticle albumin-bound (NAB) paclitaxel

Nanoparticle albumin-bound (NAB) paclitaxel (Abraxane, Abraxis) is a novel solvent-free, albumin-bound formulation of paclitaxel. It was designed to avoid solvent-related toxicities and to deliver paclitaxel to tumors via molecular pathways involving an endothelial cell-surface albumin receptor and an albumin-binding protein expressed by tumor cells and secreted into the tumor interstitium (‘secreted protein acid rich in cysteine’ [40]. Nab-paclitaxel is being evaluated for the salvage therapy of progressive UC, and as a component of combined regimens in the neoadjuvant setting.

2.7. E7389 (Eisai)

E7389 (Eisai) is a synthetic derivative of the marine sponge product halichondrin-B that inhibits tubulin polymerization and has activity in refractory breast and non-small-cell lung cancer [41]. A phase II trial is evaluating front-line E7389 in patients with advanced UC with and without renal insufficiency. Other ongoing trials are evaluating novel agents and combinations.
2.8. Vinflunine ditartrate

Vinflunine ditartrate (Javlors, Pierre Fabre Me’dicament, Boulogne-Billancourt, France) is a novel antitubulin agent obtained from a Vinca alkaloid. Fifty-one patients with recurrent advanced UC were treated with vinflunine; 9 responded, for an overall RR of 18%, and 67% achieved disease control (response + stability) [42]. Responses were predominantly in patients who had previously responded to chemotherapy.

However, 5 of 25 (20%) patients with visceral involvement had a response, and there were also responses in patients with primary chemoresistant disease. The median PFS was 3 months and the median OS was 6.6 months. There was febrile neutropenia in 5 patients (10%), of whom 2 died. Constipation was frequent but manageable and not cumulative, and was grade 3–4 in only 8% of patients; there was grade 3 nausea and vomiting in 6%, but no severe neuropathy. Salvage therapy with vinflunine plus best supportive care (BSC) is being compared with BSC in a multinational randomized trial. Another ongoing randomized trial is comparing the combination of front-line vinflunine and gemcitabine against gemcitabine alone in patients ineligible for cisplatin.

3. Monoclonal antibodies

3.1. Trastuzumab

Her-2/neu expression in urothelial cancers is variable and might be associated with a more aggressive clinical course [43]. Patients with metastatic TCC or squamous cell carcinoma that expressed Her-2/neu (by immunohistochemistry, IHC, serology or fluorescence in situ hybridization, FISH) in primary or metastatic sites were treated with trastuzumab combined with paclitaxel, carboplatin and gemcitabine [44]. Fifty-seven (52.3%) of 109 registered patients were Her-2/neu-positive using several different methods. Her-2/neu-positive patients had more metastatic sites and a higher rate of visceral metastasis than did Her-2/neu-negative patients. Forty-four of 57 Her-2/neu-positive patients were treated with the regimen. Overall, 32.6% of patients had previously received perioperative chemotherapy, and 55% had visceral metastases. The most common grade 3–4 toxicity was myelosuppression, with 2 toxic deaths. Grade 3 sensory neuropathy occurred in 14% of patients, and 22.7% had grade 1–3 cardiac toxicity. Thirty-one (70%) of 44 patients responded (5 CRs and 26 PRs), and 25 (57%) of 44 were confirmed responses. The median time to progression and survival were 9.3 and 14.1 months, respectively. Given the aggressive course of disease in this high-risk population, these outcomes are considered promising, and appear to warrant a randomized trial to definitively assess the value of adding trastuzumab to combined chemotherapy. Trastuzumab is also being evaluated in combination with paclitaxel and radiotherapy for bladder conservation.

3.2. Bevacizumab

Vascular endothelial growth factor (VEGF) receptors are expressed on UC, and preclinical evidence supports the antitumor efficacy of targeting this pathway in combination with chemotherapy [45]. Bevacizumab is administered i.v., and is commonly used in combination with chemotherapy in colorectal cancer and increasingly in other solid tumors. Separate phase II trials are evaluating neoadjuvant GC or DD-MVAC plus bevacizumab followed by RC in patients with muscle-invasive and resectable TCC of the bladder. Another phase II trial by the Hoosier Oncology Group (HOG) is evaluating first-line GC plus bevacizumab for metastatic TCC, while the Cancer and Leukemia Group B (CALGB) is planning a first-line randomized phase III trial of GC vs. GC-bevacizumab.

3.3. Cetuximab

Human TCCs overexpress epidermal growth factor receptor (EGFR) and that confers a poor prognosis [46]. Cetuximab is an intravenously administered EGFR monoclonal antibody commonly used in colorectal cancer, and in head and neck cancers. Preclinically, cetuximab alone and combined with paclitaxel inhibited tumor growth and metastasis by inhibiting neovascularization and inducing apoptosis [46]. A trial is planned to evaluate the combination of cetuximab with first-line GC and with salvage paclitaxel.

4. Targeted therapy

4.1. Farnesyltransferase inhibitors

Protein farnesylation by farnesyltransferase (FTase) is required for membrane localization and effective signal transduction by G-proteins, including Ras. Lonafarnib inhibits FTase and has shown antitumor activity in both preclinical and clinical settings [47–49]. As disturbances in Ras-signaling pathways have been implicated in the pathogenesis of TCC [50], the antitumor activity of lonafarnib was studied in a National Cancer Institute of Canada Clinical Trials Group phase II trial in 19 patients with previously treated TCC. The patients had at least 1 prior chemotherapy regimen for advanced unresectable or metastatic TCC or recurrence less than 1 year after adjuvant or neoadjuvant chemotherapy. Lonafarnib was given at an oral dose of 200 mg twice daily continuously, with cycles repeated every 4 weeks. Median time on treatment was 7.1 weeks (range 0.6–23.9 weeks). Drug-related grade 3 toxic effects included fatigue, anorexia, nausea, confusion, dehydration, muscle weakness, depression, headache, and dyspnea. Five patients discontinued the study protocol due to toxicity. No
responses were observed in 10 patients who were assessable. Of 9 patients not assessable for response, 5 had symptomatic progression, fulfilling the criteria to stop the study [51]. In a multicenter EORTC study, the pharmacokinetics and activity of a combined therapy with FTase inhibitor SCH66336 and gemcitabine in patients with advanced urothelial tract cancer were evaluated. Patients were treated with SCH66336 (150 mg in the morning and 100 mg in the evening) and gemcitabine (1000 mg/m² on days 1, 8, and 15 per 28-day cycle). A total of 152 cycles were administered in 33 patients (median 3, range 1–15). Toxicity was acceptable with no severe hematologic effects; 9 PR and 1 CR were achieved in 31 assessable patients and corresponded to an ORR of 32.3% (95% CI 17%–51%). There was no influence of exposure to SCH66336 on the plasma level of gemcitabine or 2-difluorodeoxyuridine (dFdU) in 11 assessable patients [52]. In another phase II trial, FTase inhibitor R115777 at a dose of 300 mg orally given twice daily for 21 days followed by 7 days of rest for every 4-week cycle was examined in 34 patients with metastatic TCC. Patients were allowed to have 1 prior systemic chemotherapy regimen, but not chemoradiation or neoadjuvant chemotherapy. The results showed that R115777 was absorbed rapidly after oral administration and was generally tolerated well. Grade 3–4 neutropenia was observed in 5 patients (15%). Grade 3–4 nonhematologic toxicity was rare, consisting of rash and diarrhea in 1 patient each. Two patients (6%) without prior chemotherapy demonstrated PRs. Thirteen patients (38%) achieved disease stabilization that lasted a median of 4 months. No CRs were observed [53]. To date, no further studies in TCC with FTase inhibitor as single agent or in combination are reported.

4.2. Ribozyme (RPI.4610)

RPI.4610 (Angiozyme) is a chemically stabilized ribozyme-targeting vascular endothelial growth factor receptor 1 (VEGF-R1). A study by Kobayashi et al. [54] evaluated the safety and pharmacokinetics of RPI.4610 in combination with carboplatin and paclitaxel in 12 patients with advanced solid tumors (including patients with TCC). The study used a sequential treatment design evaluating a single dose level for all 3 drugs: paclitaxel 175 mg/m² and carboplatin area under the curve (AUC) = 6 on day 1 of a 21-day cycle together with RPI.4610 100 mg/m² per day beginning on day 8 and continuing daily thereafter. The toxic effects were found to be grade 3–4 neutropenia, thrombocytopenia, pain (each 3 patients), and anemia and fatigue (each 2 patients). The ratio of the mean maximum plasma concentration (Cmax) for carboplatin when administered with paclitaxel alone vs. when administered with paclitaxel and RPI.4610 was 1.07 (90% CI 0.77–1.37). For paclitaxel, the ratio of the mean Cmax when administered with carboplatin alone versus with carboplatin and RPI.4610 was 1.17 (1.03–1.31). One complete tumor response was observed in a patient with bladder cancer and 1 patient with an esophageal cancer achieved a PR. This principal evaluation showed that a ribozyme-targeting VEGF-R (RPI.4610) can be administered safely in combination without substantial pharmacokinetic interactions with carboplatin and paclitaxel. Further efficacy or safety data are to date not available.

4.3. Histone deacetylase inhibitor (CI-994)

Histones are small basic proteins which, by complexing with DNA, form the nucleosome core. Repetitive units of this nucleosome lead to the chromatin in which all the human genome is packaged. Histones can be in 1 of the 2 antagonist forms, acetylated or deacetylated, with equilibrium regulated by the corresponding enzymes, histone acetylases, and histone deacetylases (HDACs). Inhibition of HDACs represents a new strategy in human cancer therapy since these enzymes play a fundamental role in regulating gene expression and chromatin assembly. They are potent inducers of growth arrest, differentiation, and apoptosis of tumor cells. A second generation of HDACs, synthetic benzamidine-containing HDACs such as CI-994, have reached phase I and II clinical trials [55,56]. In a phase I study by Pauer et al. [57], the maximum tolerated dose of CI-994 was determined in combination with carboplatin and paclitaxel in 30 patients with advanced solid tumors, including patients with TCC. Five cohorts of patients were treated with escalating doses (4–6 mg/m²) and alternative schedules (7 or 14 days) of CI-994. Dose escalation of paclitaxel was performed to achieve tolerability of CI-994 with a paclitaxel dose of 225 mg/m² when administered in combination with carboplatin. Maximum tolerated dose of CI-994 was determined to be 4 mg/m² administered for 7 consecutive days following paclitaxel at a dose of 225 mg/m² and carboplatin at an AUC of 6 every 21 days. Neutropenia, thrombocytopenia, and grade 3 respiratory insufficiency limited further dose escalation of CI-994. Pharmacokinetics showed that CI-994 absorption and disposition were unaffected by carboplatin and paclitaxel co-administration. Association between histone H3 acetylation levels and disease response was suggested [57]. A subset of patients with lymphocyte H3 acetylation levels at least 1.5-fold baseline achieved either a clinical response or SD. All assessable patients with progressive disease had H3 acetylation levels less than 1.5-fold baseline. Twenty-four of the 30 patients received greater than 1 cycle of treatment. Five of these patients achieved a PR [3 non-small-cell lung cancer (NSCLC), 1 colorectal cancer, and 1 unknown primary] and 2 patients achieved a CR (esophageal and bladder cancer). A phase II study in patients with TCC is not available [57].

5. Combination trials with monoclonal antibodies (epidermal growth factor receptor, Her-2/neu)

Evaluation of the therapeutic potential of the EGFR tyrosine kinase inhibitor (gefitinib, Iressa; AstraZeneca
Pharmaceuticals, London, UK) has been performed in preclinical models of bladder cancer [57–62]. To date, the CALGB is conducting a phase II trial of gemcitabine, cisplatin, and gefitinib to evaluate its clinical impact. Iressa, an orally administered EGF-R tyrosine kinase inhibitor, was approved for marketing in May 2003 for patients with NSCLC. The response rate in patients taking the drug was 10%. The approved indication was for the treatment of patients who were refractory to established cancer treatments [both a platinum drug and docetaxel (Taxotere; Hoffman-La Roche AG, Switzerland)]. Since the initial approval of Iressa, however, the Food and Drug Administration has carefully reviewed data from 2 failed clinical studies of Iressa, one of which was required by the agency as part of the drug’s accelerated approval. This trial enrolled patients with regionally advanced or metastatic NSCLC in whom 1 or 2 prior treatment regimens had failed. In this large study, 1,692 patients were randomized to gefitinib or placebo. There was no significant survival benefit in the overall study population or in patients who had high levels of a surface marker called ‘EGF-R’. It is likely that optimized therapy approaches in bladder cancer will also require an accurate ‘molecular’ diagnosis allowing effective, selective, tailored therapeutic strategies to be designed.

6. Conclusions

Human TCC of the bladder is genetically heterogeneous, and it is surrounded by a complex tissue microenvironment involving vasculature, stromal cells, and connective tissue. One of the most challenging problems facing cancer researchers is the lack of correlation between in vitro cell lines and animal tumor models and human in vivo tumors. Today, the optimal therapy for advanced urothelial carcinoma beyond cystectomy and urinary diversion remains a challenge. In metastatic disease, cisplatin-based therapy (particularly MVAC and GC) has had the best track record thus far. As a result, these regimens are recognized as the standard of care for metastatic and unresectable bladder cancer. Carboplatin-based therapy is, however, a viable therapeutic approach for patients who are poor candidates for cisplatin-based therapy. The decision on who should receive which combination of agents seems largely determined by the individual’s comorbidities, performance status, and disease extent. While not statistically significant, the results of several phase III trials using MVAC and of phase II trials using carboplatin suggest a small benefit of cisplatin over carboplatin in median survival, which is balanced by the treatment-related toxicity [63]. Whether or not this implies that

Table 1
Agents, categories, toxicities and author (response reported where available)

<table>
<thead>
<tr>
<th>Agents</th>
<th>Categories</th>
<th>Toxicities</th>
<th>Author (response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallium Nitrate</td>
<td>Near metal compound</td>
<td>Nephrotoxicity, gastrointestinal toxicity, myelosuppression minimal Hypocalcemia, nausea, anemia</td>
<td>McCaffrey (12%)</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Alkylating agent</td>
<td>Gastrointestinal, hematologic, renal and in the central nervous system</td>
<td>Witte RS (20%)</td>
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<tr>
<td>Pemetrexed</td>
<td>Multi-targeted antifolate agent</td>
<td>Anemia, thrombocytopenia, neutropenia, febrile neutropenia and neutropenic sepsis</td>
<td>Sweeney CJ (27%)</td>
</tr>
<tr>
<td>Epothilones</td>
<td>Non-taxane tubulin polymerization agents</td>
<td>Neutropenia, fatigue, and sensory neuropathy</td>
<td>Dreicer R (12%)</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Platinum analogue</td>
<td>Neutropenia and sensory neuropathy</td>
<td>Winquist (6%)</td>
</tr>
<tr>
<td>Nanoparticle Albumin-Bound (NAB) Paclitaxel</td>
<td>Novel solvent-free, albumin-bound formulation of paclitaxel</td>
<td>Neutropenia and peripheral neuropathy</td>
<td>Nyman DW (13%)</td>
</tr>
<tr>
<td>E7389 (Eisai)</td>
<td>Synthetic derivative of the marine sponge product halichondrin-B</td>
<td>Unavailable data in humans</td>
<td>Kuznetsov G (unavailable data in humans)</td>
</tr>
<tr>
<td>Vinflunine Ditartrate</td>
<td>Antitubulin agent obtained from a Vinca alkaloid</td>
<td>Febrile neutropenia; constipation, nausea, vomiting and no severe neuropathy</td>
<td>Lonn U (18%)</td>
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<tr>
<td>Trastuzumab</td>
<td>Monoclonal antibodies</td>
<td>Myelosuppression, sensory neuropathy, cardiac toxicity</td>
<td>Hussain MH (70%)</td>
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<td>Bevacizumab</td>
<td>Monoclonal antibodies</td>
<td>Myelosuppression, sensory neuropathy</td>
<td>Srilakich S (36%)</td>
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<tr>
<td>Cetuximab</td>
<td>Monoclonal antibodies</td>
<td>Unavailable data in humans</td>
<td>Inoue K (unavailable data in humans)</td>
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<td>Farnesyltransferase Inhibitors</td>
<td>Targeted therapy</td>
<td>Neutropenia, rash and diarrhea</td>
<td>Theodore C (30%)</td>
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<tr>
<td>Ribozyme (RPL4610)</td>
<td>Targeted therapy</td>
<td>Neutropenia, thrombocytopenia, pain, anemia and fatigue</td>
<td>Kobayashi (8%)</td>
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<tr>
<td>Histone Deacetylase Inhibitor (CI-994)</td>
<td>Targeted therapy</td>
<td>Neutropenia, thrombocytopenia and respiratory insufficiency</td>
<td>Pauer LR (phase II study for bladder cancer unavailable)</td>
</tr>
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</table>
younger patients with aggressive and extensive disease should receive cisplatin regimens while elderly patients with a poor performance status receive carboplatin-based treatment has not been definitively evaluated. During malignant transformation, tumor cells acquire a series of molecular characteristics resulting in growth factor independence, insensitivity to antiproliferative signals, escape from apoptosis, (neo)angiogenesis, proliferative capacity, and the ability for invasion and metastasis. The knowledge of the molecular pathways allows the identification of novel molecular targets. Translational research plays a major role in taking the results of research from the laboratory bench to the bedside. Data from high-throughput genomics and proteomics lead to the development of new technologies, ultimately resulting in rational drug design for cancer therapy. A targeted clinical trial in bladder cancer must take into account molecular characteristics and known prognostic variables of bladder tumors, and employ agents that are based on mechanism, risk of progression, and chemoresponsiveness. Individualization of both established and investigational treatment options based on molecular characteristics of the tumor is the future of bladder cancer therapy. Novel drug agents for bladder cancer are few, but the anti-EGF-R agents and antiangiogenic agents may have promise; the development of antiapoptotic agents and antisense gene therapy may also become a component of the future multimodality management of this tumor. The tremendous amount of data accumulated through genomics and proteomics have not led to a definitive understanding of the mechanisms underlying cancer. The challenge remains as to how to integrate all of the relevant knowledge and data in a systematic manner so that researchers can gain the knowledge needed to devise the best therapeutic and diagnostic strategies. Future improvements in the treatment of advanced bladder cancer will rely not only on the optimization of currently available cytotoxic agents but also on the biologic profile of individual patient tumors and the appropriate therapies that target molecular aberrations unique to this malignancy (Table 1).

References


