Review article

Current chemotherapeutic options for the treatment of advanced bladder cancer: A review

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Abstract

Advanced bladder cancer is a disease with a high recurrence rate and metastatic capacity exhibiting a poor outcome. The pathologic stage and nodal involvement are independent prognostic factors for survival after cystectomy, and in locally advanced or metastatic disease, the performance status and the presence of visceral metastases have been correlated with treatment outcome. The regimen methotrexate-vinblastine-adriamycin-cisplatin (MVAC) has been the treatment of choice for decades and later the combination of cisplatin with gemcitabine became also the new standard of care, by demonstrating a more favorable toxicity profile. Also, carboplatin-gemcitabine and taxanes have been useful alternatives for patients unfit for cisplatin-based treatment. Additionally, the evaluation of certain chemotherapeutic agents has produced promising results in the second-line setting. Lastly, the past decade has provided information on the molecular mechanism of bladder cancer offering a personalized approach and optimizing the management of the disease. © 2013 Elsevier Inc. All rights reserved.

Keywords: Bladder cancer; Chemotherapy; Toxicity profile; Targeted therapy

1. Introduction

Bladder cancer is the second most common malignancy of the genitourinary tract with 357000 new cases and 145000 deaths worldwide per year [1]. It is also the fourth most common neoplasm in men and accounts for 68,810 new cases and 14,100 deaths in USA for 2008 or 7% and 2.5% of new cancer cases, in males and females, respectively [2]. Urothelial carcinoma, formerly known as transitional cell carcinoma, comprises 90% of all bladder carcinomas, while 5% of them are identified as squamous and 2% as adenocarcinomas. Papillary or non-muscle-invasive tumors of the bladder exhibit an infrequent progression to muscle invasion or metastases [3]. On the contrary, muscle invasive disease exhibits a poor outcome. Although most cases are not clinically advanced at presentation, the disease eventually recurs or develops metastases [4].

Advanced bladder cancer comprises 3 distinct groups: inoperable disease due to local extension or grossly involved pelvic or paraortic lymph nodes, metastatic disease at presentation or recurrent disease after radical cystectomy. The recurrence rate after cystectomy for muscle-invasive disease has been affected by a number of independent risk factors, such as advanced pathologic stage, nodal involvement, size of tumor > 3 cm, and lymphovascular invasion [5,6]. Also, pathologic stage and nodal involvement are independent prognostic factors for survival [7]. Similarly, in locally advanced or metastatic disease, performance status (Karnofsky performance score) and the presence of visceral metastases correlate with treatment outcome [8].

The introduction of combination chemotherapy regimens, such as methotrexate, vinblastine, adriamycin, cisplatin (MVAC) and gemcitabine, cisplatin (GC), has been shown to be useful options for surgically incurable disease. However, despite initial high response rates, overall 5-year survival is suboptimal, ranging from 5% to 20% [9], showing the need for the development of new treatment modalities, including new combinations of the conventional chemotherapeutic agents and the incorporation of new drugs and targeted agents.
Additionally, the role of induction and adjuvant chemotherapy has also been evaluated in advanced disease. The rationale of neoadjuvant chemotherapy is to treat micro-metastatic disease present at diagnosis. To date, available data suggest that a substantial benefit may be seen in high-risk patients with T3b tumors and meta-analysis has revealed cisplatin-containing regimens as more effective. However, the available trials on adjuvant chemotherapy do not provide sufficient evidence to support its use and, therefore, larger international trials are needed [10].

Moreover, during the past decade there has been ongoing research on molecular markers, biomarkers which enhance the predictive ability based on clinicopathologic features and might lead to a personalized approach of advanced bladder cancer in the future [11,12].

This review focuses on the data of advanced bladder cancer chemotherapy and emphasizes on the promising role of novel agents.

2. Single agent chemotherapy

Although bladder cancer is considered to be a chemosensitive neoplasm, only a minority of the patients responds to single-agent therapy. Initially, in 1976, a study of 24 advanced bladder cancer patients treated with cisplatin demonstrated 8 partial and 4 minor responses [13]. The studies that followed based on cisplatin monotherapy showed a modest activity, producing response rates of 17% and, specifically, 12% in phase III trials [14]. Similarly, carboplatin monotherapy achieved response rates of 12% to 14%, as shown in phase II studies [15].

Several other chemotherapeutic agents, including gemcitabine, the taxanes (paclitaxel, docetaxel), pemetrexed, the epothilones, oxaliplatin, ifosfamide, and vinflunine [16–23] have also demonstrated single-agent activity in urothelial carcinoma. Paclitaxel monotherapy has produced a high response rate of 42%, including 27% complete response rate [24]. Gemcitabine, as single-agent treatment, has shown a significant activity, achieving response rates between 23% and 29%, with 4% to 13% complete responses [25]. Therefore, these agents have been extensively investigated in combination regimens in phase II and III studies.

3. Cisplatin-based combination chemotherapy

Initially, the first combination chemotherapy regimen tried in advanced urothelial cancer was developed by the addition of methotrexate, vinblastine, and doxorubicin to cisplatin (M-VAC) at the Memorial Sloan-Kettering Cancer Center (MSKCC), producing response rates > 50% and a median overall survival > 1 year [26–29]. Its demonstrated activity led to a prospective trial by Loehrer, et al. comparing M-VAC with cisplatin monotherapy in 269 patients with advanced urothelial carcinoma [14]. Response rates were superior for the M-VAC regimen compared with single-agent cisplatin (39% vs. 12%; P < 0.0001) and, similarly, the progression-free survival (PFS) (10.0 vs. 4.3 months) and overall survival (12.5 vs. 8.2 months) were significantly greater for the combined therapy arm. As expected, the M-VAC regimen was associated with a greater toxicity, especially leukopenia, mucositis, granulocytopenic fever, and drug-related mortality. Although a more toxic regimen, M-VAC was found superior to single-agent cisplatin with respect to response rate, duration of remission, and overall survival in patients with advanced urothelial carcinoma. Other extensively studied combination regimens in metastatic urothelial carcinoma are cisplatin-methotrexate (CM) and cisplatin-methotrexate-vinblastine (CMV) [30–32]. In a randomized study of 214 patients, CMV was shown to be superior to methotrexate-vinblastine (MV) [33], underlining and justifying the routine use of cisplatin-based combination therapy. The addition of ifosfamide to CMV led to the combination CIMV [34], and the omission of vinblastine from MVAC led to the development of CISCA regimen (cisplatin, cyclophosphamide and doxorubicin) [35]. The above M-VAC-like regimens have produced comparable results with M-VAC but have never been compared with M-VAC in randomized studies. However, most clinicians have considered MVAC as the standard of care in advanced urothelial carcinoma before the introduction of the combination of cisplatin with gemcitabine.

The toxicity profile of MVAC includes grade 3 or 4 myelosuppression in most of the patients and grade 3 or 4 gastrointestinal toxicity occurring in 1/3 of the patients. Also, the majority of the patients require dose adjustments during treatment. In addition, MVAC therapy is associated with significant morbidity (3%–4%). The use of colony-stimulating factors has allowed patients to complete their planned treatment schedule [36–38]. Also, G-CSF support has enabled patients to receive the intensified MVAC schedule in which high-dose MVAC is administered every 2 weeks. The last regimen demonstrated responses in up to 40% in initial trials with patients with disease refractory to prior systemic chemotherapy including standard dose MVAC.

A randomized phase III trial conducted by the EORTC Genitourinary Group compared high dose MVAC (HD-MVAC) with G-CSF support given every 2 weeks with conventional MVAC [39]. Toxicities were equivalent in the 2 arms of the study. Median PFS was in favor of the high-dose arm (9.5 months vs. 8.1 months, P = 0.03), and 2-year survival rates were 36.7% and 26.2% for the high-dose and conventional arms, respectively. However, the trial did not demonstrate the 50% improvement in median overall survival it was designed to detect. Therefore, to date, high dose MVAC is not considered a regimen offering any significant benefit to patients.

The toxicity and relative efficacy of MVAC have prompted a search for new agents and combinations. The 2 most promising agents are gemcitabine and paclitaxel. Phase II studies have explored the use of gemcitabine and cisplatin together
(GC) in advanced bladder cancer [40–42], with overall response rates ranging from 41% to 57% and complete responses ranging from 13% to 22%. Median survival time ranged from 12.5 months to 14.3 months. Primary toxicity was hematologic, easily manageable, with rare hospitalizations for febrile neutropenia and no toxic deaths. Based on these encouraging results, GC was compared with the standard of care regimen MVAC in a large phase III multinational trial [43]. Four hundred five patients were randomized to 1 of the 2 treatment arms. Median survival was statistically comparable, 13.8 months and 14.8 months for the GC arm and the MVAC arm, respectively. GC was less toxic than MVAC and, therefore, the risk-benefit ratio favored GC. Since this study was designed to demonstrate a 4-month improvement in survival with GC, some researchers have interpreted the results favoring GC as non-inferior. However, it does appear that GC compared with MVAC is a valuable option with a roughly similar efficacy but with markedly less toxicity.

The next step to the treatment of advanced bladder cancer had been the investigation of taxanes’ activity in combination with cisplatin. Regimens with the combination of paclitaxel and cisplatin (PC) have been evaluated in 3 phase II trials [44–46] involving a total of 106 patients. The overall response rates ranged from 50% to 70%. The combination of docetaxel and cisplatin every 3 weeks has also been evaluated in phase II trials. In approximately 120 patients the overall response rate ranged from 52% to 62%, and the median survival ranged from 8.2 months to 13.6 months [47–49]. Additionally, the Hellenic Cooperative Oncology Group conducted a randomized study comparing the combination of docetaxel-cisplatin with the standard MVAC. The difference in survival was not statistically significant \( P = 0.089 \), and the difference in time to tumor progression favored MVAC \( P = 0.005 \) [50].

Conclusively, the 2 regimens, MVAC and GC, remain the standard of care in advanced bladder cancer. Unfit patients may, however, be treated with taxane-based regimens. Table 1 summarizes the randomized studies on advanced bladder cancer.

### Table 1
 Trials on advanced bladder cancer with cisplatin-based regimens

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment</th>
<th>Patients (n)</th>
<th>RR (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loehrer et al. [14]</td>
<td>MVAC vs. DDP</td>
<td>126/120</td>
<td>39 vs. 12</td>
<td>12.5 vs. 8.2</td>
</tr>
<tr>
<td>Sternberg et al. [39]</td>
<td>HD-MVAC vs. MVAC</td>
<td>134/129</td>
<td>62 vs. 50</td>
<td>14.5 vs. 14.1</td>
</tr>
<tr>
<td>Von der Maase et al. [43]</td>
<td>MVAC vs. GC</td>
<td>202/203</td>
<td>46 vs. 49</td>
<td>14.8 vs. 13.8</td>
</tr>
<tr>
<td>Bamias et al. [50]</td>
<td>MVAC vs. DC</td>
<td>109/111</td>
<td>54 vs. 37</td>
<td>14.2 vs. 9.3</td>
</tr>
</tbody>
</table>

**Table Notes:**

- MVAC = cisplatin, methotrexate, Adriamycin, vinblastine; CDDP = cisplatin; GC = gemcitabine, cisplatin; HD-MVAC = high dose MVAC; DC = docetaxel, cisplatin.

5. **Non-platinum-based doublets**

The effort to reduce cisplatin-related renal and gastrointestinal toxicity has led to the development of non-platinum combinations. The doublet of gemcitabine and paclitaxel has been evaluated in phase II studies demonstrating response rates ranging from 40% to 60%. Specifically, a phase II study by Kaufman, et al. [59] reported an overall response rate of 40% by using paclitaxel and gemcitabine showing a 66% response rate in the cisplatin arm vs. 35% in the carboplatin arm, while no significant difference in toxicity was reported [58].

In summary, carboplatin has not been shown to be as active as cisplatin in advanced bladder cancer. However, carboplatin-based regimens are a reasonable option for unfit patients for cisplatin.

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ated, as grade 3 and 4 myelotoxicity occurred in 56% of the patients, with 3 patients experiencing grade 4 pulmonary toxicity. Also, in another phase II trial [60] of 36 advanced unresectable transitional cell carcinoma patients who were treated with weekly paclitaxel and gemcitabine, the response rate was 69.4%, including 15 patients (41.7%) with complete responses. The median survival time was 15.8 months, and grade 3 and 4 toxicities included granulocytopenia (36.1%), thrombocytopenia (8.3%), and neuropathy (16.7%). Five patients (13.9%) had grades 3 to 5 pulmonary toxicity, and 1 patient had grade 2 pulmonary toxicity.

Another non-platinum combination studied in bladder cancer included the combination of docetaxel and gemcitabine. Three phase II studies reported response rates of 33% to 50% [61–63]. Also, 2 phase II studies [64,65] of 108 patients with locally advanced or metastatic disease have evaluated the combination of pemetrexed with gemcitabine demonstrating response rates between 20% and 28%. In 1 of the 2 studies by Li, et al. [64] grade 4 myelotoxicity in 18 patients and 2 treatment-related deaths were observed.

Lastly, the combination of oxaliplatin with gemcitabine has been assessed in a randomized phase II trial by Carles, et al. in 46 unfit patients with locally advanced or metastatic urothelial cancer [66]. The overall response rate was 48% (3 patients with complete response, 19 patients with partial response, 7 patients with stable disease, and 17 patients with progressive disease) and the median time to disease progression was 5 months. Hematologic toxicity was mild with grade 3–4 peripheral neuropathy occurring in 4% of the patients. Theodore, et al. has also evaluated the combination of gemcitabine with oxaliplatin in 30 urothelial tract cancer patients [67]. Three complete responses, 11 partial responses, and an overall response rate of 47% were observed. Median overall survival was 15 months and toxicity was minimal.

Conclusively, non-platinum combinations should only be used in the context of clinical trials, since the evidence supporting these combinations is limited. Also, the combination of gemcitabine and oxaliplatin (GEMOX) has shown activity that needs to be further tested in clinical trials in comparison with other regimens.

6. Triplet combination chemotherapy

In an effort to improve the efficacy of chemotherapy in advanced urothelial cancer, several investigators have tested triplet combinations. The first study that actually addressed the issue of triplet combination chemotherapy was developed at MSKCC where the combination of ifosfamide, paclitaxel, and cisplatin (ITP) was tested [68]. Response rate was 68% (complete response 23%, partial response 45%) and median survival was 20 months. Based on these results, the same group tested sequential chemotherapy using 5 drugs: 6 cycles of doxorubicin and gemcitabine (AG) followed by 4 cycles of ITP [69]. A phase II study of 56 patients treated with the above regimen reported an overall response rate of 73%. However, these results have not been confirmed by phase III trials.

Also, the Spanish Group (SOGUG) tested the combination of paclitaxel-gemcitabine-cisplatin in a phase I/II trial in 58 patients showing a high response rate of 78% (complete response 28%, partial response 50%) [70]. In the first report of the phase I trial, the investigators cited a mean survival time of 24 months. In the multicenter phase II study the median survival was 15.6 months. These encouraging results led to a phase III EORTC/Intergroup Study (30987) comparing the doublet of gemcitabine-cisplatin vs. paclitaxel-gemcitabine-cisplatin in 627 chemotherapy-naïve patients [71]. Although the response rate was better in the triplet regimen compared with GC (57.1% vs. 46.4%, P = 0.02), the difference in terms of PFS (8.4 months and 7.7 months for PGC and GC, P = 0.1) and overall survival (15.7 months for PGC and 12.8 months for GC, P = 0.12) was not statistically significant. However, the subgroup analysis showed that the patients with primary bladder cancer had a survival benefit with the triplet combination (P = 0.03), suggesting a different pattern of chemosensitivity among urinary tract tumors.

The triplet combination of carboplatin-gemcitabine-paclitaxel has also been studied in a phase II trial of 47 previously untreated patients by Hussein, et al. [72] This combination obtained an overall response rate of 64% (complete response 32%, partial response 32%) with a reported 14.7-month median survival time and 1-year survival rate of 59%. Conversely, in a similarly designed study by Hainsworth, et al. in 60 patients, the response rate and median survival were lower (43% and 11 months, respectively) [73].

Additionally, De Santis, et al. [74] conducted a phase III trial of 175 chemotherapy-naïve patients who were randomly assigned to receive either gemcitabine-carboplatin (GC) or M-CAVI (methotrexate-carboplatin-vinblastine). Serious acute toxicity was reported in 13.6% of the patients on GC and in 23% on M-CAVI. Overall response rates were 42% and 30% for the GC and M-CAVI, respectively. Interestingly, the patients with performance status 2 and renal function impairment did not benefit as much from combination chemotherapy (response rates of 26% and 20%, respectively), confirming the need for alternative therapies in this subgroup of patients.

Further triplet combinations have been assessed with responses ranging from 40% to 69%, such as paclitaxel-cisplatin-methotrexate or paclitaxel-carboplatin-methotrexate. Specifically, Pectasides, et al. [75] studied a 3-weekly regimen of epirubicin, docetaxel, and cisplatin in 30 untreated patients (7 with locally advanced and 23 with metastatic disease). There were 9 (30.0%) complete responses (2 in locally advanced and 7 in metastatic disease) and 11 (36.7%) partial responses (3 in locally advanced and 8 in metastatic disease) with an overall response rate of 66.7%. Overall median survival was 14.5 months (15 months for locally advanced, 12.5 months for metastatic disease). In
terms of toxicity, febrile neutropenia and sepsis occurred in 4 patients. The results of this study showed a comparable activity of epirubicin-docetaxel-cisplatin with MVAC and need to be further evaluated in phase III trials.

Conclusively, although some triplet combinations demonstrate effectiveness in the treatment of advanced urothelial disease, the precise role of these combinations would only be identified through randomized studies.

7. Treatment options for locoregional disease after chemotherapy

Patients with inoperable or recurrent locoregional disease represent a group of favorable prognosis compared with patients with visceral metastases and, therefore, definitive local management (surgery or radiotherapy) has been studied [76]. There are data supporting surgical resection of isolated metastatic disease after chemotherapy and there are reports on patients who underwent metastasectomy resulting in long-term responses. However, there are no identified criteria on the optimal candidates [77]. In particular, Herr, et al. demonstrated that 41% of unresectable or regionally metastatic bladder cancer patients who underwent post-chemotherapy surgery and had residual disease survived up to 5 years [78]. In another study, surgical resection of residual disease after chemotherapy with CMV in 64 patients resulted in a 55% complete response rate with 22% of the patients being disease free at 23 to over 98 months [79]. Also, in a study of 30 patients who underwent metastasectomy, 5-year survival was 33%, while 5 patients were disease-free for more than 3 years after surgery [80].

Lastly, patients who are not surgical candidates could be offered radiotherapy, although the data on this issue are limited [76].

8. Second-line chemotherapy

In general, objective responses of patients failing first-line platinum-based chemotherapy are poor. Objective remission rates of up to 30% have been reported based on single-agent treatment, such as paclitaxel, docetaxel, gemcitabine, ifosfamide, oxaliplatin, pemetrexed, ixabepilone (Table 2).

A promising agent tested in the second-line setting has been pemetrexed, an antifolate inhibitor of multiple folate-dependent enzymes. In a study by Sweeney, et al. [81], the drug was tested in 47 patients with locally advanced, relapsed, or metastatic urothelial cancer. The study showed an overall response rate of 27.7% and a median duration of response of 5 months. The median time to tumor progression was 2.9 months and median overall survival was 9.6 months. Grades 3 or 4 hematologic events were thrombocytopenia (8.5%), neutropenia (4.3%), and anemia (2.1%). Other toxicities included grade 4 stomatitis/pharyngitis (1 patient), sepsis syndrome (1 patient), grade 3 fatigue (3 patients), and diarrhea (2 patients).

Finally, vinflunine, a third generation, semisynthetic derivative of vinca-alkaloids, has been evaluated in a phase III multinational study [82]. The study compared the administration of vinflunine plus best supportive care vs. best supportive care alone in 357 urothelial cancer patients who had failed first-line platinum-based therapy. The median overall survival was significantly longer for the vinflunine arm (6.9 vs. 4.3 months, P = 0.4), and so were overall response rate (P = 0.006), disease control (P = 0.002), and progression-free survival (P = 0.001). Main grades 3 or 4 toxicities for the vinflunine arm were neutropenia (50%), febrile neutropenia (6%), anemia (19%), fatigue (19%), and constipation (16%). Based on the above data, vinflunine seems to be a reasonable option for transitional cell urothelial tract cancer progressing after first-line platinum-based therapy with an acceptable toxicity profile.

9. Targeted therapy

During the last years, targeted agents have been investigated alone or in combination with chemotherapy, but information on their activity in bladder cancer is still limited.

The 2 classes of agents that may be of interest in urothelial cancer are the inhibitors of epidermal growth factor receptors (EGFR), including EGFR1 and EGFR2 (HER2/neu), and the inhibitors of vascular endothelial growth factor (VEGF) or its receptors.

EGFR is overexpressed in high-grade bladder cancer tumors and is associated with aggressive clinical behavior. Preclinical data showed that many bladder tumors express members of the EGFR family, and that inhibition of these pathways may have an antitumor effect [91,92]. Gefitinib, an EGFR tyrosine inhibitor, has been evaluated in a phase II study (CALGB 90102) of 54 untreated advanced urothelial cancer patients in combination with gemcitabine-cisplatin [93]. There were 23 objective responses for an overall response rate of 42.6%, median time to progression was 7.4 months, and median survival was 15.1 months. This study did not show any benefit in terms of response or survival by

### Table 2

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>n</th>
<th>RR%</th>
<th>OS (m)</th>
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<td>Paclitaxel</td>
<td>31</td>
<td>10</td>
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<td>Paclitaxel</td>
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<td>31</td>
<td>13</td>
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<td>Gencitabine</td>
<td>24</td>
<td>29</td>
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<tr>
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<td>Gencitabine</td>
<td>46</td>
<td>25</td>
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<tr>
<td>Pronzato et al. [88]</td>
<td>Ifosfamide</td>
<td>20</td>
<td>5</td>
<td>8.0</td>
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<tr>
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<td>6</td>
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<td>28</td>
<td>9.6</td>
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<td>12</td>
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<td>Vinflunine</td>
<td>357</td>
<td>NR</td>
<td>6.9</td>
</tr>
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</table>
the addition of gefitinib compared with historic controls of cisplatin and gemcitabine alone.

HER-2 is another potential target overexpressed in bladder cancer. Trastuzumab is a monoclonal antibody that targets HER-2 and has been tested in a trial that investigated its activity in combination with paclitaxel, carboplatin, and gemcitabine in 44 HER-2(+) advanced urothelial cancer patients [94]. Thirty-one patients responded (5 complete and 26 partial responses, 70%) and median time to progression and survival were 9.3 and 14.1 months, respectively. The most common grades 3 or 4 toxicity was myelosuppression. Grade 3 sensory neuropathy occurred in 14% of patients, and 22.7% experienced grade 1 to 3 cardiac toxicity. Also, there were 3 therapy-related deaths. The study results, despite the high response rate of 70%, did not demonstrate any survival benefit of the combination over treatment without trastuzumab. An ongoing prospective, randomized phase II study comparing gemcitabine-cisplatin vs. gemcitabine-cisplatin-trastuzumab in metastatic HER-2 positive bladder cancer is underway [95].

Also, dual HER1/HER2 inhibition may be another therapeutic option as combined expression of both receptors appears in 34% of the patients with bladder cancer and at least 1 of the receptors is overexpressed in 90% of the patients. Lapatinib, a tyrosine kinase inhibitor of both receptors, HER1 and HER2, has been evaluated in a phase II study in 34 pretreated bladder cancer patients with prior platinum-based chemotherapy [96]. The primary endpoint of objective response > 10% was observed in only 1.7% of the patients, and in 18 patients stable disease was achieved. The median time to disease progression and overall survival were 8.6 weeks and 17.9 weeks, respectively. Clinical benefit was found to be correlated with EGFR overexpression (P = 0.029) and median overall survival was significantly prolonged in patients with tumors that overexpressed EGFR and/or HER-2 (P = 0.0001). Although the study did not meet its primary endpoint, the improvement in overall survival demonstrated in the subset of tumors overexpressing EGFR and/or HER-2 is encouraging and needs to be further evaluated. Recently, EORTC has designed studies investigating the combination of lapatinib with cisplatin-gemcitabine or the use of lapatinib as maintenance therapy in patients responding to standard chemotherapy.

Additionally, tumor angiogenesis appears to play a major role in the development of bladder cancer and holds potential promise clinically. Mediators of angiogenesis have been implicated in the clinical progression of bladder cancer, although the role of angiogenesis inhibitors as treatment has not yet been defined. Bevacizumab, a recombinant humanized murine monoclonal antibody that targets VEGF, has shown clinical activity against urothelial cancer. In a case report [97], a heavily pretreated 78-year-old man with metastatic, poorly differentiated, transitional-cell carcinoma with squamous differentiation responded dramatically to the monoclonal antibody agent, bevacizumab. After having received therapy for 24 months, there had been a positive response with minimal toxicity. Recently, the combination of bevacizumab with gemcitabine and cisplatin is being studied by CALGB. Also, the MSKCC is planning to investigate the combination of gemcitabine-carboplatin and bevacizumab in patients unable to receive cisplatin in the first-line setting.

The anti-angiogenic multi-kinase inhibitors sunitinib and sorafenib, which have been approved for renal cancer, have been also studied in phase II trials in urothelial cancer. In a phase II trial by Gallagher, et al. [98], 77 advanced urothelial cancer patients received sunitinib in 2 schedules (50 mg for 4 weeks and 2 weeks off, cohort A, and 37.5 mg daily continuously, cohort B). Three out of 45 patients in cohort A had a partial response and 1 out of 32 patients in cohort B. Clinical regression or stable disease was achieved in 33 of 77 patients (43%), and tumor regression lasted longer than 3 months in 29% of the patients. The PFS (2.4 vs. 2.3 months, P = 0.4) and overall survival (7.1 vs. 6.0 months, P = 0.4) were similar in both cohorts. However, 47 patients experienced grades 3 or 4 toxicity, and also a treatment-related death was observed. Also a phase II trial of sunitinib in patients unfit for platinum-based chemotherapy is underway by the Spanish Group (SOGUG).

Sorafenib has also been tested by Dreier, et al. [99] in 27 advanced urothelial cancer patients who had failed cisplatin chemotherapy. The study showed no objective response, with a 4-month PFS rate of 9.5% and a median overall survival of 6.8 months. The most common grade 3 toxicities included fatigue and hand-foot syndrome. Sorafenib will also be tested with conventional chemotherapy regimens, such as gemcitabine-cisplatin, in the first-line setting.

The application of targeted therapy has proven to be beneficial in several neoplasms. However, in advanced bladder cancer, there is still little information, and the role of targeted agents as monotherapy, in combination with chemotherapy and maintenance therapy, is still under investigation.

Lastly, there are conflicting reports from several studies examining the link between p53 status and chemosensitivity in bladder cancer. The data from a retrospective analysis showing benefit after adjuvant cisplatin-based chemotherapy in patients with p53 mutations led to a still ongoing randomized study testing the role of p53 expression. Conversely, paclitaxel seems to act independently from p53 expression. Recently, the combination of paclitaxel and carboplatin, by demonstrating a more favorable profile, has been established as the new standard of care. For
the patients who are unfit for cisplatin due to impaired renal function, poor performance status, and comorbidities, the combination of carboplatin-gemcitabine or taxanes may be useful alternatives. Furthermore, the incorporation of new agents or the triplet combinations need further evaluation through randomized trials. In the second line setting, vinflunine is a reasonable option and also pemetrexed has produced promising results. Finally, new biologic agents have raised the expectations, and investigators should enroll patients in well-designed studies to define the role of these targeted therapies, improve clinical outcome, and individualize treatment.

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