



# First- and second-line therapy for metastatic urothelial carcinoma of the bladder

*F.A. Yafi MD,\* S. North MD,† and W. Kassouf MD\**

## ABSTRACT

Urothelial cancer of the bladder is the 4th most common malignancy in American men and the 9th most common in women. Although it is a chemosensitive disease, advanced bladder cancer seems to have reached a plateau with regard to median survival of patients. Standard first-line therapy remains gemcitabine plus cisplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). In patients deemed unfit to receive cisplatin, gemcitabine plus carboplatin or gemcitabine plus paclitaxel can be considered. To date, no standard therapy has been established for patients who recur or are refractory to first-line therapy. Second-line vinflunine, by way of superiority over best supportive care, has shown promise in a phase III trial. Cisplatin-based therapy (MVAC or GC) can also be offered to patients previously treated with cisplatin, especially if they responded previously and are considered platinum-sensitive. Novel targeted therapies are sorely needed to further improve the delivery and efficacy of chemotherapy.

## KEY WORDS

Bladder cancer, first-line therapy, second-line therapy, targeted therapy, chemotherapy, metastasis

## 1. INTRODUCTION

Urothelial cancer of the bladder (BC) is the 4th most common cancer in American men and the 9th most common in women, leading to 14,330 new deaths annually<sup>1</sup>. Although most newly diagnosed tumours are still superficial, up to 25% will initially present with muscle invasion, half of which will be metastatic disease. Furthermore, of tumours that are initially superficial, 20% will progress despite intravesical chemo- and immunotherapy and will become muscle-invasive<sup>2,3</sup>. Conventional chemotherapy in the neoadjuvant setting—and more particularly, platinum-based regimens—has shown promising results in the management of locally invasive tumours,

but little improvement has been achieved in the outcomes of patients with advanced or metastatic disease. Almost 90% of those patients eventually succumb to their cancer.

For patients who relapse after first-line chemotherapy, the prognosis is generally poor. To date, there is no real consensus on how to best treat these patients, and most of the available evidence stems from small phase II trials that have mostly failed to show survival benefit over supportive care. The present review provides an update on the management of metastatic BC, with a focus on first-line and second-line therapies.

## 2. FIRST-LINE THERAPY

### 2.1 Single-Agent Therapy

Single-agent therapy has generally failed to provide adequate results in patients with advanced BC. In a phase III trial of patients randomized to receive either cisplatin alone or in combination [methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC)], the overall response rate (OR) was only 12% in the cisplatin arm, with only 4 of 122 patients (3.3%) remaining alive at 3 years of follow-up<sup>4</sup>. Similar results were observed in phase II trials with carboplatin [OR: 18%; median duration of survival (MDS): 16 months]<sup>5</sup>. In a phase III trial examining the role of lobaplatin, 2 of 17 patients (12%) achieved a partial response (PR), but the study was terminated because of high toxicity rates<sup>6</sup>. Other drugs investigated in phase II trials have manifested variable activity against advanced urothelial cancer: oral piritrexim (OR: 23%; MDS: 22 weeks)<sup>7</sup>, trimetrexate (OR: 17%; MDS not reported)<sup>8</sup>, and docetaxel (OR: 13%; MDS: 9 months)<sup>9</sup>. However, some improved results were obtained with other single agents such as paclitaxel and gemcitabine<sup>10,11</sup>. In a phase II trial of 26 patients with advanced BC treated with paclitaxel, the OR was 42%, and the MDS, 8.4 months<sup>10</sup>. Similarly, in a phase II trial of gemcitabine in 40 patients, an OR of 28% was reported, with a MDS of 54 weeks<sup>11</sup>.

Overall, although single-agent therapy produced some promising responses in these tumours, the generally disappointing survival data have set researchers to investigating combinations of these potentially beneficial agents in the hope of improving outcomes.

## 2.2 Combination Chemotherapy

The so-called modern era in the management of advanced BC probably started when two landmark cisplatin-based chemotherapy studies set the tone for future management of these tumours<sup>12,13</sup>. Before those reports, life expectancy without chemotherapy for this subset of patients was about 6 months<sup>14,15</sup>.

In the first of the two trials (Northern California Oncology Group), a regimen consisting of cisplatin, methotrexate, and vinblastine was used, achieving an OR of 56% and a complete response (CR) rate of 28%, with a median overall survival (OS) of 8 months<sup>12</sup>. The second trial used the MVAC regimen to greater success, with OR and CR rates of approximately 70% and 35% respectively, and an improved median OS of 13 months<sup>13</sup>. Two prospective trials were therefore initiated to validate the role of MVAC in this patient population<sup>16,17</sup>.

In the first prospective trial, the European Cooperative Oncology Group (ECOG) randomized 246 patients to receive either cisplatin alone or MVAC, and with the latter, they observed a significantly higher OR (12% vs. 39%,  $p < 0.0001$ ) and MDS (8 months vs. 12.5 months)<sup>16</sup>. However, on long-term follow-up, the survival benefit associated with MVAC was only 4.3%, and only 3.7% of patients experienced disease-free survival at 6 years<sup>4</sup>. The second prospective trial compared MVAC with a regimen consisting of cisplatin, cyclophosphamide, and doxorubicin, and similarly showed that MVAC resulted in a higher OR (65% vs. 46%,  $p < 0.05$ ) and OS (62.6 weeks vs. 40.4 weeks)<sup>17</sup>.

In an effort to improve outcomes and lower toxicity with MVAC therapy, the European Organisation for Research and Treatment of Cancer investigated the potential role of high-dose MVAC (HD-MVAC), which consisted of rapid 2-week cycles (instead of the standard 4 weeks). A total of 246 patients were randomized to receive either standard MVAC or HD-MVAC. Although the OR and OS rates were similar, progression-free survival (PFS) was significantly improved (9.5 months vs. 8.1 months,  $p = 0.037$ ) and toxicity was decreased in patients treated with HD-MVAC<sup>18</sup>.

### 2.2.1 Cisplatin-Based Doublets

Other single agents that had shown antitumour activity in BC were examined in combination with cisplatin<sup>19</sup>. Most notably, 220 patients were randomized to receive either MVAC or a regimen of cisplatin and docetaxel. Results were unflattering to the cisplatin–docetaxel doublet, and the MVAC group continued to display a better relative risk (RR: 54.2% vs. 37.4%,

$p = 0.017$ ) and MDS (14.2 months vs. 9.3 months,  $p = 0.026$ )<sup>20</sup>. However, in three phase II trials, a gemcitabine–cisplatin (GC) regimen showed activity comparable to that for MVAC<sup>19</sup>. Those findings were subsequently assessed in a randomized phase III study of 405 patients with advanced BC who received either MVAC or GC<sup>21</sup>. The latter study did not achieve its initial goal of showing superiority of GC, but the 2 groups displayed similar RR (49% with MVAC vs. 46% with GC), MDS (14.8 months with MVAC vs. 13.8 months with GC), and PFS (7.4 months for both). Importantly, the GC group experienced significantly fewer side effects. With longer 5-year follow-up, similar survival was maintained between the groups, indicating that GC shows therapeutic non-inferiority together with less toxicity as compared with MVAC. As such, GC has become a standard of care for patients with metastatic BC<sup>22</sup>. To date, no phase III trials have compared HD-MVAC and GC.

Although cisplatin-based therapy had been shown to offer improved results in patients with advanced BC, its nephrotoxic properties continued to make it undesirable, especially in this subset of patients, who often have compromised renal function. And so carboplatin, an alkylating agent with properties similar to, but less nephrotoxic than, those of cisplatin, was investigated for its potential alternative role. Initial reports from phase II trials with paclitaxel and carboplatin were encouraging in patients deemed unfit for cisplatin, with ORs ranging from 21% to 63% and fewer associated toxicities<sup>23–25</sup>. Subsequently, a phase III ECOG trial compared MVAC with a regimen consisting of carboplatin and paclitaxel in patients with advanced BC. Preliminary results were promising, showing similar MDS (13.8 months for carboplatin–paclitaxel vs. 15.4 months for MVAC,  $p = 0.65$ ), but patient accrual was too low ( $n = 85$ ). The study was closed early, and no conclusions could be made<sup>26</sup>. Similarly, a carboplatin regimen was investigated alongside gemcitabine in phase II trials that did not exclude patients fit to receive cisplatin, resulting in ORs of 56% and 59% and a median OS of only 10 months<sup>27–29</sup>. In a phase II randomized trial of GC versus gemcitabine with carboplatin, better response rates were observed with GC (66% vs. 35%) without significant differences in toxicity profile<sup>30</sup>. Based on the foregoing findings, it became evident that carboplatin is inferior to cisplatin. Carboplatin is currently reserved only for patients who are ineligible to receive cisplatin.

### 2.2.2 Platinum-Free Doublets

In an additional effort to avoid cisplatin-related toxicities, trials were conducted using platinum-free agents. One such regimen consisted of paclitaxel and gemcitabine; it showed response rates of 40%–60%<sup>31</sup>. In a phase II trial of the same regimen in a weekly schedule, a CR of 42% (MDS: 11.9 months) was achieved, but the excitement with these results was damped by the high level of associated pulmonary

toxicity (including 1 death)<sup>32</sup>. Furthermore, a regimen consisting of docetaxel and gemcitabine showed promising response rates of 30%–50% and median OS times of 13–15 months in phase II trials<sup>33–35</sup>. Finally, gemcitabine was also combined with pemetrexed in phase II trials, resulting in modest response rates of about 25%, but with increased toxicity<sup>36</sup>.

### 2.2.3 Doublets Compared with Triplets

Finally, to improve on outcomes obtained with dual therapy, attempts were made to combine 3 or more agents. In the first study, consisting of a regimen of ifosfamide, paclitaxel, and cisplatin, 23% of assessable patients achieved a CR with a MDS of 20 months<sup>37</sup>. Based on those results, a phase II study investigated the benefit of dose-dense sequential chemotherapy with doxorubicin and gemcitabine followed by ifosfamide–paclitaxel–cisplatin, achieving a RR of 73% and a MDS of 24 months<sup>38</sup>. After that success, paclitaxel was incorporated into a regimen with gemcitabine and cisplatin (PGC) in a phase II trial that showed an excellent OR of 78%<sup>31</sup>. That result led to the largest-to-date randomized trial in advanced BC, which compared GC with PGC. The PGC combination was found to be associated with a significantly better CR rate (10% vs. 15%,  $p = 0.02$ ), but no significant improvement in PFS or OS was demonstrated<sup>39</sup>. A phase II trial with a regimen of gemcitabine, paclitaxel, and carboplatin in 49 patients resulted in a CR of 32% and a MDS of 14.7 months<sup>40</sup>, but in another phase II trial using the same regimen, the reported CR was only 12%, and the MDS, 11 months<sup>41</sup>.

At the present time, data from randomized phase III trials suggest that systemic cisplatin-based combination chemotherapy (MVAC or GC) remains the only current modality to have shown improved survival in patients with advanced BC. Accordingly, both the National Comprehensive Cancer Network and the European Society of Medical Oncology recommend either MVAC or GC as first-line treatment in those patients<sup>42,43</sup>.

## 3. PROGNOSTIC FACTORS

In the long follow-up of the ECOG study comparing MVAC with cisplatin, the Karnofsky performance status (KPS  $\geq 80$  vs. KPS  $< 80$ ;  $p = 0.000011$ ) was found to be an independent predictor of survival. Furthermore, the presence of liver or bone metastases was also a predictor of poor outcome ( $p = 0.0022$  and  $p = 0.0032$  respectively)<sup>4</sup>. Later analysis further established that those two prognostic factors—KPS less than 80% and visceral (lung, liver, bone) metastasis—were both predictive of response and survival<sup>44</sup>. Accordingly, three risk categories were established depending on the number of risk factors (0, 1, or 2). Median survival times were 33 months, 13 months, and 9 months respectively for those risk factors ( $p = 0.0001$ )<sup>44</sup>. Similar results were also reported in the

long-term follow-up of the MVAC and GC comparative study and in a phase I/II trial of paclitaxel, cisplatin, and gemcitabine<sup>22,45</sup>.

## 4. SECOND-LINE THERAPY

Patients who recur after first-line therapy have a very poor prognosis. Because of the lack of randomized trials showing benefit for any therapy over supportive care, most evidence comes from small phase II trials of single agents, combinations of agents, and new targeted therapies.

### 4.1 Single-Agent Second-Line Therapy

Multiple single agents have been assessed for their benefit in patients who relapse despite first-line therapy (Table 1). In examining older agents, only ifosfamide seemed to have shown any promise in this subset of patients. In a phase II trial, 56 cisplatin-pretreated patients received ifosfamide and achieved an OR of 20%, with a MDS of 5.3 months<sup>49</sup>.

Paclitaxel was investigated in three small phase II trials. In a cohort of 31 pretreated patients, OR and PR rates of 10% were observed, with a MDS of 7.2 months<sup>56</sup>. However, in the other two trials, lower response rates of 5%–7% were achieved, with a MDS of 6.5 months<sup>47,58</sup>. Similarly, docetaxel was investigated in 31 cisplatin-refractory patients. The result was a better OR rate of 13% and a MDS of 9 months. However, 60% of the patients developed myelosuppression, and dose reduction was required<sup>9</sup>.

An evaluation by ECOG of epothilone B in a phase II trial involving 45 patients with recurrence after cisplatin- or carboplatin-based chemotherapy showed an OR of 12% and a MDS of 8 months; however, because of high toxicity and 1 related fatality, the drug was dropped from further evaluation<sup>62</sup>. Similarly, pyrazoloacridine was investigated in 14 patients with chemo-refractory advanced BC. No responses were observed (0%), and the associated toxicities were elevated; further trials were therefore discontinued<sup>53</sup>.

Gemcitabine was also studied for its potential role in previously treated patients. As in first-line trials, it was associated with a wide spectrum of response and survival outcomes depending on the various scheduling and dosing regimens used<sup>11,66,67</sup>. In a phase I study of patients previously treated with MVAC, an OR rate of 27% was achieved when various doses of gemcitabine were used<sup>68</sup>. However, in two phase II trials of platinum-refractory patients receiving 1250 mg/m<sup>2</sup> in 4- and 3-week cycles, the OR rates were 23% and 11%, with MDS durations of 5 months and 8.7 months respectively<sup>50,54</sup>.

Piritrexim, a second-generation oral antimitabolite, has resulted in ORs ranging between 7% and 23%, but more importantly, considerable toxicity<sup>46,55</sup>. Those results have been further confirmed by another phase II trial in 23 previously treated patients, among

TABLE 1 Single-agent second-line chemotherapy trials for advanced bladder cancer

Reference	Agent	Patients (n)	Response (%)	TTP (months)	Survival (months)
Khorsand <i>et al.</i> , 1997 <sup>46</sup>	Piritrexim	17	23	NA	NA
McCaffrey <i>et al.</i> , 1997 <sup>9</sup>	Docetaxel	31	13	NA	9.0
Papamichael <i>et al.</i> , 1997 <sup>47</sup>	Paclitaxel	14	7	NA	NA
Pronzato <i>et al.</i> , 1997 <sup>48</sup>	Ifosfamide	20	5	6	8.0
Witte <i>et al.</i> , 1997 <sup>49</sup>	Ifosfamide	60	20	2.2	5.1
Lorusso <i>et al.</i> , 1998 <sup>50</sup>	Gemcitabine	35	23	3.8	5.0
Witte <i>et al.</i> , 1998 <sup>51</sup>	Topotecan	46	9	1.4	6.2
Gebbia <i>et al.</i> , 1999 <sup>52</sup>	Gemcitabine	24	29	NA	13.0
Dodd <i>et al.</i> , 2000 <sup>53</sup>	Pyrazoloacridine	14	0	NA	9.0
Albers <i>et al.</i> , 2002 <sup>54</sup>	Gemcitabine	30	11	4.9	8.7
Roth <i>et al.</i> , 2002 <sup>55</sup>	Piritrexim	35	7	2.1	7.0
Vaughn <i>et al.</i> , 2002 <sup>56</sup>	Paclitaxel	31	10	2.2	7.2
Moore <i>et al.</i> , 2003 <sup>57</sup>	Oxaliplatin	20	6	NA	NA
Joly <i>et al.</i> , 2004 <sup>58</sup>	Paclitaxel	45	5	3	6.5
Sweeney <i>et al.</i> , 2006 <sup>59</sup>	Pemetrexed	47	28	2.9	9.6
Culine <i>et al.</i> , 2006 <sup>60</sup>	Vinflunine	58	18	3.0	6.6
Akaza <i>et al.</i> , 2007 <sup>61</sup>	Gemcitabine	46	25	3.1	12.6
Dreicer <i>et al.</i> , 2007 <sup>62</sup>	Epothilone B	45	12	2.7	8.0
Galsky <i>et al.</i> , 2007 <sup>63</sup>	Pemetrexed	13	8	NA	NA
Bellmunt Molins <i>et al.</i> , 2008 <sup>64</sup>	Vinflunine	253	9	3.0	NA
Vaughn <i>et al.</i> , 2008 <sup>65</sup>	Vinflunine	175	15	2.8	7.9

TTP = time to progression; NA = not available.

whom only 2 demonstrated stable disease after 2–4 cycles; further enrolment was therefore halted<sup>69</sup>. Another anti-folate, pemetrexed, was investigated in a phase II trial in 47 patients who had a performance status of 0 or 1 and adequate organ function, and who had been treated with one prior chemotherapy regimen<sup>59</sup>. Of the 47 patients, 13 (27.7%) achieved an OR (6% CR, 21% PR), with a median duration of response of 5 months and a MDS of 9.6 months. Importantly, the drug was well tolerated. The most serious toxicities were grades 3 and 4 hematologic events in 14.9% and 6.4% of patients respectively. However, in another phase II trial of the same drug, only 1 of 12 evaluable patients attained a response (OR: 8%), and the trial was therefore halted<sup>63</sup>.

The third-generation semi-synthetic vinca alkaloid vinflunine (VFL) has been assessed as second-line therapy in two phase II trials. In the first of those trials, 51 patients completed the study, attaining an OR rate of 18% and a PFS of 3 months. Toxicity consisted mainly of grade 3 or 4 neutropenia (67%) and febrile neutropenia (5%)<sup>60</sup>. The second trial included 175 patients with platinum-refractory BC, and in 150 patients, the OR rate was 15%, with a MDS of 8.2 months and a more favourable toxicity profile<sup>65</sup>. Based on those results, a large phase III trial randomized 370 patients to receive either VFL with BSC or BSC alone<sup>64</sup>. The study was limited to platinum-pretreated patients

with ECOG performance scores of 0 or 1. In the VFL arm, toxicities included grades 3 and 4 neutropenia (50% of patients), febrile neutropenia (6%), fatigue (19%), and constipation (16%); 1 toxic death occurred. In the eligible population, the median OS was prolonged in the VFL group (6.9 months vs. 4.3 months,  $p = 0.04$ ). Importantly, by intention-to-treat analysis, the difference was not statistically significant ( $p = 0.29$ ). On adjusted multivariate analysis, addition of VFL was an independent prognostic factor for improved OS ( $p = 0.036$ ), reducing the risk of death by 23% (hazard ratio: 0.77)<sup>64</sup>. Currently, an ongoing phase III clinical trial is randomizing cisplatin-ineligible patients with advanced BC to VFL and gemcitabine or to placebo and gemcitabine (search for NCT00389155 at [www.clinicaltrials.gov/ct2/search](http://www.clinicaltrials.gov/ct2/search)).

## 4.2 Multi-Agent Second-Line Therapy

Multidrug combinations have been thoroughly investigated as second-line therapy for BC and have generally yielded better response rates, but not necessarily better survival outcomes, and often higher toxicity (Table II). In patients progressing on GC or relapsing within 6 to 12 months and still eligible for cisplatin therapy, recent data have shown that a second-line regimen of MVAC can offer acceptable outcomes, with an OR of 30% and a MDS of 10.9 months<sup>87</sup>.

TABLE II Multi-agent second-line chemotherapy trials for advanced bladder cancer

Author	Regimen	Patients (n)	Response rate (%)	Survival (months)
Logothesis <i>et al.</i> , 1994 <sup>70</sup>	5-Fluorouracil, interferon alfa, cisplatin	28	61	NA
Tu <i>et al.</i> , 1995 <sup>71</sup>	Paclitaxel, methotrexate, cisplatin	25	40	NA
Sweeney <i>et al.</i> , 1999 <sup>72</sup>	Paclitaxel, ifosfamide	13	15	8
Kaufman <i>et al.</i> , 2000 <sup>32</sup>	Gemcitabine, paclitaxel	6	0	NA
De Mulder <i>et al.</i> , 2000 <sup>73</sup>	5-Fluorouracil, interferon alfa, cisplatin	43	13	4.9
Krege <i>et al.</i> , 2001 <sup>74</sup>	Docetaxel, ifosfamide	22	25	4
Meluch <i>et al.</i> , 2001 <sup>75</sup>	Gemcitabine, paclitaxel	15	47	NA
Sternberg <i>et al.</i> , 2001 <sup>76</sup>	Gemcitabine, paclitaxel	41	60	14.4
Bellmunt <i>et al.</i> , 2002 <sup>77</sup>	Methotrexate, paclitaxel	20	32	5
Pagliaro <i>et al.</i> , 2002 <sup>78</sup>	Cisplatin, gemcitabine, ifosfamide	51	41	9.5
Chen <i>et al.</i> , 2004 <sup>79</sup>	Docetaxel, gemcitabine, carboplatin	NA	56	NA
Vaishampayan <i>et al.</i> , 2005 <sup>80</sup>	Carboplatin, paclitaxel	44	16	6
Fechner <i>et al.</i> , 2006 <sup>81</sup>	Gemcitabine, paclitaxel	30	44	NA
Takahashi <i>et al.</i> , 2006 <sup>82</sup>	Gemcitabine, paclitaxel	23	30	12.1
Lin <i>et al.</i> , 2007 <sup>83</sup>	Gemcitabine, ifosfamide	23	22	4.8
Albers <i>et al.</i> , 2008 <sup>84</sup>	Gemcitabine, paclitaxel	102	50	NA
Kanai <i>et al.</i> , 2008 <sup>85</sup>	Gemcitabine, paclitaxel	20	30	11.5
Suyama <i>et al.</i> , 2009 <sup>86</sup>	Gemcitabine, paclitaxel	33	33	11.3

NA = not available.

The most extensively studied second-line combination regimen is paclitaxel and gemcitabine. As with other second-line treatments, large discrepancies can easily be noted when dosing and scheduling regimens are modified. In an early phase II trial in which 21- or 14-day cycles with various concentrations of the drugs were used in chemo-resistant patients, the OR was 44% for the entire population, but the MDS was higher with the longer cycle (13 months vs. 9 months)<sup>81</sup>. In two more recent phase II studies in platinum-refractory patients, an OR of 33% and a MDS of 11.3 months were achieved with 180 mg/m<sup>2</sup> paclitaxel on day 1 and 1000 mg/m<sup>2</sup> gemcitabine on days 1, 8, and 15 every 28 days; and an OR of 30% and a MDS of 11.5 months were achieved with a lesser dose of paclitaxel (150 mg/m<sup>2</sup>) and a higher dose of gemcitabine (2500 mg/m<sup>2</sup>) at a shorter interval of every 2 or 3 weeks<sup>85</sup>. In a phase III trial in chemo-refractory patients, a temporary 6-cycle course of paclitaxel and gemcitabine (3-week schedule) was compared with a maintenance treatment until progression, and results showed an OR of 50% in the latter group, but no survival difference between the two arms<sup>84</sup>.

Finally, and only recently, interest has arisen in metronomic therapy, which consists of the use of

cytostatics administered at frequent intervals and which has been shown to offer benefit for patients with other cancers<sup>88-91</sup>. Spurred by those results, a phase I/II study of paclitaxel in combination with oral cyclophosphamide was conducted in 44 patients pre-treated with GC. The PR and OR rates of 31% were attained with a MDS of 8 months, and the regimen was well tolerated<sup>88</sup>. Similarly, a phase II trial in which 22 MVAC-pre-treated patients received weekly paclitaxel and carboplatin found an OR of 36% and a MDS of 7.9 months; however, 1 treatment-related death occurred<sup>92</sup>.

In the absence of conclusive data, no definitive recommendations can be put forth with regard to second-line systemic therapy. However, some evidence supports the use of cisplatin-based second-line therapy in patients who previously responded to first-line cisplatin-based therapy (more than a 6-month duration from last treatment to progression) and who are considered platinum-sensitive.

## 5. QUALITY OF LIFE WITH CHEMOTHERAPY FOR ADVANCED OR METASTATIC BLADDER CANCER

Historically, quality of life (QOL) in patients receiving chemotherapy as compared with BSC has not been

adequately addressed in metastatic BC. One study that appears to better examine this issue is the phase III trial in chemo-refractory patients with metastatic BC randomized to VFL or to BSC<sup>64</sup>. It was judged that VFL resulted in improved clinical benefit because in the VFL arm, as compared with the BSC arm, fewer patients received at least 1 palliative radiotherapy treatment (4% vs. 24%), the palliative treatment was delivered significantly later, and more importantly, as compared with BSC alone, VFL did not result in decreased health-related QOL ( $p = 0.66$ ). These data show that chemotherapy, though often associated with some level of toxicity, may not necessarily correlate with worse QOL in this subset of fragile patients with advanced disease.

## 6. TARGETED THERAPY

Advances in molecular research are helping to develop reliable biomarkers that may allow physicians to more accurately use targeted, pathway-based therapies. In a phase II trial of bortezomib in patients refractory to cisplatin, 70% progressed, with a MDS of 5.7 months<sup>93</sup>. In another trial, 14 previously treated patients received vorinostat, none achieved a response, the median OS was 2.1 months, and associated toxicities were elevated<sup>94</sup>. Furthermore, in a phase II trial of 27 patients receiving sorafenib, the OR rate was nil, and the median PFS was 2.2 months<sup>95</sup>. Similarly, in a phase II trial in 45 previously treated patients receiving sunitinib, an OR rate of 7.3% was achieved, but the associated toxicities were major<sup>96</sup>. Finally, bevacizumab was associated with a good response in the case report of a 78-year-old man with metastatic BC who, at last follow-up, had received 24 months of bevacizumab with minimal toxicity<sup>97</sup>. This result has spurred interest in bevacizumab, and future studies are awaited.

## 7. ONGOING CLINICAL TRIALS FOR ADVANCED BLADDER CANCER

A review of current clinical trials shows that multiple therapeutic regimens are being investigated as first- and second-line regimens (search using “advanced bladder cancer” at [www.clinicaltrials.gov/ct2/search](http://www.clinicaltrials.gov/ct2/search)). In chemotherapy-naïve patients, sorafenib, sunitinib, tipifarnib, and combination therapies such as paclitaxel–cisplatin–gemcitabine, paclitaxel–carboplatin–gemcitabine, cisplatin–gemcitabine–bevacizumab, carboplatin–gemcitabine–bevacizumab, and gemcitabine–carboplatin–sorafenib are being offered in phase II trials. Additionally, three phase III trials are randomizing patients to VFL–gemcitabine or to placebo–gemcitabine; gemcitabine–cisplatin–bevacizumab or gemcitabine–cisplatin–placebo; and cisplatin–larotaxel or GC (search for NCT00389155,

NCT00234494, and NCT00625664 at [www.clinicaltrials.gov/ct2/search](http://www.clinicaltrials.gov/ct2/search)). However, the latter study was prematurely closed because of two other negative larotaxel studies.

With regard to second-line therapy, ongoing phase II trials are investigating agents such as sunitinib, pralatrexate, romidepsin, gefitinib, irinotecan, paclitaxel, oral rubitecan, AZD 8477, everolimus, and the combinations lonafarnib–gemcitabine and sorafenib–bevacizumab (search using “advanced bladder cancer second-line therapy” at [www.clinicaltrials.gov/ct2/search](http://www.clinicaltrials.gov/ct2/search)).

## 8. SURGERY FOR ADVANCED DISEASE

Current evidence suggests that, although advanced BC is an aggressive disease that tends to spread rapidly, surgical consolidation after a major and durable response to systemic chemotherapy is beneficial in a highly select group of patients. This topic is, however, beyond the scope of the present review and will not be addressed here. We recommend that readers refer to our article that covers this subject in detail<sup>98</sup>.

## 9. SUMMARY

A plateau has been reached in the management of patients with advanced BC, because the addition of cytotoxic, high-dose, and doublet and triplet therapies have failed to significantly improve outcomes. Currently, the established standard of care for first-line therapy is GC and MVAC in platinum-eligible patients. Carboplatin–paclitaxel or gemcitabine–carboplatin are being considered for those unable to receive cisplatin. In patients who recur or who are refractory to first-line therapy, response rates and outcomes are grim, and to date, no second-line therapy has been clearly established. As such, most practice relies on small phase II studies, case reports, or consensus opinions. In patients previously treated with first-line cisplatin-based therapy and considered to be platinum-sensitive, with more than a 6-month duration from last treatment to progression, the same cisplatin regimen remains a viable option. Novel targeted therapies are sorely needed to further improve the delivery and efficacy of chemotherapy.

## 10. CONFLICT OF INTEREST DISCLOSURES

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership, or options, expert testimony, grants, or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

## 11. REFERENCES

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225–49.
- Cookson MS, Herr HW, Zhang ZF, Soloway S, Sogani PC, Fair WR. The treated natural history of high risk superficial bladder cancer: 15-year outcome. *J Urol* 1997;158:62–7.
- Yafi FA, Duclos M, Correa JA, *et al*. Contemporary outcome and management of patients who had an aborted cystectomy due to unresectable bladder cancer. *Urol Oncol* 2009;[Epub ahead of print].
- Saxman SB, Propert KJ, Einhorn LH, *et al*. Long-term follow-up of a phase III Intergroup study of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1997;15:2564–9.
- Waxman J, Barton C. Carboplatin-based chemotherapy for bladder cancer. *Cancer Treat Rev* 1993;19(suppl C):21–5.
- Sternberg CN, De Mulder P, Fossa S, *et al*. on behalf of the Genitourinary Group of the European Organisation for Research and Treatment of Cancer. Lobaplatin in advanced urothelial tract tumors (EORTC). *Ann Oncol* 1997;8:695–6.
- De Wit R, Kaye SB, Roberts JT, Stoter G, Scott J, Verweij J. Oral piritrexim, an effective treatment for metastatic urothelial cancer. *Br J Cancer* 1993;67:388–90.
- Witte RS, Elson P, Khandakar J, Trump DL. An Eastern Cooperative Oncology Group phase II trial of trimetrexate in the treatment of advanced urothelial carcinoma. *Cancer* 1994;73:688–91.
- McCaffrey JA, Hilton S, Mazumdar M, *et al*. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997;15:1853–7.
- Roth BJ, Dreicer R, Einhorn LH, *et al*. Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1994;12:2264–70.
- Stadler WM, Kuzel T, Roth B, Raghavan D, Dorr FA. Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *J Clin Oncol* 1997;15:3394–8.
- Harker WG, Meyers FJ, Freiha FS, *et al*. Cisplatin, methotrexate, and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group study. *J Clin Oncol* 1985;3:1463–70.
- Sternberg CN, Yagoda A, Scher HI, *et al*. Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. *J Urol* 1985;133:403–7.
- Babaian RJ, Johnson DE, Llamas L, Ayala AG. Metastases from transitional cell carcinoma of urinary bladder. *Urology* 1980;16:142–4.
- Yagoda A. Progress in treatment of advanced urothelial tract tumors. *J Clin Oncol* 1985;3:1448–50.
- Loehrer PJ Sr, Einhorn LH, Elson PJ, *et al*. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1982;10:1066–73.
- Logothetis CJ, Dexius FH, Finn L, *et al*. A prospective randomized trial comparing MVAC and cisCA chemotherapy for patients with metastatic urothelial tumors. *J Clin Oncol* 1990;8:1050–5.
- Sternberg CN, de Mulder PHM, Schornagel JH, *et al*. Randomized phase III trial of high dose intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus classic MVAC in advanced urothelial tract tumors: European Organisation for Research and Treatment of Cancer protocol no. 30924. *J Clin Oncol* 2001;19:2638–46.
- Garcia JA, Dreicer R. Systemic chemotherapy for advanced bladder cancer: updates and controversies. *J Clin Oncol* 2006;24:5545–51.
- Bamias A, Aravantinos G, Deliveliotis C, *et al*. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus MVAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study from the Hellenic Cooperative Oncology Group. *J Clin Oncol* 2004;22:220–8.
- Von der Maase, Hansen SW, Roberts JT, *et al*. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multiinstitutional, multicenter, phase III study. *J Clin Oncol* 2000;18:3068–77.
- Von der Maase, Sengelow L, Roberts JT, *et al*. Long-term survival results of a randomized trial comparing gemcitabine and cisplatin with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602–8.
- Redman BG, Smith DC, Flaherty L, Du W, Hussain M. Phase II trial of paclitaxel and carboplatin in the treatment of advanced urothelial carcinoma. *J Clin Oncol* 1998;16:1844–8.
- Small EJ, Lew D, Redman BG, *et al*. Southwest Oncology Group Study of paclitaxel and carboplatin for advanced transitional-cell carcinoma: the importance of survival as a clinical trial end point. *J Clin Oncol* 2000;18:2537–44.
- Vaughn DJ, Malkowicz SB, Zoltick B, *et al*. Paclitaxel plus carboplatin in advanced carcinoma of the urothelium: an active and tolerable outpatient regimen. *J Clin Oncol* 1998;16:255–60.
- Dreicer R, Manola J, Roth BJ, *et al*. Phase III trial of methotrexate, vinblastine, doxorubicin, and cisplatin versus carboplatin and paclitaxel in patients with advanced carcinoma of the urothelium. *Cancer* 2004;100:1639–45.
- Bellmunt J, de Wit R, Albanell J, Baselga J. A feasibility study of carboplatin with fixed dose of gemcitabine in “unfit” patients with advanced bladder cancer. *Eur J Cancer* 2001;37:2212–15.
- Nogue-Aliguer M, Carles J, Arrivi A, *et al*. Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. *Cancer* 2003;97:2180–6.
- Shannon C, Crombie C, Brooks A, Lau H, Drummond M, Gurney H. Carboplatin and gemcitabine in metastatic transitional cell carcinoma of the urothelium: effective treatment of patients with poor prognostic features. *Ann Oncol* 2001;12:947–52.
- Dogliotti L, Carteni G, Siena S, *et al*. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. *Eur Urol* 2007;52:134–41.

31. Bellmunt J, Albiol S, Suarez C, Albanell J. Optimizing therapeutic strategies in advanced bladder cancer: update on chemotherapy and the role of targeted agents. *Crit Rev Oncol Hematol* 2009;69:211–22.
32. Kaufman DS, Carducci MA, Kuzel TM, *et al.* A multi-institutional phase II trial of gemcitabine plus paclitaxel in patients with locally advanced or metastatic urothelial cancer. *Urol Oncol* 2004;22:393–7.
33. Ardavanis A, Tryfonopoulos D, Alexopoulos A, Kandyliis C, Lainakis G, Rigatos G. Gemcitabine and docetaxel as first-line treatment for advanced urothelial carcinoma: a phase II study. *Br J Cancer* 2005;92:645–50.
34. Dumez H, Martens M, Selleslach J, *et al.* Docetaxel and gemcitabine combination therapy in advanced transitional cell carcinoma of the urothelium: results of a phase II and pharmacologic study. *Anticancer Drugs* 2007;18:211–18.
35. Gitlitz BJ, Baker C, Chapman Y, *et al.* A phase II study of gemcitabine and docetaxel therapy in patients with advanced urothelial carcinoma. *Cancer* 2003;98:1863–9.
36. Dreicer R, Li S, Cooney M, Wilding G, Roth B. Phase II trial of pemetrexed disodium and gemcitabine in advanced carcinoma of the urothelium: a trial of the Eastern Cooperative Oncology Group. *Cancer* 2008;112:2671–5.
37. Bajorin DF, McCaffrey JA, Dodd PM, *et al.* Ifosfamide, paclitaxel, and cisplatin for patients with advanced transitional cell carcinoma of the urothelial tract: final report of a phase II trial evaluating two dosing schedules. *Cancer* 2000;88:1671–8.
38. Bellmunt J, Guillem V, Paz-Ares L, *et al.* Phase I–II study of paclitaxel, cisplatin, and gemcitabine in advanced transitional-cell carcinoma of the urothelium. Spanish Oncology Genitourinary Group. *J Clin Oncol* 2000;18:3247–55.
39. Bellmunt J, von der Maase H, Mead G, *et al.* Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy; EORTC30987/Intergroup Study [abstract LBA5030]. *J Clin Oncol* 2007;25: [Available online at: [www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=47&abstractID=31229](http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=31229); cited December 17, 2010]
40. Hussain M, Vaishampayan U, Du W, Redman B, Smith DC. Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. *J Clin Oncol* 2001;19:2527–33.
41. Hainsworth JD, Meluch AA, Litchy S, *et al.* Paclitaxel, carboplatin, and gemcitabine in the treatment of patients with advanced transitional cell carcinoma of the urothelium. *Cancer* 2005;103:2298–303.
42. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer*. Version 1.2011. Fort Washington, PA; NCCN; 2010. [Available online at: [www.nccn.org/professionals/physician\\_gls/PDF/bladder.pdf](http://www.nccn.org/professionals/physician_gls/PDF/bladder.pdf) (free registration required); cited December 30, 2010]
43. Bellmunt J, Albiol S, Kataja V. Invasive bladder cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2008;19(suppl 2):ii47–8.
44. Bajorin DF, Dodd PM, Mazumdar M, *et al.* Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol* 1999;17:3173–81.
45. Bellmunt J, Abanell J, Pez-Anes L, *et al.* Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. *Cancer* 2002;95:751–7.
46. Khorsand M, Lange J, Feun L, Clendeninn NJ, Collier M, Wilding G. Phase II trial of oral piritrexim in advanced, previously treated transitional cell cancer of bladder. *Invest New Drugs* 1997;15:157–63.
47. Papamichael D, Gallagher CJ, Oliver RT, Johnson PW, Waxman J. Phase II study of paclitaxel in pretreated patients with locally advanced/metastatic cancer of the bladder and ureter. *Br J Cancer* 1997;75:606–7.
48. Pronzato P, Vigani A, Pensa F, Vanoli M, Tani F, Vaira F. Second line chemotherapy with ifosfamide as outpatient treatment for advanced bladder cancer. *Am J Clin Oncol* 1997;20:519–21.
49. Witte RS, Eison P, Bono B, *et al.* Eastern Cooperative Oncology Group phase II trial of ifosfamide in the treatment of previously treated advanced urothelial carcinoma. *J Clin Oncol* 1997;15:589–93.
50. Lorusso V, Pollera CF, Antimi M, *et al.* A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. *Eur J Cancer* 1998;34:1208–12.
51. Witte RS, Manola J, Burch PA, Kuzel T, Weinschel EL, Loehrer PJ Sr. Topotecan in previously treated advanced urothelial carcinoma: an ECOG phase II trial. *Invest New Drugs* 1998;16:191–5.
52. Gebbia V, Testa A, Borsellino N, *et al.* Single agent 20,20-difluorodeoxycytidine in the treatment of metastatic urothelial carcinoma: a phase II study. *Clin Ter* 1999;150:11–15.
53. Dodd PM, McCaffrey JA, Mazumdar M, *et al.* Phase II trial of pyrazoloacridine as second-line therapy for patients with unresectable or metastatic transitional cell carcinoma. *Invest New Drugs* 2000;18:247–51.
54. Albers P, Siener R, Härtlein M, *et al.* Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma—prognostic factors for response and improvement of quality of life. *Onkologie* 2002;25:47–52.
55. Roth BJ, Manola J, Dreicer R, Graham D, Wilding G on behalf of the Eastern Cooperative Oncology Group. Piritrexim in advanced, refractory carcinoma of the urothelium (E3896): a phase II trial of the Eastern Cooperative Oncology Group. *Invest New Drugs* 2002;20:425–9.
56. Vaughn DJ, Broome CM, Hussain M, Gutheil JC, Markowitz AB. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *J Clin Oncol* 2002;20:937–40.
57. Moore MJ, Winquist E, Vokes E, *et al.* Phase II study of oxaliplatin in patients with inoperable, locally advanced or metastatic transitional cell carcinoma of the urothelial tract (TCC) who have received prior chemotherapy [abstract 1638]. *J Clin Oncol* 2003;22: [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=23&abstractID=100319](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=100319); cited December 22, 2010]
58. Joly F, Tchen N, Chevreau C, *et al.* Clinical benefit of second line weekly paclitaxel in advanced urothelial carcinoma (AUC): a GETUG phase II study [abstract 4619]. *J Clin Oncol* 2004;22: [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=26&abstractID=2217](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=26&abstractID=2217); cited December 22, 2010]

59. Sweeney CJ, Roth BJ, Kabbinner FF, *et al.* Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol* 2006;24:3451–7.
60. Culine S, Theodore C, De Santis M, *et al.* A phase II study of vinflunine in bladder cancer patients progressing after first-line platinum-containing regimen. *Br J Cancer* 2006;94:1395–401.
61. Akaza H, Naito S, Usami M, *et al.* Efficacy and safety of gemcitabine monotherapy in patients with transitional cell carcinoma after cisplatin containing therapy: a Japanese experience. *Jpn J Clin Oncol* 2007;37:201–6.
62. Dreicer R, Li S, Manola J, Haas NB, Roth BJ, Wilding G. Phase 2 trial of epothilone B analog BMS-247550 (ixabepilone) in advanced carcinoma of the urothelium (E3800): a trial of the Eastern Cooperative Oncology Group. *Cancer* 2007;110:759–63.
63. Galsky MD, Mironov S, Iasonos M, Scattergood J, Boyle MG, Bogorin DF. Phase II trial of pemetrexed as secondline therapy in patients with metastatic urothelial carcinoma. *Invest New Drugs* 2006;25:265–70.
64. Bellmunt Molins J, von der Maase H, Theodore C, *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelium. *J Clin Oncol* 2009;27:4441–5.
65. Vaughn DJ, Srinivas S, Stadler WM, *et al.* Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma: results of a large phase II study. *Cancer* 2009;115:4110–17.
66. Castagneto B, Zai S, Marengo D, *et al.* Single-agent gemcitabine in previously untreated elderly patients with advanced bladder carcinoma: response to treatment and correlation with the comprehensive geriatric assessment. *Oncology* 2004;67:27–32.
67. Moore MJ, Tannock IF, Eanst DS, Huan S, Murray N. Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. *J Clin Oncol* 1997;15:3441–5.
68. Pollera CF, Ceribelli A, Crecco M, Calabresi F. Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. *Ann Oncol* 1994;5:182–4.
69. Lassiter LK, Tummala MK, Hussain MH, Stadler WM, Petrylak DP, Carducci MA. Phase II open-label study of oral piritrexim in patients with advanced carcinoma of the urothelium who have experienced failure with standard chemotherapy. *Clin Genitourin Cancer* 2008;6:31–5.
70. Logothetis CJ, Hossan E, Recondo G, *et al.* 5-Fluorouracil and interferon-alpha in chemotherapy refractory bladder carcinoma: an effective regimen. *Anticancer Res* 1994;14:1265–9.
71. Tu SM, Hossan E, Amato R, Kilbourne R, Logothetis CJ. Paclitaxel, cisplatin and methotrexate combination chemotherapy is active in the treatment of refractory urothelial malignancies. *J Urol* 1995;154:1719–22.
72. Sweeney CJ, Williams SD, Finch DE, *et al.* A phase II study of paclitaxel and ifosfamide for patients with advanced refractory carcinoma of the urothelium. *Cancer* 1999;86:514–18.
73. De Mulder PH, Theodore C, Sella A, *et al.* Phase II EORTC trial with 5-fluorouracil, cisplatin and interferon-alpha as second-line treatment of advanced transitional cell cancer of the urothelial tract. *Ann Oncol* 2000;11:1391–4.
74. Krega S, Rembrink V, Borgermann C, Otto T, Rubben H. Docetaxel and ifosfamide as second line treatment for patients with advanced or metastatic urothelial cancer after failure of platinum chemotherapy: a phase 2 study. *J Urol* 2001;165:67–71.
75. Meluch AA, Greco FA, Burris HA, *et al.* Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol* 2001;19:3018–24.
76. Sternberg CN, Calabro F, Pizzocaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer* 2001;92:2993–8.
77. Bellmunt J, Cos J, Cleries R, *et al.* Feasibility trial of methotrexate–paclitaxel as a second line therapy in advanced urothelial cancer. *Cancer Invest* 2002;20:673–85.
78. Pagliaro LC, Millikan RE, Tu SM, *et al.* Cisplatin, gemcitabine, and ifosfamide as weekly therapy: a feasibility and phase II study of salvage treatment for advanced transitional-cell carcinoma. *J Clin Oncol* 2002;20:2965–70.
79. Chen AC, Hovey E, Shelton G, *et al.* Phase I/II study of docetaxel (D), gemcitabine (G), carboplatin (C) in poor prognosis and previously treated patients (pts) with urothelial carcinoma (UTC) [abstract 4580]. *J Clin Oncol* 2004;22: [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=26&abstractID=4051](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=26&abstractID=4051); cited December 16, 2010]
80. Vaishampayan UN, Faulkner JR, Small EJ, *et al.* Phase II trial of carboplatin and paclitaxel in cisplatin-pretreated advanced transitional cell carcinoma: a Southwest Oncology Group study. *Cancer* 2005;104:1627–32.
81. Fechner G, Siener R, Reimann M, Kobalz L, Albers P, on behalf of the German Association of Urologic Oncology (AUO) Bladder Cancer Study Group. Randomised phase II trial of gemcitabine and paclitaxel second-line chemotherapy in patients with transitional cell carcinoma (AUO Trial AB 20/99). *Int J Clin Pract* 2006;60:27–31.
82. Takahashi T, Higashi S, Nishiyama H, *et al.* Biweekly paclitaxel and gemcitabine for patients with advanced urothelial cancer ineligible for cisplatin-based regimen. *Jpn J Clin Oncol* 2006;36:104–8.
83. Lin CC, Hsu CH, Huang CY, *et al.* Gemcitabine and ifosfamide as a second-line treatment for cisplatin-refractory metastatic urothelial carcinoma: a phase II study. *Anticancer Drugs* 2007;18:487–91.
84. Albers P, Siener R, Park S, *et al.* Randomized phase III trial of 2nd line gemcitabine/paclitaxel chemotherapy in patients with advanced bladder cancer: temporary versus maintenance treatment (German Association of Urologic Oncology (AUO) Trial AB 20/99) [abstract 5030]. *J Clin Oncol* 2008;26: [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=55&abstractID=31706](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=31706); cited December 16, 2010]
85. Kanai K, Kikuchi E, Ohigashi T, *et al.* Gemcitabine and paclitaxel chemotherapy for advanced urothelial carcinoma in patients who have received prior cisplatin-based chemotherapy. *Int J Clin Oncol* 2008;13:510–14.
86. Suyama T, Ueda T, Fukasawa S, *et al.* Combination of gemcitabine and paclitaxel as second-line chemotherapy for advanced urothelial carcinoma. *Jpn J Clin Oncol* 2009;39:244–50.
87. Han KS, Joung JY, Kim TS, *et al.* Methotrexate, vinblastine, doxorubicin and cisplatin combination regimen as salvage

- chemotherapy for patients with advanced or metastatic transitional cell carcinoma after failure of gemcitabine and cisplatin chemotherapy. *Br J Cancer* 2008;98:86–90.
88. Di Lorenzo G, Montesarchio V, Autorino R, *et al.* Phase 1/2 study of intravenous paclitaxel and oral cyclophosphamide in pretreated metastatic urothelial bladder cancer patients. *Cancer* 2009;115:517–23.
  89. Di Lorenzo G, Autorino R, De Laurentiis M, *et al.* Thalidomide in combination with oral daily cyclophosphamide in patients with pretreated hormone refractory prostate cancer: a phase I clinical trial. *Cancer Biol Ther* 2007;6:313–17.
  90. Garcia AA, Hirte H, Fleming G, *et al.* Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago and Princess Margaret Hospital phase II consortia. *J Clin Oncol* 2008;26:76–82.
  91. Bottini A, Generali D, Brizzi MP, *et al.* Randomized phase II trial of letrozole and letrozole plus low-dose metronomic oral cyclophosphamide as primary systemic treatment in elderly breast cancer patients. *J Clin Oncol* 2006;24:3623–8.
  92. Kouno T, Ando M, Yonemori K, *et al.* Weekly paclitaxel and carboplatin against advanced transitional cell cancer after failure of a platinum-based regimen. *Eur Urol* 2007;54:1115–22.
  93. Rosenberg JE, Halabi S, Sanford BL, *et al.* Phase II study of bortezomib in patients with previously treated advanced urothelial tract transitional cell carcinoma: CALGB 90207. *Ann Oncol* 2008;19:946–50.
  94. Cheung EM, Quinn DI, Tsao-Wei DD, *et al.* Phase II study of vorinostat (suberoylanilide hydroxamic acid, SAHA) in patients with advanced transitional cell urothelial cancer (TCC) after platinum-based therapy: California Cancer Consortium/University of Pittsburgh NCI/CTEP-sponsored trial [abstract 16058]. *J Clin Oncol* 2008;26:. [Available online at: [www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=55&abstractID=36428](http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=36428); cited December 16, 2010]
  95. Dreicer R, Li H, Stein MN, *et al.* Phase II trial of sorafenib in advanced carcinoma of the urothelium: a trial of the Eastern Cooperative Oncology Group [abstract 5083]. *J Clin Oncol* 2008;26:. [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=55&abstractID=31628](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=31628); cited December 16, 2010]
  96. Gallagher DJ, Milowsky MI, Gerst SR, *et al.* Final results of a phase II study of sunitinib in patients (pts) with relapsed or refractory urothelial carcinoma (UC) [abstract 5082]. *J Clin Oncol* 2008;26:. [Available online at: [www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst\\_detail\\_view&confID=55&abstractID=33136](http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=33136); cited December 16, 2010]
  97. Osai WE, Ng CS, Pagliaro LC. Positive response to bevacizumab in a patient with metastatic, chemotherapy-refractory urothelial carcinoma. *Anticancer Drugs* 2008;19:427–9.
  98. Yafi FA, Kassouf W. Management of patients with advanced bladder cancer following major response to systemic chemotherapy. *Expert Rev Anticancer Ther* 2009;9:1757–64.
- Correspondence to:** Wassim Kassouf, Division of Urology, McGill University Health Center, 1650 Cedar Avenue, Room L8-315, Montreal, Quebec H3G 1A4.  
**E-mail:** [wassim.kassouf@muhc.mcgill.ca](mailto:wassim.kassouf@muhc.mcgill.ca)
- \* Department of Surgery (Urology), McGill University, Montreal, QC.  
 † Division of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, AB.