Systemic chemotherapy in inoperable or metastatic bladder cancer

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Urothelial cancer is a common malignancy. The management of patients with recurrent disease after cystectomy or initially metastatic or unresectable disease represents a therapeutic challenge. Systemic chemotherapy prolongs survival but long-term survival remains infrequent. During recent years there has been improvement due to the use of novel chemotherapeutic agents, mainly gemcitabine and the taxanes. The long-considered-standard MVAC has been challenged by combinations showing more favourable toxicity profiles and equal (gemcitabine–cisplatin) or even improved (dose-dense, G-CSF-supported MVAC) efficacy. Specific interest has also been generated in specific groups of patients (elderly patients, patients with renal function impairment or comorbidities), who are not fit for the standard cisplatin-based chemotherapy but can derive significant benefit from carboplatin- or taxane-based treatment. Retrospective analyses have enabled the identification of groups of patients with different prognoses, who possibly require different therapeutic approaches. Modern chemotherapy offers a chance of long-term survival in patients without visceral metastases, possibly in combination with definitive local treatment. Finally, the progress of targeted therapies in other neoplasms seems to be reflected in advanced bladder cancer by recent studies indicating that biological agents can be combined with modern chemotherapy. The true role of such therapies is currently being evaluated.

Key words: bladder cancer, chemotherapy, gemcitabine, MVAC, taxanes

introduction
Bladder cancer is a common human malignancy and is the second most common genitourinary malignancy. The crude incidence in the European Union is 23 cases/100,000/year and the mortality 10 cases/100,000/year. Most cases present with superficial disease [1]. Nevertheless, ~20% have muscle-invasive disease at presentation, while 5% present with metastatic disease. In addition, ~50% of patients undergoing radical surgery for invasive bladder cancer will relapse. Relapses cannot be cured by local treatment in the majority of cases. Therefore, surgically inoperable disease comprises three distinct groups: inoperable disease due to local extension or grossly involved pelvic or paraortic lymph node (stages T4b, N2, N3), metastatic disease at diagnosis or recurrent disease after radical cystectomy.

Systemic chemotherapy represents the most useful option for patients with surgically incurable disease. This review will summarize the evolution of systemic chemotherapy in this disease, focusing on recent developments and on specific groups of patients, who probably require different therapeutic approaches. It should be mentioned that some of the studies considered in this review have included patients with carcinoma of the urothelial tract in general and not only of the urinary bladder. Nevertheless, bladder cancer represents >85% of the neoplasms of the urothelial tract [1] and, therefore, the results of these studies are mainly applicable to this neoplasm.

systemic chemotherapy in inoperable bladder cancer

single-agent chemotherapy
Several chemotherapeutic agents have demonstrated single-agent activity against advanced bladder cancer. Among older agents, cisplatin and methotrexate have been described as the most active single agents, with responses rates (RRs) of ~30% [1, 2], while doxorubicin, 5-fluorouracil, vinblastine, ifosfamide and mitomycin C have shown lower RRs of between 13% and 21% [1]. Piritrexim is an oral antimetabolite which has shown a 23% overall RR (ORR) as single agent in previously treated patients [3]. Carboplatin is the second most widely tested platinum compound. Response rates after treatment with single-agent carboplatin are inferior to those with cisplatin, usually <20% [1, 4].

Recent studies have identified new agents that have activity against urothelial carcinoma, the most important being the taxanes (paclitaxel and docetaxel) and gemcitabine. The taxanes...
are antimicrotubule agents that have a mechanism of action as a promoter of microtubule assembly and a stabilizer of tubulin polymers against depolymerization. Paclitaxel has produced the highest RR ever reported for single-agent treatment for advanced urothelial cancer at 42% including 27% complete response (CR) [5], while docetaxel also produced an RR of 38% in previously untreated patients [6]. The nucleoside analogue gemcitabine has been shown to have significant single-agent activity in metastatic urothelial cancer, with RRs of 23–29% and with a CR rate of 4–13%, in both previously treated and untreated patients [7, 8].

combination chemotherapy

The encouraging efficacy of several agents in advanced bladder cancer has led to several phase II and III studies (Table 1) of combination chemotherapy with the goal of increasing response rates and survival.

cisplatin-based combinations. The landmark of systemic chemotherapy in advanced urothelial cancer was the development of the combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) at the Memorial Sloan-Kettering Cancer Center (MSKCC) in 1983 [9]. Its activity against urothelial cancer has been considerable with response rates of >50%, 3-year survival of 20–25% and median survival of >1 year [9–11]. Furthermore, MVAC was shown to be superior to single-agent cisplatin in a randomized trial [12] establishing the role of combination chemotherapy in advanced bladder cancer. Several MVAC-like regimes have also been studied. The combination of cisplatin, methotrexate and vinblastine (CMV) was contemporary with MVAC and was developed at Stanford University. In a randomized study of 214 patients it was shown to be superior to the combination of methotrexate and vinblastine [13], underlying the importance of cisplatin in prolonging survival and establishing the routine use of cisplatin-based combination chemotherapy. The addition of ifosfamide to CMV led to the development of CIMV [14], the omission of vinblastine from CMV led to the CM [15] regime, while the omission of vinblastine from MVAC led to the MD Anderson CISCIA regimen (cisplatin, cyclophosphamide and doxorubicin) [16]. All four MVAC-like regimes (CMV, CIMV, CM, CISCIA) produced results comparable to those of MVAC in phase II studies [14–17]. The CISCIA regimen was the only one which was formally compared and found to be inferior to MVAC in a randomized trial [18]. Although the other regimens were never compared with MVAC, most centres worldwide have considered this regimen as the standard treatment for advanced urothelial cancer for almost two decades.

Although MVAC has shown considerable efficacy in advanced urothelial carcinoma, clinical research has been focused on the possibilities of improving its results. Long-term survival is low with only 10–15% of these patients surviving at 5 years. In addition, toxicity of this combination is significant. Neutropenic sepsis has been reported in >10% of patients treated with MVAC, while it has also been associated with a toxic death rate of 3–4%. Two strategies have been used in order to improve over MVAC: the use of granulocyte-colony stimulating factor (G-CSF) and the study of new combinations.

The encouraging efficacy of several agents in advanced bladder cancer has led to several phase II and III studies (Table 1) of combination chemotherapy with the goal of increasing response rates and survival.

**Table 1. Randomized trials in advanced urothelial cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n</th>
<th>RR (%)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loehler [12]</td>
<td>MVAC</td>
<td>126</td>
<td>39</td>
<td>NR</td>
<td>12.5*</td>
</tr>
<tr>
<td>Logothetis [18]</td>
<td>MVAC</td>
<td>65</td>
<td>65</td>
<td>NR</td>
<td>12.6*</td>
</tr>
<tr>
<td>MRC [13]</td>
<td>CMV</td>
<td>108</td>
<td>46</td>
<td>5.3*</td>
<td>7</td>
</tr>
<tr>
<td>Maase [34]</td>
<td>GC</td>
<td>203</td>
<td>49</td>
<td>7.4</td>
<td>13.8</td>
</tr>
<tr>
<td>HECOG [36]</td>
<td>MVAC</td>
<td>109</td>
<td>54</td>
<td>9.4*</td>
<td>14.2*</td>
</tr>
<tr>
<td></td>
<td>DC</td>
<td>111</td>
<td>57</td>
<td>6.1</td>
<td>9.3</td>
</tr>
</tbody>
</table>

*Difference statistically significant.

The use of G-CSF can reduce myelotoxicity but also allowed for the administration of MVAC in a more dose-dense fashion [19–22]. The results of phase II studies indicated that the efficacy of MVAC might be improved by dose intensification.

In order to change the toxicity profile and possibly increase the efficacy of MVAC, other combinations based on cisplatin have been studied.

The development of novel cisplatin-based combinations has focused on gemcitabine and the taxanes, mainly because of their aforementioned single-agent activity but also because of their synergic effects with cisplatin. The gemcitabine–cisplatin combination (GC) has been evaluated in three studies that used different administration schedules [23–25]. All studies showed high ORR and CR rate, while median survival was also encouraging at 12–14 months.

Regimens of combined paclitaxel and cisplatin, usually given every 3 weeks, were evaluated in three studies, involving a total of 106 patients. The ORR ranged from 50% to 72% (CR rate 8–32%) [26–28]. The combination of docetaxel and cisplatin every 3 weeks has also been evaluated in three studies. In a total of 123 patients, the ORR ranged from 52% to 62% and the median overall survival was reported to be 8–14 months [29–31].

The promising efficacy and the favourable toxicity profile shown in the above-mentioned studies led to three more recent randomized studies comparing MVAC with other combinations of cisplatin (Table 1). An EORTC study showed that intensified MVAC (HD MVAC) with G-CSF support was less toxic than classic MVAC. Overall RR, CR rate and progression-free survival (PFS) were superior for HD MVAC but the difference in survival was non-significant in the initial publication [32]. With longer follow-up, the initial results have been confirmed with PFS and mortality hazard ratios of 0.73 and 0.76, respectively and 2-year and 5-year survival rates of 36% compared with 26% and 21% compared with 13% for HD MVAC and classic MVAC, respectively [33]. In another randomized study the combination of GC was found to be equally effective with regard to response time to progression and
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survival but less toxic than classic MVAC [34]. The study was designed to demonstrate a 4-month survival benefit of GC and non-equivalence of the two combinations. Long-term results of this study have also been published recently, confirming similar 5-year survival and PFS rates for GC (13% and 9.8%) and MVAC (15.3% and 11.3%) [35].

In spite of the statistical limitations, the results of these two studies indicate that the standard in chemotherapy for advanced urothelial tract cancer may be changing. In the third randomized study the combination docetaxel–cisplatin was compared with G-CSF supported MVAC [36]. Docetaxel–cisplatin was found to be inferior to MVAC, although the difference in survival did not reach statistical significance due to an imbalance in performance status between the two arms.

carboplatin-based combinations. The more favourable toxicity profile of carboplatin, especially regarding emesis, nephrotoxicity and neurotoxicity, as well as ease of administration, makes this agent an attractive alternative to cisplatin. The substitution of carboplatin for cisplatin in the MVAC or MVAC-like regimes has been studied in phase II studies [37]. Most studies using carboplatin included patients who could not receive cisplatin due to impaired renal function, poor performance status or comorbidities precluding the hydration required for cisplatin administration. In contrast, data regarding the efficacy of carboplatin-containing chemotherapy in patients who are fit for cisplatin-based treatment are scarce. More recently, the combination of carboplatin with gemcitabine has been studied. In two phase II studies, which did not specifically include patients unfit for cisplatin treatment, RRs of 36% and 59% were reported but with a median survival of 10 months in both studies [38, 39]. The combination of paclitaxel and carboplatin has also been recently studied. Five studies using this combination including a total of 149 patients have been published [40–44]. Overall RR ranged from 21% to 65% (lowest RRs in studies including substantial numbers of pretreated patients) but again median survival was <10 months in all studies.

Carboplatin-based chemotherapy has generally produced inferior results (both in RR and median survival) to cisplatin-containing combinations, although data from direct comparisons are limited. Two randomized phase II studies showed inferior RR with carboplatin as opposed to cisplatin-based chemotherapy indicating the inferiority of carboplatin-based chemotherapy [45, 46]. The only phase III study, which was designed to compare MVAC with carboplatin–paclitaxel [47] never completed accrual and, therefore, no conclusions can be drawn. Presently, cisplatin-based chemotherapy represents the standard of care for patients who can tolerate such regimes. Nevertheless, the role of carboplatin in ‘fit-for-cisplatin’ patients remains an unresolved issue.

non-platinum based chemotherapy. In an effort to reduce cisplatin-related gastrointestinal and renal toxicity, while maintaining the therapeutic benefit, novel non-platinum combinations have been tested. The need for such treatment is also underlined by the fact that there is no accepted standard second-line treatment for metastatic urothelial cancer progressing after platinum-based chemotherapy. Paclitaxel and gemcitabine represent the best-studied non-platinum combination. In four phase II studies using different schedules [48–51] RRs of over 40% in previously treated and untreated patients were reported. Specifically in patients who had previously received MVAC as adjuvant or first-line treatment for metastatic disease, Sternberg et al. [48] showed a 60% RR and a median survival of 14.4 months. Nevertheless, a more recent study, using the same schedule, did not confirm such high RRs, even after adjusting for prognostic factors [50]. Finally, an impressive RR of 69% with CR rates of 42% in 36 patients were reported with a weekly schedule [51]. However, because of the high incidence of pulmonary toxicity associated with this schedule, the authors recommend against the use of this regimen in advanced bladder cancer. There has been more limited study of the other taxane, docetaxel, in combination with gemcitabine. In two phase II studies, including 27 and 31 patients, respectively, RRs of 33% and 51% were reported [52, 53]. The combination was well tolerated and the authors in both studies concluded that this might be a useful option for patients with impaired renal function, although none of the two studies was specifically aimed at this population.

novel agents and triplet combination chemotherapy

Several new agents and combinations are currently being evaluated in advanced urothelial cancer. Pemetrexed is a novel antifolate, which showed a 33% RR in chemo-naïve patients [54]. More importantly, a 27% RR was achieved as second-line therapy. Finally, a new semi-synthetic derivative of vinca alkaloids, vinflunine, has shown a 16% ORR in patients failing platinum [55] and is now being evaluated as second-line treatment in a phase III trial.

As shown above the last decade has been characterized by the use of chemotherapy doublets, some of which were compared with standard MVAC. Nevertheless, the development of several active agents, as well as the wider application of haemopoietic growth factors, led to the study of three or more drug combinations in advanced urothelial cancer. The first triplet was developed at the MSKCC, who tested the combination of ifosfamide, paclitaxel and cisplatin (ITP) [56]. They reported a 68% RR and an impressive median survival of 18 months. Based on these results the same group developed a five-drug regimen. Sequential administration was used to facilitate drug delivery [57]: six cycles of doxorubicin and gemcitabine (AG) were followed by four cycles of ITP. Fifty-six patients have been treated at the MSKCC with an ORR of 73%, which is higher than expected with either AG or ITP [58].

The promising activity of paclitaxel led to the development of new triplets by the addition of this agent to the recently established CG or to the carboplatin–gemcitabine combination. Bellmunt et al. [59] and the Spanish Oncology Genitourinary Group have conducted a phase I/II trial of the combination of paclitaxel, cisplatin and gemcitabine (GCP). The ORR and CR rates at the phase II part of the study were 76% and 26%, respectively, and the median survival was 15.6 months. In a randomized phase II study, Lorusso et al. [60] reported an RR of 43% with a CR rate of 12% among 42 patients treated with this combination. RRs were similar to those of GC. Nevertheless, this study was underpowered to detect significant differences in
C225 (cetuximab) has shown promising efficacy in colorectal tumors and has been found to be associated with prognosis [68].

Hussain et al. [63] conducted a phase II trial evaluating the efficacy of the combination paclitaxel–carboplatin–gemcitabine in patients with advanced urothelial cancer. Most of the 49 patients who were enrolled would have been eligible for cisplatin-based chemotherapy. The ORR was 68%, with a CR rate of 32% and a median survival of 14.7 months. In a similarly designed study, Hainsworth et al. [64] failed to duplicate these results: lower RR (43%), CR rate (12%) and median survival (11 months) in 60 patients with similar prognostic features were reported.

The preliminary results of a phase I/II study by Law et al. [65] reported the use of a non-cisplatin triplet built up with paclitaxel, methotrexate and gemcitabine. In 20 evaluable patients the ORR was 45% (six complete responses and three partial responses, median overall and progression-free survival were 18 and 6.3 months, respectively and the most common toxicity was neutropenia.

Data from triplet studies so far demonstrate the feasibility of such combinations, since treatment was generally well tolerated. The precise role of these combinations will be clarified by the EORTC 30987 and other future randomized studies.

molecular factors and targeted therapy
The concept of individualized treatment through identification of molecular prognostic and predictive factors and the application of targeted therapy have gained considerable interest and is already used in other neoplasms, such as breast, colorectal and non-small-cell lung cancer. Nevertheless, there is relatively little information and no established role yet for targeted therapy in metastatic bladder cancer. Several studies have indicated that alterations of oncogenes or tumour suppressor genes or the expression of cell proteins, enzymes or angiogenesis-related factors may have prognostic value in advanced bladder cancer [66]. Nevertheless, the number of patients included was usually small, some of these studies did not include patients with advanced disease, while few of them studied the association of such factors with response to chemotherapy. Recent data have indicated that altered expression of p53 may be associated with resistance to neoadjuvant MVAC [67] but data from another retrospective analysis indicated that patients with p53 mutations benefited from adjuvant cisplatin-based chemotherapy [68]. These last data formed the basis of a randomized study, which uses p53 expression as a stratification factor for randomization [66].

A molecular target which holds promise for the development of effective therapies in bladder cancer is the epidermal growth factor receptor (EGFR). EGFR is highly expressed in bladder cancer and has been found to be associated with prognosis [68]. EGFR can be targeted at the level of the receptor using a monoclonal antibody against the receptor or at the respective tyrosine kinase. The anti-EGFR monoclonal antibody IMC-C225 (cetuximab) has shown promising efficacy in colorectal and head and neck cancer but data regarding its activity in metastatic bladder cancer are not available so far. Several tyrosine kinase inhibitors (TKIs) of the EGFR have been developed and already tested in other neoplasms but information on their activity in bladder cancer is limited. An inhibitor of the tyrosine kinases of both EGFR and HER2/neu, lapatinib (GW572016), has been tested as second-line treatment in bladder cancer showing only a 2% RR [69], while preliminary results of a Cancer and Leukemia Group B (CALGB) study showed promising activity of a first-line GC combination with an EGFR TKI ZD1839 (Iressa) in metastatic or unresectable bladder cancer [70]. The receptor coded by the HER2/neu gene also represents a promising target for bladder cancer and a monoclonal antibody targeting this receptor (trastuzumab) is already approved for the treatment of breast cancer overexpressing the receptor. Overexpression of this receptor has also been found in muscle-invasive bladder cancer [71], although its association with prognosis has not been proved. Based on the efficacy of the combination of paclitaxel–gemcitabine–carboplatin and the synergy of trastuzumab with paclitaxel and cisplatin, the NCI sponsored a multi-centre phase II clinical trial of this combination in metastatic bladder cancer [72]. The combination was administered to 44 patients with HER-2-positive tumours. A promising 72.7% RR and a median survival of 15.2 months have been reported in abstract form.

prognostic factors in patients with advanced bladder cancer treated with systemic chemotherapy
Long-term follow-up of patients who participated in large trials has helped to identify subgroups of patients with distinctly different prognoses. Indeed, long-term survival may range from 6% to 40% depending on certain baseline characteristics [33, 35, 36, 73–76]. The most comprehensive analyses have been reported for patients who were uniformly treated with cisplatin-based chemotherapy and in particular with MVAC or GC. Two factors have been consistently associated with independent prognostic significance: PS and the presence of visceral (lung, liver, bone) metastases.

In a retrospective analysis of 203 patients treated in five different MVAC trials, patients with a Karnofsky PS of ≥80 had a median survival of 18.5 months as opposed to 10.5 months for patients with worse PS. In the same study, patients with visceral metastases had a median survival of 11.1 months compared with 22.3 months for patients without visceral metastases [73]. The combination of these two factors created three risk categories: 0, 1 or 2 risk factors. Median survival of these groups was 33, 13.4 and 9.3 months, respectively, with respective 5-year survival rates of 33%, 11% and 0%. The median survival of patients’ cohorts varied from 9 to 26 months simply by altering the proportions of patients from different risk categories.

More recent analyses have also identified the same factors to be associated with prognosis. Among 121 patients treated with GC the presence of visceral metastases was the only independent prognostic factor [74]. Patients without visceral metastases had a 24% chance of 4-year survival. Long-term survival results of a randomized trial, which included patients treated with MVAC...
Table 2. Long-term survival in patients with advanced bladder cancer treated with platinum-based chemotherapy

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>MVAC [73]</th>
<th>PGC [74]</th>
<th>GCP [75]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant metastases</td>
<td>Median survival (%)</td>
<td>5-year survival (%)</td>
<td>Median survival (%)</td>
</tr>
<tr>
<td>Karnofsky PS &lt;80%</td>
<td>33</td>
<td>33</td>
<td>16.9</td>
</tr>
<tr>
<td>0</td>
<td>13.4</td>
<td>11</td>
<td>10.6</td>
</tr>
<tr>
<td>1</td>
<td>9.3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>GC</td>
<td>32.8</td>
<td>44%</td>
<td>26%</td>
</tr>
<tr>
<td>0</td>
<td>18</td>
<td>36%</td>
<td>9%</td>
</tr>
<tr>
<td>1</td>
<td>10.6</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td>2</td>
<td>9.9</td>
<td>24%</td>
<td>9%</td>
</tr>
</tbody>
</table>

GC, gemcitabine–cisplatin; PGC, paclitaxel–gemcitabine–cisplatin.

or GC, also showed that Karnofsky PS of > 70 and the absence of visceral metastases were the most important favourable prognostic factors, with respective 5-year survival rates of 16% and 21% [35]. Another recent study, which used the combination GCP [75], showed identical median survival times for patients within the same risk categories treated with MVAC (Table 2).

These results underline the important differences that can be caused simply by patient selection and their application has been proposed as a means for comparison of the results of various phase II studies [73]. Other factors apart from PS and the presence of visceral metastases, which have also been associated with prognosis are: baseline haemoglobin [73, 77], alkaline phosphatase [35, 78, 79], number of disease sites [35] and non-transitional histology [76]. Nevertheless, the prognostic significance of these factors was not always confirmed in different studies, analyses were performed in heterogeneous groups regarding treatment [77, 79] and small numbers of patients within the groups of interest [73, 77]. More importantly, these factors have not been shown to offer additional prognostic information when considered together with PS and the presence of visceral metastases [35, 73].

specific groups of patients

patients without distant metastases

Patients with inoperable or recurrent locoregional disease without distant metastases represent a group with favourable prognosis compared with patients with visceral metastases [35, 36, 75–79]. These patients derive a substantial benefit from platinum-based combination chemotherapy, with high CR rates of and 5-year survival rates consistently above 10% and up to 30%. Nevertheless, most patients will relapse and die from bladder cancer. Obtaining a complete response after chemotherapy has been shown to be an important factor for long-term remission [73]. Since most patients achieve only a partial remission, the role of post-chemotherapy consolidative local treatment (surgery or radiotherapy) has been studied [80–82]. The scope of applying definitive local management in this group of patients is also supported by reports showing that patients presenting with locoregional disease and responding to chemotherapy tend to recur locally rather than with visceral metastases [83].

Surgery can be used when a response adequate for radical resection has been achieved with systemic chemotherapy. Patients who achieve a complete response after sequential chemotherapy and excision of residual disease have 5-year survival rates exceeding 30% in many cases [73, 80]. There have been no studies directly comparing the outcome with or without radical surgery following the response to systemic chemotherapy. Nevertheless, data from MSKCC have shown that patients with no residual disease after chemotherapy fared better when they had cystectomy compared with patients with similar response who refused surgery [81]. Based on these data, it seems reasonable to offer radical surgery to patients with an adequate response to chemotherapy. Patients who are not candidates for surgery could be offered radiotherapy [82], although data regarding this modality in this setting are much more limited than for surgery.

patients unfit for cisplatin-based combination chemotherapy

At least one-third of patients with inoperable bladder cancer are unfit to receive cisplatin-based chemotherapy [60]. The definition of ‘fitness’ reflects the level of susceptibility to drug toxicity and is related to a variety of factors. The median age of these patients is ~70 years and elderly patients have age-related renal function impairment or comorbidities, which preclude the use of cisplatin. Renal function impairment may also be related to the disease itself, while cardiovascular and pulmonary comorbidities are particularly frequent in this population, since they are both associated with smoking, a well-established risk factor for the development of bladder cancer. Finally, patients with poor performance status (ECOG PS > 1) are poor candidates for cisplatin-based treatment [60].

In patients unfit for cisplatin therapy carboplatin is usually substituted for cisplatin in everyday practice to produce less nephrotoxic and more tolerable regimes. In addition to carboplatin, taxanes have also been used, especially in patients with impaired renal function, because they are cleared via hepatic metabolism. Nevertheless, few studies have specifically addressed this issue [84–89] (Table 3). In three studies a combination of carboplatin (at a dose of AUC 4–5) and gemcitabine (at a dose of 1000 mg/m² on days 1 and 8) was used. The combination was well tolerated. In the larger study, which included 56 patients, a 36% RR (9% CR) and a 26% 1-year survival were reported [86], while 44% and 56% ORRs were reported in two smaller studies [84, 85]. In three studies including patients with renal insufficiency, treatment with paclitaxel (175–225 mg/m²) or docetaxel (100 mg/m² with G-CSF) was well tolerated and RR of 24–45% were reported [87–89].

From the above data it can be concluded that patients who are unfit for cisplatin can tolerate systemic chemotherapy and
derive significant benefit from this treatment. This is underlined by the results of a recently reported phase II study, which showed that dose-dense sequential chemotherapy with adriamycin–gemcitabine and paclitaxel–carboplatin is feasible in patients with mild renal function impairment (creatinine clearance 30–60 ml/min) [90]. In addition, the ongoing randomized phase II/III EORTC 30986 is addressing the question of the optimal treatment in this group by comparing the long-used combination methotrexate–carboplatin–vindesine (MCAVI) with the doublet carboplatin–gemcitabine [61].

elderly patients

Carcinoma of the urothelial tract is a disease of primarily elderly people, since most patients are diagnosed beyond the age of 65 [1]. The use of cisplatin can be problematic for elderly patients who have age-related renal function impairment and frequently comorbidities, which preclude the adequate hydration required for cisplatin administration [91]. There is limited information regarding the tolerability of treatment by elderly patients with advanced urothelial carcinoma and their outcome following systemic chemotherapy, since they form only a small percentage of patients included in clinical trials [92]. Nevertheless, the reluctance observed in the decision process in this context is not justified by the data available so far. Old age has not been shown to be an independent adverse prognostic factor in patients with advanced urothelial cancer. In a retrospective analysis of 381 patients with advanced urothelial cancer treated with cisplatin or carboplatin-based chemotherapy, including 106 patients aged over 70, the elderly experienced more frequent neutropenia grade 3/4 (55.2% compared with 37.4%) and renal toxicity (27.6% compared with 10.5%) than younger patients [77]. These differences, however, did not result in clinically significant sequelae in most cases. Response rates and survival did not differ significantly between elderly and younger patients (median survival 9.3 compared with 10.8 months). Elderly patients with a PS of <2 and haemoglobin ≥10 g/dl had a median survival of 13.9 months as opposed to 5 months for patients with PS ≥2 or haemoglobin <10 g/dl (P <0.001). In a recent study, 25 patients aged over 70 were treated with single-agent gemcitabine [93]. Treatment was tolerated extremely well, while an impressive 45.5% RR was reported. Furthermore, comprehensive geriatric assessment showed improvement of the examined parameters in 17% and deterioration in only 9% during treatment.

The above data, albeit limited, indicate that elderly patients with advanced urothelial cancer can tolerate treatment well when they do not suffer from other comorbidities. Besides, they seem to derive the same benefit as their younger counterparts and, therefore, they should be offered the same treatment and the chance to participate in clinical studies.

second-line treatment

There are few data regarding the treatment of patients failing first-line platinum-based chemotherapy. One of the main reasons is the fact that after progressing following first-line treatment there is frequently a significant deterioration in PS and/or renal function, which make the enrolment of patients in clinical studies or even the administration of systemic chemotherapy outside the context of a clinical trial difficult. As already mentioned in other sections, non-platinum combinations and especially taxanes with gemcitabine have shown promising results after failure of MVAC [48, 49]. Nevertheless, these studies did not specifically include patients failing first-line chemotherapy for advanced disease. In addition, the clinical significance of taxane–gemcitabine combination as second-line treatment is diminished by the emergence of GC as a new standard, since many of the patients on progression will have been exposed to gemcitabine. Relative to this is the absence of sufficient data on the role of MVAC as second-line treatment after failure of GC. Lorenzo et al. [94] used the combination of oxaliplatin with fluorouracil and folinic acid (FOLFOX-4) in pre-treated patients with advanced transitional cell carcinoma of the bladder. Oxaliplatin has minimal single-agent activity in previously treated patients with bladder cancer, but it has a pronounced synergic effect with fluorouracil, which has been proved in colon cancer. The ORR was 19% (three of the 16 eligible patients). This response rate is low in comparison with FOLFOX-4 in colon cancer, but it is important to consider that the treatment was a third-line approach in patients pretreated with platinum compounds.

Another combination, which also showed activity in the second-line setting was gemcitabine–ifosfamide [95]. This combination resulted in 21% RR in 34 platinum and/or taxane pretreated patients with advanced urothelial cancer. Probably the most important finding was the significant symptomatic improvement achieved in a significant number of patients. Probably the most promising approach for second-line treatment are novel agents, like pemetrexed and vinflunine, which have shown efficacy in pretreated patients [53–55]. Vinflunine is currently being compared with best supportive care as second-line treatment after progression following platinum-based chemotherapy. This is the first phase III trial in

Table 3. Chemotherapy in patients unfit to receive cisplatin-based treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Reason for ‘unfitness’</th>
<th>Treatment</th>
<th>ORR (%)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellmunt 2001 [84]</td>
<td>16</td>
<td>PS 2 and/or CrCl &lt;60</td>
<td>Carboplatin–gemcitabine</td>
<td>44</td>
<td>NR</td>
</tr>
<tr>
<td>Linardou 2004 [86]</td>
<td>56</td>
<td>PS &gt;2 and/or age &gt;75 and/or CrCl &lt;50</td>
<td>Carboplatin–gemcitabine</td>
<td>36</td>
<td>7.2</td>
</tr>
<tr>
<td>Vaughn 2002 [88]</td>
<td>37</td>
<td>Cr 1.6–4</td>
<td>Paclitaxel</td>
<td>24.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Dimopoulos 1998 [87]</td>
<td>11</td>
<td>Cr &gt;1.6</td>
<td>Docetaxel</td>
<td>45</td>
<td>11</td>
</tr>
<tr>
<td>Yang 2000 [89]</td>
<td>13</td>
<td>Cr &gt;1.5</td>
<td>Paclitaxel</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>Carles 2000 [85]</td>
<td>17</td>
<td>CrCl &lt;60</td>
<td>Carboplatin–gemcitabine</td>
<td>56</td>
<td>NR</td>
</tr>
</tbody>
</table>

N, number of patients; ORR, overall response rate; OS, overall survival.
a setting with no standard treatment, underlining the necessity for expanding clinical research in this area. The development of effective second-line treatment may result in further improvement of prognosis in patients with advanced bladder cancer. In addition, targeted therapies alone or in combination with chemotherapy may prove useful after failure of first-line chemotherapy, especially due to their favourable toxicity profile for chemotherapy-pretreated patients. Two inhibitors of the tyrosine kinases of the EGFR and HER-2 receptor are currently being evaluated in clinical studies [70, 72].

conclusions and future perspectives

Advanced bladder cancer is a chemosensitive neoplasm. The long-considered-standard regimen, MVAC, has consistently proved the efficacy of cisplatin-based combination chemotherapy and shown that long-term survival is possible, although for a minority of patients. The current decade has been characterized by the effort to improve on the results of MVAC in terms of both efficacy and toxicity. These efforts have been successful and new standards have emerged (GC and intensified MVAC) based on new agents or intensification by using haemopoietic growth factors. It should be stressed that the acceptance of the novel combinations as potential new standards has been predominantly based on their more favourable toxicity profile and not a survival benefit.

The treatment of choice for advanced bladder cancer remains cisplatin-based combination chemotherapy. Nevertheless, a substantial proportion of patients cannot receive such treatment, mainly due to renal function impairment, poor performance status and other comorbidities. For these patients the combination of carboplatin–gemcitabine or the taxanes are useful alternatives. Elderly patients tolerate chemotherapy well and derive the same benefit as younger patients. Therefore, elderly patients who are fit for cisplatin-based chemotherapy should be offered this option and advanced age per se should not be an exclusion criterion in clinical trials.

Retrospective analyses have identified performance status and the presence of visceral metastases as the most useful independent prognostic factors in advanced bladder cancer. The combination of these factors can identify groups of patients with significantly different prognosis and should be used in order to compare results of different phase II studies. In addition, they should be used as stratification factors in randomized trials. Based on these analyses patients with ECOG PS 0 or 1 and without visceral metastases have a 30% chance of 5-year survival following MVAC chemotherapy. Surgery following an initial response to chemotherapy appears to be important in achieving long-term survival. In contrast, patients with poor PS and visceral metastases have a poor outcome with effectively no chance of long-term survival.

In spite of the recent advances in systemic chemotherapy for bladder cancer, long-term survival is not achieved in most cases and this represents the most important target of basic and clinical research. The incorporation of new agents in two- or three-drug combinations is currently being tested in randomized trials. In addition, treatment optimization can be achieved using molecular markers. Their application could help to identify patients with different prognosis who possibly require different therapeutic approaches or result in precise prediction of response to various chemotherapeutic and biological agents. Furthermore, the use of new biological agents aimed at specific targets on cancer cells (erb-2, EGFR) may lead to the design of individualized treatments.

references
