Choosing chemotherapy in patients with advanced urothelial cell cancer who are unfit to receive cisplatin-based chemotherapy

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***Abstract*:** Transitional cell carcinoma of the urothelial tract is the second most common cancer of the genitourinary system and the fifth most common cancer in Western countries with more than 300,000 new cases per year worldwide. Following the introduction of cisplatin-based chemotherapy, median overall survival in patients with metastatic disease has doubled, demonstrating chemotherapy as an important treatment modality in advanced or metastatic disease. Patients 'unfit' to receive cisplatin-based chemotherapy are characterized by impaired renal function, impaired performance status, and/or comorbidity that preclude the use of cisplatin. In this review we summarize the different chemotherapeutic schemes, focusing on treatment options in cisplatin 'unfit' patients.

***Keywords*:** bladder cancer, chemotherapy, cisplatin, treatment options

Introduction

Transitional cell carcinoma of the urothelial tract is the second most common cancer of the genitourinary system and the fifth most common cancer in Western countries with an estimated 300,000 new cases per year worldwide. The incidence in the European Union is 23 cases per 100,000 inhabitants per year and mortality reaches 10 cases per 100,000 inhabitants per year [Shipley *et al.* 2008]. A third of these new cases have muscle-invasive or metastatic disease at time of diagnosis. In addition, half of the patients who undergo radical surgery for invasive disease will relapse. As relapses are mostly incurable with locoregional treatment modalities, systemic therapies have a major role in the treatment of bladder cancer. Median overall survival of patients with metastatic bladder cancer treated with best supportive care ranges between 4 and 6 months. Following the introduction of cisplatin in chemotherapeutic schemes, such as methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) and gemcitabine and cisplatin (GC), median overall survival has doubled to 12–14 months, demonstrating chemotherapy as an important treatment modality in this stage of the disease. However, the toxicity profile of the M-VAC scheme is considerable with frequent hospital admissions due to neutropenic fever and mucositis-related complications. Careful patient selection and management should be attempted to avoid serious treatment related toxicities such as cisplatin-induced nephtotoxicity.

Defining being 'unfit' is related to the frailty of patients to receive cisplatin-based chemotherapy and mostly depends on impaired renal function, impaired performance status (PS), and/or comorbidity that preclude the use of cisplatin. Normal renal function is an important requisite to receive cisplatin, as the drug causes tubular toxicity. Renal impairment is defined as a creatinine clearance of less than 60 ml/min as calculated by Cockroft–Gault formula. Although commonly used to assess renal function, Cockroft–Gault and other mathematical formulas can be inaccurate, thus categorizing patients unfit to receive cisplatin, who in fact have a measured clearance of >60 ml/min. Without sufficient renal clearance, sensitive systems such as the cardiovascular, pulmonary and neurological systems are exposed longer to toxic metabolites of cisplatin, resulting in more frequent and higher grades of toxicity. After radical cystectomy plus ureter-deviating surgery, the renal function is impaired in up to 17% of patients [Dash *et al.* 2006]. Although age is not an independent prognostic factor for bladder cancer treatment, age-related

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decrease in glomerular filtration rate impairs the patients' ability to receive cisplatin. Owing to a median age at diagnosis of 68 years, and smoking as an associated risk factor, many patients have pulmonary and/or cardiovascular disease, leading to accelerated deterioration of renal function. As the median age of patients with invasive bladder cancer approaches the seventh decade, this specific patient population is more susceptible for age-related comorbidities. Impaired PS, defined as Eastern Cooperative Oncology Group PS of two and above, is another patient category not able to receive cisplatin, as this type of patient is more susceptible to treatment-related toxicity. PS appears to be adversely related to treatment outcome. Cardiac dysfunction, vascular disease or chronic obstructive pulmonary disease may preclude cisplatin-based therapy. At least 30–40% of patients with advanced and/or metastatic bladder cancer are unfit to receive cisplatin-based chemotherapy [de Wit, 2003].

In this review we summarize the different chemotherapeutic schemes and future developments, focusing on treatment differences between fit and unfit patients.

Chemotherapy for fit patients who are able to receive cisplatin-based chemotherapy

The long-time standard treatment for transitional-cell carcinoma of the urothelial tract has been the four-drug Memorial Sloan–Kettering Cancer Center regimen based on methotrexate 30 mg/m^2 on days 1, 15 and 22, vinblastine 3 mg/m^2 on days 2, 15 and 22, doxorubicin 30 mg/m^2 on day 2 and cisplatin 70 mg/m^2 on day 2, on a 28-day cycle (M-VAC), that in the initial report gave a 72% response rate (RR) and median survival of 13 months [Sternberg *et al.* 1989]. Treatment-related toxicity was significant: 25% of the 133 participating patients had neutropenic fever, 58% expressed National Cancer Institute Common Toxicity Criteria (CTC) myelosuppression grade $\geq$3 and 49% severe mucositis. Four patients died due to drug-related toxicity. Two subsequent phase III trials revealed a RR of 39–65% and median survival of 12.5–14.6 months [Loehrer *et al.* 1992; Logothetis *et al.* 1990]. Although overall median survival was improved, this achievement was at a considerable cost of toxicity. Grade 3–4 leukocytopenia was observed in 24% of patients treated with M-VAC compared with 1% when treated with cisplatin alone ($p < 0.0001$) [Loehrer *et al.* 1992]. This resulted in 10% of patients with granulocytopenic fever and even 6% of patients with sepsis in the M-VAC group, while only 1% of patients had sepsis when treated cisplatin alone ($p = 0.0002$ and 0.04, respectively). Five deaths due to sepsis were recorded in the combination treatment group. In addition, grade 3 or 4 mucositis, nausea and vomiting were reported (17% of patients in the M-VAC group versus 0% of patients in the cisplatin alone group; $p < 0.0001$ and 12% versus 1%; $p = 0.0004$). In these two phase III studies; nephrotoxicity was observed in 7–48% of the patients with two recorded deaths due to acute renal failure. The large range of renal toxicity of the two studies was due to the different eligibility criteria. While Loehrer and colleagues included patients with a minimal creatinine clearance rate of 60 ml/min, Logothetis and colleagues allowed a minimal creatinine clearance rate of 40 ml/min in a relatively young patient population (median age 66 years). Thus, following along the lines of inclusion criteria used in these studies and the resulting toxicity profiles, at least 30–40% of patients with advanced and/or metastatic bladder cancer are unfit to receive cisplatin-based chemotherapy [de Wit and Bellmunt, 2003].

Impact of prognostic factors on treatment outcome

Around the turn of the century, an important meta-analysis was published on prognostic factors in transitional cell carcinoma [Bajorin *et al.* 1999]. Two hundred and three patients with unresectable or metastatic transitional cell carcinoma treated with M-VAC in five trials were pooled for the evaluation of possible prognostic factors. Univariate survival analysis showed nine variables associated with an adverse prognosis: low hemoglobulin level, high leukocytes count, high platelet count, high lactate dehydrogenase level, high alkaline phosphatase level, low albumin, low PS according to Karnofsky, previous surgery to remove the primary tumor, presence of bone, lung, liver metastases and any visceral metastases. Multivariate survival analysis reduced the influencing factors to low hemoglobin level, Karnofsky PS less than 80% and presence of visceral metastases (respectively, associated hazard ratios [HRs] of 1.12, 1.93 and 1.99). As PS and hemoglobin level have a similar clinical impact, hemoglobin was omitted due to its lower HR. As the survival impact of each factor was nearly identical, three risk group profiles emerged: zero, one and two risk

with a significant difference in median survival (33, 13 and 9 months and 33%, 11% and 0% likelihood of 5-year survival, respectively; $p < 0.0001$). Similarly, major response to chemotherapy or even achieving complete response differed by risk group (78%, 74% and 36%; 35%, 11% and 0%, respectively). The study elegantly showed the importance of patient selection on outcome of patients entered into a trial. Overall, with only 3.7% of all patients treated with M-VAC had a disease-free survival of more than 6 years, this treatment schedule should be reserved for patients with good prognostic factors, keeping in mind the high toxicity profile [Saxman *et al.* 1997; Connor *et al.* 1989].

New standard treatment option: the gemcitabine–cisplatin regimen

The high toxicity profile of M-VAC led to the search for an alternative, less-toxic combination chemotherapeutic scheme with an equal survival rate. Gemcitabine has demonstrated effectiveness as a single-agent treatment with an overall RR of 24–28%. [Moore *et al.* 1997; Stadler *et al.* 1997] Gemcitabine 1000 mg/m^2 on days 1, 8 and 15 and cisplatin 70 mg/m^2 on day 2 (GC) in a 28-day cycle was compared with the M-VAC regimen in a randomized phase III trial, revealing similar RR and survival (13.8 versus 14.8 months, $p = 0.75$; HR = 1.04) [von der Maase *et al.* 2000]. Sixty three per cent of all GC cycles were administered without the need for dose adjustments compared with only 37% of all M-VAC cycles. Grade 3 or 4 neutropenia was less frequent in GC treated patients compared with M-VAC treated patients (71% versus 82%, respectively), resulting in lower rates of granulocytopenic fever (2% versus 14%) with significantly less cases of neutropenic sepsis (1% versus 12%, $p < 0.001$). Although more grade 3 and 4 anemia and thrombocytopenia was observed in the GC arm compared with the M-VAC arm (27% versus 18% and 57% versus 21%, respectively), this did not resulted in higher need for transfusion or higher risk for bleeding. The number of patients with grade 3 or 4 chemotherapy-related mucositis was significantly reduced in the GC arm (1% versus 22%, respectively; $p = 0.001$). Eight patients (two in the GC arm and six in the M-VAC, $p > 0.05$) died during the study: seven due to complications of neutropenia and one due to complications of mucositis. Although the primary endpoint of the study was not reached with no benefit in survival, the HR (adjusted for prognostic factors) was 0.95, 95% confidence interval [CI] 0.74–1.22. An upper bound CI of 1.2 is generally accepted to reflect noninferiority. Therefore, as toxicity data proved more favorable for the GC regimen, GC was accepted as a new standard treatment regimen for metastatic bladder cancer.

In view of the frequent thrombocytopenia in the 4-weekly regimen and that frequent gemcitabine dose omissions on day 15 resulted in a decreased dose-intensity of gemcitabine, the GC scheme has been adapted to gemcitabine given on day 1 and day 8 of a 21-day cycle [Moore *et al.* 1999]. Although there is limited information on the tolerability of platinum-based treatment in elderly patients, it is suggested that otherwise healthy elderly patients with advanced urothelial cancer can tolerate a standard treatment such as GC similarly to their younger counterparts [Bamias *et al.* 2006].

Chemotherapy for unfit patients due to renal dysfunction and/or impaired PS

Carboplatin-based chemotherapy

In order to reduce renal toxicity, attempts were made to replace cisplatin in the M-VAC scheme, while trying to obtain equal RRs and survival in patients unable to receive cisplatin due to impaired PS, renal function or comorbidities precluding prehydration schemes required for cisplatin administration. These substitution schemes were studied in several phase II studies [Linardou *et al.* 2004; Nogué-Aliguer *et al.* 2003; Bellmunt *et al.* 1997, 2001; Petrioli *et al.* 1996]. However, a RR of 30–50% consistently appeared which is lower than obtained with the M-VAC regimen. Also median survival data seem inferior to those obtained with the cisplatin-based regimens.

These inferior results may in part be explained by worse characteristics, especially worse PS of patients enrolled in the carboplatin-based studies, but to date it is generally assumed that carboplatin is slightly less effective in bladder cancer, as it is felt to be less effective as compared with cisplatin in most solid tumors. Various combinations with taxanes and carboplatin have been studied [Kouno *et al.* 2007; Vaughn *et al.* 2002; Small *et al.* 2000]. Although the toxicity profiles were more favorable, the efficacy results again seemed slightly inferior to those obtained with the cisplatin-based regimens.

There has been only one randomized trial to directly compare cisplatin and carboplatin [Dogliotti *et al.* 2007]. This randomized phase II study compared gemcitabine 1250 mg/m^2 on days 1 and 8 plus carboplatin AUC 5 on day 2 with gemcitabine 1250 mg/m^2 on days 1 and 8 plus cisplatin 70 mg/m^2 on day 2. The study produced no relevant toxicity differences, which was the primary outcome measure and design of the study. The study was stopped prematurely for reasons of poor accrual after 114 chemonaive patients had been enrolled. The results on 110 patients showed similar RR, respectively 49.1 versus 40.0%, but again the study was designed and powered to test for toxicity differences and not in efficacy outcome measures. Moreover, the vast majority of the patient population had a PS of 0 or 1, and only 10% of patients had a PS of 2, and all patients had a creatinine clearance of more than 60 ml/min.

Following the establishment of GC as a new standard regimen, the European Organization for Research and Treatment of Cancer (EORTC) defined two separate strategies for further investigation; one strategy was directed at the improvement of the chemotherapy in 'fit' patients by adding a third drug to the GC regimen aiming to improve survival. The other strategy was to develop a regimen in patients with a slightly impaired PS or renal function impairment aiming for an improved toxicity/palliative benefit profile. A regimen frequently used in Europe in patients with either impaired PS or impaired renal function was the M-CAVI regimen. As GC became the standard treatment in advanced bladder cancer patients able to receive cisplatin, substituting carboplatin for cisplatin seemed logical in patients unable to receive cisplatin. Combining gemcitabine with carboplatin had already shown a favorable toxicity profile in patients with non-small-cell lung cancer [Iaffaiolli *et al.* 1999]. Under the assumption that the combination of gemcitabine–carboplatin (GCa) would be less toxic than M-CAVI, the EORTC planned to conduct a randomized phase II/III study in advanced bladder cancer patients with impaired PS and/or renal function. For this purpose, however, it was decided to conduct a formal dose-finding study of the GCa regimen in this compromised patient group first.

The dose-finding study was conducted at the Vall d'Hebron University Hospital, Barcelona and the Erasmus University Medical Center, Rotterdam [Bellmunt *et al.* 2001]. The initial dose level of gemcitabine 1000 mg/m^2 on days 1 and 8 and carboplatin AUC 5 on day 1 in a 21-day schedule was chosen based on phase II data obtained in patients with non-small-cell lung cancer [Iaffaiolli *et al.* 1999]. This regimen proved not to be feasible in the frail patient population with metastatic bladder cancer, as dose-limiting myelotoxicity was observed in four of eight patients with grade 4 thrombocytopenia and in two patients with febrile neutropenia, requiring dose reduction or delay in five patients. After reducing the carboplatin AUC to 4.5 and maintaining the gemcitabine dose at 1000 mg/m^2, hematological toxicity was less pronounced and there were no clinical sequelae. This schedule and dose was chosen for the randomized phase II/III study. This observation of unexpected severe myelotoxicity in the compromised patient population demonstrates that extrapolating a chemotherapeutic scheme based on the feasibility in another disease type and/or different patient characteristics cannot be done without taking into consideration the different patient characteristics between the two tumor-specific groups. Selecting the carboplatin AUC 4.5 as recommended dose, the EORTC conducted a randomized phase II/III trial in patients with unresectable or metastatic transitional cell carcinoma of the urinary tract [de Santis *et al.* 2009]. Patients randomized in the M-CAVI arm or in the GCa arm. The goal of the randomized phase II part of the study was to evaluate the antitumor activity of GCa compared with M-CAVI and to assess the toxicity of the two treatment arms. A RR of 45% or higher with a severe acute toxicity rate of 15% or less was considered to be sufficient to proceed with the phase III part, comparing overall survival, complete remission rates, progression-free survival of the two treatment arms and assessing quality of life. A total of 178 patients were enrolled onto the phase II part of the study. All patients were 'unfit' to receive cisplatin due to a PS of 2 and/or a creatinine clearance between 30 and 60 ml/min. The obtained overall RR was 38% on GCa and 20% on M-CAVI. Less severe acute toxicity (SAT) was seen in GCa arm (14% versus 23%, respectively): grade 3 or 4 neutropenic fever (5.7% versus 13.8%), grade 4 thrombocytopenia with active bleeding (3.4% versus 0%), grade 3 mucositis (1.1% versus 5.7%), and grade 3 or 4 renal toxicity (3.4% versus 2.3%). Treatment-related deaths were observed in two patients treated with GCa (due to thrombocytopenia-related hemorrhage and

Table 1. Results according to stratification parameters and Bajorin risk groups [de Santis *et al.* 2009].

	Only 1 cycle given		RR		SAT	
	N	%	*N*	%	*N*	%
Stratification parameters						
PS 2 or GFR <60 ml/min	7/129	5	51/129	39.5	20/129	15.5
PS 2 and GFR <60 ml/min	9/46	20	12/46	26.1	12/46	26.1
Bajorin risk factors						
0	4/68	6	32/68	47	11/68	16
1	2/58	3	21/58	39	9/58	16
2	10/49	20	10/49	20	12/49	25

GRF, glomerular filtration rate; PS, performance status; RR, response rate; SAT, severe acute toxicity.

neutropenia-related complications) versus four patients treated with M-CAVI (due to neutropenia-related complications). The important finding in this part of the study was, irrespective of the regimen, the impact on the numbers of stratification factors on both RR and SAT (Table 1). Stratified for either a PS of 2 or an impaired renal function, the RR was 39.5% which declined to 26.1% in patients with both factors present. Likewise, the number of stratification characteristics had an impact on the SAT rate, which was less frequent in patients with one characteristic as compared with patients with both characteristics present (15.5% versus 26.1%, respectively). The analysis was extended to incorporating the prognostic factors for response and survival previously published by Bajorin and colleagues, namely an impaired PS and the presence of visceral metastases [Bajorin *et al.* 1999]. This analysis also showed the impact of the number of factors present (0, 1, or 2) on both RR and SAT accordingly (47% in the zero-risk group, 39% in the one-risk group *versus* 20% in two-risk group and 16%, 16% versus 25%, respectively). Thus, both stratification schemes showed low RR and high toxicity in poor-profile patient groups (Table 1).

The authors concluded that GCa and M-CAVI produce acceptable RR and SAT rates in patients who are scheduled to receive these regimens for reasons of either an impaired renal function or PS, but that if multiple factors are present in view of poor RR and high SAT this type of chemotherapy rarely benefits these patients. In these patient subgroups, alternative treatment modalities are to be considered. One randomized phase III trial comparing M-VAC versus carboplatin and paclitaxel in previously treated patients with advanced urothelial cancer was set up as ECOG 4897. As stated earlier, few attempts are made to compare M-VAC with other chemotherapeutic schemes. However, the accrual goal of 330 patients was never met and thus conclusions could not be made from this underpowered trial.

Platinum-free-based doublets

Of interest for patients with invasive bladder cancer unable to receive cisplatin, is the development of platinum-free regimens, aiming at therapeutic efficacy while avoiding renal toxicity. Paclitaxel and gemcitabine in pretreated and chemonaive patients showed RR ranging between 40% and 60% [Calabro *et al.* 2009; Li *et al.* 2005; Meluch *et al.* 2001]. Alternative platinum-free doublets have comprised docetaxel and gemcitabine, producing a RR of 33–53% and median survival figures of 14–15 months [Dumez *et al.* 2007; Ardavanis *et al.* 2005; Gitlitz *et al.* 2003]. Other agents such as pemetrexed, epirubicin or vinorelbine combined with gemcitabine have also been evaluated in phase II trials [Dreicer *et al.* 2008; von der Maase *et al.* 2006; Türkölmez *et al.* 2003; Ricci *et al.* 2002]. However, as evidenced by the experience learned in the dose-finding study of GCa in renal function and/or PS compromised patients with bladder cancer [Bellmunt *et al.* 2001], dose levels and administration schemes of these regimens cannot be extrapolated if developed in better patient populations [Calabro *et al.* 2009]. Relative patient selection by good PS and other risk factors may confound the toxicity profile as well as antitumor efficacy and eventual survival benefit [Bajorin *et al.* 1999]. Randomized data of platinum-free-based doublets, stratified for adverse prognostic factors, are needed to determine the potential of platinum-free two or three drug regimens. Owing to scarce data in both 'fit' and 'unfit' patients treated with platinum-free regimens, no recommendations for its clinical use

Table 2. Systemic treatment options in different patient groups.

Bajorin risk groups	Stratification parameters	Systemic treatment options
0	GFR >60 ml/min	Gemcitabine-cisplatin (M-VAC)
	GFR ≥30 to ≤60 ml/min	Gemcitabine-carboplatin (M-CAVI)
	GFR < 30 ml/min	No data
1	Visceral metastases	Gemcitabine–cisplatin
	GFR ≥30 to ≤60 ml/min or PS 2	Gemcitabine–carboplatin
2		Benefit from any chemotherapy unlikely

GRF, glomerular filtration rate; M-CAVI, methotrexate + carboplatin + vinblastine; M-VAC, methotrexate + vinblastine + doxorubicin + cisplatin; PS, performance status.

can be made at this point and these regimens should be used in a trial setting.

Conclusions

In the palliative setting, recommended first-line chemotherapy in muscle-invasive bladder cancer depends on the ability of the patients to receive cisplatin. As toxicity data proved more favorable for the GC compared with M-VAC regimen, GC was accepted as a new standard treatment regimen for metastatic bladder cancer, but only in patients able to receive cisplatin [von der Maase *et al.* 2000]. Although lacking randomized studies, RR and survival of carboplatin-substitution schemes seems inferior to those obtained with the cisplatin-based regimens in patients unable to receive cisplatin. These inferior results may in part be explained by worse characteristics of patients enrolled in the carboplatin-based studies. In a meta-analysis, major response to chemotherapy differed by risk group characterized by impaired PS and/or the presence of visceral metastases [Bajorin *et al.* 1999]. The introduction of Bajorin and colleagues' risk group has led to patient selection bias in several trials. Two strategies for further investigation were defined by the EORTC; improving survival by chemotherapeutic triplets in 'fit' patients and improving toxicity profile by chemotherapy in 'unfit' patients. The study by Bellmunt and colleagues revealed that extrapolating a chemotherapeutic scheme from one patient population to another cannot be done blindly [Bellmunt *et al.* 2001]. A randomized EORTC study comparing M-CAVI and GCa in patients unable to receive cisplatin not only proved acceptable RR and SAT rates of the GCa arm, but also the large impact of impaired or renal function on RR and SAT [de Santis *et al.* 2009]. Therefore, when choosing a chemotherapeutic scheme, the impact of the prognostic factors should always be taken into account (Table 2).

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