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Paclitaxel and carboplatin in bladder cancer: recent developments

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Abstract

Paclitaxel demonstrates significant single-agent activity in advanced urothelial carcinoma. Paclitaxel/carboplatin is an active and tolerable outpatient chemotherapy treatment regimen for these patients. This regimen has been studied in several phase II trials with response rates ranging from 14 to 65%. Paclitaxel/carboplatin may be considered in patients with advanced urothelial cancer and renal insufficiency, and a recent Eastern Cooperative Oncology Group (ECOG) phase II trial investigates this regimen specifically in this patient population. Ongoing ECOG trials are comparing paclitaxel/carboplatin with M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) in both the advanced disease and adjuvant settings.

Keywords: Urothelial cancer; Bladder cancer; Paclitaxel; Carboplatin

1. Introduction

In 1999, an estimated 54 200 Americans were diagnosed with bladder cancer, resulting in 12 100 deaths [1]. Most of these patients present with superficial tumours confined to the mucosa and lamina propria of the bladder. Although these superficial bladder cancers frequently recur and may be multifocal, survival is excellent. However, the prognosis markedly worsens when the tumour invades the muscle of the bladder wall. Muscle-invasive bladder cancer may result in metastatic disease in approximately half of patients. Thus, there is a definite need for effective systemic chemotherapy for this disease.

2. Lessons from the M-VAC era

Transitional cell carcinoma of the urothelium is a chemotherapy-sensitive neoplasm. Significant antitumour activity has been demonstrated with a variety of single agents. Cisplatin-based combination regimens such as methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) have been extensively studied. In the 1980s, investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) developed M-VAC and reported objective response rates as high as 72%, including a 36% complete response rate [2]. Results of subsequent randomised trials demonstrated that M-VAC was superior to single-agent cisplatin (the Intergroup trial) and to CISCA (cyclophosphamide, doxorubicin, and cisplatin) [3,4]. Based on these results, M-VAC became standard treatment for patients with metastatic urothelial carcinoma. The most important limitations of M-VAC are toxicity and poor patient tolerability. In the Intergroup trial comparing M-VAC with single-agent cisplatin, M-VAC was associated with substantially more toxicity including mucositis, myelosuppression and treatment-related deaths than single-agent cisplatin [3].

Attempts to improve results with M-VAC have focused on intensifying the dose and/or preventing toxicity. Dose intensification of M-VAC using haematopoietic growth factors has been attempted in several studies, with generally disappointing results, largely due to excessive toxicity [5–7]. In an effort to improve the tolerability of M-VAC, investigators have incorporated haematopoietic growth factors. Gabrilove and colleagues demonstrated that the addition of granulocyte colony-stimulating factor (G-CSF) to M-VAC decreased the number of days of significant granulocytopenia, the need for antibiotics for granulocytopenic fever, and the incidence and severity of mucositis. In addition, G-CSF allowed planned chemotherapy doses to be delivered on time [8].

Despite the toxicity and narrow therapeutic index of M-VAC, enthusiasm for the regimen emerged because of its potential to cure patients with advanced urothelial cancer. However, in the Intergroup trial comparing M-VAC and single-agent cisplatin in patients with advanced urothelial cancer, the chance of long-term cancer-free survival in patients treated with M-VAC

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was only 3.7% at 6 years of follow-up. Predictors for poor outcome in this study included non-transitional histology, poor performance status, and/or bone/visceral metastases [9].

More recently, Bajorin and colleagues reported on a series of 203 patients with advanced bladder cancer treated with M-VAC. Poor prognostic factors in this study were the presence of visceral (lung, liver, or bone) metastases and a baseline Karnofsky performance status less than 80. Five-year survival amongst patients with both of these risk factors was 0% (median survival, 9.3 months), and amongst those with neither risk factor was 33% (median survival, 33 months) [10]. Clinicians may utilise the identified poor prognostic factors to help predict which patients have the potential for long-term benefit from combination chemotherapy regimens such as M-VAC. Understanding the importance of these prognostic factors may also be useful in evaluating reported trials of new chemotherapy regimens, since patient selection may significantly influence results.

In summary, M-VAC is an active but toxic regimen for advanced bladder cancer. Given the small chance for long-term survival for most patients treated with this regimen, efforts to identify new agents and combinations with improved efficacy and/or tolerability are ongoing. New agents with significant activity include the taxanes paclitaxel and docetaxel, gemcitabine, ifosfamide and the methotrexate analogues trimetrexate and piritrexim. This review will discuss the evolving role of paclitaxel in urothelial cancer, with an emphasis on the paclitaxel/carboplatin combination.

3. Paclitaxel in bladder cancer

Paclitaxel is a novel antimicrotubule agent with broad solid tumour activity. In preclinical studies, paclitaxel significantly inhibits the growth of human bladder cancer cell lines [11]. Paclitaxel is metabolised and excreted via the hepatobiliary route, which is a potential advantage for patients who may have abnormal renal function, including certain patients with advanced urothelial carcinoma. Preliminary studies have demonstrated that paclitaxel may be used in the setting of renal insufficiency [12]. Therefore, development of this agent in urothelial cancer has both a preclinical and pharmacological rationale.

Roth and colleagues of the Eastern Cooperative Oncology Group (ECOG) performed a phase II trial of single-agent paclitaxel 250 mg/m^2 administered over 24 h every three weeks with prophylactic G-CSF in patients with previously untreated advanced transitional cell carcinoma of the urothelium [13]. The median patient age was 63 years (range: 34–80); 14 patients had multiple metastatic disease sites. 11 of 26 patients demonstrated an objective response (response rate, 42%; 95% confidence interval (CI), 23–63%), with 7 complete responses. Toxicities included granulocytopenia, anaemia, mucositis and neuropathy. These results demonstrated that paclitaxel is an active single agent in urothelial cancer.

Based on this initial trial, paclitaxel-based regimens, including both doublet and triplet combinations have been developed. Despite minimal data using single-agent paclitaxel given over shorter infusion times in bladder cancer, most of these combinations have administered paclitaxel over 3 h. Paclitaxel has been combined with cisplatin, carboplatin, gemcitabine, ifosfamide, methotrexate and other agents. Paclitaxel/cisplatin-based regimens have demonstrated significant activity in advanced urothelial carcinoma.

Dreicer and colleagues reported results of an ECOG phase II trial of paclitaxel 175 mg/m^2 over 3 h plus cisplatin 75 mg/m^2 every 3 weeks in patients with advanced urothelial cancer [14]. 26 of 52 patients demonstrated an objective response (response rate, 50%; 95% CI, 36–64%). The primary toxicities were myelosuppression and neurotoxicity [14]. The median overall survival was 10.6 months. Burch and colleagues performed a phase II trial of paclitaxel 135 mg/m^2 over 3 h plus cisplatin 70 mg/m^2 administered every 3 weeks. Amongst 29 treated patients, 21 (72%) responded (95% CI, 56–90%), and the reported median survival was 13 months [15].

Bajorin and colleagues completed a phase II trial of the triplet combination paclitaxel/ifosfamide/cisplatin (ITP) in patients with advanced urothelial carcinoma. Patients received ifosfamide 1.5 g/m^2/day on days 1, 2 and 3, paclitaxel 200 mg/m^2 over 3 h on day 1 and cisplatin 70 mg/m^2 on day 1 every 4 weeks with prophylactic mesna and G-CSF. 29 patients were evaluable; 10 had locally advanced or recurrent disease, and 19 had metastatic disease. 23 of 29 patients demonstrated objective response for a response rate of 79% (95% CI, 60–92%), including 6 complete responses. The median overall survival was 18.3 months. The significant toxicities were haematological, nephrotoxicity and neuropathy [16]. An update of the ITP experience was recently reported including results of an every-3-week administration schedule [17].

4. Carboplatin in bladder cancer

Many patients with advanced urothelial tract cancer cannot receive cisplatin-based regimens. Urothelial carcinoma frequently occurs in older individuals, some of whom have a poor performance status rendering regimens such as M-VAC potentially dangerous. In addition, the presence of age- and/or disease-related renal dysfunction can make cisplatin-based regimens problematic and sometimes unfeasible. Although cisplatin has traditionally been considered the preferred platinum

analogue in urothelial cancer, pooled results of phase II studies involving 274 advanced urothelial carcinoma patients who received single-agent carboplatin showed a 14% response rate [18].

The lack of nephrotoxicity and the ability to calculate carboplatin dose based on glomerular filtration rate using the Calvert formula [19] are potentially important advantages of this agent, especially amongst patients who may have age- and disease-related alterations in renal function. Results of studies of carboplatin-based combination regimens have been reported previously. In one such trial, Small and colleagues treated 23 advanced transitional cell carcinoma patients with a regimen including methotrexate, vinblastine, mitoxantrone and carboplatin (M-VNCa) [20]. The median patient age was 70 years (range: 52–83 years) and median creatinine clearance was 0.83 ml/s (range: 0.50–1.77 ml/s). 13 of 23 patients responded, for an overall response rate of 56.5% (95% CI, 34.5–76.8%) and the median overall survival was 10 months.

To date, prospective randomised phase III trials comparing regimens in which the only variable is the inclusion of carboplatin versus cisplatin have not been performed. A randomised phase II study in which 57 patients received M-VEC (methotrexate, vinblastine, epirubicin, cisplatin) or M-VECa (methotrexate, vinblastine, epirubicin, carboplatin) demonstrated response rates of 71% and 41%, respectively ($P = 0.04$). M-VEC was associated with more significant gastrointestinal tract toxicity, nephrotoxicity and neurotoxicity. The authors suggested comparing the two regimens in a larger randomised, phase III trial [21]. In a small randomised trial comparing M-CAVI (methotrexate, carboplatin and vinblastine) with M-VAC, response rates amongst 47 assessable patients were 39% and 52%, respectively ($P = $ NS). M-VAC was associated with more gastrointestinal tract toxicity, stomatitis, alopecia and grade 4 granulocytopenia. Median disease-related survival was 16 months in the M-VAC arm versus 9 months in the M-CAVI arm ($P = 0.03$) [22]. However, the choice of platinum analogue was not the only variable in this trial, because M-CAVI also did not include doxorubicin. Thus, one cannot assume that carboplatin has efficacy equivalent to that of cisplatin, either as a single agent or in combination, given the lack of direct comparative data. Moreover, no conclusive data are available demonstrating the superiority of cisplatin.

5. Phase I and II trials of paclitaxel/carboplatin in bladder cancer

In an effort to develop an active and tolerable outpatient chemotherapy regimen that can be administered to patients of advanced age and with abnormal renal function, paclitaxel/carboplatin regimens have been developed for advanced urothelial cancer. Several trials of the paclitaxel/carboplatin regimen have been completed and are reviewed in Table 1.

We performed a phase I/II trial of paclitaxel/carboplatin in patients with advanced urothelial carcinoma at the University of Pennsylvania Cancer Center [23]. Paclitaxel doses included 150, 175, 200 or 225 mg/m^2 over 3 h followed by carboplatin at an AUC of 6 every 3 weeks. During the phase I component of the trial, 16 patients were treated. The maximum tolerated dose of the regimen was not defined. Subsequently, in the phase II portion of the trial, 17 additional patients received paclitaxel 225 mg/m^2 over 3 h followed by carboplatin (AUC = 6). The median patient age was 70 years (range: 47–82) and median estimated creatinine clearance was 0.87 ml/s. 18 patients had locally advanced or nodal/soft tissue only disease. A total of 156 treatment cycles were administered; the median number of cycles per patient was 5 (range: 1–8).

Significant granulocytopenia was common at all dose levels, but significant thrombocytopenia was not. Granulocytopenic sepsis occurred in 1 patient and uncomplicated granulocytopenic fever in 4 patients during phase I accrual. During the phase II portion of the study G-CSF was administered as a prophylaxis to patients who had previously received adjuvant chemotherapy or pelvic radiation therapy; no episodes of granulocytopenic fever were observed in these 8 patients whilst two additional episodes of granulocytopenic fever occurred amongst the 9 patients who did not receive G-CSF. Sensorimotor neuropathy was the principal non-haematological toxicity. Grade 3 neuropathy developed in 5 patients. No treatment-related deaths occurred during the study. Objective responses were demonstrated at all dose levels. Fifty-two per cent of all patients treated in the phase I/II study demonstrated objective responses including 10 of 18 patients with soft tissue/nodal disease and 4 of 10 with liver metastases. At the phase II dose level, 10 of 20 patients responded (50%; 95% CI, 28–72%). Median overall survival was 8.5 months for all treated patients.

Table 1
Paclitaxel/carboplatin trials in advanced bladder cancer

Author [Ref.]	No. evaluable pts	RR (%)	Median overall survival (months)
Vaughn [23]	33	52	8.5
Redman [24]	35	51	9.5
Zielinski [25]	20	65	NR
Droz [26]	38	37	NR
Bauer [27]	23	43.5	NR
Small (SWOG) [28]	29	14	9.0

SWOG, Southwest Oncology Group; RR, response rate; NR, not reported.

In a subsequent phase II trial by Redman and colleagues, 36 patients with previously untreated advanced urothelial carcinoma received paclitaxel 200 mg/m^2 over 3 h plus carboplatin at an AUC of 5 every 3 weeks [24]. The median patient age was 66 years (range: 38–82 years). 23 patients had lymph node only metastases. A total of 184 treatment cycles were administered, with a median of six cycles per patient. 18 of 35 evaluable patients demonstrated an objective response (51%; 95% CI, 35–68%), including 7 complete responses. The median overall survival was 9.5 months, with an estimated 1-year survival of 38%. Toxicities included granulocytopenia, myalgia/arthralgia and neuropathy.

Zielinski and colleagues treated 20 patients with paclitaxel 175 mg/m^2 over 3 h plus carboplatin (AUC = 5) every three weeks. 9 patients were older than 70 years of age; 13 patients had nodal metastases and only 3 had liver metastases. A response rate of 65% (13 of 20 patients) was reported, with a complete response rate of 40%. Leucopenia and neuropathy were the most significant toxicities. After a mean follow-up of 11.4±4.8 months, the median survival had not been reached [25].

Droz and colleagues administered paclitaxel 225 mg/m^2 over 3 h plus carboplatin at an AUC of 6 every 3 weeks to 47 advanced urothelial carcinoma patients. An objective response rate of 37% was reported (14 of 38 evaluable patients responded) [26]. Bauer and colleagues reported 10 responses (43.5%) amongst 23 evaluable patients who received paclitaxel 175 mg/m^2 over 3 h plus carboplatin dosed to an AUC of 5 every 3 weeks [27].

The Southwest Oncology Group (SWOG) initiated a phase II trial of the paclitaxel/carboplatin regimen in patients with advanced urothelial carcinoma. This cooperative trial included two patient cohorts: previously untreated patients and those who had previously received cisplatin. A preliminary report by Small and colleagues [28] regarding the previously untreated patients showed responses in only (4 of 29) 14% (95% CI, 4–32%) of patients who received paclitaxel 200 mg/m^2 over 3 h plus carboplatin (AUC = 5) every three weeks. The median progression-free survival was 4 months, and median overall survival was 9 months, similar to survival noted in other paclitaxel/carboplatin trials. Significant toxicities included grade 4 granulocytopenia (39%), grade 3 thrombocytopenia (11%) and grade 3 sensory neuropathy (18%).

The authors have offered a potential explanation regarding the significantly lower response proportion observed in this SWOG trial compared with that in previous studies: the SWOG patient population included only 24% with node-only disease, and 76% with extranodal metastatic disease. This differed from the relative proportion of nodal versus visceral metastatic disease reported in some of the other trials in which a greater proportion of patients had nodal disease. As discussed previously, patients with visceral metastatic disease derive less benefit from chemotherapy than those with nodal or soft tissue disease sites [9, 10]. Thus, the broad range of response rates in the paclitaxel/carboplatin trials may relate partly to the specific characteristics of the patients in each trial.

6. Eastern Cooperative Oncology Group (ECOG) trials of paclitaxel/carboplatin in bladder cancer

Further evaluation of the paclitaxel/carboplatin regimen in the cooperative group setting is ongoing by ECOG (Table 2). E2896 is a phase II trial of paclitaxel plus carboplatin in advanced urothelial cancer patients who have renal insufficiency (serum creatinine concentration of 142–354 μmol/l). Such patients are often excluded from clinical trials. This trial reached the accrual goal of 42 patients in November 1999.

E4897 is a recently activated phase III trial in which previously untreated patients with advanced urothelial cancer are randomly assigned to receive paclitaxel plus carboplatin versus the 'gold standard' M-VAC regimen. In addition to the primary endpoint of survival and the secondary endpoints of response rate, response duration and toxicity, this trial includes a comparative assessment of quality of life using the FACT-BL measurement scale. The accrual goal is 330 patients. E1897 is a randomised phase III trial of adjuvant therapy with four cycles of paclitaxel/carboplatin versus four cycles of M-VAC for patients with pathologically staged pT3b–pT4 and/or node-positive disease postcystectomy. This trial was activated in March 1999 and has an accrual goal of 490 patients. Thus, these important trials will help to define further the role of paclitaxel/carboplatin in patients with bladder cancer.

Table 2
ECOG trials of paclitaxel/carboplatin in bladder cancer

Trial	Phase	Patient eligibility	Treatment	Accrual goal
E2896	II	Advanced disease, renal insufficiency	P/C	42
E4897	III	Advanced disease	P/C versus M-VAC	330
E1897	III	pT4 and/or node positive, postcystectomy	P/C versus M-VAC	490

ECOG, Eastern Cooperative Oncology Group; P/C, paclitaxel/carboplatin; M-VAC, methotrexate/vinblastine/doxorubicin/cisplatin.

7. Paclitaxel/carboplatin-based triplets

Based on the activity and tolerability of the paclitaxel/carboplatin regimen, some investigators are incorporating an additional drug to form triplet combinations. One such drug, gemcitabine, has significant single-agent activity in urothelial cancer [29]. Investigators from Wayne State University and the University of Michigan have built upon their previous work by incorporating gemcitabine 800 mg/m^2 on days 1 and 8 with a combination of paclitaxel 200 mg/m^2 over 3 h and carboplatin (AUC = 5) on day 1 every 3 weeks [30]. In a preliminary report of 19 evaluable patients, 11 (58%) demonstrated objective responses. Edelman and colleagues performed a phase I trial of paclitaxel 200 mg/m^2 over 3 h, carboplatin dosed to an AUC of 6, and escalated doses of methotrexate [31]. G-CSF and calcium leucovorin were administered to prevent toxicity. Initial data on 19 patients showed that a methotrexate dose level of 50 mg/m^2 had been administered without reaching dose-limiting toxicity. The overall response rate was 50% (95% CI, 25–75%). Thus, investigation of paclitaxel/carboplatin-based triplets is ongoing, and whether adding agents to the paclitaxel/carboplatin regimen will significantly increase efficacy remains to be determined.

8. Conclusion

Use of new chemotherapy agents such as the taxane paclitaxel has expanded the treatment options for patients with advanced urothelial carcinoma. Studies have demonstrated that paclitaxel/carboplatin is an active and tolerable outpatient treatment regimen for this disease. Randomised ECOG trials comparing paclitaxel/carboplatin to M-VAC in both the advanced disease and the adjuvant settings will help to define the role of this combination in patients with bladder cancer. In addition, an ECOG trial of paclitaxel/carboplatin in advanced urothelial cancer patients with renal insufficiency may help to define treatment options for this patient subset which is usually excluded from clinical trials. Patients should be offered the opportunity to participate in these and other well-designed clinical trials to advance our understanding of the role of chemotherapy in invasive bladder cancer.

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