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Gemcitabine/paclitaxel-based three-drug regimens in advanced urothelial cancer

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Abstract

Transitional cell carcinoma (TCC) of the urothelium is a highly chemosensitive tumour. Combination chemotherapy can provide both palliation and a modest survival advantage in patients with advanced disease. At present, the combination of cisplatin, methotrexate, doxorubicin and vinblastine (M-VAC) is the most widely used for advanced TCC with an overall response rate of 40–72% in phase II, and 35–45% in phase III studies, and a median survival of approximately 12 months. These modest results and the unsuccessful attempts to increase efficacy with dose intensive M-VAC schedules have prompted the identification of new active agents in TCC, such as the taxanes and gemcitabine. The overall response rates for two-drug regimens of cisplatin–paclitaxel, carboplatin–paclitaxel and cisplatin–gemcitabine range from 63 to 72%, 14 to 65% and 42 to 66%, respectively. The overall response rates for platinum–paclitaxel–gemcitabine three-drug regimens range from 58 to 80%. The potential clinical benefit of these new three-drug combinations in the treatment of TCC needs to be tested in future phase III studies.

Keywords: Transitional cell carcinoma; Advanced bladder cancer; M-VAC; CISCA; Cisplatin; Carboplatin; Gemcitabine; Paclitaxel; Two-drug regimen chemotherapy; Three-drug regimen chemotherapy

1. Introduction

Urothelial tumours are chemosensitive, and objective tumour regression has been documented following administration of various agents with different mechanisms of action. Although a substantial number of agents are active against this disease, the percentage of patients who respond to single agents is modest. Most patients experience a partial response (PR) of short (3–4 months) duration. The number of patients who achieve a lasting complete response (CR) is anecdotal [1,2].

Until now, cisplatin (response rate (RR), 30%; 95% confidence interval (CI) 25–35%) and methotrexate (RR, 29%; 95% CI, 23–35%) have been described as the most active single agents, with response rates of approximately 30% [3]. Although recent data on cisplatin therapy in phase II and III trials have not been as encouraging [4–9], in clinical practice this drug remains the mainstay of current combination chemotherapy to treat advanced bladder cancer, and it is a component of most commonly used regimens.

Carboplatin, doxorubicin, vinblastine, cyclophosphamide, 5-fluorouracil and several other agents have also demonstrated activity against advanced urothelial cancer [3]. The aim for patients with metastatic disease is palliation, but by combining these classic agents into three- or four-drug combinations, overall outcomes have improved to the point where cure is now possible in selected patients with advanced disease.

Recent studies have identified new agents that have single-agent activity against urothelial carcinoma, including gallium nitrate, with a response rate (RR) of 17% (95% CI, 2–33%) [10], ifosfamide (RR, 21% 95% CI, 10–32%) [11], trimetrexate (RR, 17% 95% CI, 7–30%) [12], gemcitabine (RR, 24–28% 95% CI, 8–37%, 15–45%) [13–15] and paclitaxel (RR, 42% 95% CI, 23–63%) [16]. Amongst these new agents, paclitaxel and

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gemcitabine have shown highly promising single-agent activity against this disease.

Paclitaxel, a member of the novel taxane family, stabilises microtubules and promotes their assembly, resulting in M phase cell cycle arrest [17]. In preclinical studies, paclitaxel has proved to be an active anticancer agent against a broad range of cancer cell lines, including human bladder cancer cells [18,19]. In patients with advanced urothelial carcinoma, first-line chemotherapy with paclitaxel, given at a dose of 250 mg/m^2 by 24-h continuous infusion every 3 weeks [16], resulted in a response rate of 42%, including 27% CRs. Because the kidney excretes paclitaxel only minimally, this agent can be evaluated appropriately in patients with urothelial neoplasms since such patients often have impaired renal function. Early clinical experience has confirmed the utility of this agent in patients with compromised renal function [20].

Gemcitabine, a novel nucleoside analogue, has also demonstrated promising single-agent activity against urothelial cancer. This drug was initially evaluated in an Italian phase I study conducted in 15 patients with metastatic bladder cancer [21]. The doses ranged from 875 to 1370 mg/m^2. One CR and 2 PRs occurred in 14 previously treated patients, and 1 PR was observed in a chemotherapy-naive patient. The overall response rate was 27% (95% CI, 4.3–49.1%). In a subsequent phase II trial in previously treated patients, a response rate of 28% was recorded [13]. Two recent trials that evaluated gemcitabine in previously untreated patients confirmed the high activity of this agent. Stadler and colleagues [14] treated 40 patients with gemcitabine 1200 mg/m^2 three times weekly, repeated every 28 days, and reported an overall response rate of 28% (95% CI, 15–45%). Three CRs occurred in patients with liver metastases. Moore and colleagues [15] reported an overall response rate of 24.3% (95% CI, 12–41%) in 37 assessable patients.

2. Classic combination chemotherapy regimens

2.1. The right regimen for the right patient

The choice of a particular chemotherapy programme depends on patient- and tumour-related factors that can affect the tolerability of the therapy and its outcome. Careful consideration must be given to pretreatment patient-related factors (presence of long ileal conduits, previous radiation therapy, underlying cardiac dysfunction and renal dysfunction) that can influence the individual ability to tolerate the planned chemotherapy programme. Several pretreatment disease-related prognostic factors that can also affect outcome have been identified. The positive prognostic factors include high initial performance status, nodal versus metastatic disease, absence of bone or liver metastasis and no history of weight loss [22]. A recent multivariate analysis that examined prognostic factors for survival determined that the presence of baseline performance status below 80% or visceral metastases (lung, liver or bone) or both had a profound impact on survival [23].

2.2. 'Standard' cisplatin-containing combination regimens

Cisplatin-based combination chemotherapy regimens, such as M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) and CMV (cisplatin, methotrexate, vinblastine) are standard treatment for patients with metastatic carcinoma of the urothelium [24–26]. The overall response rates (CR plus PR) for standard cisplatin-based combination regimens range from 40 to 72%, with CRs occurring in 15–25% [27–30]. None the less, disease ultimately relapses in almost all responding patients, with a median survival of approximately 12 months [31]. The M-VAC combination continues to be the most common regimen for patients with advanced urothelial cancer.

In randomised trials, M-VAC produced a modest, albeit significant, survival benefit when compared with cisplatin as a single agent [8], with CAP or CISCA (cisplatin, cyclophosphamide, doxorubicin) [32], and with carboplatin-based regimens [33]. The CMV regimen, used widely in Europe, proved to be superior to methotrexate and vinblastine in a randomised trial [34]. Long-term follow-up of M-VAC-treated patients in the Intergroup trial showed that only 3.7% were continuously free of urothelial cancer at 6 years [35]. This dismal long-term outcome with currently available regimens has led to the search for new treatment approaches.

2.3. 'Standard' carboplatin-containing combination regimens

Many patients with bladder cancer have a poor performance status and abnormal renal or cardiovascular function. These patients require particular care when combination chemotherapy programmes are being designed, with emphasis placed on the patients' quality of life. Conventional doses of carboplatin cause little, if any, renal toxicity, no neurotoxicity or ototoxicity and less emesis than cisplatin [36]. Carboplatin has been shown to be effective against transitional cell bladder cancer. The total response rate in 138 assessable patients from seven phase II trials that used a dose of 400 mg/m^2 was 16% (95% CI, 13–19%), with CRs occurring in 4% and PRs in 12% [37]. There were no long-lasting responses.

The presence of impaired renal function, older age, poor performance status or underlying cardiac dys-

function in the so-called unfit patient population has led to several modifications of the standard programs. Epirubicin (M-VEC) and mitoxantrone have substituted doxorubicin in an attempt to reduce cardiac toxicity [38], and cisplatin has been replaced by carboplatin (M-CAVI) in patients with compromised renal function [37,39–42]. The overall response rate in these carboplatin-substituted studies is approximately 50% (range: 39–63%) and the median reported overall survival is approximately 9 months [33,37,39–42]. A formal comparison of carboplatin-containing regimens and M-VAC has been undertaken in patients who have adequate renal function in two randomised trials [33,43].

Bellmunt and colleagues reported a randomised phase III trial that compared M-VAC with a three-drug regimen of methotrexate, carboplatin, and vinblastine (M-CAVI) [33]. In addition to substituting carboplatin for cisplatin, we dropped doxorubicin in order to compensate for the added myelotoxicity of carboplatin. 47 patients were evaluated. The overall response rate was higher in patients treated with M-VAC (52 versus 39%), but the difference was not statistically significant. Although the M-VAC regimen was more toxic, it produced a significantly longer median disease-related survival (16 months versus 9 months).

Another randomised phase II study, reported by Petrioli and colleagues, compared a regimen of methotrexate, vinblastine, epirubicin and cisplatin (M-VEC) with a carboplatin-substituted version of this regimen (M-VECa) in 57 patients with recurrent or metastatic bladder cancer [43]. The overall rates of response (71 versus 41%) and CR (25 versus 11%) significantly favoured M-VEC. Even though the number of patients was limited, the results of these two trials seem to suggest that carboplatin cannot routinely replace cisplatin for reasons of toxicity without compromising therapeutic outcome.

Carboplatin-based chemotherapy like M-CAVI or M-VECa may only benefit patients whose medical condition precludes the use of cisplatin [37]. Future studies are needed to determine whether the activity of carboplatin is lower than or equivalent to that of cisplatin in advanced bladder cancer.

3. New two-drug regimens

Because of the high antitumour activity reported with various new agents, particularly the taxanes and gemcitabine, a great deal of effort has been aimed at integrating these drugs into combination regimens, mainly with cisplatin and, in some instances, with carboplatin (especially in paclitaxel-containing regimens). These newly designed two- and three-drug combination therapies are being evaluated in patients with advanced disease.

3.1. Cisplatin–taxanes

Several reports have described the antitumour activity of the taxanes in combination with cisplatin. Regimens of combined paclitaxel and cisplatin, usually given every three weeks, were evaluated in three studies [44–46] involving a total of 67 patients, with overall response rates ranging from 63 to 72%. A regimen that used docetaxel combined with cisplatin every 3 weeks resulted in a response rate of 60% in one study involving 25 patients [47]. In the aforementioned studies [46,47], median survival was reported to be 13 and 13.6 months with the cisplatin–taxane two-drug regimen (Table 1).

3.2. Carboplatin–paclitaxel

Carboplatin has the advantages of easier administration and individualised dosing. Although carboplatin has similar mechanism of action and preclinical spectrum of activity as cisplatin, it does not have the same clinical efficacy in all platinum-sensitive tumours. Since Langer and colleagues reported their study [48], the paclitaxel–carboplatin combination has become popular for treating non-small cell lung cancer because it appears to be active and patient-friendly, with modest haematological and non-haematological toxicity. The use of this combination in bladder cancer was justified because of the high level of activity of paclitaxel in urothelial cancers and because carboplatin dosing based on Calvert formula results in predictable haematological toxicity in patients with age- and disease-related alterations in renal function.

Table 1
Taxanes–cisplatin: overview of phase II studies

Author [Ref.]	Paclitaxel/docetaxel (mg/m^2)	Cisplatin (mg/m^2)	No. of evaluable patients	Prior chemotherapy	ORR (95% CI)
Murphy [44]	Paclitaxel 170 24 h	75	18	No	72% 4 CR, 9 PR
Burch [46]	Paclitaxel 135	70	29	No	72% (56–90%) 10 CR, 9 PR MS 13 mo.
Dreicer (ECOG) [45]	Paclitaxel 225	75	20	No	63% (42–81%) 1 CR, 11 PR
Sengelov [47]	Docetaxel 75	75	25	No	60% (39–79%) 7 CR, 8 PR MS 13.6 mo.

ORR, overall response rate; ECOG, Eastern Cooperative Oncology Group; MS, median survival; mo., months; CI, confidence interval; CR, complete response; PR, partial response.

Table 2
Paclitaxel–carboplatin: overview of phase II studies

Author [Ref.]	Paclitaxel (mg/m^2)	Carboplatin (AUC)	No. of evaluable patients	Prior chemotherapy	ORR (95% CI)
Zielinski [51]	175	5	20	No	65% 8 CR, 5 PR MRD 8.5 mo.
Vaughn [49]	150–225 (phase I–II)	6 (Cr range, 62–239 μmol/l)	16 + 17 (phase I + II)	No (6 adjuvant > 6 mo.)	52% (28–72%) MS 8.5 mo.
Redman [50]	200	5 Cr < 177 μmol/l	35	No (2 adjuvant > 6 mo.)	51% (35–68%) 7 CR, 11 PR MS 9.5 mo.
Droz [52]	225	6	38	No (10 adjuvant > 12 mo.)	37% 2 CR, 12 PR
Bauer [53]	175	5	23	No	43.5% (23–65%) 3 CR, 7 PR
Small (SWOG) [54]	200	5 Cr clearance > 0.5 ml/s	29	No (2 adjuvant ⩾6 mo.)	14% (4–32%) MS 9 mo.

AUC, area under the concentration–time curve; ORR, overall response rate; MRD, median duration of response; MS, median survival; SWOG, Southwest Oncology Group; mo., months; CI, confidence interval; CR, complete response; PR, partial response, Cr, creatinine.

The paclitaxel–carboplatin regimen has been evaluated rather extensively in bladder cancer (Table 2). Three studies involving a total of 88 patients have been published [49–51]. In these studies, the inclusion criteria permitted some degree of impaired renal function, usually represented by serum creatinine concentrations up to 177 μmol/l; levels as high as 239 μmol/l were permitted in one study [49]. The mean overall response rate in all these studies was 54%, with an overall median survival of 8.5 months. Reports of similar activity have been described in abstract form by Droz and colleagues [52] in 38 patients (RR, 37%) and by Bauer and colleagues [53] in 23 patients (RR, 44%). A recently presented Southwest Oncology Group phase II trial [54] involving 29 patients reported a response rate of only 14% (95% CI, 4–32%). The lower than expected overall response might be explained by the high percentage of study patients with extranodal metastases. In terms of response, these results are substantially poorer than those reported in previous trials. Nevertheless, the 9-month median survival time was similar to that reported in previous studies and also similar to that achieved with standard carboplatin-containing regimens discussed previously.

3.3. Cisplatin–gemcitabine

The two-drug regimen of gemcitabine and cisplatin has been evaluated in patients with bladder cancer in at least three studies that used different administration schedules [55–57] (Table 3). Gemcitabine was administered on days 1, 8 and 15 every 4 weeks and cisplatin once every four weeks either on day 1 or 2, or weekly on days 1, 8 and 15. In all, 113 patients were treated with the combination, with an overall response rate ranging from 42 to 66% and CRs ranging from 18 to 28%. The median survival was consistently reported to be approximately 13 months in two of the studies [55,57].

Because of the high response rates in these phase II trials, randomised phase III trials comparing M-VAC with cisplatin–gemcitabine and with carboplatin–paclitaxel are ongoing.

4. Gemcitabine–paclitaxel-based three-drug regimens

Given the noteworthy activity of two-drug combinations with gemcitabine or paclitaxel (cisplatin–gemcitabine, cisplatin–paclitaxel and carboplatin–paclitaxel), the partially non-overlapping toxicity of these agents and their different mechanisms of action, combinations

Table 3
Gemcitabine–cisplatin: overview of phase II studies

Author [Ref.]	Gemcitabine (mg/m^2)	Cisplatin (mg/m^2)	No. of evaluable patients	Prior chemotherapy	ORR (95% CI)
von der Maase [55]	1000 Days 1,8,15 q28d	35 Days 1,8,15	38	No	42% (26–59%) 7 CR (18%) 9 PR MS 12.5 mo.
Kaufman [56]	1000 Days 1,8,15 q28d	100/75[a] Day 1	47		66% (51–79%) 13 CR (28%) 18 PR
Moore [57]	1000 Days 1,8,15 q28d	70 Day 2	28	No (4 adjuvant > 12 mo.)	57% (37–76%) 6 CR (21%) 10 PR MS 13.2 mo.

ORR, overall response rate; MS, median survival; mo., months; CI, confidence interval; PR, partial response; CR, complete response.
[a] The first 13 patients received 100 mg/m^2 and 34 patients received 75 mg/m^2.

of these compounds in three-drug regimens is the next logical step.

4.1. Paclitaxel–cisplatin–gemcitabine

The Spanish Oncology Genitourinary Group (SOGUG) recently reported the preliminary results of a phase I–II trial [58] in 61 patients treated with a combination of paclitaxel, cisplatin and gemcitabine (TCG). The rationale for the TCG combination was based on the high single-agent activities of these drugs, the low haematological toxicity of paclitaxel given weekly and existing data that demonstrated the feasibility of combined administration of gemcitabine plus paclitaxel. The sequence of administration to avert possible drug interactions was also considered [59,60] and the type of schedule [61]. A phase I–II trial was started in March 1997 to determine the maximum tolerated dose, the dose-limiting toxicities and the efficacy of this combination in patients with advanced carcinoma of the urothelium in an attempt to develop a practicable regimen with high activity.

Patients with measurable, locally advanced or metastatic transitional cell carcinoma of the urothelium with a creatinine clearance $\geqslant 0.92$ ml/s and an Eastern Cooperative Oncology Group performance status $\leqslant 2$ were candidates for the study. Four dose levels were defined to determine the optimal doses of paclitaxel, given in a 1-h infusion, and gemcitabine, both given on days 1 and 8, combined with a fixed dose of cisplatin (70 mg/m^2) on day 1 of a 21-day cycle. The respective doses of gemcitabine and paclitaxel given on days 1 and 8 at each dose level were: level 1, 800 and 60 mg/m^2; level 2, 1000 and 60; level 3, 1000 and 80; and level 4, 1000 and 90. During the phase I study, 15 patients were accrued. Once the dose for the phase II study was determined, 46 additional patients were enrolled, making a total of 49 patients treated at dose level 3 as of March 1999.

During phase I accrual, dose-limiting toxicity, which consisted of early onset (after the first cycle) grade 2 asthenia — in 2 of 6 patients — and grade 3 asthenia — in 1 of 6 patients — was observed at dose level 4. Thus, the recommended doses for phase II evaluation were paclitaxel 80 mg/m^2 and gemcitabine 1000 mg/m^2 (dose level 3). A total of 177 cycles were administered at this dose level, with a median of four cycles (range: 1–6 per patient). The principal non-haematological toxicity was grade 2 asthenia in 19 of the 43 patients (44%) assessable for toxicity, with early onset (after the first cycle) in 5 patients. Grade 3 asthenia was present in 4 patients (9%). Other grade 3 or 4 non-haematological toxicities consisted of nausea and vomiting, mucositis, diarrhoea, neurotoxicity, ototoxicity and infection. 27 patients (63%) developed grade 3–4 neutropenia, 11 patients (26%) grade 3–4 thrombocytopenia and 13 (30%) grade 3–4 anaemia. Febrile neutropenia occurred in 8 patients (19%), 1 of whom died of neutropenic sepsis.

Objective responses were demonstrated at all dose levels. At the phase II dose level (40 assessable, 7 too early, 1 ineligible, 1 early death) 32 patients had objective responses. 10 were CRs (25%) and 22 PRs (55%), for an overall response rate of 80% (95% CI, 65–97%).

Some points from this study merit comment. Firstly, we demonstrated that therapeutic doses of the two drugs can be reached in combination, and we confirmed the clinical appropriateness of this treatment sequence. Secondly, the regimen was administered to most patients on an outpatient basis and demonstrated a good toxicity profile, with the predominant toxicities being grade 2 asthenia and myelosuppression. Despite the frequency and severity of asthenia, none of the patients required withdrawal of treatment. Neutropenia was common, but had no clinical relevance in the majority of cases being detected during weekly haematological monitoring. As mentioned, 8 patients developed neutropenic fever, which resulted in neutropenic sepsis and death in 1 patient. Antitumour responses were seen at all dose levels and at all sites of disease, even in patients with visceral metastases.

The results of this trial confirm the high response rate observed using these new drugs to treat advanced urothelial carcinoma. Nevertheless, it must be noted that our study population presented some favourable prognostic factors that could have biased the results. It is recognised that chemotherapy is more effective for patients with advanced nodal disease than for those with visceral metastases and that presence of baseline Karnofsky performance status below 80 or visceral metastases (lung, liver or bone) or both has a profound impact on survival [23]. 44 of 61 (72%) of the registered patients exhibited an Eastern Cooperative Oncology Group performance status less than 2 and approximately two-thirds of the patients had non-visceral disease sites.

Histology is another factor known to affect outcome in urothelial carcinomas. The regimens in common use have limited efficacy against non-transitional cell histologies like adenocarcinomas and squamous cell tumours. Because these drugs have been shown to be active in the non-transitional cell histologies of other malignancies such as non-small cell lung cancer [62,63] the role of the new combination regimens in mixed and pure non-transitional cell histologies needs to be assessed. At our institution, 1 patient with a pelvic recurrence of a pure squamous cell carcinoma after radical cystectomy was treated with the three-drug regimen out of protocol. He experienced a pathologically verified CR.

Although survival data for this three-drug regimen are still immature and long-term follow-up is needed, the high level of activity and good tolerability of the regimen holds promise for the treatment of advanced bladder cancer.

4.2. Paclitaxel–carboplatin–gemcitabine

Carboplatin and paclitaxel have been combined to treat bladder cancer, with good results in terms of tolerability and efficacy [49–51]. Based on their previous experience [50] with this combination and the significant single-agent activity of gemcitabine, investigators at the Barbara Ann Karmanos Cancer Institute and at the University of Michigan Comprehensive Cancer Center conducted a phase II trial using carboplatin, paclitaxel and gemcitabine in patients with advanced urothelial malignancy [64]. Patients with advanced urothelial cancer of any histology and no previous chemotherapy (previous adjuvant–neoadjuvant chemotherapy more than 6 months before was permitted) and a Southwest Oncology Group performance status of $\leqslant 2$ were considered eligible. Inclusion required serum creatinine $\leqslant 177$ μmol/l and adequate bone marrow and hepatic function. Treatment consisted of paclitaxel 200 mg/m^2 as a 3-h infusion followed by carboplatin (area under the concentration–time curve (AUC) dosing of 5 with Calvert formula) as a 15-min infusion on day 1, and gemcitabine at 800 mg/m^2 on days 1 and 8, repeated every 21 days.

23 patients (18 males, 5 females) with a median age of 65 years (range: 33–82 years) and a median creatinine clearance of 1.32 ml/s (range: 0.38–2.75 ml/s) were enrolled between October 1997 and September 1998. One patient's disease was staged as T4 Nx M0, 6 patients had lymph node only metastases and 16 had visceral metastases (liver, bone, lung and ascites). A total of 92 cycles were administered (range: 1–8 per patient). Grade 4 neutropenia appeared in 12 patients (52%) and grade 3 and 4 thrombocytopenia in 12 patients (52%). 4 patients (17%) experienced febrile neutropenia and 14 patients (61%) required dose reductions. Of 19 response-assessable patients, 11 (58%) demonstrated a major response (5 CRs and 6 PRs). Responses were seen in the lymph nodes and in visceral and bony metastatic sites. The preliminary results of this trial indicate that combination chemotherapy with carboplatin, paclitaxel and gemcitabine is active and well tolerated in patients with advanced urothelial cancer. The major toxicities, neutropenia and thrombocytopenia, resolved when doses were modified.

Quite interestingly, the preliminary response rate was especially promising in a patient population in which the majority had visceral metastases. In light of these results, larger trials are warranted to validate the efficacy and toxicity of this regimen and to evaluate it in relation to standard therapy and other taxane–gemcitabine regimens, such as the TCG three-drug regimen.

Although carboplatin has replaced cisplatin in chemotherapy regimens for several diseases, such as ovarian carcinoma, it is still unclear whether its efficacy is equivalent or inferior to that of cisplatin across all disease types and especially in bladder cancer. Even with the results of the two small randomised trials discussed previously [37,43], the fact that this drug is currently being combined with new and highly active drugs that could overcome its reported inferior activity needs to be considered. Further studies are needed to determine whether carboplatin is as active as cisplatin in advanced bladder cancer, particularly when used in combination with new agents.

5. Other platinum-based three-drug regimens

Before the availability of gemcitabine, Memorial Sloan-Kettering Cancer Center investigators assessed the addition of ifosfamide to the two-drug regimen cisplatin–paclitaxel in 30 patients with metastatic or unresectable transitional cell carcinoma [65]. 23 of 29 assessable patients, i.e. 79% (95% CI, 60–92%), demonstrated a major response, with 6 CRs. Response duration ranged from 5 to 24+ months. Febrile neutropenia was observed in 17% of patients and 4% of cycles. The median survival was 18.3 months (95% CI, 12.2–29.2 months).

Other authors have investigated the incorporation of paclitaxel into the classic combination of cisplatin or carboplatin–methotrexate. The combination methotrexate–paclitaxel–cisplatin (TMP) was evaluated in a pilot study in 1995 by Tu and colleagues at the M.D. Anderson Cancer Center [66]. They assessed the activity of the TMP combination in a total of 25 consecutive patients with cisplatin refractory metastatic urothelial malignancy. Of these 25 patients, 10 (40%), including 3 of 7 with liver metastases, had a PR. Duration of response ranged from 2+ to 9+ months.

A phase I–II trial of paclitaxel, carboplatin and escalating doses of methotrexate with granulocyte colony-stimulating factor and leucovorin support was conducted by Meyers and colleagues [67] in 24 previously untreated patients with advanced disease. Paclitaxel 200 mg/m^2 (3 h), carboplatin (AUC 5) and methotrexate 60 mg/m^2 were administered sequentially every 21 days. The overall response rate was 50% (95% CI, 29–71%), with 3 CRs and 9 PRs and a median survival of 17.7 months (Table 4).

It is too soon to draw definitive conclusions about the impact of these triple regimens on survival. None the less, the median survival reported seems promising in view of the consistently observed median survival of 12 months reported in the M-VAC series. Additional follow-up data from these studies are needed to confirm these encouraging results and to determine whether they will translate into long-term benefit.

Table 4
Other paclitaxel–platinum-based three-drug regimens

Author [Ref.]	Schedule	No. of evaluable patients	Prior chemotherapy	ORR (95% CI)
Bajorin [65]	Ifosfamide 1.5 g/m^2×3 d Paclitaxel 200 mg/m^2, 3 h, day 1 Cisplatin 70 mg/m^2 day 1, q21d	29	No	79% (60–92%) 6 CR, 17 PR MS 18.3 mo. (95% CI, 12.2–29.2 mo.)
Meyers [67]	Paclitaxel, 200 mg/m^2 3 h, day 1 Carboplatin AUC 5 day 1 Methotrexate 10–60 mg/m^2 day 1 q21d	24	No	50% (29–71%) 3 CR, 9 PR MS 17.7 mo.
Tu [66]	Methotrexate 30 mg/m^2 Paclitaxel 200 mg/m^2 Cisplatin 70 mg/m^2 All day 1, q21d	25	Yes	40% 10 PR

ORR, overall response rate; MS, median survival; AUC, area under the concentration–time curve; mo., months; CI, confidence interval; PR, partial response; CR, complete response.

6. Conclusions

Although several active combination regimens incorporating new agents are now available, there are currently no data demonstrating that these regimens improve patient survival, prolong response duration, or are less toxic than M-VAC or CMV. The results of the ongoing multinational phase III study of M-VAC versus gemcitabine/cisplatin and other trials comparing M-VAC with other two-drug regimens, such as paclitaxel–carboplatin, will further define the role of the new agents in combination for treating urothelial malignancies. We hope that a new standard or an alternative option to M-VAC will soon be available.

Even though the existing new two-drug regimens have significant activity, the antineoplastic effect might be improved further by adding a third cytostatic agent with a different mechanism of action. Results of current studies show that three-drug regimens of gemcitabine and paclitaxel with either cisplatin or carboplatin are feasible and have promising response rates. Whether the carboplatin triplet is as effective as the cisplatin triplet and whether the activity of the triplets is superior to the existing two-drug regimens remains to be resolved from future studies.

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