

The Role of Taxanes in the Management of Bladder Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. List the prognostic factors that are the best predictors of outcome for patients with metastatic bladder cancer.
2. Interpret the results of the completed phase III trials comparing MVAC with taxane-based regimens in patients with metastatic bladder cancer.
3. Describe the ongoing multinational phase III trial using taxane-based therapy in patients with metastatic bladder cancer.
4. Define the role of taxanes as perioperative therapy in patients with localized bladder cancer.

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ABSTRACT

Transitional cell carcinoma of the bladder is a chemosensitive neoplasm. Whereas the MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimen was long considered the standard of care for patients with advanced disease, the evaluation of newer agents with retained activity and improved tolerability has been the focus of much investigation over the past decade. Among

the most important of these newer agents are taxanes. Whereas taxane-containing regimens have not yet been shown to improve the survival of patients with transitional cell carcinoma in randomized trials, ongoing phase III trials will further define the role of these agents in both the perioperative and advanced disease settings. *The Oncologist* 2005;10:792–798

INTRODUCTION

Transitional cell carcinoma (TCC) of the urinary bladder is a chemosensitive neoplasm. The development of the MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimen in the 1980s marked a big step forward in the treatment of patients with advanced disease [1]. Despite the unprecedented activity of this regimen, its limitations were readily apparent; response durations were relatively

short, and treatment related toxicities were significant. As a result, newer agents were sought with both improved activity and tolerability. Among the most important of these newer agents are taxanes.

This review will focus on the clinical development of the taxanes in TCC, both as single agents (Table 1) and as components of multidrug regimens, in phase II (Table 2) and phase III (Table 3) trials.

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SINGLE-AGENT TAXANES IN ADVANCED TCC

Paclitaxel

Multiple trials have evaluated single-agent paclitaxel in metastatic TCC [2–5]. In an Eastern Cooperative Oncology Group (ECOG) trial, 26 previously untreated patients received paclitaxel 250 mg/m² by 24-hour continuous infusion every 21 days with granulocyte colony-stimulating factor (G-CSF) support [4]. Eleven of 26 patients (42%; 95% confidence interval [CI], 23%–63%) responded to treatment, with seven complete responses (27%; 95% CI, 12%–48%). Treatment was generally well tolerated. This study established paclitaxel as one of the most active single agents in TCC.

Docetaxel

In a phase II trial, 30 chemotherapy-naïve patients with metastatic TCC were treated with docetaxel 100 mg/m² every 3 weeks [6]. Of the 29 evaluable patients, the overall response rate was 31% with four complete responses and five partial responses. Toxic effects consisted mainly of neutropenia, although infectious complications were rare (5%). Docetaxel has also shown activity in patients with TCC who failed to respond to prior cisplatin-based therapy [7].

TAXANE-BASED DOUBLETS IN ADVANCED TCC

Paclitaxel Plus Cisplatin

Several phase II trials have been performed exploring the combination of paclitaxel and cisplatin. In an ECOG study, 52 patients were treated with paclitaxel 175 mg/m² and cisplatin 75 mg/m² every 21 days [8]. Twenty-six patients achieved an objective response (50%; 95% CI, 36%–64%), with four (8%) complete responses. The toxicity of this regimen was considered moderate with neutropenia (without fever) and neurotoxicity being most common. In a study by Burch et al., slightly lower doses of paclitaxel (135 mg/m²) and cisplatin (70 mg/m²) were used [9]. Thirty-four patients were treated, with partial responses in 38% and complete responses in 32%. There were no episodes of grade 4 neutropenia or thrombocytopenia.

Docetaxel Plus Cisplatin

At least three trials have evaluated the combination of docetaxel and cisplatin (DC). In a multicenter phase II trial, 38 previously untreated patients with advanced/metastatic TCC received docetaxel 75 mg/m² and cisplatin 75 mg/m² every 21 days [10]. There were seven (19%) complete responses and 15 (39%) partial responses for an overall response rate of 58% (95% CI, 41%–74%). The median overall survival was 10.4 months. Notably, grade ≥ 3 neu-

tropenia occurred in 27 patients, with five episodes of febrile neutropenia. A second trial used the same dose and regimen [11]. A total of 25 patients were evaluable with an overall response rate of 60% (95% CI, 39%–79%), including seven (26%) complete responses. Grade 3 or 4 neutropenia occurred in 56% of patients. Less common side effects included neuropathy and fluid retention. A third trial exploring the same DC regimen, given with G-CSF support, yielded similar response proportions with slightly less hematologic toxicity [12].

A phase III randomized trial comparing DC with MVAC has been reported by the Hellenic Cooperative Oncology Group [13]. Patients randomized to DC received docetaxel 75 mg/m² and cisplatin 75 mg/m² repeated every 3 weeks. Both treatment arms received G-CSF support. Of the 224 patients enrolled, 109 were randomized to MVAC and 111 were randomized to DC. Although DC was associated with less hematologic toxicity and febrile neutropenia, overall response rate (54.2 versus 37.4; $p = .017$), median time to progression (9.4 versus 6.1 months; $p = .003$), and median survival (14.2 versus 9.3 months; $p = .026$) favored the MVAC arm. Importantly, whereas stratification was performed for disease site (visceral metastases versus locoregional disease) in this trial, there was no stratification according to performance status, the other major prognostic indicator in patients with advanced urothelial carcinoma [14]. There was a higher proportion of patients with poor performance status on the DC arm (ECOG performance status 2: MVAC = 12%, DC = 24.5%), which may have contributed, in part, to the poor outcomes on the DC arm.

Paclitaxel Plus Carboplatin

In a pilot study, paclitaxel was dose-escalated from 150 to 225 mg/m² with a fixed dose of carboplatin (area under the curve [AUC] 6) [15]. No maximum tolerated dose was reached, and of the 16 patients treated, two achieved a complete response and seven achieved a partial response. The dose of paclitaxel recommended for phase II study was 225 mg/m². Subsequently, several phase II trials have been performed with varying doses of paclitaxel (150–225 mg/m²) and carboplatin (AUC 5–6) reporting overall response rates of 14%–65%, with complete responses in 0%–40% [16–21]. This regimen has proven well tolerated with predominantly mild hematologic and neurologic toxicities.

A phase III trial conducted by ECOG compared MVAC with paclitaxel plus carboplatin [22]. Patients with previously untreated metastatic TCC were randomized to either standard MVAC or paclitaxel (225 mg/m²) plus carboplatin (AUC 6) administered every 21 days. After 2.5 years, the study was terminated due to slow accrual. Of the planned

330 patients, only 85 were enrolled. Compared with carboplatin/paclitaxel (CP), patients treated with MVAC had more severe myelosuppression, mucositis, and renal toxicity. Interestingly, a quality-of-life instrument revealed no significant differences between the two arms. At a median follow-up of 32.5 months, there was no significant difference in response rate (35.9% MVAC versus 28.2% CP, $p = .34$) or median survival (15.4 months MVAC versus 13.8 months CP, $p = .41$) between the two arms. However, definitive conclusions are not possible given that the trial was severely underpowered.

Paclitaxel Plus Ifosfamide

In an alternative attempt to improve the efficacy and tolerability of combination chemotherapy in advanced TCC, regimens devoid of platinum analogues have been developed. Sweeney et al. reported the combination of ifosfamide 1,000 mg/m² given on days 1–4 plus paclitaxel 135 mg/m² given over 24 hours on day 4 [23]. Treatment was recycled every 21 days, and GCSF was given for prophylaxis. Twenty-six patients were treated, and 12 developed \geq grade-3 hematologic toxicity. There were no episodes of febrile neutropenia. Among the 13 previously untreated patients, there were three complete responses and one partial response (overall response rate 30.7%; 95% CI, 9%–61%).

Paclitaxel Plus Gemcitabine

Paclitaxel plus gemcitabine has been studied in at least three phase II trials. Two of these trials used alternate doses and schedules of this combination in patients previously treated with platinum-based therapy and demonstrated encouraging activity [24, 25]. A recently published phase II trial performed by the Hoosier Oncology Group explored gemcitabine plus paclitaxel in patients with previously untreated metastatic TCC [26]. Patients initially received paclitaxel 110 mg/m² and gemcitabine 1,000 mg/m² on days 1, 8, and 15 every 28 days. However, after the first 24 patients were treated, the dose of paclitaxel was decreased to 90 mg/m² and gemcitabine was decreased to 800 mg/m² due to a concerning incidence of pulmonary toxicity. The overall response rate was 69%, with 41% complete responses. Despite the encouraging activity, the authors recommended against further use of this dose and schedule given the high rate of pulmonary toxicity (14% grade 3–5). This excessive rate of pulmonary toxicity was not encountered in the other trials of gemcitabine and paclitaxel using different doses and schedules.

Docetaxel Plus Gemcitabine

An ECOG trial evaluated the combination of docetaxel and gemcitabine in previously treated patients with advanced

TCC [27]. Twenty-nine patients received docetaxel 40 mg/m² plus gemcitabine 800 mg/m², both agents administered on days 1 and 8, with cycles repeated every 21 days. The overall response rate was 17% (90% CI, 7%–33%) with one complete response. The median survival was 7.7 months. Toxicity was moderate and included neutropenia, anorexia, and fatigue.

TAXANE-BASED TRIPLETS IN ADVANCED TCC

Paclitaxel, Cisplatin, and Ifosfamide

The three-drug regimen of ifosfamide, paclitaxel, and cisplatin (ITP) has been explored at Memorial Sloan-Kettering Cancer Center (MSKCC) [28]. Thirty previously untreated patients with advanced TCC received ifosfamide (1.5 g/m² per day for 3 days), paclitaxel (200 mg/m² on day 1), and cisplatin (70 mg/m² on day 1) given every 28 days with prophylactic GCSF. Twenty-nine patients were evaluable, with six complete responses and 17 partial responses for an overall response rate of 79% (95% CI, 60%–92%).

Based on these results and the emerging evidence supporting the benefits of increasing dose-density, an additional 15 patients were treated with the same doses of ITP given every 3 weeks with GCSF support. Subsequently, the results of all 44 patients were reported [29]. There was no significant difference in toxicity with the every-3-week regimen. Overall, myelosuppression was the predominant toxicity (45% grade 3 to 4 neutropenia) although the risk of febrile neutropenia was low (3.3% of all cycles). The median survival of patients treated with ITP was 20 months, among the best reported results for patients with metastatic/advanced TCC. However, favorable baseline prognostic factors and aggressive post-treatment surgery may have contributed to these results.

Paclitaxel, Cisplatin, and Gemcitabine

The combination of paclitaxel, gemcitabine, and cisplatin has been investigated in a phase I/II study by Bellmunt et al. [30]. The phase II dose of this combination was determined to be cisplatin 70 mg/m² on day 1 with paclitaxel 80 mg/m² and gemcitabine 1,000 mg/m² given on both day 1 and 8 with cycles repeated every 21 days. Toxicities consisted mainly of asthenia, thrombocytopenia, and neutropenia with a 22% incidence of febrile neutropenia and one toxic death. This regimen demonstrated substantial activity in the 58 evaluable patients, with 16 complete responses (28%) and 29 partial responses (50%) for an overall response rate of 77.6% (95% CI, 60%–98%). The median survival for the phase I portion was 24 months, while the median survival of the entire group had not been reached at the time of the initial report. This regimen is currently being compared with

gemcitabine plus cisplatin in an international, randomized, phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), which has recently completed accrual. This trial was designed to detect a difference in survival of 4 months (from 14 to 18 months) enrolling 610 patients.

Paclitaxel, Carboplatin, and Gemcitabine

Investigators at Wayne State University (Detroit, MI) treated 49 patients on a phase II study exploring paclitaxel 200 mg/m², carboplatin AUC 5, and gemcitabine 800 mg/m² on day 1 (with gemcitabine repeated on day 8) [31]. Treatment was recycled every 21 days. With this regimen, hematologic toxicity was common although febrile neutropenia was rare (1.4%). Of the 47 evaluable patients, 15 (32%) achieved a complete response, and 17

(36%) achieved a partial response for an overall response rate of 68% (95% CI, 56%–83%). Responses were seen at all sites, including 15/22 patients with visceral metastases. The median survival with this regimen was 14.7 months. This regimen has become commonly used in patients with TCC and impaired renal function but has not yet been compared with doublet-therapy in a randomized trial.

COMPARING PHASE II TRIALS IN ADVANCED TCC: THE IMPACT OF PRE-TREATMENT PROGNOSTIC FACTORS

The association between pretreatment prognostic factors and clinical outcomes in patients with advanced TCC treated with chemotherapy has been underscored by several analyses [14, 32–34]. In one such study, a database of 203 patients with advanced TCC treated with chemotherapy was retrospectively subjected to multivariate analysis to determine which patient characteristics predicted response rate and survival [14]. Two factors, KPS (Karnofsky performance status) $\leq 80\%$ and visceral (lung, liver, or bone) metastases, had independent prognostic significance. The median survival for patients with zero, one, or two risk factors was 33, 13.4, and 9.3 months, respectively ($p = .0001$). This report highlighted that the median survival of patient cohorts could vary from 9 to 26 months simply by altering the proportion of patients from different risk categories. Notably, the same two prognostic fac-

Table 1. Results with single-agent taxanes in patients with advanced bladder cancer (cumulative results, data compiled irrespective of dose and schedule)

Agent	First-line		Previously treated	
	OR	95% CI	OR	95% CI
Paclitaxel [2–5]	42%	23%–63%	9%	0%–17%
Docetaxel [6, 7]	31%	14%–48%	13%	4%–30%

Abbreviations: CI, confidence interval; OR, overall response.

Table 2. Phase II trials of taxane-based doublets and triplets as first-line treatment in metastatic transitional cell carcinoma (cumulative results, data compiled irrespective of dose and schedule)

Regimen	n	OR (95% CI)	CR (95% CI)
Paclitaxel + cisplatin [8, 9]	86	45% (34%–55%)	16% (2%–24%)
Docetaxel + cisplatin [10–12]	129	43% (34%–52%)	23% (16%–30%)
Paclitaxel + carboplatin [16–18, 20, 21]	153	45% (37%–53%)	18% (12%–24%)
Paclitaxel + ifosfamide [23]	13	31% (6%–56%)	23% (0%–46%)
Paclitaxel + gemcitabine [24]	39	56% (40%–72%)	8% (0%–17%)
Paclitaxel, gemcitabine, cisplatin [30]	61	78% (60–98%)	28% (18%–40%)
Paclitaxel, gemcitabine, carboplatin [31]	49	68% (56%–83%)	32% (20%–56%)
Paclitaxel, ifosfamide, cisplatin [29]	44	68% (52%–81%)	23% (13%–37%)

Abbreviations: CI, confidence interval; CR, complete response; OR, overall response.

Table 3. Randomized trials involving taxane-based therapy in advanced transitional cell carcinoma

Regimen	OR	CR	Survival (months)	p
MVAC [13]	54%	23%	14.2	.025
Docetaxel + cisplatin	37%	13%	9.3	
^a MVAC [22]	40%	13%	15.4	.41
Paclitaxel + carboplatin	28%	3%	13.8	

^aTrial terminated early with only 85 patients.

Abbreviations: CR, complete response; MVAC, methotrexate, vinblastine, doxorubicin, cisplatin; OR, overall response.

Table 4. The proportion of patients with poor prognostic factors in selected phase II trials in advanced transitional cell carcinoma

Regimen	<i>n</i>	Poor PS	Visceral metastases	OR	Median survival (months)
Paclitaxel [4]	26	12%	NA	42%	8.4
Paclitaxel + carboplatin [16]	29	7%	76%	20%	9
Paclitaxel + cisplatin [9]	34	6%	30%	70%	12.7
Paclitaxel, gemcitabine, cisplatin [42]	56	7%	36%	78%	15.8
Paclitaxel, gemcitabine, carboplatin [31]	49	10%	49%	68%	14.7

Abbreviations: NA, not available; OR, overall response; PS, performance status.

tors have proven to be independent predictors of survival in patients treated with taxane-based chemotherapeutic regimens [35].

Clearly, attention to these baseline prognostic factors is critical when comparing outcomes among different phase II trials in patients with advanced TCC. The wide variation in the proportion of patients with poor prognostic factors, and the associated clinical outcomes, in selected phase II trials using taxane-based therapy is shown in Table 4.

NEW TREATMENT APPROACHES: THE INTEGRATION OF TAXANES INTO SEQUENTIAL TREATMENT REGIMENS FOR ADVANCED TCC

Sequential “Dose-Dense” Therapy

Despite the promising activity and improved tolerability of these newer combination regimens in TCC, the majority of patients still succumb to their disease, and new approaches are needed. Rather than simply adding additional agents, which increases toxicity and limits the drug delivery of each agent, the Norton-Simon hypothesis [36] predicts that the efficacy of chemotherapy is increased with a sequential “dose-dense” approach.

Given the promising results with the ifosfamide, paclitaxel, and cisplatin (ITP) triplet, a study of sequenced therapy with doxorubicin and gemcitabine (AG) followed by ITP was initiated at MSKCC [37]. In a pilot trial, 15 patients were treated with six cycles of AG repeated every 2 weeks (with GCSF support) followed by four cycles of ITP given every 21 days (with GCSF support). Treatment was generally well tolerated, and after completion of the AG-ITP sequence, nine of 14 evaluable patients (64%) had a major response (three complete responses and six partial responses). This regimen has subsequently been studied in a phase II trial that has completed accrual. A preliminary analysis of 21 patients has been reported with a major response seen in 18 patients (87%; 95% CI, 71%–100%) and a complete response rate of 43% (95% CI, 22%–64%) [38]. A similar regimen consisting of sequential AG followed by paclitaxel plus carboplatin is currently being explored in patients with impaired renal function.

ROLE OF TAXANES AS SECOND-LINE THERAPY FOR ADVANCED TCC

The outcome for patients with advanced TCC who relapse or progress on first-line chemotherapy is extremely poor. Given that MVAC or gemcitabine-based combinations are often used as first-line chemotherapy in advanced TCC, several trials have explored the activity of the taxanes in the second-line setting. In a small phase II trial (14 patients) involving paclitaxel 200 mg/m² administered every 21 days, there was only one partial response (7%) and no complete responses [3]. A trial of 31 previously treated patients exploring weekly paclitaxel (80 mg/m²) yielded a similarly modest response rate of 10% [5]. A study exploring docetaxel 100 mg/m² every 21 days in 30 patients with previously treated advanced TCC reported a response rate of 13%.

While the activity of single-agent taxanes in these heavily pretreated patients appears modest at best, it is worthwhile noting that these response proportions are similar to those experienced with single-agent docetaxel as second-line therapy in patients with advanced non-small cell lung cancer. Docetaxel has been approved by the U.S. Food and Drug Administration for use as second-line therapy in advanced non-small cell lung cancer based on randomized trials demonstrating an improvement in survival and palliation compared with placebo. Ultimately, phase III trials are needed to determine if the taxanes confer the same benefit in the second-line setting in advanced urothelial cancer.

ROLE OF TAXANES IN PERIOPERATIVE THERAPY FOR TCC

Two randomized trials and a meta-analysis have confirmed the survival advantage associated with the use of cisplatin-containing combination chemotherapy in the neoadjuvant setting in patients with muscle-invasive TCC [39–41]. While the data supporting adjuvant therapy are less compelling, this is likely the result of poor trial design and the use of suboptimal chemotherapy, leading most oncologists to extrapolate the data derived from the neoadjuvant trials to the adjuvant setting.

There have been no randomized trials of taxane-containing chemotherapy regimens in the perioperative setting. However, given the promising activity of the sequential doublet of AG-ITP in advanced disease, the Cancer and Leukemia Group B/Clinical Trial Support Unit initiated a phase III randomized trial comparing the sequential doublet of AG-TP (doxorubicin plus gemcitabine followed by paclitaxel plus cisplatin) versus gemcitabine-cisplatin as adjuvant therapy for patients with high-risk ($\geq pT3$ and/or node-positive) TCC after cystectomy. This trial was designed to enroll 800 patients to detect a 30% decrease in the hazard rate (or increase in median survival from 4.4 to 6.3 years). Unfortunately, this trial was recently closed due to poor accrual, leaving the oncologic community without an answer to this important question.

CONCLUSION

The taxanes are among the most active of the newer cytotoxic agents to be explored in TCC. As single agents and as components of multidrug regimens, the taxanes have proven tolerable and have demonstrated promising activity in chemo-naïve patients. While the addition of the taxanes has not yet led to improved survival in randomized trials, the recently completed EORTC trial will further define the role of the taxanes in advanced disease.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The author indicate no potential conflicts of interest.

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