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Chemotherapy of advanced transitional-cell carcinoma of the bladder*

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Summary. A number of single agents and multidrug combinations are useful in the therapy of advanced transitional-cell carcinoma of the bladder. Phase II studies have identified cisplatin, Adriamycin (doxorubicin), methotrexate, and vinblastine as the most active cytotoxic agents. Combination chemotherapy based on cisplatin has shown greater efficacy than older regimens based on Adriamycin or methotrexate. Trials of regimens containing both cisplatin and methotrexate, such as those conducted by the Northern California Oncology Group using CMV (cisplatin, methotrexate, and vinblastine), have reported that a significant number of patients respond to treatment, with frequent complete responses being noted. Anthracycline-containing regimens such as M-VAC (methotrexate, vinblastine, Adriamycin, and cisplatin) have also played an important role in the therapy of advanced bladder cancer. Trials comparing cisplatin- and methotrexate-containing regimens with single-agent cisplatin or other cisplatin combinations have shown the apparent superiority of the former in terms of greater overall response rates and improved survival. However, the toxicity of such regimens can be significant, and phase III studies are under way to validate their use in the neoadjuvant setting.

Introduction

According to data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program, an estimated 51,600 new cases of cancer of the bladder and 9,500 deaths will have been recorded in the United States for 1992 [4]. Although >70% of cases are localized at the time of diagnosis and many remain confined to the bladder for their entire natural history, tumors that invade into the smooth muscle of the bladder wall carry a poor prognosis. Despite advances in surgical and radiotherapy techniques, there has been little change in survival rates over the past 40 years, with <50% of patients with invasive tumors living for 5 years or longer after conventional therapy [61]. Since a significant number of patients with sustained local control subsequently develop distant metastases, it has been suggested that improvement in survival will be seen only with the development of more effective systemic therapies for micrometastatic disease [71].

In the past decade, progress has been made in the development of effective chemotherapy for the treatment of advanced transitional-cell carcinoma (TCC) of the urothelium, once regarded as being largely unresponsive to conventional agents. The identification of single drugs that are active against this disease has led to trials of various multidrug combinations, and regimens have been developed that produce objective response rates exceeding 60%, with a significant number of complete responses being reported [8]. To date, the majority of trials evaluating combination chemotherapy for advanced bladder cancer have been single-arm phase II studies, and claims for the superiority of combination regimens over single agents have been made without full accounting for differences in patient selection and response criteria. However, the first reports of prospective randomized trials are now being published [36, 37], and further phase III trials are under way. This review summarizes the current status of chemotherapy for advanced TCC of the bladder and highlights the direction of future investigations.

Single agents

A variety of individual agents have shown activity against TCC of the bladder [8, 86, 101] (Table 1). Cisplatin is the single most active drug, with Adriamycin, methotrexate,

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Table 1. Single-agent activity in advanced bladder cancer

Drug	CR + PR/ evaluable patients	% CR + PR	References
Cisplatin	8/ 23	35	[103]
	10/ 28	36	[100]
	19/ 51	37	[43]
	4/ 8	50	[58]
	9/ 21	43	[26]
	7/ 27	26	[55]
	9/ 27	33	[74]
	10/ 50	20	[75]
	11/ 17	65	[13]
	30/ 50	60	[60]
	17/ 48	35	[32]
	3/ 15	20	[56]
	7/ 48	15	[89]
	17/ 55	31	[28]
	10/110	9	[36]
Total	171/578	30[a]	
Carboplatin	2/ 20	10	[56]
	3/ 48	6	[42]
	1/ 11	9	[53]
	2/ 13	15	[21]
	8/ 28	29	[41]
	0/ 15	0	[70]
	3/ 20	15	[90]
	4/ 19	21	[46]
Total	23/174	13[a]	
Adriamycin	14/ 39	36	[51]
	1/ 10	10	[44]
	1/ 19	5	[97]
	5/ 35	14	[105]
	11/ 65	17	[52]
	6/ 15	40	[15]
	8/ 41	20	[19]
	5/ 45	11	[34]
Total	51/269	19[a]	
Epirubicin	5/ 33	15	[16]
Methotrexate	23/ 64	36	[91]
	7/ 31	23	[54]
	11/ 42	26	[49]
Total	41/137	30[a]	
5-Fluorouracil	7/ 46	15	[34]
	3/ 10	30	[15]
	4/ 15	27	[72]
Vinblastine	5/ 28	18	[3]
Vincristine	3/ 37	8	[62]
Etoposide	0/ 13	0	[50]
	1/ 16	6	[57]
	1/ 17	6	[94]
Cyclophosphamide	2/ 26	7	[104]
Ifosfamide	8/ 20 (bilharzial)	40	[18]
Mitoxantrone	0/ 28	0	[92]
Mitomycin C	10/ 48	21 (?)	[86]

[a] Overall value
CR, Complete response; PR, partial response

and vinblastine also possessing important activity. The wide range of response rates reported for any single agent is likely due to patient selection, differences in staging (especially clinical versus pathological staging), schedule and dose differences, and variability in the criteria for response. Modern trials tend to employ more stringent definitions of response than do trials reported in the 1970s and early 1980s, which sometimes included patients showing either minor responses (i.e., a 25%–50% reduction in the sum of the perpendicular diameters of measurable lesions) or responses in evaluable sites such as the bladder that are difficult to measure objectively. Another cause for variability is that response rates for a given drug are often derived from studies including patients with both locally advanced primary tumors and metastatic disease, and there are likely to be differences in drug sensitivity between these two groups [95].

Cisplatin and platinum analogues

In 1976, Yagoda et al. [103] first reported an overall response rate of 35% in 23 evaluable patients with advanced measurable bladder cancer who were treated with cisplatin at a dose of 1.25–1.6 mg/kg every 3 or 4 weeks, including 8 partial responses in 14 patients who had received no prior chemotherapy. The activity of cisplatin has been confirmed in a number of subsequent trials, and data from 15 separate studies are shown in Table 1 [13, 26, 28, 32, 36, 43, 55, 56, 58, 60, 74, 75, 89, 100, 103]. This list includes trials in which cisplatin was given as neoadjuvant therapy prior to definitive local treatment for the primary tumor and studies in which single-agent cisplatin was compared with drug combinations. At doses ranging from 50 to 100 mg/m^2, cisplatin as a single agent has yielded response rates ranging from 9% to 65%. Pooled data from these studies result in an overall response rate of 30%. Interestingly, the trial with the largest sample size, the Intergroup study comparing single-agent cisplatin with the M-VAC combination (methotrexate, vinblastine, Adriamycin, and cisplatin), reported the lowest response rate for cisplatin as a single agent [36]. The complete response rate obtained in these studies was low (26/578 patients, or 4%), and the median duration of response was generally 5–9 months. The expected toxicities of peripheral neuropathy, renal dysfunction, and nausea and vomiting were frequently encountered, and the latter was particularly severe for patients treated in the pre-metoclopramide era. In all, 2 deaths documented in these 15 trials were attributable to therapy. Although cisplatin was given at a dose of 70 mg/m^2 in most of these studies, the optimal dose is not known. It is not clear whether a dose-response relationship exists for the drug, as may be the case for other solid tumors such as testicular or ovarian carcinomas.

Carboplatin, a less nephrotoxic and neurotoxic analogue of cisplatin, has shown promising activity against a variety of solid tumors that are responsive to cisplatin. In studies in advanced TCC, carboplatin has generally shown less activity than cisplatin. Giving carboplatin at a dose of 400 mg/m^2 as a short infusion every 4 weeks, a number of groups have obtained response rates ranging from 0 to 29%

[21, 41, 42, 53, 56, 70, 90] (Table 1). Complete responses were very rare. It is possible that the schedule of administration may have some effect of the response rate, as one group recorded somewhat more promising results when the drug was given as a 24-h infusion every month [46]. In general, hematologic toxicity, particularly thrombocytopenia, was dose-limiting for carboplatin, and other toxicities were less severe than those produced by cisplatin.

Anthracyclines

Adriamycin (doxorubicin) has been extensively studied in advanced TCC. In early drug-oriented trials using Adriamycin at a dose of 60–75 mg/m^2 every 3 weeks, objective remissions were achieved by 14 of 39 patients with bladder cancer [51]. Further data are reported in Table 1. Rates of response to Adriamycin as a single agent range from 5% to 40%. One trial has suggested a dose-response relationship [52]. The most recent study cited, an Eastern Cooperative Oncology Group (ECOG) phase II trial in 108 patients with advanced bladder carcinoma randomized to either 5-fluorouracil or Adriamycin, yielded 5 partial responses in 45 evaluable patients who had not received prior chemotherapy [34]. No complete response was obtained, and the median survival was only 20 weeks. Overall, Adriamycin as a single agent produces a cumulative response rate of 19% with tolerable gastrointestinal, hematologic, and cardiac toxicity.

In an attempt to diminish the cardiac toxicity of anthracyclines, analogues of Adriamycin have been developed. Epirubicin, the 4′ epimer of doxorubicin, has shown activity in the intravesical treatment of superficial bladder tumors. In a study by the European Organization for Research on Treatment of Cancer (EORTC), 33 evaluable patients were treated with 90 mg/m^2 epirubicin every 3 weeks; 5 partial responses were seen [16]. This agent may be more useful in multidrug combinations, and further studies are in progress.

Antimetabolites

Methotrexate has been used as a single agent in a variety of schedules and routes of administration. Using three different regimens consisting of methotrexate doses of 50 mg given i.v., 100 mg given i.v., and 200 mg given i.m., with folinic acid rescue being carried out, at 2-week intervals, Turner [91] found objective clinical responses in 3/25, 12/23, and 8/16 patients, respectively, for an overall response rate of 36% in 64 patients. Using a dose of 100 mg/m^2 weekly with leucovorin rescue, Oliver [54] reported responses in 0/6 patients with bone metastases, in 3/9 patients with clinically measurable metastases, and in 4/16 patients with primary bladder lesions recurrent after initial radiotherapy. Natale et al. [49] reported 1 objective response in 9 patients with measurable lesions who received a "high-dose" methotrexate regimen of 250 mg/m^2 with folinic acid rescue and 10 responses in 33 patients receiving "low-dose" (0.5–1.0 mg/kg) methotrexate weekly. Mucositis was the most common toxicity encountered, but it was rarely severe enough to compromise therapy. No treatment-related death was reported. The overall response rate for methotrexate ranges from 18% to 38% (median, approximately 30%) [8]. Complete responses to methotrexate as a single agent are quite rare. As yet, no randomized study has compared low-dose methotrexate with high-dose regimens, although in a small number of patients treated at higher doses, response rates of up to 45% have been obtained [101].

Drug-oriented trials using 5-fluorouracil, some dating back to the early 1960s, showed a wide range of response rates, which may have been due to patient selection and inadequately defined response criteria. In a more modern phase II trial conducted by the ECOG, in which 5-fluorouracil (5-FU) was given as a weekly bolus at a dose of 400–600 mg/m^2, 2 complete and 5 partial responses were observed in 46 evaluable patients with measurable metastatic lesions [34]. Mild to moderate myelosuppression was noted. Two additional trials using a similar schedule of 5-FU reported responses in 3/10 and 4/15 patients [15, 72].

Plant alkaloids

A limited number of patients have been treated with vinblastine as a single agent. Using doses of 0.10–0.15 mg/kg each week, Blumenreich et al. [3] obtained 5 partial responses in 28 patients, the majority of whom had received prior chemotherapy. In a study by the EORTC, vincristine given on a weekly schedule showed little antitumor efficacy and produced prohibitive toxicity as a single agent [62].

Etoposide (VP-16) given as a 30-min infusion twice weekly at varying dose levels has been studied by the Cancer and Leukemia Group B (CALGB) in a drug-oriented trial [50]. No complete or partial response was observed in 13 evaluable patients with bladder cancer. Another phase II study using 130 mg/m^2 oral VP-16 daily for 5 days every 3 weeks produced only 1 complete response in 16 evaluable patients [57]. In a Southeastern Cancer Study Group report [94], VP-16 failed to show any greater activity when given on a more conventional schedule (130 mg/m^2 given i.v. daily for 3 days); only 1 partial response was seen in 17 evaluable patients, and there was 1 probable treatment-related death.

Other drugs

Among other commercially available agents, cyclophosphamide has been studied in several older trials, with response rates of up to 52% being reported [8]. However, its single-agent efficacy as judged using strict response criteria appears to be considerably poorer, with the analysis of Yagoda et al. [104] revealing only 2 partial responses in 26 evaluable patients. Ifosfamide is active in bilharzial bladder cancer, usually of squamous histology [18], but its activity against TCC is unknown. Ifosfamide is currently being studied in a phase II trial by the ECOG. In a phase II study by the EORTC, mitoxantrone given at a dose of 12 mg/m^2 every 3 weeks produced no objective response

in 28 evaluable patients, many of whom had been heavily pretreated [92]. Mitomycin C has been reported to yield an overall response rate of 21% in trials completed before 1975 [86]. No recent trial has assessed its single-agent efficacy using modern response criteria.

Investigational agents

Multiple investigational agents have been studied in advanced TCC [8, 102]; few have shown sufficient promise to warrant phase III testing or incorporation into established multidrug regimens. Trimetrexate, a quinazoline antifolate, has been evaluated in a phase II trial conducted by the ECOG. In a preliminary report, the administration of daily i.v. bolus injections for 5 days at a dose of 8 mg/m^2 resulted in 1 complete response and 4 partial responses in 31 evaluable patients [99]. Gallium nitrate, a heavy metal employed in the therapy of hypercalcemia, showed early promising activity, but its usefulness was limited by renal toxicity when it was given as a bolus injection [101]. When it was given as a 5-day continuous infusion, the nephrotoxicity was eliminated, but the drug was inactive in heavily pretreated patients [78]. Hexamethylmelamine is another drug that appears to be active in bilharzial bladder cancer [18]; however, when it was compared with 5-FU, Adriamycin, and cyclophosphamide in a randomized study of the Southwest Oncology Group (SWOG), no activity could be demonstrated in TCC [20].

Few studies have used cytokines or other biologic agents in the therapy of TCC. An early report of i.m. injections of alpha-interferon showed regressions of grades I and II superficial bladder papilloma in a few patients [69]. In addition, alpha-interferon can produce complete remissions in carcinoma-in-situ when used intravesically [87]. In another report, interleukin-2 produced three local complete responses in six patients treated with intralesional injection of primary bladder tumors [59]. However, no report has yet documented the systemic activity of these agents when they are used in bladder tumors that are no longer superficial.

Combination chemotherapy

The highest rates for complete and partial responses in TCC have been obtained using multidrug combinations. The most efficacious regimens contain cisplatin, and the greatest activity is associated with regimens incorporating both cisplatin and methotrexate in a variety of doses and schedules. As noted, most trials investigating combination chemotherapy in advanced TCC have been relatively small single-institution studies, and the majority have not demonstrated clear superiority for multidrug treatment over single-agent therapy. Yagoda [102] has outlined some of the difficulties in the interpretation of multiple trials over time. "Stage migration," the phenomenon by which more accurate modern staging techniques define disease status more precisely than those used in the past, accounts for some of the differences in response rates over time. This is particularly true when clinical staging (the results obtained by transurethral resection and bimanual examination) is compared with pathologic staging (the depth of muscle invasion and nodal status determined at the time of cystectomy), and many trials do not adequately address this issue. The majority of older trials used clinical criteria alone. In addition, modern trials of bladder cancer chemotherapy tend to enroll patients showing a better performance status and less prior therapy than those entered in older studies, and this also has an impact on reported rates of tumor response. Further enrollment of patients in randomized phase III studies, in which all patients are similarly staged and treated, will serve to clarify these issues.

Table 2. Adriamycin- and methotrexate-based regimens

Regimen	CR + PR/ evaluable patients	% CR + PR	References
ADR + CTX	9/18	50	[44]
	3/18	17	[104]
ADR + 5-FU	7/20	35	[9]
	21/52	40	[73]
	8/21	38	[39]
ADR + 5-FU + CTX	3/17	18	[72]
	0/16	0	[40]
	1/15	7	[20]
ADR + VM-26	5/27	19	[63]
ADR + CTX + BLEO	8/23	35	[35]
MTX + MMC	5/16	31	[83]
MTX + ADR + CTX	15/38	39	[84]
MTX + VLB	19/47	40	[1]

ADR, Adriamycin (doxorubicin); CTX, Cytoxan (cyclophosphamide); 5-FU, 5-fluorouracil; VM-26, teniposide; BLEO, bleomycin; MTX, methotrexate; MMC, mitomycin C; VLB, Velban (vinblastine); CR, complete response; PR, partial response

Non-cisplatin-based regimens

Adriamycin-based regimens. The earliest combination regimens used for advanced TCC were based on Adriamycin. Adriamycin has been combined with cyclophosphamide, 5-FU, teniposide (VM-26), and bleomycin (Table 2). In an early study, Merrin et al. [44] obtained a 50% response rate in 18 patients treated with cyclophosphamide and Adriamycin, but subsequent investigators have been unable to reproduce these results, even using higher doses of cyclophosphamide [104]. In studies of Adriamycin in combination with 5-FU, the Yorkshire Urological Cancer Research Group [9] obtained 3 complete responses and 4 partial responses in 20 patients using 500 mg/m^2 5-FU and 50 mg/m^2 Adriamycin every 3 weeks. The largest experience with this regimen was reported by the EORTC, whereby 4 complete responses and 17 partial responses were observed in 52 evaluable patients [73]. Using similar doses, Martino et al. [39] found 8 objective responses in 21 patients; however, 12 subjects developed severe leukopenia, and 1 septic death occurred. Several groups have reported on the combination of Adriamycin, cyclo-

Table 3. Cisplatin-based regimens[a]

Regimen	CR + PR/ evaluable patients	% CR + PR	References
CDDP + ADR	14/ 26	54	[100]
	16/ 37	43	[19]
	20/ 35	57	[64]
CDDP + CTX	15/ 32	47	[106]
	7/ 59	12	[75]
	6/ 17	35	[12]
CDDP + ADR + CTX	10/ 12	83	[80]
	26/ 50	52	[67]
	19/ 23	83	[31]
	13/ 34	38	[88]
	17/ 42	40	[48]
	13/ 28	46	[68]
	15/ 45	33	[32]
	15/ 36	42	[2]
	8/ 18	44	[6]
	9/ 42	21	[89]
Total	145/330	44[b]	
CDDP + ADR + 5-FU	18/ 39	46	[98]
CDDP + VM-26	21/ 41	51	[81]
CDDP + infusion 5-FU	5/ 11	45	[33]

[a] Non-methotrexate-containing regimens
[b] Overall value
ADR, Adriamycin (doxorubicin); CDDP, cisplatin; CTX, Cytoxan (cyclophosphamide); 5-FU, 5-fluorouracil; CR, complete response; PR, partial response

phosphamide, and 5-FU (Table 2). The Southeastern Cancer Study Group found no significant advantage for 500 mg/m^2 cyclophosphamide, 50 mg/m^2 Adriamycin, and 500 mg/m^2 5-FU given every 3 weeks over weekly bolus 5-FU [72]. Among 15 evaluable patients, 1 partial response and 1 toxic death were observed in a study of the same regimen conducted by the SWOG [20]. The apparent inferiority of the three-drug regimen as compared with combinations of Adriamycin and cyclophosphamide or Adriamycin and 5-FU may be a function of overlapping 95% confidence intervals or may reflect the more stringent response criteria employed in the more recent studies. In other trials, an M. D. Anderson report on Adriamycin combined with the podophyllotoxin VM-26, which had shown modest single-agent activity in early studies, suggested that the combination was less effective than Adriamycin alone [63]. Adriamycin-based regimens lacking cisplatin have demonstrated no superiority to Adriamycin alone.

Methotrexate-based regimens. There has been limited experience with regimens containing methotrexate and lacking cisplatin. The combination of methotrexate and mitomycin C was studied by the Princess Margaret Hospital group, but the trial was terminated because of prohibitive toxicity [83]. Tannock et al. [84] subsequently reported on the combination of methotrexate, Adriamycin, and cyclophosphamide (MAC) and showed objective responses in 15/38 patients with measurable tumor parameters, including 2 complete respones. The Memorial Sloan-Kettering group used 4 mg/m^2 vinblastine and 40 mg/m^2 methotrexate given as weekly outpatient doses and obtained 3 complete and 16 partial responses in 47 evaluable patients with measurable disease [1]. It was noted that the median duration of response was slightly longer than that historically seen for single-agent methotrexate. It was also noteworthy that four of the responders subsequently developed brain metastases, suggesting that this combination was effective in controlling systemic disease but not in inhibiting progression in sanctuary sites such as the central nervous system.

Cisplatin-based regimens

Non-methotrexate-containing cisplatin combinations. Cisplatin has been combined with Adriamycin, cyclophosphamide, 5-FU, and VM-26 (Table 3). Yagoda [100] initially described the activity of the combination of cisplatin and Adriamycin. Subsequently, in a randomized study conducted by the SWOG in the late 1970s [19], patients with measurable T3, T4 bladder lesions or M1 disease received either 50 mg/m^2 Adriamycin or 50 mg/m^2 cisplatin plus 50 mg/m^2 Adriamycin at 3-week intervals. In the Adriamycin-alone arm, 8 of 41 patients (19%) responded as compared with 16/37 (43%) in the combination arm ($P = 0.02$). However, no statistically significant difference in median duration of response or median survival was found between the two treatment arms. Significantly greater leukopenia and gastrointestinal toxicity were noted in the combination arm. The University of Minnesota group used monthly injections of 60 mg/m^2 cisplatin and 60 mg/m^2 Adriamycin given as part of a chronotherapy protocol that specified precise drug order and timing. In 35 evaluable patients with metastatic TCC, 20 objective responses, including 8 complete responses, were obtained [64]; toxic side effects included 5 episodes of sepsis and 1 death related to myelosuppression.

The combination of cisplatin and cyclophosphamide has been studied by several groups, and it has shown no clear superiority over cisplatin alone. In the Memorial Sloan-Kettering series [106] using doses of 1.6 mg/kg cisplatin and 50–1000 mg/m^2 cyclophosphamide given every 3–4 weeks, 15 partial remissions were observed in 32 evaluable patients. There was no obvious improvement in survival as compared with historical controls treated with single-agent cisplatin. A trial by the National Bladder Cancer Collaborative Group [75] randomized patients to 70 mg/m^2 cisplatin or to 70 mg/m^2 cisplatin plus 750 mg/m^2 cyclophosphamide; 10 of 50 evaluable patients in the cisplatin-alone arm and 7 of 59 in the combination arm responded. No statistically significant difference in response or survival was observed. The results obtained in a small series from M. D. Anderson using cyclophosphamide and weekly cisplatin [12] are shown in Table 3.

The combination of cisplatin, Adriamycin, and cyclophosphamide (CISCA or CAP) is one of the most extensively studied combination regimens used in the therapy of advanced TCC. It was first reported by the M.D. Anderson group in 1977 to produce objective responses in 10 of 12 patients with metastatic TCC [80]. A larger follow-up series from the same institution reported 26 responses in

50 patients with metastatic disease, including 9 complete responses [67]. A number of additional trials using the same regimen, including those conducted by the EORTC, the Memorial Sloan-Kettering Cancer Center, the ECOG, the SWOG, and the Southeastern Cancer Study Group, have subsequently been reported and are summarized in Table 3 [2, 6, 31, 32, 48, 68, 88, 89]. The regimen consists of 250–650 mg/m^2 cyclophosphamide, 40–50 mg/m^2 Adriamycin, and 40–100 mg/m^2 cisplatin given at 3- to 4-week intervals. Response rates for these 10 trials ranged from 21% to 83%, with a cumulative response rate of 44% being noted in 330 patients. The proportion of complete responses noted was typically in the range of 12%–18% of the patients treated. No consistent dose-response relationship was observed, although the two trials using a cisplatin dose of 100 mg/m^2 reported responses in 83% and 52% of the patients treated [67, 80]. The regimen was moderately toxic, with frequent episodes of renal, hematologic, and gastrointestinal toxicity being seen. A total of four septic deaths were reported. The median duration of response ranged from 3 to 7 months, and the median overall survival was 5–8 months.

Two cooperative groups have compared single-agent cisplatin given at 60 mg/m^2 with the combination of 400 mg/m^2 cyclophosphamide, 40 mg/m^2 Adriamycin, and 60 mg/m^2 cisplatin in a randomized fashion. In a trial conducted by the ECOG [32] from 1978 to 1981, 135 patients with disseminated TCC were randomized, and among the patients with measurable disease parameters, 48 received cisplatin alone and 45 received the combination. In all, 33% of the patients on the combination arm achieved a partial response as compared with 17% of those on the cisplatin-alone arm ($P = 0.09$). The complete response rate was 2% for the cisplatin-alone arm and 22% for the combination arm ($P<0.01$). The median duration of response was 9 months for the cisplatin-alone arm and 7 months for the combination arm, with only four of ten patients on the latter arm achieving a complete response lasting for 6 months or longer. The median survival of patients on the cisplatin-alone arm was 6.0 months as compared with 7.3 months for patients on the combination arm ($P = 0.17$). The combination regimen was significantly more toxic, with 34% of patients developing grade III or IV hematologic toxicity and one septic death being noted. The Southeastern Study Group trial of the same randomized comparison [89] showed objective responses in 7/45 (16%) patients treated with single-agent cisplatin as compared with 9/42 (21%) treated with the combination regimen. The combination regimen again proved to be more toxic, and no difference in overall survival was found between the two groups. Despite the improvement in response rates and the increased number of durable complete responses obtained using the combination of cisplatin, Adriamycin, and cyclophosphamide, the unequivocal superiority of this regimen over single-agent cisplatin has not been demonstrated.

Reports on other cisplatin-containing regimens [81, 98], including combinations with Adriamycin, 5-FU, or VM-26 are shown in Table 3. Experience with them is limited, and there is no evidence to suggest their superiority over either regimen described above or cisplatin alone. A recent preliminary report from Wayne State University [33] has shown promising results using cisplatin combined with a 5-day continuous infusion of 5-FU, perhaps taking advantage of the theoretical synergy between these two drugs. Responses occurred in 45% of 11 evaluable patients; however, mucositis and myelosuppression were significant.

Cisplatin- and methotrexate-based regimens. Combination regimens containing both cisplatin and methotrexate have yielded impressive clinical results, with reproducible response rates being as high as 70% and a significant number of complete responses being reported [101]. Toxicity has been significant and prohibitive in some patients, especially the elderly and those with decreased renal function. The potential enhancement of methotrexate toxicity due to cisplatin-induced tubular damage remains a concern in patients treated with these regimens. However, a pharmacokinetics study in a small number of patients at the University of Glasgow in 1984 failed to demonstrate any decrease in methotrexate clearance by the simultaneous administration of cisplatin at 50 mg/m^2 [30].

Several groups have reported on two-drug combinations of cisplatin and methotrexate. An initial report by Carmichael et al. [7] from Edinburgh demonstrated both the substantial activity of the combination (68% objective response rate, including complete responses in 3/19 patients with lung metastases) and the acceptable toxicity. Subsequent reports from other groups, including the EORTC, confirmed this level of activity [28, 56, 82]. These studies used cisplatin at a dose of 70–100 mg/m^2 and methotrexate at 40–200 mg/m^2 (in the presence or absence of folinic acid rescue). Simultaneous administration of methotrexate and cisplatin was generally avoided. The response rates obtained in these four studies ranged from 45% to 68%, and a cumulative response rate of 49% was seen, with 22/135 patients (16%) achieving a complete response. In one of these trials, conducted by the Australian Bladder Cancer Study Group [28], 108 patients with metastatic or recurrent disease were randomized to cisplatin alone or to cisplatin and methotrexate. The response rate obtained in the combination arm was 45% as compared with 31% in the cisplatin-alone arm ($P = 0.18$). An equal percentage of complete responses was seen in the two arms. The median duration of relapse-free survival and median overall survival were slightly longer for patients in the combination arm, but this difference did not achieve statistical significance. Grade III and IV hematologic toxicity and mucositis were significantly greater in the combination arm. Once again, this study failed to show any statistically significant advantage for combination chemotherapy over single-agent cisplatin.

Cisplatin, methotrexate, and vinblastine. One of the most active regimens used to date in the treatment of advanced TCC of the bladder consists of cisplatin, methotrexate, and vinblastine (CMV, Table 4). The regimen was developed at Stanford University Medical Center and was investigated by the Northern California Oncology Group (NCOG). The results achieved have been described in a series of reports [11, 23, 24, 45]. Harker et al. [24] reported the results obtained in 58 patients with advanced TCC of

Table 4. Stanford CMV regimen for advanced transitional-cell carcinoma

Drugs	Dose (mg/m^2)		
	Day 1	Day 2	Day 8
Cisplatin		100	
Methotrexate	30		30
Vinblastine	4		4

Cycles are repeated every 21 days

Modification of methotrexate and vinblastine doses for myelosuppression, expressed as a percentage of the initial calculated dose[a]:

WBC ($/mm^3$)	Platelet count ($/mm^3$)			
	≥150,000	100,000–149,000	75,000–99,000	<75.000
$\geq 3.5 \times 10^4$	100	100	50	0
$3.0-3.4 \times 10^4$	75[b]	75[b]	50	0
$2.5-2.9 \times 10^4$	50	50	0[c]	0
$<2.5 \times 10^4$	0	0	0	0

[a] If the day-1 dose of subsequent cycles (day 22) falls into the 0–50% range, the initiation of cycles is delayed for up to 2 weeks

[b] 100% of the calculated dose to be given for platelet and WBC counts at this level on day 8

[c] 50% of the calculated dose to be given for platelet and WBC counts at this level on day 8

Modification of the cisplatin dose for nephrotoxicity, expressed as a percentage of the initial calculated dose:

Creatinine clearance (ml/min)	% Calculated cisplatin dose
>60	100
45–60	50
<45	0

Modification of the methotrexate dose for nephrotoxicity:

No methotrexate is given if either of the following occur:
1. Decrease of >30 ml/min in creatinine clearance
2. Serum creatinine values of ≥2.0 mg/dl, regardless of creatinine clearance

the urinary tract who received this regimen between 1981 and 1984. Of 50 evaluable patients with measurable disease parameters, 14 achieved a complete response to CMV and 14 others showed a partial response, for an overall response rate of 56%. Complete responses were noted in all sites, including the bladder, retroperitoneal and peripheral lymph nodes, liver, lung, and bone. The median survival of these 50 patients was 8 months. Toxicities included moderate to severe mucositis in 26% of the patients; fever and neutropenia in 28%; and elevations in serum creatinine of >2.0 mg/dl, usually transient, in 30%. Two patients who were treated during the pilot experience at higher doses of methotrexate and vinblastine (40 and 5 mg/m^2, respectively) than those specified by the current protocol showed elevations in serum creatinine of ≥4.0 mg/dl and died of complications related to sepsis. The doses of methotrexate and vinblastine were subsequently reduced, and the protocol was modified to include a requirement for creatinine clearance measurements on day 8 to ensure adequate renal function. No further toxic deaths occurred.

The Stanford group has increasingly used surgical restaging to biopsy or to resect sites of residual disease after treatment with four cycles of CMV chemotherapy [11]. This is customarily followed by two additional cycles of CMV as consolidative therapy. In the original series of 50 patients reported by Harker et al. [24], 3 additional patients treated with CMV were rendered disease-free after surgical resection of residual disease. In the most recent update of this experience, a total of 64 previously untreated patients received CMV at Stanford for advanced TCC [47]. Of 55 evaluable patients, 36 underwent surgical restaging of known disease sites; 14 of these subjects had residual tumor resected, and an additional 11 were found to be pathologically free of disease after chemotherapy alone. Of these 11 patients, 9 are alive and disease-free at 24–98 months. The median duration of survival for all evaluable patients was 17 months.

Additional reports confirm the activity of this combination. Rosenberg and Williams [65] employed the same doses and schedule used by the NCOG and found a 47% complete response rate and a 12% partial response rate in 17 evaluable patients. Using a once-monthly three-day regimen, whereby cisplatin was given in two divided doses of 45 mg/m^2, Walther and Walker [93] achieved a 74% response rate in a small number of patients. The EORTC has also reported the preliminary results of a phase II study in which patients were randomized either to the combination of 70 mg/m^2 cisplatin (day 1) and 40 mg/m^2 methotrexate (days 8 and 15) with leucovorin rescue or to 6 mg/m^2 vinblastine (day 1), 200 mg/m^2 methotrexate (days 1 and 15) with leucovorin rescue, and 70 mg/m^2 cisplatin (day 1) [10]. The response rate for the two-drug combination was 56% vs 35% for the three-drug regimen. However, the sample size was not adequate for this finding to constitute a statistically significant comparison between these two regimens.

Carboplatin- and methotrexate-containing regimens. Two preliminary reports describe the activity of the two-drug combination of carboplatin and methotrexate in patients with advanced disease [25, 76]. Overall response rates were 45% and 44% respectively, with toxicity being acceptable. One advantage of this regimen is that it can be given in the outpatient setting. An interesting study in Great Britain used a combination of carboplatin, methotrexate, mitoxantrone, and vinblastine. Of 32 evaluable patients, 27% achieved a complete response and 36% showed a partial response [96]. Despite the greater myelosuppressive effects of carboplatin versus cisplatin, hematologic toxicity was relatively mild, although nine patients were admitted with fever and neutropenia. Combinations of carboplatin with methotrexate or other active agents deserve further study. Despite these encouraging preliminary results, however, substantial concern remains about substituting carboplatin for cisplatin in established active regimens because of the low response rate obtained using carboplatin in single-agent studies.

Role of anthracyclines in the combination chemotherapy of advanced bladder cancer

The important role of anthracyclines in several combination regimens used in the therapy of advanced TCC has been described above. One of the most active and widely used regimens is M-VAC, which was developed at the Memorial Sloan-Kettering Cancer Center and has been described in a series of reports [77, 79, 102]. The regimen incorporates 30 mg/m^2 methotrexate (days 1, 15, and 22), 3 mg/m^2 vinblastine (days 2, 15, and 22), 30 mg/m^2 Adriamycin (day 2), and 70 mg/m^2 cisplatin (day 2) given at monthly intervals. In the initial study, of 24 evaluable patients with bidimensionally measurable disease who were treated prior to 1985, 12 achieved a complete clinical response and 5 showed a partial clinical response, for an overall response rate of 71% [77]. All sites of metastatic disease responded, including 75% of visceral indicator lesions. Hematologic toxicity was significant, with 24% of patients having a WBC nadir of $\leq 1000/mm^3$. A follow-up study of 83 evaluable patients resulted in a complete response rate of 37% and a partial response rate of 31% [79]. The complete responders included ten patients who were found to be pathologically free of disease at the time of surgical restaging and ten subjects who had residual disease resected after chemotherapy. The median duration of survival for all treated patients was 12 months. Toxicity was significant, with 17 patients having fever and neutropenia and 4 subjects dying of complications related to treatment. Relapses in the brain occurred in 18% of responders, half of whom did not have a systemic relapse, suggesting that the central nervous system may be a sanctuary site in patients who achieve a remission at other sites.

A number of other groups have reported their experience with the M-VAC regimen. Tannock et al. [85] treated 41 patients and noted 4 complete and 8 partial responses, for an overall response rate of only 40% in 30 evaluable patients. Toxicity was formidable, with 90% of patients having a WBC of $<500/mm^3$ and at least one dying of sepsis. This series included a larger percentage of patients with M+ disease than did the Memorial series, and this may partially explain the diminished response and enhanced toxicity. A report of the Japanese experience [29] duplicated the high level of activity found by the Memorial group, showing an overall response rate of 57% in 58 evaluable patients. However, the response in liver and bone was disappointing, with a 21% response rate being obtained at these sites. The median duration of survival for all patients was 8 months. Severe myelosuppression was noted, with two toxic deaths being recorded; however, nephrotoxicity was not prominent. The GU Group of the French Federation of Cancer Centers has reported their experience with M-VAC in an abstract [5]. The overall response rate was 59% in 64 evaluable patients. Hematologic and renal toxicity was tolerable.

The results of two important phase III comparisons using M-VAC are currently available. The Intergroup trial [36] compared single-agent cisplatin given at 70 mg/m^2 with the M-VAC regimen. A total of 266 patients with advanced TCC were entered from October 1984 to April 1989. In 224 evaluable patients, the rate of response to cisplatin alone was 9% and that for M-VAC was 33% (P <0.001). The median duration of survival was 8.7 months for cisplatin and 12.6 months for M-VAC (P = 0.002). M-VAC was significantly more toxic than single-agent cisplatin, and only 18% of the scheduled M-VAC cycles were given without dose reductions or delays. The M. D. Anderson group has reported the results of a prospective randomized trial [37] comparing the M-VAC regimen with CISCA (cisplatin, cyclophosphamide, and Adriamycin). Of the 110 patients who were randomized, 102 were evaluable for response; responses were reported using clinical criteria, and pathologic restaging was not required. The complete response rates for M-VAC and CISCA, respectively, were 35% and 25%, and the partial response rates were 30% and 21%. Only a comparison of the total response rate (65% for M-VAC vs 46% for CISCA) achieved statistical significance (P <0.05). However, the median duration of survival significantly favored M-VAC (62.6 weeks vs 40.4 weeks for CISCA; P = 0.0003). No significant difference in toxicity was found between the two regimens.

The increasing availability of hematopoietic growth factors in clinical practice may enable investigators to use higher doses of myelosuppressive drugs in combination chemotherapy for advanced bladder cancer. In a study conducted by the Memorial Sloan-Kettering Cancer Center, 27 patients with advanced TCC receiving M-VAC at standard doses were also treated with recombinant human granulocyte colony-stimulating factor (rhG-CSF) [17]. A significant reduction in the number of days of neutropenia and in the incidence and severity of mucositis was observed, as was a significant increase in the number of patients whose hematologic indices were adequate for further chemotherapy at mid-cycle. In another study, human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) was investigated in a phase I trial using escalated doses of M-VAC [38]. The maximum tolerated dose of rhGM-CSF was 250 μg/m^2 daily given s.c. for 10 days. Complete and partial responses were seen in 12 of 30 evaluable patients, all of whom had received previous systemic chemotherapy. Although the administration of hematopoietic growth factors may enable the escalation of doses of standard agents, it is not known whether this will enhance the antitumor efficacy of these regimens in advanced TCC.

The anthracycline epirubicin, an analogue that may be less cardiotoxic than Adriamycin, has been substituted for the latter drug in the M-VAC regimen. In a series from West Germany [66], 53 patients with advanced TCC were treated with M-VEC, with 30 mg/m^2 epirubicin replacing Adriamycin in the standard M-VAC schedule. The overall response rate was 70%, and only one case of "decreased" cardiac function was noted. In another preliminary report, the combination of methotrexate, vindesine, epirubicin, and cisplatin given every 3–4 weeks produced 14 responses in 19 evaluable patients [22]. Subsequent studies should define the role of this agent more fully and confirm these early promising results in the combination chemotherapy of advanced TCC.

Neoadjuvant chemotherapy

The impressive results reported for combination chemotherapy based on cisplatin and methotrexate have led many investigators to use these drugs in a neoadjuvant fashion prior to definitive therapy for the primary bladder lesion. The theoretical benefits of this approach include down-staging of the original tumor so as to improve the chances for curative resection or to reduce the extent of surgery, identification of tumors that are "sensitive" to chemotherapy for purposes of postoperative adjuvant chemotherapy, treatment of micrometastatic disease at a time during which the tumor burden is smallest and most kinetically active, and sterilization of the primary bladder tumor to prevent dissemination of malignant cells in the operative field at cystectomy [27]. Potential disadvantages of the neoadjuvant approach include the risk of tumor progression during the period of chemotherapy, the difficulties in determining the response of the primary bladder lesion on clinical grounds, and the observation that some patients who receive neoadjuvant therapy would likely have been cured with definitive local therapy alone and are thus exposed to unnecessary and potentially fatal toxicity [14]. There has been a proliferation of trials of neoadjuvant chemotherapy prior to cystectomy, with most using the CMV or M-VAC regimens and the vast majority being single-arm phase II studies. In some cases, chemotherapy has been given by the intra-arterial route. There is considerable variability in these trials because of differences in patient selection, the inclusion of some patients with T2 lesions, the extent of restaging, and the criteria for response [101].

Although it is clear that often dramatic down-staging of bulky bladder lesions does occur, the exact role of neoadjuvant chemotherapy remains uncertain. In light of the heterogeneity of the patient populations treated in these nonrandomized trials, a definitive answer must await the completion of large phase III comparative studies of sufficient sample size. The United States Intergroup study, which is being conducted by the SWOG, the ECOG, and the CALGB, is currently enrolling patients with muscle-invasive tumors in a randomized trial for treatment in the presence and absence of M-VAC prior to radical cystectomy. The EORTC has also initiated a randomized trial testing the addition of neoadjuvant CMV chemotherapy to definitive local treatment of invasive bladder cancer. We must await the results of such studies to determine whether initial chemotherapy will improve upon the outcomes achieved by definitive local treatment.

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Note added in proof: New data have demonstrated the activity of continuous infusion gallium nitrate in advanced TCC. Four partial responses were seen in 23 patients, all of whom had prior therapy with cisplatin-based regimens, who received gallium nitrate at a dose of 350 mg/m^2/d for 5 or more days. See Seidman AD et al. (1991) Continuous infusion gallium nitrate for patients with advanced refractory urothelial tract tumors. Cancer 68: 2561. Gallium nitrate is currently undergoing study in combination with established regimens.