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The Current and Future Application of Adjuvant Systemic Chemotherapy in Patients with Bladder Cancer Following Cystectomy

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Urothelial transitional cell cancer has a high rate of response ($\geq$50%) to combination cytotoxic therapy, especially regimens that are designed around cisplatin. Approximately 50% of patients with high-grade bladder cancer and deep muscle invasion ultimately die of disseminated disease. High-risk patients with pT3-pT4 and node-negative disease have no more than a 5-year overall survival of 47% after cystectomy; patients with lymph node metastases have an overall 5-year survival rate of up to 31% after radical cystectomy [1,2]. However, translating the high response seen in locally advanced disease into long-term survival in the metastatic setting and to improved survival in the advanced setting has proved difficult [3,4]. This article reviews the use of adjuvant chemotherapy in localized or locally advanced transitional cell cancer. The chemotherapy of urological malignancies, including bladder cancer, has recently been reviewed in detail [5]; this article does not contain an extensive review of the drugs used.

Role of systemic therapy in urothelial cancer: regimen selection

Cisplatin has been the cornerstone of systemic therapy for advanced urothelial cancer for 25 years and remains so (Table 1) [6–21]. Table 2 details the acronyms, schedule, and dosing of more commonly used chemotherapy regimens for urothelial cancer [20,22–25]. Sequential trials in this setting tell us that: cisplatin is superior to supportive care, at least in contemporaneous controls; combination therapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) is superior to cisplatin alone [14] and to cyclophosphamide, doxorubicin, and cisplatin (CISCA) [15]; and therapy with gemcitabine and cisplatin is equivalent to MVAC but has less morbidity [20]. Several other platin-based combinations have shown promising activity in phase II trials, including ifosfamide, paclitaxel, and cisplatin and cisplatin or carboplatin, gemcitabine, and a taxane [23,25–27]. Whether triplet therapy carries any advantage over doublet therapy has yet to be demonstrated. The European Organization for the Research and Treatment of Cancer (EORTC) with the assistance of the Southwest Oncology Group (SWOG) and several other groups have concluded a trial comparing gemcitabine and cisplatin (GC) with GC plus paclitaxel in advanced transitional cell cancer (TCC) with results available soon [21]. Carboplatin is a popular alternative to cisplatin in some centers, but its equivalence to cisplatin has not be shown in transitional cell carcinoma and its use should probably be reserved for patients with impaired renal function or other contraindication to cisplatin except in the context of a clinical trial [28].

In terms of duration of therapy for advanced transitional cancer, most clinicians do not continue therapy indefinitely until progression or extreme

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Table 1
A brief history of systemic chemotherapy for metastatic transitional cell cancer

Year	Advance made	References
1976	Cisplatin enters clinical trials and demonstrates single agent activity in TCC as does doxorubicin	[6–8]
1981–1982	Methotrexate and vinblastine demonstrate single agent activity in TCC	[9,10]
1985	MVAC and CMV combinations reported	[11–13]
1990–1992	MVAC demonstrated superior to cisplatin alone and cisplatin, cyclophosphamide, doxorubicin in combination	[14–16]
1993	Taxanes demonstrates single agent activity in TCC Ifosfamide "active" in TCC	[17,18]
1996	Gemcitabine demonstrates single agent activity in TCC	[19]
2000	Gemcitabine and cisplatin equivalent in efficacy to MVAC with less toxicity	[20]
2004	EORTC trial of GC versus GC plus paclitaxel completed	[21]

Abbreviations: CMV, cisplatin, methotrexate, and vinblastine; EORTC, European Organization for the Research and Treatment of Cancer; GC, gemcitabine and cisplatin; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; TCC, transitional cell cancer.

toxicity. Rather, a defined course of therapy is given until maximal response is assessed to be achieved. While there is little definitive evidence for this, experience in non–small cell lung cancer and breast cancer suggests that this response is generally obtained in the first 9 weeks of therapy and further response is unlikely after 12 to 18 weeks and certainly after 24 weeks.

A historical review of the clinical trials of adjuvant chemotherapy

Multiple cisplatin-based combinations have been evaluated in the adjuvant setting after the promising results of cisplatin-based therapy for patients with metastatic disease (Table 3) [29–37]. Logothetis and colleagues [38] administered CISCA to a group of 71 postcystectomy patients with resected nodal metastases, extravesicular extension, lymphovascular invasion, or pelvic visceral invasion. These patients were compared in a nonrandomized fashion with 62 high-risk patients and 206 low-risk patients who did not receive adjuvant chemotherapy. The authors concluded that adjuvant CISCA conferred a 2-year disease-free survival advantage to patients with unfavorable pathologic findings (70% vs 30%; $P = .00012$). The earliest randomized control trial of combination chemotherapy administered to patients after radical cystectomy was conducted at the University of Southern California (USC) [39]. Ninety-one patients with p3, p4, or node-positive TCC were randomized to four cycles of cyclophosphamide, adriamycin (doxorubicin), cisplatin (CAP) or to observation. Chemotherapy resulted in a significant improvement in the risk of disease recurrence at 3 years (0.30 vs 0.54; $P = .011$ [unstratified Wilcoxon test]) and in the overall risk of death (0.34 vs 0.50; $P = .099$ [unstratified Wilcoxon]). The median survival of patients on chemotherapy was reported to be 4.25 years versus 2.4 years for patients in the observation group. This study has been criticized for the fact that only 33 out of 44 patients assigned to the chemotherapy arm received one or more cycles of CAP, for the small sample size, and for deficiencies in statistical analysis such as the use of the Wilcoxon test emphasizing early differences. Nonetheless, the study was provocative in revealing the potential benefit of adjuvant chemotherapy and in highlighting the difficulties involved in conducting such trials.

A subsequent trial of adjuvant chemotherapy with three cycles of cisplatin alone did not result in any survival benefit in a randomized study of 77 patients [40]. Potential explanations for the lack of significant benefit include the use of single-agent cisplatin, the small sample size, the inclusion of patients with lower T stage and lymph node–negative disease, and the administration of the three planned cycles of chemotherapy to only 65% of patients in the treatment arm.

Given the superiority of the MVAC combination over single-agent cisplatin in the metastatic setting [14], it became important to evaluate the MVAC or methotrexate, vinblastine, epirubicin, and cisplatin (MVEC) combinations in the adjuvant setting. Stockle and colleagues [41] randomized patients with pT3, pT4, and/or pelvic lymph nodes to three cycles of MVAC or MVEC versus observation. Although the study intended to accrue

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