Systemic Therapy for Invasive Bladder Cancer

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Combined systemic chemotherapy and local treatment may improve outcomes for patients with locally advanced bladder cancer.

Introduction

Bladder cancer is one of the most common malignancies in Western society. This year, approximately 52,900 new cases will be identified in the United States, with the majority of incident cases representing superficial bladder cancer.[1] However, approximately 10,000 of these patients will have invasive disease at first presentation, and additional cases will subsequently become invasive after failure of treatment of superficial disease.

Because more than 50% of newly diagnosed patients with invasive bladder cancer will develop metastases despite treatment of the primary tumor, invasive bladder cancer can be regarded as a systemic disease.[2] The hypothesis that foci of micrometastatic disease are present early in the course of the disease has led to the use of systemic chemotherapy in addition to locoregional treatment in an attempt to improve cure rates (Figs 1 and 2).[3]

Evolution of Systemic Chemotherapy for Bladder Cancer

Most chemotherapy programs for bladder cancer evolved through the management of patients with metastatic disease. The early clinical trials showed limited activity of several single agents, including cyclophosphamide, the vinca alkaloids, methotrexate, fluorouracil, doxorubicin, and cisplatin,[4] and the list has been recently expanded to include mitomycin, ifosfamide, gallium nitrate, paclitaxel, and gemcitabine.[2,5-7]

Several initial trials assessing the impact of combination chemotherapy vs single agents failed to demonstrate a survival benefit from the combination regimens, despite a higher response rate.[2] However, an international randomized trial[8] revealed that the M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimen yields increased response rate, as well as progression-free and total survival, when compared with single-agent cisplatin. These results were confirmed in another comparison of M-VAC vs the combination of cyclophosphamide, doxorubicin, and cisplatin.[9] At the Annual Scientific Meeting of the American Society of Clinical Oncology in May 1996, a report on the long-term follow-up of the international trial revealed 2% five-year survivors following treatment with cisplatin alone compared with 17% alive after treatment with the M-VAC regimen.[10] Thus, M-VAC constitutes the current standard treatment for patients with metastatic disease, although the low cure rate with this regimen demonstrates the need for more effective treatments. - See hard copy of journal for table 1.

Neoadjuvant Chemotherapy for Invasive Disease

The rationale for the use of initial (neoadjuvant) chemotherapy in this clinical context has been addressed earlier.[3] In brief, possible benefits include tumor downstaging with the increased possibility of resection, the potential for in vivo assessment of anticancer efficacy, improved access to tumor tissues before the onset of the vascular effects of irradiation, and possible radiosensitization. A possible drawback is the use of ineffective treatment, thus delaying the onset of potentially active treatment approaches (such as radiotherapy or surgery).

The early clinical trials of neoadjuvant chemotherapy were predominantly of noncomparative phase I-II design and thus were subject to accrual biases such as patient selection factors, increased sophistication of staging (with stage migration), and premature reporting of immature survival data. As a result, the early assessment of the clinical relevance of these studies may have been unduly optimistic. Despite the encouraging results of the early nonrandomized single-agent trials, randomized clinical trials that tested single-agent chemotherapy plus local treatment vs local treatment alone did not show any benefit from this strategy (Table 2).[20,21,23] Similarly, the...
use of combination chemotherapy regimens as neoadjuvant treatment initially appeared attractive, but most later follow-up studies did not indicate any apparent long-term benefit.[24] By contrast, the Nordic Cooperative Bladder Cancer Study Group has reported that two cycles of neoadjuvant cisplatin and doxorubicin confer a reduced death rate in patients with T3 and T4 bladder cancer who are treated by cystectomy, albeit with a relatively weak statistical power.[25]

A recent meta-analysis[26] of all known randomized trials reviewed 479 cases and compared local treatment vs neoadjuvant chemotherapy followed by local treatment. The use of neoadjuvant chemotherapy was associated with an overall hazard ratio of 1.02 (favoring local treatment) and a 2% increase in relative risk of death. However, this study was dominated by single-agent trials. Similar findings were provided by the International Intergroup (MRC/EORTC) Trial[22] in which nearly 1,000 patients were randomly allocated to receive either neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) plus local treatment or local treatment alone. The first report of this study failed to reveal a significant survival difference between the two arms.

Although an important United States intergroup trial has not yet been reported, little current evidence supports the routine use of neoadjuvant chemotherapy. It is our belief that such treatment programs should be conducted only in the context of a randomized clinical trial.

**Adjuvant Chemotherapy**

The beneficial use of adjuvant systemic chemotherapy, in which cytotoxics are delivered after the control of local tumor (by complete resection or by radical radiotherapy), has its paradigms in the management of breast cancer and colorectal cancer. In the context of bladder cancer, several early nonrandomized phase II trials have been reported but without useful conclusions. More recently, Skinner and colleagues[27] conducted a randomized trial for patients with deeply invasive bladder cancer that was staged at cystectomy. Half of the patients enrolled on this trial received adjuvant treatment with cyclophosphamide, doxorubicin, and cisplatin. Although the interpretation of this study has been controversial, survival benefit achieved by this strategy is small, as the survival curves had already crossed at four years. The interpretation of this study has been controversial, survival benefit achieved by this strategy is small, as the survival curves had already crossed at four years. The results of a randomized trial by Stockle et al[28] may hold more interest for future strategic planning. In this study, patients with stages pT3b or pT4 bladder cancer (defined at cystectomy and lymph node dissection) were randomly allocated to receive adjuvant M-VAC or equivalent chemotherapy vs observation. A disease-free survival benefit was reported (73% vs 19%, respectively). However, the statistical power of the study was diminished by limited patient enrollment due to early closure when it was recognized that the trial design required patients on the observation arm to forego salvage chemotherapy at the time of relapse. Thus, this study assessed only the impact of chemotherapy at some time after cystectomy and was not a true test of adjuvant treatment.

Of greater relevance to this hypothesis is a randomized trial[29] in which cystectomy plus adjuvant CMV was compared with cystectomy alone (but with CMV offered at the time of relapse). While this study also was limited by small patient numbers, it demonstrated a statistically significant increase in disease-free survival and a trend toward improved overall survival from the use of adjuvant CMV chemotherapy. However, caution is indicated by the report of a nonrandomized experience involving 56 patients with adjuvant CMV chemotherapy for stages pT2 through pT4 and node-positive disease.[30] The median disease-free survival was 15.5 months, but the three-year disease-free survival probability was only 28%. Again, a definitive statement regarding the role of adjuvant chemotherapy requires the results of a statistically valid randomized trial, although the current weight of evidence suggests a survival benefit from adjuvant M-VAC or CMV chemotherapy.

**Perioperative Chemotherapy**

Another variant of the combination of systemic chemotherapy with definitive locoregional treatment is the use of cytotoxic agents administered before and after the local therapy. The first major trial[20] of such an approach predominantly assessed the impact of neoadjuvant methotrexate but also included a component of adjuvant therapy after completion of definitive treatment. No survival gain was noted when this approach was compared with standard treatment.

In a pilot study conducted by the Eastern Cooperative Oncology Group,[31] two cycles of M-VAC were administered before cystectomy, followed by two additional cycles. Seventeen patients had T3 disease and one had a stage T2 tumor, and nearly half the cases showed downstaging in response to M-VAC. However, at a median follow-up of 23 months, 50% had died. Logothetis and colleagues[32] tested a similar hypothesis in a randomized trial in which 100 patients were randomized to receive either two cycles of M-VAC followed by cystectomy and three adjuvant cycles of M-VAC or initial cystectomy followed by five cycles of adjuvant M-VAC. Survival was equivalent in both arms, despite the significant level of downstaging after neoadjuvant chemotherapy. Both trials revealed an unexpectedly high rate of intercurrent deaths from vascular complications, which further demonstrates the importance of randomized trials in the assessment of these novel strategies of management.

![Table 2](https://example.com/table.png)
Concurrent Chemoradiation

Doxorubicin, fluorouracil, mitomycin C, carboplatin, and cisplatin exhibit the characteristic of radiosensitization, ie, altering the responsiveness of both tumor and normal tissues to the cytotoxic effects of irradiation. Predicated on this feature, clinical trials have been initiated in which these cytotoxic agents are given during the period of radiotherapy to increase the level of tumor kill, with the hope that a sufficient discriminant in toxicity between normal and malignant tissues will protect the patient from excessive side effects.

Several phase II trials have assessed the impact of single agents (fluorouracil, carboplatin, doxorubicin, and cisplatin) and combination regimens (fluorouracil and cisplatin) in radiosensitizing protocols[33-36] and have demonstrated significant tumor reduction (Table 3). In most of these studies, chemotherapy has been combined with radiotherapy as the definitive local treatment, although one study assessed the use of doxorubicin-induced radiosensitization as adjuvant therapy after surgery. To date, it is unclear if these approaches confer a survival benefit, notwithstanding their efficacy in achieving local tumor control.[40] In a report of a randomized trial conducted by the National Cancer Institute of Canada, Coppin et al[37] showed that a statistically significant increase in local tumor control could be achieved by the concurrent use of cisplatin and radiotherapy (compared with radiotherapy alone), but a survival benefit from the combination regimen was not seen. No other randomized trials have assessed the potential survival benefit of this approach. Given the changes in tumor classification, staging, available cytotoxics, and support therapy, it is our view that at least one convincing randomized trial is required to establish the role of chemoradiation as a standard of therapy. However, this view is not universally held. For example, Shipley has expressed the view that the Canadian NCIC study has established the role of chemoradiation in achieving local control and that this should be incorporated into other randomized trials to assess innovations in neoadjuvant or adjuvant systemic therapy (personal communication, 1996).

Conclusions

After more than a decade of investigation on the combination of systemic chemotherapy and definitive local treatment, it appears that this regimen may be beneficial in the management of locally advanced bladder cancer. However, the optimal schedules and the extent of true survival benefit have not yet been demonstrated. Current data indicate that the most promising future strategy will be the incorporation of adjuvant systemic chemotherapy in some way into treatment programs. However, the design and implementation of well-structured, randomized clinical trials are needed to resolve these issues. In this era of managed care and contained medical costs, it may be difficult to conduct these studies unless the academic leaders of the medical community take a stand on these issues and secure cooperation from community practitioners to enroll eligible patients in these trials.

References


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