Perioperative chemotherapy for muscle-invasive bladder cancer

Peter Black, MD, FRCSC; Alan So, MD FRCSC

Abstract

Considerable debate exists concerning the combined use of systemic chemotherapy and radical surgery for muscle-invasive bladder cancer. While there is evidence for a survival benefit after neoadjuvant chemotherapy, the benefit is modest and the potential toxicity and delay of time to surgery prior to cystectomy appears to be deterring many surgeons from its administration. The evidence for adjuvant chemotherapy, on the other hand, is less compelling and substantial. Furthermore, the role of adjuvant compared to salvage chemotherapy requires further investigation. Similarly, research continues on identifying molecular and clinical markers to best stratify patients for optimal perioperative therapy. In this article, the evidence for radical cystectomy and chemotherapy, given either in a neoadjuvant or adjuvant setting, will be reviewed.

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Transitional cell carcinoma of the bladder is chemosensitive,[1-3] but its use in the neoadjuvant and adjuvant settings combined with radical cystectomy remains controversial. Despite aggressive surgical management, up to 50% of patients with muscle-invasive bladder cancer will develop tumour recurrence, suggesting that a significant proportion of these patients have micro-metastases at the time of surgery.[4] Early application of multimodal therapy in bladder cancer is therefore an attractive paradigm.

The case for neoadjuvant chemotherapy

The level I evidence demonstrating a survival benefit with neoadjuvant chemotherapy has now been established for several years. The data have been compiled in multiple prior reviews and have also been analyzed in three pertinent meta-analyses.[5-7] The primary data include, most notably, two Nordic trials,[8-10] a combined UK Medical Research Council/European Organizations for Research and Treatment of Cancer (MRC/EORTC) trial[11] and an Intergroup trial in the United States.[12] These trials have been conducted on patients with T2-T4a, N0 M0 disease and incorporated various cisplatin-based regimens.

Improvements in survival rates with neoadjuvant chemotherapy have been modest. The Intergroup trial showed the widest 5-year survival margin, namely 57% in 153 patients undergoing cystectomy after chemotherapy compared to 43% in 154 patients undergoing cystectomy alone.[12] This translates into a median survival increase from 46 to 77 months. This trial was also noteworthy because it used MVAC (methotrexate, vinblastine, adriamycin, cisplatin), the most efficacious chemotherapy regimen. In the larger MRC/EORTC trial of 976 patients there was a 6% absolute increase in overall survival at 5 years.[11] A similar magnitude of survival benefit was found in the 3 meta-analyses comprising about 3000 patients, with a survival advantage at 5 years of 50% compared to 45%. These meta-analyses included patients who underwent radiotherapy for local treatment, although this did not appear to influence survival.

Secondary reasons to support the use of neoadjuvant chemotherapy for muscle-invasive bladder cancer include an increased probability of having no residual cancer in the cystectomy specimen (pT0) and a reduced rate of positive surgical margins.[12,13] The pT0 rate increased from 15% to 38% in the Intergroup trial and from 12.3% to 32.5% in the MRC/EORTC trial. Patients with pT0 disease have an excellent survival rate, and those with positive surgical margins invariably succumb to the disease.

A further advantage of neoadjuvant chemotherapy is the ability to monitor tumour response during therapy. This offers prognostic information and allows modification of therapy based on response. This is not only of clinical utility but it also makes the neoadjuvant setting particularly attractive for testing novel agents. The efficacy of novel agents can be assessed by gross tumour response and by molecular markers of response (pharmacodynamics) in the surgical specimen.

Controversy remains regarding the selection of patients for neoadjuvant therapy. While some centres encourage its use in any patient with muscle-invasive disease (clinical T2 or greater),[14,15] others reserve it only for locally advanced disease (cT3/T4a). Further risk stratification may include patients with cT2 tumours associated with hydronephrosis or lymphovascular invasion, since patients with these risk factors fare as poorly as patients with cT3

tumours.[13,16] The argument against use in patients with cT2 tumours is that these patients have an excellent likelihood of cure with cystectomy alone and the incremental benefit of neoadjuvant chemotherapy may not be worth the risk of toxicity. The absolute survival benefit of neoadjuvant chemotherapy appears to be the same across all stages but the relative improvement is greater for higher stages.[6,17] While an improvement from 55% to 60% in T2 disease is only a relative benefit of 9%, an improvement from 25% to 30% for pT4a disease is a relative increase of 20%.

Further controversy surrounds the choice of chemotherapy. The level I evidence for neoadjuvant chemotherapy is based on MVAC, CMV (cisplatin, methotrexate, vinblastine) and similar regimens and MVAC must therefore be considered the gold standard. Most medical oncologists, however, have abandoned MVAC in favour of gemcitabine and cisplatin (GC) due to the reduced toxicity.[2] This choice is based on extrapolation of data using GC in patients with metastatic disease and has not been adequately tested for neoadjuvant therapy. Limited single-institution retrospective data are conflicting.[15,18] While a careful balance must be found between toxicity and efficacy in patients with metastatic disease where the goal is palliation, there is no tolerance for poorer efficacy in the neoadjuvant setting especially in younger healthier patients. Dose-dense MVAC, which has also only been tested for metastatic disease, is used by some instead of traditional MVAC to reduce toxicity.[3]

The case against neoadjuvant chemotherapy

The main shortcoming of neoadjuvant chemotherapy is the potential toxicity, especially when balanced with the modest benefit and the risk of overtreatment in a large proportion of patients. There is a paucity of data for assessing toxicity from neoadjuvant chemotherapy.[12,13,19] and the fear of toxicity relates more to traditional MVAC or similar regimens, even though most patients are currently receiving the less toxic GC.[2,20] It would therefore appear that the hesitation to administer neoadjuvant chemotherapy may be exaggerated. There is some data to indicate that surgical complications are not increased after neoadjuvant chemotherapy.[19] Many urologists offer anecdotal reports that the surgery itself is more difficult after neoadjuvant chemotherapy. The big experience at MD Anderson Cancer Center has revealed an increased risk of prolonged post-cystectomy ileus after neoadjuvant MVAC (Colin Dinney, personal communication)

If ineffective chemotherapy is delivered, there is a delay in definitive local therapy, which can be potentially detrimental to overall survival.[21] The evidence would indicate that only those patients with a major response to neoadjuvant chemotherapy benefit from it, and there is also the presumption that those without a major response may be harmed by the delay in cystectomy. It will be important in the future to develop better tools for risk stratification and response prognostication in patients with locally advanced disease to direct a more efficient use of neoadjuvant chemotherapy.[22]

The benefit of neoadjuvant chemotherapy is uncertain is some clinical scenarios. Aberrant histologies such as micropapillary and sarcomatoid bladder carcinoma have either a reduced or an unknown response to common urothelial chemotherapy regimens.[23] Lack of efficacy would make the additional delay in surgery detrimental, so that primary radical cystectomy is preferred by most. Small cell carcinoma is an exception; it requires immediate multiagent chemotherapy.[24]

Additional challenges are posed by the elderly and patients with renal failure. Older patients are less likely to tolerate both surgery and chemotherapy and for this reason may not be offered neoadjuvant therapy. Many elderly but otherwise healthy patients will tolerate both modalities, however, and their treatment should not be compromised based on age alone. The use of cisplatin is restricted in patients with renal failure and has led to the investigation of carboplatin as an alternative,[25] but we know from the metastatic setting that this agent is less efficacious against transitional cell carcinoma, so alternate regimens require investigation.[26]

The case for adjuvant chemotherapy

The primary advantage of adjuvant chemotherapy is that it can be tailored to individual patient risk based on pathological criteria. Such risk stratification is superior to any preoperative clinical assessment and may therefore prevent the overtreatment of good prognosis patients, especially those with ≤pT2 disease who have a 5-year recurrence-free survival of up to 80%.[4,27] Since cystectomy is the single most effective therapy for resectable disease, it may be advantageous to perform surgery first, thereby avoiding the delay necessary when neoadjuvant chemotherapy is administered.[28-30] Furthermore, compared to salvage chemotherapy, adjuvant chemotherapy allows treatment of potential metastatic disease when tumour burden is at its minimum rather than waiting for clinically recognizable metastatic disease to occur. Thus, adjuvant therapy may allow for optimal timing of surgery and personalization of chemotherapy.

The case against adjuvant chemotherapy

A theoretical disadvantage of adjuvant chemotherapy is the delay in treatment of potential micro-metastatic disease while the patient undergoes and recovers from surgery. The delay from time of initial diagnosis to radical cystectomy, combined with the delay from time of surgery to the time of starting chemotherapy, may represent a

clinically significant delay to systemic treatment. This delay may further escalate if patients develop surgical complications. Moreover, fewer patients will receive systemic chemotherapy in the adjuvant setting compared to a neoadjuvant setting.[13] An additional disadvantage of adjuvant chemotherapy is the lack of measurable disease from which to assess tumour response.[31] It is therefore impossible to tailor therapy to response, and efficacy of adjuvant therapy may only be assessed after tumour recurrence or death.

The ultimate argument against adjuvant chemotherapy at this time is the lack of evidence supporting its clinical efficacy. Although several randomized controlled trials (RCTs) evaluating adjuvant chemotherapy have been conducted, most have significant shortcomings and the evidence is therefore less convincing than for neoadjuvant chemotherapy. The data are summarized in Table 1. The University of Southern California trial, for example, showed enhanced time to progression and median overall survival in patients with pT3/T4 or pN+ bladder cancer receiving cisplatin-based combination chemotherapy after radical cystectomy.[32] This was the first trial to demonstrate a potential benefit for adjuvant chemotherapy but has been criticized for methodological flaws, including heterogeneity in chemotherapy regimens and small sample size.

Similar results were obtained in 2 even smaller studies in Germany[33-35] and Stanford.[36] Both studies were stopped early due to the benefit in time to progression found at interim analysis. Both studies continued to show enhanced disease-free survival at 10 and 5 years, respectively, but there was no improvement in overall survival (OS) at the same time points. This may be related to small sample size. The German study, in which the OS advantage is nearly significant, has been criticized because most patients with recurrences in the observation arm did not receive salvage chemotherapy.[35] The Stanford study, on the other hand, cites the administration of salvage chemotherapy as a possible reason for the lack of benefit for OS.[36] Another problem with some of these trials is that up to 25% of patients randomized to chemotherapy did not receive it.[35] The Swiss trial is considered deficient because single-agent cisplatin has been shown in other trials to be insufficient therapy.[37]

The most recent results assessing the efficacy of adjuvant chemotherapy have been reported by the National Research Council in Italy where patients with pT2 or higher-staged disease were randomized to receive 4 cycles of GC given adjuvantly or at time of relapse (salvage). This study accrued 194 patients and preliminary results at 3 years showed that OS was 48% in patients receiving adjuvant chemotherapy compared to 67% in the salvage arm, but the differences were not statistically significant.[38,39]

A recent meta-analysis assessing adjuvant chemotherapy from six RCTs with a total of 491 patients showed a 9% improvement in absolute survival at 3-year (HR 0.75, 95% CI 0.60-0.96, $p = 0.019$).[40] However, the authors point out that the sample sizes for all of the studies were too low and a definitive recommendation for adjuvant chemotherapy could not be made.

Although methodologically imperfect and inadequately powered, these RCTs show that adjuvant chemotherapy is feasible and safe. The data indicate that patients most likely to benefit are those with high-risk disease (pT3/4 and/or pN+).[41] Further risk stratification may be possible with

Table 1. Randomized control trials of adjuvant chemotherapy after radical cystectomy for muscle-invasive bladder cancer

Study	Chemotherapy	No. patients		Benefit	Benefit
		Chemotherapy	No chemotherapy		
USC – Skinner, 1991[32]	CAP	47	44	Yes	3-yr DFS: 70% vs. 46% ($p = 0.001$) median survival: 4.3 vs. 2.4 yrs ($p = 0.006$)
German – Stockle, 1992[34]	MV(A/E)C	26	23	Yes	10-yr DFS: 41.7% vs. 17.4% ($p = 0.007$) 10-yr OS: 26.9% vs. 17.4% ($p = 0.069$)
Swiss – Studer, 1994[37]	Cisplatin	40	37	No	5-yr OS: 57% vs. 54% ($p = 0.65$)
Stanford – Freiha, 1996[36]	CMV	25	25	Yes	5-yr DFS:50% vs. 22% ($p = 0.01$) 5-yr OS: 54% vs. 34% ($p = 0.32$)

CAP = cyclophosphamide, doxorubicin and cisplatin; MV(A/E)C = methotrexate, vinblastine, doxorubicin or epirubicin, and cisplatin; CMV = cisplatin, methotrexate and vinblastine; DFS = disease-free survival; OS = overall survival.

molecular characterization of bladder cancer, although a multi-centre trial randomizing patients to adjuvant chemotherapy based on p53 status was recently closed early after an interim analysis demonstrated insufficient benefit.[42]

Conclusion

There continues to be considerable controversy around the use of systemic chemotherapy for muscle-invasive bladder cancer. While there is high-level evidence for a survival benefit after neoadjuvant chemotherapy, the benefit is modest and the potential toxicity before planned cystectomy appears to be deterring many physicians from its administration. The evidence for adjuvant chemotherapy, on the other hand, is less compelling and the role of adjuvant compared to salvage chemotherapy requires further investigation. At the same time, research continues on identifying molecular and clinical markers to best stratify patients for optimal perioperative therapy. Finally, with the advent of targeted therapies, one can anticipate new treatment paradigms and improved patient outcomes in the near future.

From the Department of Urologic Sciences, UBC, Vancouver, BC

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Correspondence: Dr. Alan So, The Prostate Centre at the Vancouver General Hospital, 2660 Oak Street, Vancouver, BC V6H-3Z6; fax: 604-875-5654; alan.so@ubc.ca