Symposium

Role of systemic peri-operative chemotherapy in management of transitional cell carcinoma of bladder

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ABSTRACT

Bladder cancer has variable biological behavior pattern in different individuals and the debate regarding peri-operative use of systemic chemotherapy with the surgical management remains. The optimal treatment strategy, regimen and the timing of peri-operative chemotherapy are not yet known. Here we review the existing literature for the use of systemic peri-operative chemotherapy in management of advanced bladder cancer.

Key words: Bladder cancer

INTRODUCTION

Bladder cancer is among the common urological cancers, being second only to prostate cancer in terms of prevalence among middle aged and elderly men.[1] It is more common in men than women (3:1).[2] About 20-30% of cases present with invasive tumors at diagnosis. Mortality from bladder cancer is also high. Approximately 5000 deaths have been reported to occur per year in UK.[3] Although radical cystectomy provides excellent long-term progression-free survival, recurrences remain a concern particularly for cases with higher stage and grade of disease. Overall 5-year survival rates after cystectomy fall from 50 to 60% for stage T1-T2 to 26-44% for stage pT3b-4 and 13-29% for stage N2-N3.[4] Micrometastasis, both regional and distant, has been considered as an important factor leading to local or distant failure. A report evaluating long-term outcomes after radical cystectomy in patients with T3a and T3b disease showed local and distant recurrence to occur in 9 and 29% of patients, respectively.[5] It is this relatively high incidence of distant failure which implies a potential role for early peri-operative chemotherapy in management of bladder cancer by eradicating the synchronously existing micrometastasis. This theoretical potential to impart survival benefits is similar to the proven role of peri-operative chemotherapy in other visceral tumors like breast, lung and colon cancer. Here we review the existing literature concerning the use, problems and outcomes with the use of systemic peri-operative chemotherapy in management of operable localized or locally advanced bladder cancer.

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CHEMOTHERAPY REGIMENS, REPORTED EFFICACIES AND TOXICITIES

Bladder cancer is a reasonably chemosensitive tumor and as many as 40-70% of cases show some response to chemotherapeutic drugs initially. Several drugs have been used in the past in different clinical settings for treatment of bladder cancer. Single agent therapies have been used, most commonly cisplatin and methotrexate, with limited efficacy and response rates ranging from about 5 to 50%.[6] Combination chemotherapy using multiple drugs has been shown to be superior to the use of single agents in sequential manner.[7,8] Methotrexate, vinblastine, adriamycin and cisplatin (MVAC) regimen, first developed by Sternberg *et al.*,[9] has repeatedly shown survival benefits in several randomized trials and is currently considered the standard to compare efficacy of newer regimens.[8,10] A 14% overall survival advantage

was shown at 5 years in patients receiving neoadjuvant MVAC (57%) compared to those receiving cystectomy alone (43%).[10] This regimen is, however, significantly toxic and may not be tolerated well by many. Cisplatin, methotrexate and vinblastine (CMV) regimen though less toxic and better tolerated is considered to be less efficacious,[11,12] though no head to head direct comparative trials are available. The most significant side effects (grade 3 and 4) include myelosuppression, mucositis, alopecia, nausea, vomiting, infection and diarrhea, which occur frequently enough to merit dose adjustment, or withholding chemotherapy. Only 37% of cycles of chemotherapy were given without needing dose adjustment in one phase III study.[13]

Strategy using dose escalation has been tried to good effect with the availability of recombinant hematopoetic growth factors. High-dose MVAC with granulocyte colony-stimulating factor (GCSF) showed improved overall response rates of 61% (95% CI 54–70%) versus 50% (95% CI 42–59%) for standard MVAC, at comparable toxicity.[14] Other combinations have also been tried in an effort to search less toxic combinations with equal or better efficacy. Gemcitabine and cisplatin (GC) has shown statistically equal response rates and disease free or overall survival times compared to MVAC regimen for patients with advanced bladder cancer, though with lower toxicity and lower treatment-related morbidity and mortality.[13] Presently as per 2010 NCCN guidelines, it is considered as the standard of care ahead of MVAC therapy, which remains a relatively cheaper option.

A host of other chemotherapeutic agents and regimens have been assessed[6] in various clinical settings, but none has demonstrated improved response seen consistently with other standard regimens.

NEOADJUVANT VERSUS ADJUVANT CHEMOTHERAPY

Neoadjuvant therapy refers to systemic chemotherapy when given before a planned radical surgery to be done with a curative intent. It targets to kill micro-metastatic deposits which remain undetermined on present day imaging modalities. Its purported advantages include dealing with micro-metastasis early without any further delay, while waiting for surgery and its outcome. The patient is also in best physiological frame to tolerate the side effects of chemotherapeutic drugs, since radical cystectomy entails a major anatomical resection and alteration in physiological and biochemical mileu of the patient. Also, the response to chemotherapy can be clinically gauged better than in the adjuvant setting, using *in vivo* decrease in size of the bladder lesion before the surgery as a surrogate marker to the chemosusceptibility of the tumor.[15] It is not presently clear as to what percentage of bladder tumors is chemoresistant at presentation and to what drugs. At best, the reported pathological complete response rates of various regimens in neoadjuvant setting are not more than 14-38% and overall response rates not more than 30-65% when used in adjuvant setting.[16,17]

The clinical response of the disease to chemotherapy regimen used in neoadjuvant setting may be used as a benchmark for the use of same or different regimen in the post-op period as adjuvant therapy. Although rare and unproven, neoadjuvant therapy also has the potential of bladder preservation in cases that show complete response. Availability of the tumor tissue biopsy both before and after the chemotherapy is also helpful for research purposes in developing molecular or biological markers to grade chemosensitivity of tumors.[17]

Potential disadvantages of giving chemotherapy before the surgery include delaying the definitive surgical treatment of the locoregional disease by 3 or more months, more so because the biological response of the tumor to the chemotherapy is unknown when the neoadjuvant chemotherapy is to be planned. Whether delay in surgery, in cases that turn out to have chemoresistant tumors, ultimately has any deleterious effect over long-term outcomes is not known. However, some studies do suggest delaying surgery results in poorer outcomes for patients of carcinoma bladder.[18-20] Extrapolating these findings, it seems logical that methods be devised to preoperatively identify that subgroup of cases who are chemoresistant, so that alternative regimens are planned in those cases at the outset. Moreover, the presently available chemotherapy regimens have associated toxicities in a significant proportion of patients, becoming an aversive factor for many clinicians to use neoadjuvant chemotherapy. Besides, neoadvujant therapy is planned based on clinical staging rather than pathological staging. Therefore, some patients may be subjected to overtreatment and undue toxicity of drugs. Staging errors to the tune of 30% have been reported in literature. However, as of now, neoadjuvant treatment has not been shown to increase morbidity or recovery from surgery.

The Medical Research Council and European Organization for Research and Treatment of Cancer (MRC/EORTC) conducted a large randomized multi-institutional trial using CMV as three cycles of neoadjuvant therapy in T_2G_3, T_3, T_{4a}, N_0-N_X and M_0 disease.[21] Local treatment-included radical cystectomy and/or radiotherapy. This trial showed only a 5.5% (non-significant, P=0.075) survival difference at 3 years favoring the chemotherapy arm (55.5%) compared to non-chemotherapy arm (50%). Although small, this difference in survival has been shown to be maintained even at longer follow up of 5 and 8 years (50% versus 44% and 43% versus 37%, respectively) and even attained statistical significance.[22] Statistically significant differences in favor of neoadjuvant chemotherapy have also been reported by the Grossman group using MVAC,[10] and Abol Enein group using carboplatin and MV for T_{2-4} disease.[23] There are other several trials which have shown benefit in the chemotherapy

arm compared to only local treatment though the difference did not reach level of significance.[24-26] A meta-analysis of various studies comprising more than 2600 patients with high-risk bladder cancer showed a significantly improved (5%) overall survival at 5 years (P=0.016) regardless of the type of local treatment used.[27] Thus to say, present literature does favor the use of neoadjuvant chemotherapy in high-risk patients undergoing radical cystectomy.

Chemotherapy is also given preoperatively in cases with advanced loco-regional disease to down-stage the disease so as to achieve negative surgical margins. Neoadjuvant therapy has also been tried together with preoperative radiation therapy.

Adjuvant chemotherapy refers to use of chemotherapeutic agents as an adjunct after radical surgery with curative intent. Its advantages include availability of detailed pathological staging for better prognostication of disease. Also chemotherapeutic drugs have less disease burden to counter after the surgery. It is suggested that increased turnover of the tumor cells in a patient recovering from a major surgery may make the tumor cells more susceptible to chemotherapeutic drugs. Such treatment approach may be associated with less patient anxiety since major tumor burden had already been removed during the surgery itself. This approach was used during early phase of development of chemotherapy for bladder cancer, use being mostly limited to pathologically locally advanced or metastatic disease. However, there are not many well-constructed randomized studies with large number of cases in the adjuvant setting.[28,29] Only few randomized trials have been done using this approach comparing the response to a control arm, and very few have demonstrated clinically significant overall survival advantage,[30] or improved disease-free survival.[30-32] Still, this approach is widely used currently especially for locally advanced or node-positive disease after radical local therapy (cystectomy or radiotherapy), given the inhibition of urologists to use neoadjuvant treatment, and definitive trend of improved survival in most available studies especially for node-positive disease. A summary of survival results from some major randomized studies of neoadjuvant and adjuvant chemotherapy is given in Table 1.

CLINICAL DECISION MAKING AND CURRENT STANDARDS

Radical cystoprostatectomy with regional lymphadenectomy is currently the standard choice treatment for operable clinically organ confined muscle-invasive bladder cancer in males. In females anterior exenteration is its standard counterpart operation. It provides cure in many but disease recurrence is known to occur in as many as 30-50% over the long term.[35] A 73% recurrence-free survival at 5 years

Table 1: Table depicting survival results from various randomized trials of neoadjuvant and adjuvant chemotherapy in cases of muscle-invasive bladder cancer

Study	Number of cases	Type of local therapy	Chemotherapy regimen used	Survival benefit from chemotherapy	Other remarks
Selected randomized trials of neoadjuvant chemotherapy					
Hall, 2002 (MRC/EORTC trial)[21]	976	Cystectomy ± radiation	CMV	15% at 7 years	
Grossman, 2003[22]	317	Cystectomy	MVAC	14% at 5 years	
Malmstrom, 1996 (Nordic I)[33]	325	Cystectomy + radiation	Cisplatin + Adriamycin	15% at 5 years for $T_{3 \text{ and } 4a}$	
Sherif, 2002 (Nordic II)[25]	317	Cystectomy	Cisplatin + Methotrexate	No significant difference at 5 years	
Selected randomized trials of adjuvant chemotherapy					
Skinner, 1991[30]	91	Cystectomy	Cisplatin + Cyclophosphamide + Adriamycin (CISCA)	Significant improvement in time to progression and median survival time No significant difference in overall survival at 3 years	Long accrual time, stastistically underpowered
Stockle, 1995[31]	49	Cystectomy	MVAC or Methotrexate + Vinblastine + Epirubicin + Cisplatin (MVEC)	Significant improvement in relapse free survival at 2 years	Not designed to deduct overall survival, non-chemotherapy arm fared very poorly than usual raising selection bias issues
Studer, 1994[34]	77	Cystectomy	Cisplatin	No significant difference at 5 years	
Frieha, 1996[32]	55	Cystectomy	CMV	Significant improvement in progression free survival No significant difference in overall survival at 5 years	

has been reported for organ-confined disease.[36] Since the majority of recurrences are distant, it is likely that many patients undergoing cystectomy for localized carcinoma have occult metastasis either pre-existing before the surgery which remains unidentified or develop micro-metastasis during handling of malignant tissues at the time of surgery itself. These may later on present as failure of surgery with disease recurrences. To improve upon the results of radical cystectomy, preoperative radiation therapy and peri-operative chemotherapy has been tried. Preoperative radiation therapy was routinely applied three decades earlier with the proposition of downstaging non-resectable disease, treat local micrometastasis and reduce local recurrence rates. However, improvement of disease specific survival has not been demonstrated with it.[37-39] Chemotherapy has since been used more extensively and has shown good response rates with demonstrable survival benefits in several studies.[10,33,40] It aims to impart long-term survival benefits compared to radical local therapy alone (radical surgery or radiotherapy).

Organ confined bladder cancer (T_2 and below)

There are very few studies which have evaluated the role of peri-operative chemotherapy in the setting of T2 disease. Existing evidence from available literature suggests no survival advantage in the Nordic cystectomy I trial,[33] which used the neoadjuvant approach. Since all trials using the adjuvant approach have also focused upon advanced stages of bladder cancer, there is as yet no concrete support in literature for this approach as well in pT2 disease. Since it is presently not possible to conclusively foretell which cases will have positive nodes on subsequent radical cystectomy and lymphadenectomy, current NCCN guidelines 2010 suggest the use of neoadjuvant therapy. However, the same guidelines do not suggest the use of adjuvant chemotherapy if the pathological stage shows pT_2N_0 disease.

Extravesical bladder cancer ($T_{3,4a}$ and/or N_1)

Trials using adjuvant chemotherapy based on pathological staging after cystectomy have been few, not well designed and used variable chemotherapy protocols and drugs to derive consistent observations for clinical recommendations. Millikan *et al.* conducted a large randomized trial comparing pre+postoperative MVAC with post operative adjuvant MVAC chemotherapy for patients clinically staged as T_{3b} or T_{4a} disease, or lymphovascular permeation at cystoscopic biopsy.[41] No significant difference was found in overall survival of the two groups. However, 40% of the cases in group receiving neoadjuvant chemotherapy group showed no evidence of muscle-invasive disease at radical cystectomy. This finding further consolidates the evidence in favor of neoadjuvant chemotherapy compared to adjuvant chemotherapy, and also is comparable to findings from the neoadjuvant MRC/EORTC and SWOG 8710 trials.[21,42] 2010 NCCN guidelines strongly suggest the routine use of neoadjuvant chemotherapy in clinical T_{3or4} or N_+ disease. Based on the risk adjuvant chemotherapy is suggested if neoadjuvant treatment was not used. It goes on to consider biopsy of nodes if there is no other evidence of metastasis. If the nodes turn out to be pathologically positive for metastasis, they suggest the use of primary chemotherapy with or without radiotherapy, and consider further treatment based upon the response to primary chemotherapy.

Locally advanced inoperable bladder cancer (T_{4b} and/or N_2 and above)

As per NCCN guidelines 2010, chemotherapy is used as the first-line treatment for cases with clinical stage T_{4b} and above. Based upon the response to the chemotherapy further treatment may include radical cystectomy, radiotherapy, palliative TURBT or alternative chemotherapy.

Chemotherapy in cases that cannot tolerate toxicity of combination regimens

Patients with poor renal reserve, uncorrectable obstructive uropathy, poor cardiac status, poor performance status, poor bone marrow reserve, associated comorbidities and extreme of age are poor candidates for routine standard combination regimens. Strategies that may be used in such cases include avoiding use of cisplatin, using lower dose, simultaneously using nephroprotective agents (N-acetyl cysteine, amifostine) or growth factors, or using alternative less toxic regimens or drugs.

Bladder cancer with renal insufficiency forms a special group with as many as 25-50% of cases of carcinoma bladder presenting with renal insufficiency. It is usually related to obstructive uropathy from the tumor itself, or medical renal disease related to elderly age and associated comorbidities. Renal insufficiency precludes the use of cisplatin in these patients, with the percentage of ineligibility increasing with the increasing age of the patients.[43] Carboplatin has been tried as an alternative, though several studies done so far, do not favor carboplatin in terms of overall response rate.[44-47] A clinical decision must be taken to weigh the risk versus benefits of the use of cisplatin in these patients. NCCN guidelines 2010 advise for considering a split dose regimen of cisplatin for cases with borderline renal function (category 2A). Carboplatin and taxane-based regimens should be considered for advanced renal failure cases.

Chemotherapy along with radical TURBT in the setting of bladder preservation protocol

Bladder preservation is always an option which excites the patient and clinician alike, wherever feasible. Presently, there are no head-to-head comparisons for radical surgery versus the preservation protocol in randomized fashion. Therefore, the standard of care for muscle-invasive bladder cancer remains radical surgery. Bladder preservation protocol is used only in appropriately selected cases which are either unwilling or unfit for major surgery. Chemotherapy with or without radiotherapy is used in the clinical setting

of $T_{2or3,}N_{0,}M_0$ disease, in association with radical TURBT whereby the intention is to excise all possible disease including the one which has spread into the deep muscle or out of the confines of bladder wall in to the adjacent fatty tissue. There are several studies which have shown that complete response rates of 60-80%, 5-year survival of 50-60% and survival rate with intact bladder of 40-45% can be achieved with tri-modality approach with salvage cystectomy being done only if necessary later. These outcomes are quite comparable to those achieved with early radical surgical approach in most contemporary series for muscle-invasive localized bladder cancer.[48-52] However, such an approach is associated with long time of treatment and also has treatment related toxicity like genitourinary and gastrointestinal toxicities from high-dose radiation or myelodepression from chemotherapy. Most of these toxicities occur within the first 2 years. Incidence of delayed high-grade toxicities is relatively low (2-6%). Cystectomy for palliation of treatment-related toxicity is also low (0-2%).[48,53] The option of using neoadjuvant chemotherapy before radical TURBT is one option for better bladder preservation, which needs to be explored further with better well-designed trials in the future.[54]

Future directions and advances

Despite the use of multimodal therapy, long-term survival outcomes remain dismal (<50% at 5 year) in patients with invasive bladder cancer.[55] Initially, a good percentage of cases show good or partial response following use of chemotherapy. However, relapses are common. As many as 60-70% cases of metastatic bladder cancer show recurrence of disease within the first one year.[56] Several trials with newer cytotoxic drugs are underway in various phases of development, aiming to reduce toxicity while providing same or improved survival compared to current standards. Efforts are also underway to delineate pathways involved in development of drug resistance and explore ways to bypass those resistance mechanisms.[57] Specific molecular targeted drugs may thus be developed.[58-60] Gene therapy directed toward p53 tumor suppressor gene has been explored in recent times with encouraging results.[61,62] Meanwhile more potent regimens are surely needed. Taxanes like paclitaxel and gemcitabine have increased the available pool of drugs to choose from, though much still remains elusive with plenty of scope for improvement. Several drugs are being investigated for potential role as second line chemotherapy.[63] Various molecular markers (like p53, Bcl-2, Bax, CD40 and CD40L) have been investigated to identify patients more likely to benefit from chemotherapy. Limited success has been achieved thus far in this field.[64,65]

SUMMARY

Chemotherapy forms an integral part of treatment of cases with bladder cancer, since surgery alone has not been able to provide long-term cure or survival especially in locally advanced cases. Present literature supports the routine use of neoadjuvant chemotherapy, either MVAC or GC regimen, in such cases. Data available for adjuvant chemotherapy is not robust enough to prove improved overall survival. Clinical assessment of the disease and detailed discussion with the patient regarding expected outcomes with or without the use of chemotherapy is warranted. Ideal cases for neoadjuvant chemotherapy would be those cases of muscle-invasive bladder tumor with good performance status, preserved renal function, and limited disease (T_3,N_1). These may be expected to gain maximum benefit out of receiving neoadjuvant therapy. As regards adjuvant therapy, ideal cases may be those who are found to have lymph node-positive disease on cystectomy specimen. Although the efficacy of adjuvant and neoadjuvant therapy are not very different, absence of conclusive evidence in favor of adjuvant therapy and possibility of determination of *in vivo* response with neoadjuvant chemotherapy (since pathological complete response is a powerful predictor of long-term survival) tilts the balance in favor of neoadjuvant treatment.

Overall, it is not an overstatement to say that a multimodality approach is essential to improve upon the results of radical cystectomy, particularly for patients with advanced malignancy. It is essential to properly select out cases and plan the use of peri-operative chemotherapy based on clinical setting and individual patient characteristics. It is absolutely imperative that all such administration is done under a hospital protocol in a well planned out clinical study to help improve upon the presently available evidence to this regard.

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