Perioperative chemotherapy for localized bladder cancer

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Introduction: *Survival benefits have been recently reported in meta-analyses of randomized clinical trials (RCTs) studying perioperative chemotherapy for muscle-invasive urothelial cancer. Controversy and lack of awareness of these data have diminished their impact on daily practice, and they deserve further scrutiny.*

Materials and methods: *Recently published meta-analyses of RCTs studying perioperative chemotherapy for bladder cancer were narratively reviewed, along with two reports from the most recently reported RCT of neoadjuvant chemotherapy for bladder cancer.*

Results: *Two recently published individual patient data meta-analyses report that cisplatin-based combination neoadjuvant chemotherapy is associated with an absolute survival benefit of 5% at 5 years, and adjuvant chemotherapy with an absolute survival benefit of 9% at 3 years. However, the value of the adjuvant meta-analysis is limited by the available data. Positive surgical margins and fewer than 10 lymph nodes removed are associated with poorer prognosis. Pathological complete response is associated with better survival.*

Conclusions: *Patients diagnosed with muscle-invasive urothelial cancer may benefit from perioperative chemotherapy and should be routinely referred to a medical oncologist. Surgical factors potentially have a greater impact on survival than the use of perioperative chemotherapy. RCTs studying all stages of localized muscle-invasive bladder cancer are currently enrolling patients in Canada and are a high priority.*

Key Words: bladder neoplasms, drug therapy, chemotherapy, adjuvant, neoadjuvant therapy, meta-analysis

Introduction

Recent reports of randomized clinical trials (RCTs) identifying survival benefits for patients with breast and prostate cancer have generated excitement and controversy. In an analysis presented at the American Society of Clinical Oncology annual meeting in May 2005, the addition of trastuzumab to adjuvant chemotherapy for early breast cancer was associated with a statistically significant 33% reduction in the risk of death.[1] The absolute improvement in overall survival at 4 years was 4% in this trial (number-needed-to-treat [NNT] = 25). In the New England Journal of Medicine, Bill-Axelson et al[2] reported a 26% reduction in the risk of death in men with localized prostate cancer treated with prostatectomy compared with observation. The absolute improvement in overall survival at 10 years was 5% (NNT = 20). It is of interest that similar absolute survival benefits have been recently reported with perioperative chemotherapy for muscle-invasive urothelial cancer, but with far less attention and impact on everyday practice. The rationale for studying chemotherapy in this setting is clear, as treatment with combination cisplatin-based chemotherapy prolongs survival in patients with incurable recurrent or metastatic disease.

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As bladder cancer represents the fourth most common cancer in males in Canada, and at least half of patients diagnosed with muscle-invasive disease will die of it, the recent perioperative chemotherapy data deserve further scrutiny.

Neoadjuvant chemotherapy

There are complementary advantages and disadvantages to administering chemotherapy either before (neoadjuvant) or after (adjuvant) radical cystectomy.[3] The neoadjuvant approach is most well studied in RCTs. Although trends favoring chemotherapy have been observed, no individual RCT to date has reported unequivocal survival benefits. It has been hypothesized that this might be due in part to trial designs anticipating more than the usual modest effect of perioperative chemotherapy seen in solid tumors. Nonstatistically significant trends observed have stimulated efforts to pool the results of completed RCTs using meta-analytic techniques to potentially identify benefits.

Individual patient data (IPD) meta-analysis has a number of advantages over meta-analyses done based on published or summary trial data.[4] As unpublished RCTs can be included, there is less publication and selection bias. Patient follow-up can be and usually is updated to a common time point. Data on individual patients provides the opportunity to perform intention-to-treat as well as subgroup and prognostic factor analyses. The main barriers to routine use of IPD are the necessity of cooperation and additional efforts by the individual RCT investigators, and that it is both expensive and time-consuming. The Advanced Bladder Cancer Meta-analysis Collaboration (ABCMC) has recently published IPD meta-analysis of RCTs for both neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer.[5,6]

In the neoadjuvant analysis a total of 11 RCTs considered eligible were included. None of these trials reported statistically significant results at conventional levels. Overall survival data was available from 10 RCTs including 2809 patients and 1430 deaths. Overall the hazard ratio (HR) for death was 0.89 (p=0.022) indicating an 11% reduction in the risk of death with use of chemotherapy. Seven RCTs (87% of patients) used cisplatin-based combinations, and for this group the HR was 0.86 (p=0.003) consistent with a 5% improvement in survival at 5 years (NNT=20). Three cycles of methotrexate-vinblastine-doxorubicin-cisplatin (M-VAC) (29% of patients), CMV (40%), or CM (19%) were most commonly used. There was no evidence of statistical heterogeneity or inconsistency that might raise questions about the validity of these results. Others have reviewed the toxicities and treatment-related mortality of neoadjuvant chemotherapy in these trials.[7] Severe symptomatic toxicities occurred in 20% to 30% of patients receiving M-VAC and CMV, and the rate of toxic death with CMV in the largest RCT was 1%. The ABCMC authors conclude: "Neoadjuvant platinum-based combination chemotherapy therefore remains the treatment against which all new treatments for invasive bladder cancer should be judged."

Adjuvant chemotherapy

The ABCMC recently published the first IPD meta-analysis examining adjuvant chemotherapy for muscle-invasive bladder cancer.[6] Nine RCTs were identified but data could be obtained from only six of these (66% of all patients). No RCT randomized more than 108 patients. Data for analysis was available on 491 patients and 283 deaths. Patient characteristics described 39% as age 65 or older, 73% as T3 or T4, and 34% N1 or N2. Overall the HR for overall survival was 0.75 (p=0.019) suggesting a 25% reduction in the risk of death with use of chemotherapy. Five RCTs (81% of patients) used cisplatin-based combinations, and for these the HR was 0.71 (p=0.010) consistent with a 9% absolute improvement in survival at 3 years (NNT=11). There was no evidence of statistical heterogeneity or inconsistency, and at face value these results appear superior to those of neoadjuvant chemotherapy. However, there are a number of important limitations of these data which limit their interpretation.

One-third of patients studied in adjuvant RCTs were not included in this analysis. Presumably this is because these trial investigators were either unwilling or unable to provide their data in the ABCMC. These trials are also unpublished, and unpublished RCTs are much more likely to show negative results. The effect of omitting these RCTs is likely to be an exaggeration of the treatment effect favoring adjuvant chemotherapy. As well, three of the RCTs included in the analysis were stopped earlier than planned by their investigators when the trials were showing results favoring adjuvant treatment. Although updated follow-up could mitigate this effect, it remains quite possible that if enrollment had continued the observed benefits of adjuvant chemotherapy might have lessened. The effect of this again is likely to exaggerate the treatment effect favoring adjuvant chemotherapy.

The ABCMC authors were able to confirm the use of chemotherapy at the time of relapse in the control arms of the RCTs in only 19% of patients. As cisplatin-based combination chemotherapy treatment is associated with improved survival in metastatic urothelial cancer, the likely effect of under treatment in the control arm is again to exaggerate the treatment effect in favor of adjuvant chemotherapy. The main limitation of this meta-analysis is the small number of patients and events (deaths). This analysis contained only 17% of the number of patients and 20% of the number of deaths included in the neoadjuvant meta-analysis. Statistically, 900 events are required to reliably detect an absolute difference of 9% with 80% power and 5% significance. This implies that the positive result seen is at significant risk of being "false positive" (type I error). In view of this, the ABCMC authors question the validity of their results and endorse ongoing RCTs studying adjuvant chemotherapy in localized bladder cancer in RCTs using no chemotherapy control arms.

Controversies for medical oncologists

Based on the data available, it is recommended that all patients diagnosed with muscle-invasive bladder cancer be referred to a medical oncologist for an opinion about perioperative chemotherapy. However, urologist should expect variability in the opinion they will receive. This reflects the nature of the data currently available, and should not discourage urologists from involving medical oncologists in the care of these patients.

In general, medical oncologists prefer to prescribe chemotherapy after surgery when pathological staging information is available. This avoids exposing some patients to unnecessary treatment. However, the data available from adjuvant RCTs is less convincing, and current RCTs are testing adjuvant chemotherapy versus no treatment. The data from neoadjuvant RCTs are much more convincing and identify a clinically significant survival benefit, one consistent with that seen in other solid tumors where perioperative chemotherapy is routinely employed. So the medical oncologist is left asking the question: "If I believe that neoadjuvant chemotherapy works, can I also believe that adjuvant chemotherapy does not?". Other dilemmas are the choice of chemotherapy and amount of treatment to give. The weight of RCT evidence supports use of M-VAC or CMV for three cycles if neoadjuvant or 12 weeks if adjuvant. However, most medical oncologists have abandoned use of these regimens. The commonly used gemcitabine-cisplatin regimen has not been tested in perioperative RCTs. Recent data do report nearly identical survival in the long term with M-VAC compared to gemcitabine-cisplatin in metastatic patients.[8] However, a median four cycles of M-VAC and six cycles of gemcitabine-cisplatin were given to achieve these results, suggesting that at least five cycles of gemcitabine-cisplatin be used perioperatively. Use of gemcitabine-cisplatin perioperatively also may create a dilemma regarding choice of chemotherapy if relapse occurs. Notwithstanding these dilemmas, urologists should persist in their efforts to engage medical oncologists in treatment planning for these patients.

Implications for surgeons

Information from perioperative chemotherapy RCTs also has direct implications for surgeons. Concerns about a detrimental delay in local therapy required to permit neoadjuvant chemotherapy administration seem to be refuted by the data. Conversely, it is implied that neoadjuvant chemotherapy could be considered to avoid detrimental effects of waiting a prolonged period for surgery if this is unavoidable. In their neoadjuvant RCT report, Grossman et al[9] examined overall survival in relation to whether residual tumor was identified pathologically in the cystectomy specimen or not (pT0). pT0 patients had superior survival whether they had received neoadjuvant chemotherapy or not. This may simply identify a surrogate for earlier stage disease, but benefit from maximal tumor debulking by transurethral resection prior to cystectomy consistent with current practice recommendations is also possible.

In a separate report from the same study, Herr et al[10] evaluated surgical and tumor factors in the 268 pts treated with radical cystectomy. Multivariable analyses for associations with post-cystectomy survival (PCS) and local recurrence (LR) were done, and adjusted for use of neoadjuvant chemotherapy, age, pathologic stage, and node status. Overall the 5-year PCS and LR rates were 54% and 15%, respectively. Negative surgical margins (HR=0.37, p=0.0007) and having at least 10 pelvic lymph nodes removed (HR=0.51, p=0.0001) were strongly associated with PCS. Positive surgical margins (odds ratio=11.2, p=0.0001) and having less than 10 pelvic lymph nodes removed (odds ratio=5.1, p=0.002) were strongly associated with risk of LR. The authors concluded: "Surgical factors influence bladder cancer outcomes after cystectomy, after adjustment for pathologic factors and use of neoadjuvant chemotherapy."

Implications for research and current RCTs

Grossman et al[9] observed better survival in neoadjuvantly treated patients who were pT0 at cystectomy (48/158 patients) compared to those with residual tumor, whose survival was similar to that of patients not receiving chemotherapy at all. This suggests that only a subgroup of patients truly benefit from chemotherapy treatment, and that this subgroup is identified by their response to neoadjuvant chemotherapy. Thus the difficulty in identifying the benefits of perioperative chemotherapy maybe explained: the large benefit in the minority is diluted by the lack of benefit in the majority. It also suggests that the majority of patients do not benefit from chemotherapy, and either should not receive it or receive different systemic therapy. Finally, it suggests that patients destined to benefit from perioperative chemotherapy could theoretically be identified *a priori* by preoperative tumor sampling and analysis. Identification of these subgroups using genomic approaches is now potentially possible and should be a research priority.

The Canadian Urological Oncology Group (CUOG) and National Cancer Institute of Canada (NCIC) are participating in a NCI US sponsored clinical trial (NCIC BL.10) that evaluates pT1-2 N0 patients for the presence of mutated p53. Patients with wild type p53 are observed and those with mutated p53 randomized to M-VAC for three cycles or observation, and 800 patients will be randomized. CUOG/NCIC is also participating in the EORTC 30944 trial which randomizes patients with pT3-4 and/or pN1-3 disease to four cycles of gemcitabine-cisplatin or observation with chemotherapy deferred until relapse. Recently the sample size of this trial was reduced to 660 when two similar trials in Italy and Spain were identified and an agreement to pool results was established. In the US the CALGB trial will randomize 800 patients with pT3a-4a and/or pN1-3 disease to either sequential doxorubicin-gemcitabine followed by paclitaxel-cisplatin, or gemcitabine-cisplatin, each for four cycles.

Conclusions

High quality meta-analytic data supports the effectiveness of neoadjuvant cisplatin-based combination chemotherapy in patients with muscle-invasive urothelial cancer. The absolute survival benefit is 5% at 5 years. The effectiveness of adjuvant chemotherapy is less certain due to limitations of the data provided by and the small number of patients studied in RCTs. It is recommended that all patients diagnosed with muscle-invasive urothelial cancer be referred to a medical oncologist. Current data support the use of neoadjuvant chemotherapy with a cisplatin-based combination, and removal and pathological examination of at least ten lymph nodes with radical cystectomy. Ultimately a better understanding and ability to identify the molecular characteristics of muscle invasive bladder cancers will guide optimal use of perioperative chemotherapy. RCTs studying all stages of localized muscle-invasive bladder cancer are currently enrolling patients in Canada and are a high priority. □

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