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Pooled Analysis of Clinical Outcomes with Neoadjuvant Cisplatin and Gemcitabine Chemotherapy for Muscle Invasive Bladder Cancer

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Abstract

Purpose—Neoadjuvant chemotherapy for muscle invasive bladder cancer has been shown to confer a survival advantage in phase III studies. Although cisplatin and gemcitabine are often used in this setting, a comprehensive evaluation of this regimen is lacking. In this review we summarize the efficacy of neoadjuvant cisplatin and gemcitabine chemotherapy for muscle invasive bladder cancer based on currently published studies.

Materials and Methods—A systematic literature review was conducted in April 2012 searching MEDLINE® databases. Articles were selected if they included patients with muscle invasive bladder cancer, evaluated the combination of cisplatin and gemcitabine as neoadjuvant treatment, and reported pathological data after cystectomy. Cisplatin and gemcitabine dosing regimens and clinical data were further summarized using weighted averages.

Results—Seven studies encompassing 164 patients were published between 2007 and 2012. The majority of patients (79%) received cisplatin and gemcitabine on a 21-day cycle. A weighted average of 19.2 lymph nodes was obtained at cystectomy, and 29.7% of patients were found to have pN1 disease. Pathological down staging to pT0 and less than pT2 occurred in 42 (25.6%) and 67 (46.5%) patients, respectively.

Conclusions—Neoadjuvant cisplatin and gemcitabine yield appreciable pathological response rates in patients with muscle invasive bladder cancer. Since pathological response has been implicated as a potential surrogate for survival in muscle invasive bladder cancer, these data suggest that neoadjuvant cisplatin and gemcitabine may warrant further prospective assessment.

Keywords

cisplatin; gemcitabine; neoadjuvant therapy; drug therapy; combination; urinary bladder neoplasms

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Radical cystectomy with pelvic lymphadenectomy is the recommended treatment for muscle invasive bladder cancer.¹ Despite thorough pelvic lymph-adenectomy, a certain percentage of patients will harbor micrometastatic disease, contributing to recurrence rates of up to 40% at 5 years.²⁻⁴ Neoadjuvant chemotherapy with platinum based regimens before cystectomy may optimize outcomes, possibly by treating occult disease. A meta-analysis including 11 randomized studies suggested that neoadjuvant chemotherapy followed by cystectomy (compared to cystectomy alone) was associated with a 5% improvement in overall survival and a 9% improvement in disease-free survival.⁵

The Southwest Oncology Group (SWOG) conducted a pivotal study establishing the role of neoadjuvant chemotherapy. In SWOG 8710, 317 patients with MIBC were randomized to receive a 4-drug regimen (methotrexate, vinblastine, doxorubicin and cisplatin) followed by cystectomy or cystectomy alone. Patients receiving MVAC were noted to have an improved pT0 rate (38% vs 15%, $p < 0.001$) and an improved median OS (77 vs 46 months, $p = 0.06$) compared to those receiving cystectomy alone.⁶ Despite these findings, the use of MVAC chemotherapy appears to be infrequent, perhaps due to concerns regarding myelosuppression and resultant neutropenic infections. Phase III data in the metastatic setting suggest that MVAC has efficacy similar to that of a 2-drug regimen, cisplatin and gemcitabine.⁷ In this study CG demonstrated a lesser degree of myelosuppression and other grade 3/4 events. Accordingly many clinicians have extrapolated from this data set to apply neoadjuvant CG in the setting of localized MIBC.

It would likely take a randomized, phase III study to establish neoadjuvant CG as the standard of care for MIBC. However, previous studies of neoadjuvant therapy have been plagued by slow accrual and methodological issues. While such a trial is pending, medical oncologists and urologists must rely on a heterogeneous pool of largely retrospective data to justify the use of neoadjuvant CG. Therefore, in this study we provide a pooled analysis of these existing data.

MATERIALS AND METHODS

Literature Search

A systematic literature review was conducted searching the PubMed® and MEDLINE databases in April 2012 using the medical subject heading and free text protocols with the terms gemcitabine, cisplatin, chemotherapy, muscle invasive bladder cancer, neoadjuvant and cystectomy. Only articles published in the English language were included in the search. Furthermore, American Society of Clinical Oncology abstracts were reviewed. Studies were included in analysis if they 1) included patients with MIBC, 2) evaluated the combination of cisplatin and gemcitabine as neoadjuvant treatment (series evaluating monotherapy with either agent or triplet regimens were excluded from analysis), and 3) included pathological staging subsequent to cystectomy. Of the 9 articles retrieved 7 contained data evaluable specifically for neoadjuvant CG.

For all of the included studies several variables were obtained, including 1) number of patients treated with neoadjuvant CG and 2) number of patients receiving neoadjuvant CG who were pT0 at cystectomy. When available, several data elements were also collected, such as 1) average number of lymph nodes harvested at cystectomy, 2) average time between completion of neoadjuvant CG and cystectomy, 3) number of patients with lymph node positive disease at cystectomy (ie pN1 disease), 4) number of patients with nonmuscle invasive disease (ie less than pT2 disease) at cystectomy and 5) number of cycles of chemotherapy delivered.

When available, the chemotherapy dosing schedule was recorded and classified as 1) 70 mg/m² cisplatin (single dose or split) with 2,000 mg/m² gemcitabine (split) on days 1 and 8 of a 21-day cycle, 2) 75 mg/m² cisplatin with 2,500 mg/m² gemcitabine (split) on days 1 and 8 of a 21-day cycle, or 3) 70 mg/m² cisplatin (single dose or split) with 3,000 mg/m² gemcitabine (split) on days 1, 8 and 15 of a 28-day cycle.

Statistical Analysis

A weighted average was calculated for the previously mentioned variables, provided that more than 100 patients were assessed for the variable of interest across the studies included

in this analysis. The formula, $\bar{x} = \sum_{i=1}^n w_i x_i / \sum_{i=1}^n w_i$, was used in which w represents the number of patients who received neoadjuvant CG in a selected study and x represents the number or proportion of patients who demonstrated the variable of interest. In cases in which 100 or fewer patients were assessed for a variable of interest, descriptive statistics were generated.

RESULTS

Study Identification

Seven studies were identified that met the inclusion and exclusion criteria (see supplementary table at <http://jurology.com/>).⁸⁻¹⁴ In summary, these studies included a total of 164 patients (individual study range 15 to 42), and were published between 2007 and 2012. Of these studies 6 were retrospective institutional analyses and the other study was a prospective phase II assessment. Median followup of patients ranged between 12 and 32 months.

Chemotherapy Regimen

Neoadjuvant chemotherapy was administered between 1988 and 2011. Details related to chemotherapy regimen were available for 111 of 164 (68%) patients across the 7 studies included in the analysis. Of these patients 88 (79%) received CG on a 21-day cycle while the remainder received CG on a 28-day cycle. The most frequently administered regimen was 70 mg/m² cisplatin (single dose or split) with 2,000 mg/m² gemcitabine (split) on days 1 and 8 of a 21-day cycle, rendered in 65 patients (58.5%). Completeness of CG delivery was demonstrated with more than 90% of patients receiving at least 2 cycles.

Clinical and Pathological Outcome

More than 100 patients were assessed for the variables of interest of 1) lymph node count, 2) presence or absence of pN1 disease, 3) presence or absence of pT0 disease, and 4) presence or absence of less than pT2 disease. Weighted averages for these variables are noted in the supplementary table. A weighted average of 19.2 lymph nodes was obtained at cystectomy across these studies, and 29.7% of patients had pN1 disease. Overall 25.6% and 46.5% of patients achieved pT0 and less than pT2 disease, respectively.

Toxicity

Although the general tolerability of the treatment regimen was satisfactory, only 2 studies provided an analysis of specific toxicities related to neoadjuvant CG. Herchenhorn et al reported a 38% incidence of grade 3 to 4 hematologic toxicity, although 3 complete cycles of CG were completed in all but 1 patient.⁹ Kaneko et al reported grade 3 to 4 neutropenia, anemia and thrombocytopenia in 14.3%, 2.4% and 21.4% of patients, respectively.¹⁰ There were no grade 3 to 4 gastrointestinal toxicities, although thrombocytosis was reported in 26% of CG cycles.

DISCUSSION

Several phase III studies have indicated a survival benefit in association with neoadjuvant chemotherapy for MIBC and meta-analytic data support this finding.^{5,6,15–17} Possible benefits of neoadjuvant chemotherapy compared to adjuvant include up-front treatment of micro-metastases, pathological evaluation of response to chemotherapy from the cystectomy specimen, and systemic treatment before surgery avoiding delays associated with complications or debilitation after radical surgery. Accordingly Wosnitzer et al demonstrated a statistically significant improvement with disease specific survival in patients receiving neoadjuvant vs adjuvant CG.¹⁸

However, use of neoadjuvant chemotherapy remains poor, with an estimated 13% of patients receiving this treatment in 2007.¹⁹ The limited use of this modality is due in part to toxicities associated with multidrug regimens such as MVAC. As a consequence, many practicing oncologists have turned to regimens such as CG, given the similar efficacy and a favorable adverse effect profile in the metastatic setting.²⁰ To our knowledge, no prospective randomized trials evaluating CG for neoadjuvant use in MIBC have been performed. To date, publications evaluating neoadjuvant CG have yielded variable outcomes. In our pooled analysis including 164 patients with MIBC, we demonstrate an appreciable rate of pathological complete response (25.6%) and pathological down staging (46.5%). Prospective analysis of MVAC in SWOG 8710 showed down staging to pT0 in 38% of patients⁶ compared to the 25.6% exhibited in the present analysis. However, if the SWOG data are assessed in an intent to treat fashion, the pT0 rate decreases to 32%. Nevertheless, the pT0 rate from MVAC may be slightly better than that of CG in the current analysis. In other retrospective analyses of neoadjuvant MVAC, the pT0 rate ranges between 19% and 31%.^{8,13,21} Of note, Weight et al reported on 20 patients with a pT0 rate of only 10% and concluded that neoadjuvant CG was not associated with down staging.¹² However, time to cystectomy in this study was prolonged (7 months), a much longer delay than in the remainder of studies possibly contributing to decreased response.

What is the importance of response rate in the setting of MIBC? Traditionally, phase III studies assessing neoadjuvant chemotherapy have examined OS as the primary end point. In the phase III evaluation of neoadjuvant MVAC (SWOG 8710), this end point was achieved, albeit with borderline statistical significance ($p = 0.06$).⁶ The more recently published evaluation of neoadjuvant cisplatin, methotrexate and vinblastine in the BA06 30894 study was initially powered to evaluate 2-year OS.¹⁵ Ultimately the study did suggest an absolute improvement in OS of 6% ($p = 0.037$). Although OS remains the gold standard for defining appropriate neoadjuvant treatments for MIBC, more recent phase II studies have moved toward examining unique clinical end points that can be achieved in a shorter time frame. Various studies have implicated pathological down staging as a surrogate for long-term oncologic control and survival and, thus, response rate has emerged as an attractive target.^{22,23} As noted in the Appendix, multiple phase II studies evaluating CG or CG based combinations have used the pT0 rate or less than pT2 rate as a primary end point.^{24–28} These studies underscore the importance of establishing the anticipated response rates with neoadjuvant CG through efforts such as ours. If inappropriate estimates are used to set the bar for response in these early studies, promising combinations could be rejected or underperforming regimens could be carried forward.

Several limitations of our study should be acknowledged. Although we were careful to select similar studies that included patients with MIBC who had received neoadjuvant CG, the regimen details were difficult to characterize. Information related to dosing, schedule and number of cycles of CG rendered was not available for nearly a third of the cumulative data set. The response rates cited here may be most relevant to 70 mg/m² cisplatin (single

dose or split) with 2,000 mg/m² gemcitabine (split) on days 1 and 8 of a 21-day cycle (see figure). However, the heterogeneity of treatments administered among the studies examined makes this unclear. Although several studies in this combined analysis were based on intent to treat, this was not unanimous. Therefore, patients who received CG but did not go on to undergo cystectomy may affect the pathological results. Furthermore, individual patient data were not accessible, limiting the ability to report certain clinical outcomes for which point data are mandatory (ie median DFS, median OS etc). An additional caveat of our study is an inability to assess toxicity, as 6 of the 7 studies included in our pooled analysis were retrospective. Toxicity data acquired in a retrospective fashion are always subject to investigator bias. Thus, our data cannot substantiate the popular opinion that neoadjuvant CG may carry a favorable toxicity profile compared to conventional neoadjuvant regimens such as MVAC.

Finally, our study could not account for the effect of varying surgical practices that can potentially influence clinical outcome. For instance, extended lymphadenectomy (compared to lymphadenectomy in a standard template) has been posited to improve DFS in retrospective series.²⁹ This observation is being prospectively evaluated in an ongoing phase III study (SWOG 1011).³⁰ With respect to our data set, it is unclear whether the rate of lymph node positive disease at cystectomy (approaching 30%) reflects inadequacy of the systemic regimen or more extensive lymph node retrieval.

CONCLUSIONS

The current study serves to provide justification for the further pursuit of randomized studies evaluating neoadjuvant CG chemotherapy. The cumulative pT0 rates and rates of down staging are substantial. Furthermore, given the potential surrogacy of pathological down staging for clinical outcomes such as DFS and OS, the rates of down staging reported in this review could inform the design of prospective trials powered to assess these end points in the context of CG based therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

APPENDIX

APPENDIX

Studies evaluating CG and CG based combinations for MIBC

Study Identifier	Primary End Point	Description
NCT00847015 ²⁴	pT0 rate	Evaluation of neoadjuvant CG in combination with sunitinib in patients with MIBC. Study suspended due to toxicity. ²⁵
NCT00585689 ²⁶	pT0 rate	Evaluation of neoadjuvant CG in combination with <i>nab</i> -paclitaxel in patients with MIBC. With 27 patients enrolled, pT0 rates of 30% observed.
NCT01261728 ²⁷	Less than pT2 rate	Evaluation of neoadjuvant CG in patients with muscle invasive upper tract urothelial cancers. No results available to date.
NCT01222676 ²⁸	pT0 rate	Evaluation of CG in combination with sorafenib in patients with MIBC. No results available to date.

Abbreviations and Acronyms

CG cisplatin and gemcitabine

DFS	disease-free survival
MIBC	muscle invasive bladder cancer
MVAC	methotrexate, vinblastine, doxorubicin, cisplatin
OS	overall survival

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Dose and schedule of cisplatin (*Cis*) and gemcitabine (*Gem*) administered in 4 of 7 studies in pooled analysis. Cis 70/*Gem* 2000 (q3wk) indicates 70 mg/m² cisplatin (single dose or split) with 2,000 mg/m² gemcitabine (split) on days 1 and 8 of 21-day cycle. Cis 75/*Gem* 1250 (q3wk) indicates 75 mg/m² cisplatin with 2,500 mg/m² gemcitabine (split) on days 1 and 8 of 21-day cycle. Cis 70/*Gem* 3000 (q4wk) indicates 70 mg/m² cisplatin (single dose or split) with 3,000 mg/m² gemcitabine (split) on days 1, 8 and 15 of 28-day cycle.