Neoadjuvant gem-cis in real-world bladder cancer

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**ABSTRACT**

Neoadjuvant gemcitabine/cisplatin chemotherapy for muscle invasive urothelial carcinoma of the bladder: a single institution experience

El-Gehani F, Venner P, Ghosh S, North S.

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**Introduction and Objectives:** Despite evidence of a survival advantage for neoadjuvant (NA) cisplatin-based chemotherapy (CT) prior to radical cystectomy (RC) for muscle invasive urothelial carcinoma (UC), treatment rates are low. A number of Canadian centres use NA gemcitabine/cisplatin (GC) but there is little information on pathologic response rate, an important predictor of long-term outcome. This retrospective study was undertaken to determine the rate of NA GC use prior to RC at our institution and to assess the pathologic response rates.

**Methods:** A retrospective chart review was performed on all patients (pts) undergoing RC between 2007.01.01 to 2011.06.30 at our institution. Data were collected on demographics, clinical stage, type and amount of NA administered, and postoperative pathology.

**Results:** A total of 251 RC were performed: Stage T2-T4 UC 166 patients; non-muscle-invasive UC in 85 patients; and in 6 patients as salvage treatment. Ninety-one (57%) pts received NA GC and 69 (43%) pts went straight to RC. Reasons for no NA GC being given include: medical contraindication in 37 pts (54%); pt refusal in 9 pts (13%); and lack of referral to medical oncologist in 23 pts (33%). Pathological staging and survival rates are presented in Table 1.

**Conclusions:** The rate of NA CT use prior to RC at our institution is higher than quoted in published literature. The use of NA GC combination improves the chances of achieving a pT0 status and downstaging of the UC in the RC specimen at rates comparable to those reported for MVAC.

The largest trials for neoadjuvant chemotherapy in muscle-invasive bladder cancer were performed with MVAC¹ (methotrexate, vinblastine, doxorubicin and cisplatin) and CMV² (MVAC without the doxorubicin), yet most U.S. and Canadian centres administer gemcitabine and cisplatin (gem-cis) to these patients. This is based on a trial in the metastatic setting that showed noninferiority for efficacy but better tolerability for gem-cis.³

This study from Edmonton was a single-institution retrospective review of pathologic response to neoadjuvant gem-cis. Of 168 patients who underwent radical cystectomy between 2007 and 2011 for T2-T4 urothelial carcinoma of the bladder, 91 (57%) received neoadjuvant gem-cis. Of these patients, 21% had complete downstaging (pT0N0) and 37% were downstaged to non-muscle invasive disease (T0/Tis/Ta/T1). In the patients not treated with neoadjuvant chemotherapy, 3% were pT0N0 and 10% were pT1 or less. These advantages were observed even though patients receiving neoadjuvant chemotherapy group tended to have higher-stage disease prior to treatment.

Neoadjuvant chemotherapy appeared to have a benefit also in other disease and outcome parameters. The tumour was more likely to be organ confined (60% vs 32% p=0.0006). There was a near-significant trend toward a reduction in the rate of positive lymph nodes in the cystectomy specimen (24% vs 33%, p=0.06). Finally, there was a trend toward better overall survival in the patients receiving gem-cis (54% vs 40% at median time of 51 months). The authors acknowledged the limitations and potential bias in survival data in this retrospective analysis. The patients not receiving neoadjuvant chemotherapy were older and some were considered ineligible for chemotherapy due to comorbidities.
TABLE 1. Pathologic staging and survival rates

<table>
<thead>
<tr>
<th>Variables</th>
<th>NA treated</th>
<th>RC only</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete downstaging (pT0aN0)</td>
<td>19/91 (21%)</td>
<td>2/69 (3%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-invasive only (pT0/pTis/pTaN0)</td>
<td>34/91 (37%)</td>
<td>7/69 (10%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Organ-confined disease (pT0–pT3aN0)</td>
<td>55/91 (60%)</td>
<td>23/69 (33%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Lymph node positive (pN+)</td>
<td>22/91 (24%)</td>
<td>23/69 (33%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>51 months</td>
<td>31 months</td>
<td>0.07</td>
</tr>
<tr>
<td>4-yr survival rate</td>
<td>55%</td>
<td>43%</td>
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NA=neoadjuvant; RC=radical cystectomy.

COMMENT
Alberta has been leading the way in the delivery of neoadjuvant chemotherapy in Canada. Investigators in Alberta have previously reported on the poor utilization of neoadjuvant chemotherapy, which improved after introduction of provincial guidelines recommending its use in patients with muscle-invasive disease. Poor adoption of what is considered the standard of care, however, remains an issue throughout Canada.

In this context of trying to increase the uptake of neoadjuvant chemotherapy in the genitourinary oncology community, we often lose sight of the choice of chemotherapy regimen given to these patients, even though the issues related to MVAC vs gem-cis are familiar to most urologists and medical oncologists. The purists advocate for MVAC, but most practitioners shy away from the increased toxicity and give gem-cis.

This report from El-Gehani et al is important because it demonstrates good efficacy for gem-cis in a “real world” patient cohort. We accept pT0 as a valid surrogate for survival in bladder cancer, and this group has achieved what would appear to be an acceptable rate of pT0 at 21%. The corresponding rate in the SWOG (Southwest Oncology Group) trial was 38%, yet there are reports of much worse results (e.g. 7% in Cleveland), as well as reports of similar results from single-institution retrospective series. The question must therefore be asked, how each centre has selected its patients. We would like to treat patients similar to those represented by the SWOG trial and avoid treating patients like those in the Cleveland cohort. Only patients with a major response (pT1 or less) benefit from the chemotherapy, so it would be relevant to figure out what differentiates these populations. On the other hand, even in the SWOG trial and in the Edmonton series, a majority of patients are being treated without obvious benefit, so markers of response to chemotherapy are urgently needed.

What should be made of the inability of retrospective series like this to match the 38% rate of pT0 observed in the SWOG trial? We would anticipate results to be better within a clinical trial, and the trial accrued over a long period of time, so there is likely an element of selection bias. It is also noteworthy that the pT0 rate in patients undergoing immediate cystectomy in the SWOG trial was high at 15%. Is this a reflection of particularly thorough transurethral resections of bladder tumour (TURBTs) in these trial patients, and, if so, is this relevant to the response to chemotherapy? On the other hand, the risk profile of patients in the SWOG trial is fairly high: only 32% were clinical T2, and all of these had lymphovascular invasion on the TURBT specimen. The retrospective data comparing MVAC and gem-cis are limited, but there is not obvious difference. Ultimately we cannot know if there is a difference between gem-cis and MVAC without conducting a prospective trial comparing the two in the neoadjuvant setting. This, however, seems unlikely in the current environment of bladder cancer clinical trials.

References