The Effect of Neo-adjuvant Platinum-based Combination Chemotherapy on Pathological Down-staging and Survival of Patients with Locally Advanced Bladder Cancer

by

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Curriculum Vitae

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ABSTRACT

Background

Bladder cancer (BC) is the fifth most commonly diagnosed malignancy in the United States, with more than 70,000 new cases and more than 14,000 BC deaths reported in year 2009. The overwhelming majority of deaths from BC occur among patients with muscle-invasive disease (stages T2-T4). Standard therapy for resectable (T2-T4a) muscle-invasive BC without known metastases includes radical cystectomy. Unfortunately, 30%-50% of patients with apparently resectable muscle-invasive BC (“locally advanced” disease) in fact have undiagnosed micrometastases at the time of definitive surgery.

Early treatment of micrometastatic disease with neo-adjuvant platinum-based combination chemotherapy (PBCC) administered before cystectomy has been compared to cystectomy alone in several randomized trials. A meta-analysis of these trials demonstrated that addition of a neo-adjuvant PBCC regimen to definitive surgery can substantially increase the probability of tumor down-staging to pathological stage zero (pT0) and improve survival. However, it is currently unknown whether PBCC is effective for all most commonly encountered histologic sub-types of BC, including pure urothelial carcinoma (UC) and UC with squamous and/or glandular differentiation (mixed tumors). In addition, the PBCC regimens used in the trials of neo-adjuvant chemotherapy for locally advanced BC were relatively toxic. In recent years, a less toxic regimen composed of gemcitabine and cisplatin (GC) has been introduced as an alternative to the more toxic drug combinations. However, the ability of GC to induce complete pathological response
(stage pT0) and improve survival of patients with locally advanced BC has not yet been clearly demonstrated.

**Purpose**

(1) To determine whether the effect of neo-adjuvant PBCC on pathological down-staging and survival of patients with locally advanced BC treated with radical cystectomy is influenced by the presence of non-urothelial components in the tumor (Specific Aim 1).

(2) To investigate the effect of neo-adjuvant chemotherapy with GC on pathological down-staging and survival of patients with locally advanced urothelial carcinoma of the bladder treated with cystectomy (Specific Aim 2).

**Methods**

To address Specific Aim 1, we performed a secondary analysis of the Southwest Oncology Group trial 8710 of neo-adjuvant MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) followed by cystectomy versus cystectomy alone for treatment of locally advanced UC of the bladder. For the purpose of these analyses, tumors were classified based on the presence of non-urothelial components as either pure UC (n=236) or mixed tumors (n=59). Non-urothelial components included squamous and/or glandular differentiation. Additive probability models and Cox regression analysis were used to estimate the effect of chemotherapy on pathological down-staging and survival of patients with pure UC and patients with mixed tumors and to test for the interaction of treatment with histologic type.
To address Specific Aim 2, we conducted a retrospective cohort study of patients treated with cystectomy for locally advanced BC at Strong Memorial Hospital during the years of 1999-2009. Additive probability models and Cox regression analyses were used to estimate the effect of neo-adjuvant GC on pathological down-staging and survival of these patients with adjustment for confounding factors.

**Results**

SA1: Among patients with mixed tumors, 32 were randomized to MVAC-plus-cystectomy and 27 were randomized to cystectomy-only. Among patients with pure UC, 115 were randomized to MVAC-plus-cystectomy and 121 were randomized to cystectomy only. Evidence of tumor down-staging to pT0 following chemotherapy was clearly present among patients with mixed tumors (adjusted risk difference = 27%, p=0.004) and among patients with pure UC (adjusted risk difference = 15%, p=0.004; interaction p=0.17). There was evidence of a survival benefit from chemotherapy in patients with mixed tumors (HR=0.46, p=0.02). Patients with pure UC had improved survival on the chemotherapy arm however the survival benefit was not statistically significant (HR=0.90, p=0.48). There was marginal evidence that the survival benefit of chemotherapy in patients with mixed tumors was greater than it was for patients with pure UC (interaction p=0.09).

SA2: We identified 160 eligible patients, of which 25 were treated with neo-adjuvant GC and 135 were treated without neo-adjuvant chemotherapy. There was evidence of tumor down-staging to pT0 following neo-adjuvant chemotherapy (risk difference adjusted for clinical stage = 16%, p = 0.03). The use of neo-adjuvant chemotherapy was associated
with improved survival; however this association was not statistically significant (adjusted hazard ratio 0.61, 95%CI: 0.26, 1.42, p=0.25).

**Conclusion**

Presence of squamous or glandular differentiation in locally advanced UC of the bladder does not confer resistance to MVAC and in fact may be an indication for the use of neo-adjuvant chemotherapy prior to radical cystectomy. Neo-adjuvant chemotherapy with GC is capable of down-staging the tumors in the bladder. However, its effect on survival of patients with locally advanced BC remains uncertain.
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