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Correlation of Pathologic Complete Response with Survival After Neoadjuvant Chemotherapy in Bladder Cancer Treated with Cystectomy: A Meta-analysis

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Abstract

Context: Neoadjuvant chemotherapy before radical cystectomy (RC) is the preferred initial option for muscle-invasive bladder cancer (BCa). As in rectal and breast cancer, pathologic downstaging is associated with increased overall survival (OS).
Objective: We conducted a meta-analysis to determine whether pathologic complete response (pCR) (pT0N0M0) after neoadjuvant chemotherapy is associated with a better outcome in muscle-invasive BCa.
Evidence acquisition: A systematic search was conducted in PubMed, Web of Science, Cochrane Collaboration's Central register of controlled trials, and Embase for publications reporting outcomes of patients with and without pCR. All patients underwent neoadjuvant cisplatin-based polychemotherapy and RC. The primary outcome reported as relative risk (RR) was OS. Secondary end points were recurrence-free survival (RFS) and cancer-specific survival other than distant and locoregional RFS. A meta-analysis was performed using the fixed effects model or random effects model. Overall heterogeneity for RFS and OS was assessed with forest plots and the Q test.
Evidence synthesis: A total of 13 trials were included, for a total of 886 patients analysed after neoadjuvant chemotherapy and RC, without any postoperative treatment. The pCR rate was 28.6%. Patients who achieved pCR in the primary tumour and the lymph nodes presented an RR for OS of 0.45 (95% confidence interval [CI], 0.36–0.56; $p < 0.00001$). The number needed to treat to prevent 1 death was 3.7 (absolute risk difference: −26%). The summary RR for RFS was 0.19 (95% CI, 0.09–0.39; $p < 0.00001$).
Conclusions: Patients with BCa who achieved pCR (pT0N0M0 stage) after neoadjuvant chemotherapy have a better OS and RFS than do patients without pCR.

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1. Introduction

Muscle-invasive urothelial carcinoma (UC) of the bladder is usually treated with radical cystectomy (RC) and complete pelvic lymph node dissection after an initial transurethral resection of bladder tumour (TURBT). Urothelial bladder cancer (BCa) is most sensitive to cisplatin-based combination chemotherapy. One of the most active chemotherapies is the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), which has substantially more

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activity than single-agent chemotherapy [1]. In addition, a gemcitabine plus cisplatin combination has shown efficacy results similar to those of the MVAC regimen, and both regimens are now considered adequate options for advanced disease [2].

Randomised clinical trials and meta-analyses have demonstrated a survival advantage for patients with muscle-invasive BCa who receive neoadjuvant chemotherapy prior to undergoing cystectomy compared with surgery alone [3]. In particular, the use of neoadjuvant chemotherapy permits downstaging of BCa, the possibility of bladder preservation, and assessment of the response of the primary lesion and, thus, evaluation of the prognosis of the patient in terms of long-term survival.

In one of the pivotal neoadjuvant phase 3 trials, the Southwest Oncology Group (SWOG) 8710, Grossmann et al. [4] demonstrated that in the MVAC group, 38% of the surgical specimens were pathologically free of cancer (pT0N0M0 or pathologic complete response [pCR]) at the time of RC, while 15% in the RC group were pT0 at surgery ($p < 0.001$). In addition, the overall survival (OS) rate at 5 yr was higher in the pT0 patients compared with the no-pT0 group, regardless of whether the patients received neoadjuvant chemotherapy or not. The prognostic value of a pCR after neoadjuvant chemotherapy is meaningful and indicates the chance of long-term survival in the subjects who are downstaged to pT0N0M0 disease.

Many publications have correlated the degree of pathologic response with survival after BCa surgery. However, many of these studies included radiotherapy, TURBT alone, or other unconventional monochemotherapy or polychemotherapy schedules that are not the standard of care [5–7]. In addition, the evaluation was frequently performed between non–muscle-invasive, downstaged subjects (<pT2) and all the others (≥pT2), or between pT0/any pN and >pT0/any pN subjects [8]. It is well known, in fact, that nodal downstaging is a strong prognostic factor after preoperative chemotherapy, even after a complete downstaging of the primary tumour. In addition, residual pT1 disease is not equivalent to pT0-Tis but is associated with a worse prognosis [9].

For these reasons, we undertook a pooled analysis of studies in which data were reported for the diagnosis, treatment, and prognosis of patients with and without pCR after neoadjuvant cisplatin-based chemotherapy for muscle-invasive BCa. The aim was to assess whether patients who achieve pCR had improved OS, recurrence-free survival (RFS), locoregional RFS (LR-RFS), distant RFS (D-RFS), and cancer-specific survival (CSS) compared with patients who did not achieve pCR, defined as the absence of any cancer cells in the bladder and lymph node specimens after radical or partial cystectomy.

2. Evidence acquisition

2.1. Literature search

We carried out a systematic literature search up to April 20, 2013, using PubMed, Embase, the Cochrane Collaboration's Central register of controlled trials, and Web of Science, restricted to articles published in English, using the following search keywords: *(urothelial cancer OR bladder cancer OR bladder carcinoma OR urinary bladder) AND (neoadjuvant chemotherapy OR preoperative chemotherapy OR induction chemotherapy) AND (pathological complete remission OR pathological complete response OR pathologic response OR down-staging OR pT0 OR pCR OR P0) AND (prognosis OR outcome OR survival OR OS OR DFS OR disease-free survival OR recurrence-free survival)*. We also searched the reference lists of all included studies.

2.2. Study selection criteria

Published studies were included if they (1) used a retrospective or prospective study design; (2) evaluated the association between pCR (defined as pT0N0M0 after neoadjuvant cisplatin-based chemotherapy) and outcome; (3) presented odds ratio, relative risk (RR), or hazard ratio (HR) estimates with 95% confidence intervals (CIs), standard errors (SEs), or number of events necessary to calculate these for the outcome of interest, such as OS or disease-free survival ([DFS]/RFS other than D-RFS or LR-RFS, and CSS, if available, in addition to p values); and (4) included ≥10 patients treated with RC (plus lymph node dissection) or partial cystectomy for only localised or locally advanced BCa. When multiple publications from the same study or institution were available, we used the publication with the largest number of cases and most applicable information. Studies including (definitive or neoadjuvant) radiotherapy, TURBT plus neoadjuvant chemotherapy alone, metastatic patients, other histologies, delivery of chemotherapy other than intravenously, or carboplatin-based chemotherapy were excluded. Studies in which additional postsurgical adjuvant treatment was delivered (ie, radiotherapy or adjuvant chemotherapy) were excluded so that adjuvant treatment factors did not confound results.

2.3. Data extraction

The following information was recorded for each eligible trial: authors' names, year of publication, duration of follow-up, total number of patients, median age, percentage of patients achieving pCR, systemic therapy regimen delivered, clinical TNM stage, and survival data (percentages and number of events). If the authors found a correlation between response and outcome, this finding was also recorded.

2.4. Statistical analysis

OS was the primary outcome measure, and RFS (or DFS), D-RFS, LR-RFS, and CSS were the secondary end points. In the meta-analysis, outcome of pT0N0M0 BCas were compared with outcome of any not–pT0N0M0 (eventually including pTa or pTis as well). Summary statistics of patients achieving pCR after neoadjuvant chemotherapy with RRs and 95% CI were calculated using the fixed effects model/Mantel-Haenszel method when there was minimal heterogeneity in the variables among studies, and the DerSimonian-Laird