Clinical Oncology xxx (2016) 1–7

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Association between the Absolute Baseline Lymphocyte Count and Response to Neoadjuvant Platinum-based Chemotherapy in Muscle-invasive Bladder Cancer

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Received 3 March 2016; received in revised form 6 June 2016; accepted 22 June 2016

Abstract

Aims: Platinum-based neoadjuvant chemotherapy (NAC) improves overall survival in muscle-invasive bladder cancer (MIBC). A pathological complete response (pCR) at radical cystectomy after NAC is associated with better overall survival, but there are no established predictive biomarkers of response to NAC in MIBC. The aim of this study was to find laboratory variables associated with pCR following NAC.

Materials and methods: We carried out a retrospective review of MIBC patients treated with NAC followed by radical cystectomy at the Sheba Medical Center between 2005 and 2015. Overall survival was calculated using the Kaplan–Meier product-limit method and compared between patients who achieved or did not achieve pCR using the Log-rank test. Baseline and pre-surgery laboratory values were collected and compared between patients who subsequently achieved pCR and those who did not using logistic regression.

Results: Fifty-eight patients underwent radical cystectomy after NAC, with a median follow-up of 32 (range 4.8–111.4) months from diagnosis. Of 55 patients with documented pathological outcome on radical cystectomy, 17 (31%) achieved pCR (complete responders). Of the 15 complete responders with follow-up data, 13 (87%) were still alive at time of last follow-up for this study (July 2015). Patients who did not achieve pCR had a significantly worse overall survival than complete responders ($P = 0.0007$). The baseline lymphocyte count, neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) were significantly associated with response ($P = 0.037$, $P = 0.045$, $P = 0.042$, respectively) on univariate analysis, whereas baseline albumin, haemoglobin, neutrophils, platelets and the total white blood count were not significantly associated with response. Lymphocyte counts were significantly higher in responders than non-responders throughout three time points ($P = 0.003$ using a generalised linear mixed model).

Conclusions: A high baseline level of lymphocytes is associated with the achievement of pCR at radical cystectomy after NAC, which, in turn, is associated with a significantly longer overall survival. Our results suggest that chemosensitivity in MIBC is associated with lymphocyte count.

Key words: Bladder cancer; chemosensitivity; lymphocytes; MIBC; neoadjuvant chemotherapy; urothelial carcinoma

Introduction

Muscle-invasive bladder cancer (MIBC) continues to pose significant therapeutic challenges. When the disease is localised to the bladder, standard treatment generally includes neoadjuvant chemotherapy (NAC) with a platinum-based combination followed by radical cystectomy [1]. Whereas this multidisciplinary approach was shown to increase survival in a pivotal phase III trial [2] and in several meta-analyses [3,4], the extent of benefit for the entire patient population is small. It is now well established that

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http://dx.doi.org/10.1016/j.clon.2016.07.007
0936-6555/

the achievement of pathological complete response (pCR) in the cystectomy specimen after NAC is associated with a significantly improved outcome [5], yet only about 30% of patients achieve this goal. Moreover, it is hard to specifically quantify the direct contribution of NAC to the achievement of pCR as the pre-treatment transurethral resection of the bladder tumour can also lead to a complete response in some of the patients. As there are no proven clinical, biochemical or molecular biomarkers that predict which patients are likely to respond to NAC to date, many patients receive futile toxic chemotherapy that postpones definitive surgery. Finding markers that predict the response to NAC in MIBC is therefore highly needed.

In recent years, immunotherapy has emerged as a promising systemic approach in a wide range of solid cancers; specifically, there is extensive ongoing clinical research on the use of immunotherapy in bladder cancer [6], long thought to be linked to aberrant inflammatory/immune processes [7]. Currently, it is unclear which patients are more likely to respond to an immunotherapeutic approach. Similarly, little is known about the crosstalk between the immune system and chemosensitivity in bladder cancer.

The neutrophil–lymphocyte ratio (NLR) in the blood count has emerged as a strong prognostic factor in a wide range of solid malignancies, with high values evidently associated with a worse prognosis [8]. The platelet–lymphocyte ratio (PLR) has also been linked to a poor prognosis in cancer [9]. A persistently high NLR throughout NAC was also associated with a lack of response to NAC in MIBC in a Canadian patient cohort [10]. Our aim here was to further study the relationship between the different components of the inflammatory/immune systems, as manifested in the complete blood count and the response to NAC in MIBC.

Materials and Methods

Data Collection and Definitions

This was a retrospective chart review of all patients treated with NAC followed by radical cystectomy for MIBC between October 2005 and December 2014 that were documented in the institutional electronic patient record at the Sheba Medical Center. This study received institutional review board approval. Inclusion criteria included: a histological confirmation of MIBC with predominant urothelial histology, no radiological evidence of distant or lymph node metastasis, the administration of combination platinum-based chemotherapy with neoadjuvant intent and a subsequent radical cystectomy. Patients who received NAC with adjuvant intent but did not subsequently undergo radical cystectomy (for any reason) were summarised for sake of database completeness but were not included in our primary or secondary end point analyses. Patients who underwent upfront radical cystectomy without prior NAC and patients diagnosed with MIBC that was not upfront amenable to curative therapy were excluded from this analysis as well.

Clinical and pathological data were extracted from the electronic patient record. Laboratory variables including haemoglobin, neutrophil, lymphocyte, platelet and total white blood cell (WBC) counts and albumin levels were retrieved from blood tests taken within 1 week before NAC start (designated 'Pre-NAC' or baseline), within a week before radical cystectomy (designated 'pre-surgery') and 4–6 weeks after radical cystectomy (designated 'post-surgery'). The pre-surgery laboratory variables were taken from the closest time point available before radical cystectomy (and no longer than 1 month before radical cystectomy) as long as it was at least 3 weeks after completion of the last chemotherapy cycle.

NLR and PLR were calculated as the ratio between the absolute neutrophil and lymphocyte count or the absolute platelet and lymphocyte count, respectively, in the peripheral blood. NLR measurements were not assessed for patients with known active infection, patients receiving steroid medication ($\geq$20 mg of prednisone a day or the equivalent) or patients with known haematological malignancies. pCR was defined when no evidence of invasive cancer was reported in the cystectomy sample and when all lymph nodes in the surgical specimen were free of tumour. A pathological partial response was defined when there was unequivocal down-staging of the tumour in the cystectomy specimen with remaining evidence of muscle invasion. Stable and progressive disease were defined when there was no clear evidence of response or when there was unequivocal evidence of disease progression (such as T4 disease not evident on pre-NAC radiological staging), respectively. In the current analysis, patients who achieved pCR are designated as 'complete responders', whereas all other patients are defined as 'non-complete responders' or 'non-responders' for short.

Primary End Point and Statistical Analysis

Our primary end point was to find laboratory variables that are associated with the achievement of pCR at radical cystectomy after NAC. Our secondary end point was to study the trends in laboratory variables that are associated with the achievement of pCR throughout time.

Categorical variables were summarised with counts and percentages. Continuous variables were summarised with medians/ranges and/or mean (standard deviation) accordingly. The Kolmogorov-Smirnov test was used for normality assumption of lab values and log transformation was used for those not satisfying the normality assumptions. Time to death/censoring was calculated in months from the diagnosis date to the death date or the date of the last follow-up, respectively. The overall survival rate was calculated using the Kaplan–Meier product-limit method and the Log-rank test was used to assess the effect of pCR on overall survival. A logistic regression analysis was used to determine which laboratory values were associated with the primary outcome of pCR. A generalised linear mixed model was used to account for the time trend and co-linearity when assessing changes in laboratory variables between patients who achieved pCR ('complete responders') and those who

Please cite this article in press as: Leibowitz-Amit R, et al., Association between the Absolute Baseline Lymphocyte Count and Response to Neoadjuvant Platinum-based Chemotherapy in Muscle-invasive Bladder Cancer, Clinical Oncology (2016), http://dx.doi.org/10.1016/j.clon.2016.07.007