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Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients

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Abstract

Background: The optimal time interval between the end of neoadjuvant systemic therapy (NST) and breast surgery is still unclear. It is not known if a delay in surgery might influence the benefit of primary chemotherapy. The aim of this study is to evaluate the relationship between time to surgery (TTS) and survival outcomes.

Patients and methods: According to TTS, women with diagnosis of BC treated with NST were divided into two cohorts: group A = 21 days or fewer and group B = longer than 21 days. OS and RFS were estimated and compared according to TTS and known prognostic factors.

Results: A total of 319 patients were included in the study: 61 in group A and 258 in group B. Median TTS was 34 days. No association between clinical stage, nuclear grade, type of chemotherapy, type of surgery and TTS was detected. OS and RFS were significantly worse for group B compared with group A, with a hazard ratio of 3.1 (95% CI, 1.1–8.6 p = 0.03) and 3.1 (95% CI, 1.3–7.1 p = 0.008) respectively. Multivariate analysis confirmed that TTS was an independent prognostic factor in term of OS (p = 0.03) and RFS (p = 0.01). Even in the subgroup of patients with pCR, TTS continued to be an independent prognostic factor for both OS and RFS (p = 0.05 and p = 0.03).

Conclusions: TTS after NST seems to influence survival outcomes. BC patients underwent surgery within 21 days experienced maximal benefit from previous treatment: this advantage is consistent and maintained over time.

Keywords: Breast cancer; Neoadjuvant chemotherapy; Time to surgery; pCR

Introduction

Nowadays neoadjuvant systemic therapy (NST) is an option in patients with early-stage breast cancer (BC) that provides an opportunity to study the impact of systemic therapies on cancer biology.[1] Tumor response to NST correlates with outcome and it could be considered a surrogate for evaluating the effect of chemotherapy on micrometastasis.[2] After NST, surgical management of the breast and the axilla is mandatory.[3] Nevertheless, the optimal time interval between the end of NST and definitive surgery is unclear. Many of the trials that have evaluated the survival benefit of NST arbitrarily defined the interval from the end of preoperative chemotherapy to surgery. In clinical practice, primary tumor removal is usually performed within few weeks from the completion of chemotherapy, but it is not known if a delay in surgery might influence the benefit of previous systemic treatment. To the best of our knowledge, there is only one retrospective study that have investigated the impact on survival outcomes of time to surgery (TTS) after NST without underlining statistically significant difference between three time groups.[4]

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In the adjuvant setting, experimental data suggested that physicians should start systemic treatment as soon as possible after curative surgery because the removal of the primary tumor as well as the surgical trauma might lead to an accelerated growth of micrometastasis.[5] Several retrospective studies investigated the proper timing of initiation of adjuvant chemotherapy after surgery in BC. In spite of the majority of these trials have shown a positive relationship between shorter interval of time to surgery and systemic treatment, it is still unclear how soon after surgery chemotherapy should be initiated for maximal benefit.[6–11] Available data have been shown an important decrease in adjuvant systemic therapy efficacy when it is administered more than 12 weeks after surgery.[12] Current guidelines from the European Society of Medical Oncology suggest that systemic adjuvant treatment should start preferably within 2–6 weeks after surgery, but do not recommend a specific safe maximum interval between NST and surgery.[13]

In this retrospective study we have evaluated the relationship between the length of time from the end of NST to surgery and the survival outcomes benefit in terms of Overall Survival (OS) and Relapse Free Survival (RFS). We hypothesized that surgery performed as soon as possible after preoperative chemotherapy may optimize the clinical benefit of previous systemic treatments. For this reason we evaluated a time interval of 21 days, considered as the shortest time required for recovery from chemotherapy toxicity.

Patients and methods

Patient population

We performed a retrospective review of the electronic medical records of all patients treated with NST for early BC in our institution between 1991 and 2015. All the patients with a histologically proven diagnosis of BC (stage I–III) treated with primary chemotherapy either within clinical trials or on the basis of standard service guidelines were included. No other eligibility/exclusion criteria was applied. Tumor-specific characteristics, including cancer stage, grade and tumor subtypes were collected. Tumor subtypes were defined as follow: human epidermal growth factor receptor 2 (HER2) positive BC, hormone receptor positive BC (estrogen and/or progesterone receptors expression $>1\%$ and HER2 negative) and triple negative (TN) BC (hormone receptor and HER2 negative). NST was given according to standard recommendation, dose reduction or drug discontinuation were applied in case of toxicity according with the clinician's choice. Date about pathological response and local regional treatment after NST were collected. TTS was defined as the time between the end of NST, considered as the last dose of chemotherapy $\pm$ anti-HER2 agents, and surgery. The date of the surgery was considered as the date of the primary tumor removal. According to TTS all patients have been divided into two time cohorts: group A, 21 days or fewer and group B, longer than 21 days. Ethical approval is not required due to the retrospective nature of this mono-institutional study reflecting the daily clinical practice of the physicians, without any support by sponsors.

Statistical analysis and outcome measures

Baseline differences in prognostic factors between TTS groups were assessed by chi-square test or Fisher exact test for categorical variables (*i.e.* clinical stage, BC subtypes, grade, pathological complete response, NST and adjuvant treatments) and Wilcoxon Mann–Whitney test for continuous variables (*i.e.* age at diagnosis). The association between pathological complete response (pCR), defined as complete disappearance of invasive tumor in the breast and axillary lymph nodes, and other prognostic factors such as age (dichotomized as over or below 50 years), clinical stage and BC subtypes was assessed through chi-square test. Outcomes of interest were OS and RFS. OS was defined as the time from diagnosis of BC to death/last follow up, while RFS was defined as the time from the date of the diagnosis to the date of the first documented relapse (local, regional, and/or distant). Analyses were conducted within the two cohorts defined by interval time between the end of NST and surgery (*i.e.* the last course of NST $\pm$ anti-HER2 agents). RFS and OS curves were constructed using Kaplan–Meier method. Survival estimates were calculated and reported at 5, 10 and 15 years, along with their 95% confidence intervals (95% CI), for the groups defined by TTS and other relevant prognostic factors, such as BC subtypes, clinical stage and pCR. Hazard ratios (HRs) and their 95% CIs were obtained through Cox models. Univariate and multivariable analyses were fit to determinate the association between known prognostic factors and survival outcomes. Variables in the models included TTS, BC subtypes, clinical stage and pCR. Finally, we performed multivariate analysis on the subgroup of patients with residual disease after NST in order to assess the survival impact of TTS, BC subtypes and clinical stage in these patients with worse prognosis. A p-value < 0.05 was considered statistically significant. All analyses were performed using STATA 13 (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP).

Results

A total of 319 patients were included in the study: 61 patients in group A and 258 patients in group B. Specifically, in group B, 82 patients had TTS 22–28 days, 82 had TTS 29–35 days, 47 had TTS 36–42 days and 47 had TTS >42 days. Patient, tumor and treatment characteristics stratified by TTS groups are listed in Table 1. The two cohorts of patients were well balanced according to demographic and

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