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Original article

Impact of timeliness of adjuvant chemotherapy and radiotherapy on the outcomes of breast cancer; a pooled analysis of three clinical trials

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ABSTRACT

Objective: To assess the impact of delay in initiation of adjuvant chemotherapy and/or radiotherapy on the outcomes of breast cancer patients referred for adjuvant treatment.
Methods: This is a pooled analysis of patient-level data of 3390 breast cancer patients referred for adjuvant chemotherapy in three clinical trials. Overall and relapse-free survivals were assessed according to "surgery to chemotherapy interval" through Kaplan-Meier analysis. Likewise, among patients who received adjuvant radiotherapy, relapse-free survival was assessed according to "surgery to radiotherapy interval" through Kaplan-Meier analysis. Univariate and Multivariate analysis of factors affecting overall and relapse-free survival was then conducted through Cox regression analysis.
Results: Kaplan-Meier analysis of overall survival according to surgery to chemotherapy interval (<vs. > 6 weeks) was conducted. When stratified by the hormone receptor status, the longer interval was associated with worse overall survival in hormone receptor-negative patients ($P = 0.006$); while it was not associated with overall survival difference in hormone receptor-positive patients ($P = 0.268$). In multivariate Cox regression analysis, the test of interaction between "surgery to chemotherapy interval" and hormone receptor status was significant ($P = 0.015$). Moreover, when the multivariate analysis was restricted to hormone receptor-negative patients, longer surgery to chemotherapy interval was associated with worse overall survival among this subset of patients ($P = 0.004$). On the other hand, in multivariate analysis of factors affecting relapse-free survival, surgery to radiotherapy interval did not impact relapse-free survival ($P = 0.439$).
Conclusion: Among hormone receptor-negative patients, delaying chemotherapy initiation beyond 6 weeks (after surgery) is associated with worse patient outcomes. Moreover, delaying radiotherapy initiation beyond surgery does not compromise outcomes in patients receiving long course adjuvant chemotherapy.

1. Introduction

As the most common cancer among women as well as the second most common cancer worldwide, breast cancer represents a global health challenge [1]. Moreover, breast cancer is the most common cause of cancer-related death among females in the developing countries as well as the fifth most common cause of cancer-related death overall [2].

Adjuvant chemotherapy and radiotherapy are considered as fundamental parts of the management of many cases with early-stage breast cancer. Based on the biological rationale and clinical evidence, it was suggested that early initiation of adjuvant chemotherapy would improve the outcomes of those patients [3]. Successive retrospective and prospective studies evaluating the true impact of delaying adjuvant chemotherapy initiation revealed conflicting results [4–6]. This might be related to the heterogeneous composition of the cohorts evaluated in different studies (in terms of baseline characteristics like age, stage, hormone receptors and menopausal status). This heterogeneity might have affected the outcomes of each of these studies. Likewise, numerous studies evaluating the impact of surgery to radiotherapy interval were published. However, the majority of patients in these studies received adjuvant radiotherapy without chemotherapy or with short course chemotherapy. It is still not clear if it is safe to delay adjuvant radiotherapy until the end of a long anthracycline-taxane adjuvant chemotherapy course [7].

Recently, the initiative of allowing access to raw data of selected

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landmark clinical trials (through Project Data Sphere (PDS)) was launched [8]. Accessing the raw data of breast cancer clinical trials present an unprecedented chance to answer relevant research questions utilizing the high-quality information available in these trials. These raw data are thus considered an optimal medium to examine the real impact of adjuvant therapy timelines in breast cancer management.

Assessing the true impact of timeliness in administering adjuvant treatment for breast cancer is thus of paramount significance in terms of therapeutic decision making, patient referral patterns as well as patient counseling.

2. Objective

To assess the impact of delay in initiation of adjuvant chemotherapy and/or radiotherapy on the outcomes of breast cancer patients referred for adjuvant treatment.

3. Methodology

3.1. Description of the study cohort

The study cohort of the current analysis is an individual patient pooled analysis of the raw data of three phase III trials evaluating adjuvant treatment for breast cancer. Through the PDS initiative, the raw data were obtained after relevant approvals. These trials are BIG 02/98 (NCT00174655); BCIRG001 (NCT00688740); BCIRG005 (NCT00312208) (Only the dataset of comparator arms was available for the three studies). The primary results of these clinical trials were published before [9–11]. Details of each of the included trials were summarized in Table 1. Collectively, a total of 3390 patients were included in the study cohort.

3.2. Data collection

The following data were collected from each of the three datasets; age at diagnosis; race, body mass index (calculated through weight and height), Karnofsky performance score, pathological T and N stage, lymph node ratio, hormone receptor status (estrogen and progesterone receptors), Her2 neu status, grade, histological subtype, type of surgery, protocol of adjuvant chemotherapy, whether or not adjuvant radiotherapy was administered, surgery to chemotherapy interval, surgery to radiotherapy interval and chemotherapy to radiotherapy interval, relapse status, relapse-free survival, overall survival and vital status.

According to the available protocols/manuscripts of different clinical trials, all included patients have adequate organ function (including hepatic, bone marrow, cardiac and renal functions) and all patients have performance status >70. Overall survival was defined in the three trials as: “time from randomization till death” (patients who were alive at the time of database lock for each study were censored). Relapse-free survival was defined as: “time from randomization till relapse” (patients who were alive at the time of database lock as well as those who died without relapse were censored). Surgery to chemotherapy interval was defined as “time from breast surgery to the start of adjuvant chemotherapy”; surgery to radiotherapy interval was defined as “time from breast surgery to the start of adjuvant radiotherapy”; while chemotherapy to radiotherapy interval was defined as “ time from the end of adjuvant chemotherapy to the start of adjuvant radiotherapy”. For patients who underwent more than one breast surgery (e.g. lumpectomy followed by mastectomy), only the date of last surgery was considered.

3.3. Statistical considerations

Descriptive statistics for patient characteristics were detailed. The probability of overall survival was assessed according to “surgery to chemotherapy interval” through Kaplan-Meier analysis and log-rank testing. For the sake of the current analysis and based on previously published guidance, evaluated cutoff value for surgery to chemotherapy interval was either 3 or 6 weeks [12].

Univariate and Multivariate analysis of factors affecting overall and relapse-free survival was then conducted through Cox regression analysis. Factors with $P < 0.05$ in the univariate analysis were included in the multivariate analysis. Because of the potential correlation between surgery to chemotherapy interval and surgery to radiotherapy interval (i.e. delay in chemotherapy initiation might lead later on to delay in radiotherapy initiation), both intervals were not included in the same multivariate model for either overall or relapse-free survival.

A two-sided P value < 0.05 was considered statistically significant. Statistical analyses were performed through SPSS Statistics 20.0 (IBM, NY).

4. Results

Baseline characteristics of the studied 3390 patients were detailed in Table 2. Most of the patients have an age group in the range of 40–69 years (84.4%) and the majority of cases with known

Table 1
Studies included in the current analysis.[a]

Study	Chemotherapy protocol(s)	Percent of patients included in the pooled analysis	Median follow up (range)
BIG 02/98 (Only comparator arms) (NCT00174655)	Active comparator A1: doxorubicin 75 mg/m^2 i.v. day 1 q 21 days for 4 cycles, followed by CMF (C: cyclophosphamide 100 mg/m^2 orally days 1–14, M: methotrexate: 40 mg/m^2 i.v. days 1 and 8, FU; 5-fluorouracil: 600 mg/m^2) i.v. days 1 and 8, q 28 days for 3 cycles. Active comparator A2: doxorubicin 60 mg/m^2 i.v. + cyclophosphamide 600 mg/m^2 i.v., day 1, q 21 days for 4 cycles, followed by CMF for 3 cycles.	A1: 14.4% A2: 14.9%	18.3 months (0.23–45)
BCIRG001 (TAX316) (Comparator arm only) (NCT00688740)	Active Comparator: FAC 5-fluorouracil (500 mg/m^2) in combination with doxorubicin (50 mg/m^2) and cyclophosphamide (500 mg/m^2) on day 1 every 3 weeks for 6 cycles of treatment	22%	125.99 months (0–141.1)
BCIRG005 (Comparator arm only) (NCT00312208)	Active comparator: AC x 4: Doxorubicin 60 mg/m^2 as an IV bolus in combination with cyclophosphamide 600 mg/m^2 as IV followed by docetaxel 100 mg/m^2 as 1 h IV infusion on day 1 every 3 weeks for 4 cycles.	48.7%	114.95 months (0-154)

[a] Adjuvant radiotherapy, hormonal therapy as well as trastuzumab were allowed according to institutional guidelines.