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Chemotherapy dose reduction and delay in clinical practice: evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer

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Abstract

Randomised clinical trials demonstrate the importance of maintaining chemotherapy dose and dose intensity in the systemic adjuvant treatment of breast cancer, and show that the strategies of dose delay and dose reduction carry the risk of suboptimal outcome. Such dose modifications are usually necessitated by the myelosuppressive effects, specifically neutropenia, thrombocytopenia and anaemia, resulting from the previous cycle of chemotherapy. The Canadian Database Initiative was designed to determine the incidence of neutropenic complications (an episode of febrile neutropenia or dose delay or reduction) and the frequency of complications by cycle of therapy using data from patients with breast cancer treated at centres across Canada. The centres used a variety of adjuvant chemotherapy regimens and the database covered the treatment of 444 patients, average age 47.7 years, who were treated between 1991 and 1996. Across all chemotherapy regimens, 42% of patients experienced at least one complication. Of those, 72% went on to have additional complications in subsequent cycles. The neutropenic complications usually occurred early in the treatment schedule.

Keywords: Breast cancer; Adjuvant chemotherapy; Neutropenia; Chemotherapy dose reduction; Chemotherapy dose delay

1. Introduction

Breast cancer is the most common cancer in women in the western industrialised countries and its incidence has been increasing over the last 50 years [1]. Several large clinical trials and meta-analysis of all randomised trials of adjuvant systemic therapy have demonstrated that both chemotherapy and hormone therapy decrease the risks of recurrence and cancer-related deaths in breast cancer patients [2–4].

The relationship between dose intensity and patient outcome in the management of breast cancer in the adjuvant setting is still controversial. Randomised clinical trials have provided evidence that supports the delivery of full standard doses of chemotherapy and suggests that there may be no benefit to patients at lower doses [5]. The 1998 Canadian Consensus Document, Clinical Practice Guidelines for Breast Cancer, recommends that full standard-dose chemotherapy be given when possible [5]. This recommendation is supported by several clinical trials.

A subgroup analysis of 20-year follow-up data from the study by Bonadonna's group, comparing adjuvant CMF (oral cyclophosphamide 100 mg/m^2 on days 1–14, methotrexate 40 mg/m^2 intravenous (i.v.) on days 1 and 8, and 5-fluorouracil 600 mg/m^2 i.v. on days 1 and 8, given every 4 weeks for 12 cycles) plus surgery versus surgery alone, observed that patients receiving less than 85% of the calculated total dose do not appear to have benefited from adjuvant chemotherapy. The overall survival for those receiving greater than 85% of the calculated dose and those receiving less than 65% of the calculated were 52% and 30%, respectively [6]. In a large, randomised trial conducted by the CALGB, patients receiving a lower dose intensity of CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) experienced a significantly higher rate of recurrence and reduced overall survival. Three levels of CAF dose intensity in node-positive breast cancer were explored. The disease-free survival at 3 years for patients receiving full-dose

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and half-dose were 74 and 63%, respectively. There was an 11% decrease in disease-free survival at 3 years with a 50% reduction of dose [7], a difference which was maintained at 5 years when the results of a 9-year follow-up were reported [8].

In the adjuvant setting, clinical trials have also addressed the issue of more effective chemotherapy protocols. Data from The National Cancer Institute of Canada — Clinical Trials Group (NCIC-CTG) trial MA-5 show that the Canadian version of CEF (oral cyclophosphamide 75 mg/m^2 on days 1–14, epirubicin 60 mg/m^2 i.v. on days 1 and 8, 5-fluorouracil 500 mg/m^2 i.v. on days 1 and 8, given every 4 weeks for six cycles) was associated with a statistically significant survival advantage over standard CMF therapy in pre- and postmenopausal node-positive women with breast cancer ($P = 0.03$) [9]. Thus, CEF is a proven regimen in the adjuvant setting. However, neutropenia is dose-limiting in many patients. In the NCIC-CTG MA-5 clinical trial, the mean average relative received dose intensity of the CEF regimen was 0.77 ± 0.14 (0.77 ± 0.15 for epirubicin), and 90% of patients treated with CEF experienced NCIC-CTG grade 4 granulocyte toxicity.

There is evidence that there is a dose–response relationship and that maintaining dose is important to clinical outcomes in breast cancer patients. The reduction of dose intensity of adjuvant chemotherapy may lead to suboptimal results. Thus, total dose and dose intensity play an important role in the outcome of patients receiving adjuvant chemotherapy for breast cancer. However, the clinical challenge is to maintain adequate doses of chemotherapy in the face of adverse effects of the therapy. Neutropenia is a common problem associated with cytotoxic therapy in cancer. The risk of mortality and morbidity associated with neutropenia often leads to dose reductions and dose delays in standard chemotherapy strategies.

2. The Canadian Database Initiative (CDI)

The Breast Cancer — Canadian Database Initiative (CDI) was set up with the objectives of determining the incidence of neutropenic complications, the incidence of single versus multiple complications, and the frequency of complications by cycle of chemotherapy. The initial findings from the database are presented here. Patients with early-stage breast cancer receiving adjuvant chemotherapy were assessed for neutropenic complications and the dose intensity of therapy was also reviewed [10,11].

The study was a retrospective review of the charts of women with breast cancer who had received adjuvant chemotherapy with curative intent at six centres across Canada (British Columbia Cancer Agency, Vancouver, British Columbia; Tom Cross Cancer Institute, Calgary, Alberta; St Joseph's Health Centre, London, Ontario; The Credit Valley Hospital, Mississauga, Ontario; Women's College Hospital, Toronto, Ontario; Lakeridge Health Oshawa, Oshawa, Ontario) between 1991 and 1996. Women of all ages were eligible for inclusion. Women were excluded from review if they had received palliative treatment (no curative intent), or if they had stage IV disease, bone marrow transplantation, seropositivity for the human immunodeficiency virus or use of any growth factors. Ethics approval was obtained in all sites. For the results presented in this report, all data were merged into a single database.

Data on demographics, staging, chemotherapy drugs and dosage, chemotherapy schedule, hospitalisations, and neutropenic complications were collected in 72 variables. The proportion of patients participating in clinical trials was $< 10\%$ of the entire sample reviewed.

A neutropenic complication was defined as an episode of febrile neutropenia, a dose delay of 1 week or more due to neutropenia or a dose reduction of at least 10% of the intended dose due to neutropenia. The occurrence of single and multiple complications was recorded. Multiple complications in any one cycle were counted only once (i.e. dose delay and dose reduction in cycle 2 counted as one complication). A cycle 1 neutropenic complication was counted if the patient had a febrile neutropenic episode during that cycle or, uncommonly, if the patient started at a reduced dose. Dose delays or dose reductions that were not due to neutropenia were not counted. Febrile neutropenia was defined as an absolute neutrophil count of less than 0.5×10^9/l and an oral temperature greater than 38.5°C. Neutropenia was defined as an absolute neutrophil count of $\leqslant 1.0 \times 10^9$/l that resulted in a dose delay or dose reduction on the next cycle of chemotherapy. Since this was a retrospective review, blood counts were not checked. Only blood counts on the day of scheduled chemotherapy were reviewed to make the determination of neutropenia.

Standard chemotherapies were AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 i.v. on day 1, given every 3 weeks for four cycles); CEF (oral cyclophosphamide 75 mg/m^2 on days 1–14, epirubicin 60 mg/m^2 i.v. on days 1 and 8, 5-fluorouracil 500 mg/m^2 i.v. on days 1 and 8, given every 4 weeks for six cycles); CMF i.v. (cyclophosphamide 600 mg/m^2 i.v., methotrexate 40 mg/m^2 i.v. and 5-fluorouracil 600 mg/m^2 i.v. all on day 1, given every 3 weeks for six cycles), CMF p.o. (oral cyclophosphamide 100 mg/m^2 on days 1–14, methotrexate 40 mg/m^2 i.v. on days 1 and 8, and 5-fluorouracil 600 mg/m^2 i.v. on days 1 and 8, given every 4 weeks for six cycles).

2.1. CDI results

The database included data from 444 patients with stage I–III breast cancer. The age range was 26–89 years

(average 47.7 years). The adjuvant chemotherapy was given between 1991 and 1997. The following results are an initial assessment of the database. CMF p.o. was the most common treatment regimen ($n=162$, 36% of patients), followed by AC ($n=87$, 20%), CEF ($n=61$, 14%) and CMF i.v. ($n=45$, 10%). A further 8% of patients ($n=37$) received EC (epirubicin, cyclophosphamide) and the remaining 12% of patients ($n=52$) were treated with various other regimens.

For all chemotherapies combined, 42% of patients experienced at least one complication. Of these, 72% had further complications. Neutropenic complications were assessed by chemotherapy regimen (Table 1). Regardless of the chemotherapy given, most of those patients who developed at least one neutropenic complication continued to have complications in subsequent cycles. The complications usually occurred early. For the CMF p.o. group ($n=162$), 49% of patients experienced at least one complication. Of these, 71% had further complications. Thirty-seven per cent experienced their first complication in the first two cycles of chemotherapy. For the CMF i.v. group ($n=45$), 44% of patients experienced at least one complication. Of these, 80% had further complications. Fifty per cent experienced their first complication in the first two cycles. For the Canadian CEF group ($n=61$), 71% of patients experienced at least one complication. Of these, 72% had further complications. Fifty per cent experienced their first complication in cycle 2. For the AC group ($n=87$), 24% of patients experienced at least one complication. Of these, 67% had further complications. Forty-eight per cent experienced their first complication in cycle 2. Complications that occurred that were not related to neutropenia were recorded as part of the non-neutropenic complication group for comparison with patients with neutropenic complications in terms of relative dose intensity (not reported here). The final analysis of the database is being prepared for publication.

Table 1
Incidence of neutropenic complications (febrile neutropenia or dose reduction in cycle 1, dose reduction or dose delay due to neutropenia in subsequent cycles) with various adjuvant chemotherapy regimens

Chemotherapy regimen	No. of patients (n) (%)	Patients with at least one neutropenic complication (% of all pts)	Incidence of subsequent complications (% of pts with at least one neutropenic complication)
CMF p.o.	162 (36)	49	71
CMF i.v.	45 (10)	44	80
CEF	61 (14)	71	72
AC	87 (20)	24	67
Other regimens	89 (20)	42	72
All regimens	444 (100)	42	72

3. Discussion

Data have accumulated that dose reduction and dose delay may adversely affect optimal clinical outcome. However, studies are still needed to show whether maintenance of standard chemotherapy doses and schedule improves survival outcome. The interaction of radiotherapy and chemotherapy on complications such as neutropenia will need exploration and delineation. The optimal route of delivery of chemotherapy (i.e. oral versus intravenous) requires further assessment.

Preliminary analysis of the CDI database results shows that approximately half of the patients exposed to adjuvant chemotherapy experienced neutropenic complications and a majority of these patients experienced subsequent complications. These neutropenic complications tended to occur early on during therapy. Since the database defined neutropenic complications as febrile neutropenia in cycle 1 and dose reductions or treatment delays in later cycles, it is probable that the patients included in the database were receiving adjuvant chemotherapy at dose intensities below those considered to be optimal (as judged by the findings of randomised controlled trials). The database gathered information from centres across Canada, with the intent of increasing the sample size and improving the generalisability of the results. It also seems likely, therefore, that adjuvant chemotherapy for breast cancer is routinely delivered at suboptimal doses owing to the occurrence of neutropenia. However, it is difficult to predict the likely impact on clinical practice of database findings such as ours. The dose–response relationship cannot be addressed directly since there are no survival data available. Final analysis of the CDI database is pending, and the relative dose intensity of each drug for each patient in the database will be calculated in the final analysis. Results from a similar but larger clinical practice database in the USA were recently reported [12]. They showed that, among women receiving adjuvant chemotherapy for breast cancer (CMF, AC or CAF), 21% received a dose intensity of less than 85% planned. The database was a retrospective review of 5819 patient records from 338 centres. It also showed that dose intensity was more likely to be lower in patients aged over 65 years. One reason for the incidence of dose reduction and treatment delays in clinical practice databases may be the inclusion of women with a wider range of characteristics (e.g. older age, poorer performance status) than are eligible for inclusion in clinical trials.

If the maintenance of full dose intensity of chemotherapy is as important as suggested by the findings of large, controlled trials, it may be that more strenuous efforts to administer full dose chemotherapy according to the established schedule are required. Whilst there is no substitute for the large, randomised, controlled

clinical trial, the publication of database results such as those generated by the CDI provide interesting information on how clinical practice may vary from the standards set by those clinical trials.

In Bonadonna's study [6], 20% of the 207 women received 85% or more of the optimal dose of CMF; 45% received 65–84% and 34% received <65%. Dosage was reduced for older age (>60 years) and if myelosuppression was present. Those women receiving 85% or more of the optimal dose had a superior 20-year survival. The CALGB 8541 comparison of three dose levels of CAF showed that dose was a critical determinant of outcome [7,8]. Grade 3–4 leucopenia occurred in 65% of patients receiving the highest dose (approximating to a standard dose in current terms) and 3% discontinued treatment for reasons of toxicity. In the three groups combined, over 95% of treated patients received at least 90% of the assigned dose. Data on received dose intensity are not available per group, so it is not possible to know if myelosuppression, which was dose related, led to more frequent dose reductions or delays in the highest dose group. In a more recent study, the standard treatment arm of the NCIC-CTG trial mentioned previously [9] was CMF (administered according to Bonadonna's protocol). In the 359 patients treated with CMF, 198 dose reductions were necessary for toxicity, which comprised granulocytopenia grade 3 and 4 in 38 and 41% of patients, respectively, and leucopenia grade 3 and 4 in 52 and 9% of patients. The mean average relative received dose intensity was 0.88 ± 0.13. Patients in the dose-intensified FEC arm, who received antibiotic prophylaxis routinely, had a 90% incidence of grade 4 granulocytopenia and 9% were hospitalised for febrile neutropenia. Growth factor support was not used in either arm.

Adjuvant chemotherapy at standard doses for breast cancer is not, in general, associated with a high enough incidence of febrile neutropenia to warrant a recommendation for routine haematological support. However, the patients who are at highest risk of dose reductions and dose delays are likely candidates for supportive measures to maintain planned dose intensities. For the chemotherapy regimens assessed within the CDI database, 72% of those patients who experienced a first episode of neutropenic complications went on to experience further complications. This is not surprising, since it is logical to suppose that the bone marrow response during earlier cycles of chemotherapy will impact on the response to later cycles.

Planned dose on time is a potential and worthwhile goal for patients receiving adjuvant chemotherapy for breast cancer. Tools are needed to prospectively identify patients who are at increased risk of developing neutropenia that may result in dose delay or reduction. Useful predictive models are currently being developed to allow the rational selection of patients in the adjuvant setting for haematopoietic growth factor (HGF) support [13,14]. The selective use of HGFs (e.g. recombinant G-CSF) may lessen the need for dose modifications during routine standard adjuvant chemotherapy for early breast cancer. As evidence accumulates that dose intensity of therapy is an important component of ensuring optimal clinical outcome, measures used to maintain dose intensity will become an integral part of treatment regimens.

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