Myelotoxicity and Dose Intensity of Chemotherapy: Reporting Practices From Randomized Clinical Trials

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Key Words
Chemotherapy, myelotoxicity, neutropenia, relative dose intensity, supportive care

Abstract
Delivery of cancer chemotherapy is often limited by myelotoxicity, primarily neutropenia. As part of an effort to create a model to predict the risk of chemotherapy-induced neutropenia, we reviewed the reports of randomized clinical trials with more than 50 patients per arm in early-stage breast cancer (ESBC) and non-Hodgkin’s lymphoma (NHL) published between 1990 and 2000. We observed that no hematologic toxicity data were reported in 39% and 34% of the ESBC and NHL trials, respectively. The remaining trials reported on hematologic toxicity in 16 different ways. When reported, rates of neutropenia, leukopenia, and hemotoxicity varied widely with the same and similar chemotherapy regimens. Dose-intensity data were not reported in 39% and 54% of ESBC and NHL trials, respectively. The majority of the remaining studies reported incomplete dose-intensity data such as percentages of patients completing all cycles or receiving a given percentage of planned dose intensity. Only 28% reported the mean or median relative dose intensity received by patients. Based on this review, we conclude that current practices for reporting chemotherapy treatments are inadequate for describing the risk of chemotherapy to patients or for quantitatively assessing the risk of treatment alternatives. We recommend that standard procedures for documenting and reporting hematologic toxicity and dose intensity in cancer chemotherapy trials be required for publication of chemotherapy trials. (JNCCN 2003;1:440–454).

Myelosuppression is the major dose-limiting toxicity of cancer chemotherapy. Neutropenia, in particular, increases the risk of morbidity and mortality caused by fever, infection, and sepsis. Chemotherapy-induced febrile neutropenia (FN) results in hospitalization and antibiotic treatment, and the threat of FN with severe neutropenia often triggers delays or reductions in further chemotherapy. Reductions in chemotherapy dose intensity, however, carry the risk of potentially diminished therapeutic efficacy.1–9 Balancing the risks and benefits of each cancer treatment regimen requires accurate information on its beneficial and adverse effects based on careful clinical observations.

Carefully collected clinical data are also important to guide the use of supportive care with hematopoietic growth factors. Over the past decade, colony-stimulating factors (CSFs) have been widely used to reduce the severity and duration of the neutrophil nadir and resulting neutropenic complications and to maintain chemotherapy dose intensity.10–12 The challenge has been to define the patients and populations who would be most likely to benefit from prophylactic CSF.13–16 Several recent reports have identified factors associated with severe neutropenia during myelosuppressive chemotherapy,14,17–20 but there is not yet a comprehensive predictive risk model to guide clinical practice. Furthermore, although it is clear that certain chemotherapy regimens are more likely to cause serious myelosuppression than others, no systematic evaluation to define the relative rates of neutropenic

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Received December 21, 2002; accepted for publication April 16, 2003.

Research support for this study received from Amgen Inc. (Thousand Oaks, CA).

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complications and corresponding dose intensity with these regimens has been performed.

As part of an effort to create a model to predict the risk of chemotherapy-induced neutropenia, we assessed the reporting of myelotoxicity and delivered dose intensity in randomized controlled trials of chemotherapy over the past decade. A comprehensive literature search was undertaken to summarize the results of such reporting in trials in early-stage breast cancer (ESBC) and non-Hodgkin’s lymphoma (NHL). We restricted our review to produce a comprehensive data set in a representative and manageable range of clinical situations. Our choices also emphasize settings in which chemotherapy is potentially curative and in which maintaining dose intensity has been reported to be important.

Methods

An extensive electronic search of the National Library of Medicine database MEDLINE was undertaken using the medical subject headings (MeSH) “Lymphoma, Non-Hodgkin/drug therapy” and “Breast Neoplasms/drug therapy.” The publication type was restricted to randomized controlled trials that were published in English between 1990 and 2000. Review articles also were surveyed for further references. Each abstract was read to select studies with at least 50 patients in each arm and to confirm study eligibility. Trials in breast cancer were limited to those in nonmetastatic disease. Articles that met these criteria were then retrieved. Trials reported on in more than one article (such as interim and final reports) were represented by the article with the most recent and complete data on hematologic toxicity. Data on the chemotherapy dose and schedule, patient population, protocol dose-modification requirements, delivered dose intensity, and a variety of measures of clinical consequences relating to hematologic toxicity were extracted and tabulated. The terms used in the reports for the relevant myelotoxic effects of chemotherapy included “neutropenia,” “granulocytopenia,” “leukopenia,” and simply “hematologic toxicity,” which presumably could include anemia and thrombocytopenia as well as leukopenia and neutropenia. Table 1 lists the definitions of grades 3 and 4 of these effects according to the Common Toxicity Criteria (CTC) of the National Institutes of Health (NIH) Cancer Therapy Evaluation Program. These definitions are identical to earlier criteria such as the World Health Organization (WHO) and Southwest Oncology Group (SWOG) definitions. Because the absolute granulocyte count is virtually identical to the absolute neutrophil count, the terms “granulocytopenia” and “neutropenia” were treated as equivalent.

Results

A total of 135 publications that met all the inclusion criteria were identified through the literature search. Seventy-seven ESBC and 58 NHL articles were selected for detailed assessment of myelotoxicity and delivered dose intensity reporting.

Reporting of Myelotoxicity and Dose Intensity Data

Myelotoxicity: A wide variety of measures were used to indicate myelotoxicity of the regimens tested in both tumor types. The primary variation in the form of reporting was the cytopenia used: leukocytopenia, granulocytopenia, or neutropenia (Table 1). The secondary variation in reporting was the grouping of different grades of cytopenias (Table 1). The most common incidences of particular grades of toxicity were reported separately or only grade 3 and 4 toxicities were reported, combined or separately. Variation in the method of calculating incidence of neutropenia was noted among studies. Myelotoxicity was occasionally reported as occurring in a percentage of chemotherapy cycles rather than in a percentage of patients. Another infrequently found means of reporting myelotoxicity was to provide the median nadir neutrophil or leukocyte count. Finally, the duration of severe neutropenia, as a measure of the relative severity of myelotoxicity, was also considered.

Table 1 Definitions of Grades 3 and 4 Myelotoxicity

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<thead>
<tr>
<th>Myelotoxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tbody>
<tr>
<td>Leukopenia/leukocytopenia</td>
<td>WBC ≥1000 – &lt;2000/µL</td>
<td>WBC &lt;1000/µL</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>AGC/ANC ≥500 – &lt;1000/µL</td>
<td>AGC/ANC &lt;500/µL</td>
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<tr>
<td>“Hematologic toxicity,”* may include either of above and/or:</td>
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<tr>
<td>Hemoglobin: 6.5 – &lt;8 g/dL</td>
<td>Hemoglobin: &lt;6.5 g/dL</td>
<td></td>
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<tr>
<td>Platelets: ≥10,000 – &lt;50,000/µL</td>
<td>Platelets: &lt;10,000/µL</td>
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*“Hematologic toxicity” not usually defined per se, but is presumed to possibly include anemia and thrombocytopenia. WBC = white blood cells; AGC/ANC = absolute granulocyte count/absolute neutrophil count.
toxicity, was reported in one study each in the two tumor types.

No data on myelotoxicity of the chemotherapy regimen were reported in 39% (30 of 77) of ESBC and 34% (20 of 58) of NHL articles (Table 2). Of the remaining 47 ESBC studies, 47% reported myelotoxicity as leukopenia or leukocytopenia, 17% reported it as granulocytopenia or neutropenia, and 5% reported it as “hematologic toxicity” (Table 2). The 38 NHL articles that discussed myelotoxicity similarly reported it as leukopenia or leukocytopenia (29%), or granulocytopenia or neutropenia (31%). “Hematologic toxicity” was used to describe myelotoxicity in 9% of NHL reports (Table 2). Only the clinical consequences of myelotoxicity (such as fatal infections or hospitalizations due to infection), but not the incidence of myelotoxicity, were reported in 3% of NHL trials.

Six articles on ESBC (7%) and four articles (7%) on NHL provided the incidences of two or more types of hematologic adverse events (i.e., granulocytopenia or neutropenia; leukopenia; and hematologic toxicity). Most commonly, leukopenia was reported together with neutropenia or granulocytopenia.

**Dose Intensity:** The concept of dose intensity, in which drug doses are measured per unit of time, has standardized the quantification of delivered dose when it is expressed as relative dose intensity (RDI); the administered dose is related to either the planned or a reference dose intensity. In this review, dose intensity data were reported in various degrees of detail. Four levels of reporting (type 1, best, through type 4, no data) dose intensity were identified and defined as follows: Type 1 (best) included mean or median RDI, overall or by cycle, of each agent separately or averaged; type 2 (intermediate) included the percentage of patients given a stated percentage (e.g., 85%) of the planned dose intensities or absolute dose intensity data (i.e., nonrelative); type 3 (intermediate-low) included the percentage of patients completing all cycles and percentage with dose modifications, as well as mean or median percentage of total dose given (no time component); and type 4 (no data), no information on dose intensity provided.

The percentages of trials that reported dose intensity and the level of detail (type 1 to type 4) in both tumor types are shown in Figure 1. No data on delivered dose intensity were reported in the majority (39%...
and 54%, respectively) of ESBC and NHL trials. Of the 34 studies that reported high-level (type 1) RDI data, 21 (62%) were NHL studies. ESBC study results more often reported intermediate-low data (type 3), such as the number of patients who completed all cycles or who received a given percentage of dose intensity.

The majority of trial reports in ESBC and NHL (67% and 64%, respectively) indicated in the Methods section that dose modifications were prescribed in the event of hematologic toxicity. A combination of dose delays and reductions was most often prescribed. Nevertheless, many of these trial reports did not provide data on the resultant dose intensity delivered, or reported low-level dose intensity data: 64% of ESBC reports and 46% of NHL reports provided either type 3 (intermediate-low) or type 4 (no data) data. Therefore, in those studies that reported myelotoxicity but not dose intensity, it cannot be determined how toxicity rates may have been affected by reductions in the dose intensity that patients received.

**Reported Hematologic Toxicity and Dose Intensity Data:** The variations in the form of cytopenia reported, grades of toxicity used, and the calculation of the incidence of neutropenia (per patient, per chemotherapy cycle, or as a median absolute neutrophil count [ANC] nadir) make it difficult to compare data among reports. To facilitate comparisons and provide a more uniformly derived dataset for a comprehensive overview of myelotoxicity associated with particular regimens, for further analysis we used data only from those studies that provided the combined grades 3 and 4 or grade 4 alone incidences of hematologic toxicity, leukopenia, and granulocytopenia or neutropenia. For this comparison, 65 ESBC treatment arms and 46 NHL treatment arms are included. The reported rates of grades 3 and/or 4 myelotoxocities and dose intensity are summarized graphically in Figures 2 (ESBC) and 3 (NHL).

**Early-Stage Breast Cancer**
Studies of adjuvant chemotherapy for ESBC are separated between the arms of trials that tested CMF (cyclophosphamide, methotrexate, 5-fluorouracil)-based regimens and anthracycline-containing regimens (e.g., CAF [cyclophosphamide, doxorubicin, 5-fluorouracil], FEC [5-fluorouracil, epirubicin, cyclophosphamide], AC [doxorubicin, cyclophosphamide], and AC given sequentially or alternating with CMF).

**CMF and CMF-Modified Regimens:** Grades 3 and/or 4 myelotoxicity data were reported in 30 CMF-based arms (Fig. 2A). The rates of grades 3 and/or 4 cytopenias with CMF-based regimens varied widely, from 1% to 78% of patients. As seen in the scatter plot, rates fell below 15% in the majority of trial arms, and in all but one study were less than 50%. For no obvious reason, one study with standard CMF doses reported 78% and 60% incidences of grade 3 and grade 4 granulocytopenia and leukopenia, respectively.

Relative dose intensity (RDI) data were provided in 10 CMF-based treatment arms (Fig. 2B). Fifty percent of treatment arms reported RDIs below 85%; in one arm it was as low as 66%. Therefore, of the ESBC treatment arms that reported RDI below 85%, five of seven were CMF-based regimens. This information is significant because it has been specifically reported that dose intensity of CMF regimens must be maintained to achieve a five-year disease-free survival benefit.

**Anthracycline-Containing Regimens:** The most commonly used anthracycline-containing regimen identified in this review was the cyclophosphamide, doxorubicin, 5-fluorouracil/Fratafuir (CAF, FAC, CDF) combination. The incidence of grades 3 and/or 4 cytopenias reported with these treatment regimens ranged from 18% to 100% (Fig. 2A). The study reporting a 100% incidence of grade 3 or 4 neutropenia tested FAC with the prophylactic use of granulocyte-macrophage colony-stimulating factor. The incidence of neutropenia and its consequences was therefore evaluated in greater detail; perhaps this accounts for the higher rate of neutropenia.

When the anthracycline is changed from doxorubicin to epirubicin, the regimen is referred to as...
Figure 2 Scatter plots of reported grades 3 and/or 4 myelotoxicity and relative dose intensity data from randomized clinical trials of chemotherapy in early-stage breast cancer. A. Rates of grades 3 and/or 4 myelotoxicity in randomized controlled trials of chemotherapy for early-stage breast cancer. The rates of grades 3 and 4 effects combined that were reported in the clinical trials are shown grouped by chemotherapy regimen. †With prophylactic granulocyte-colony-stimulating factor (G-CSF) or granulocyte-macrophage-CSF (GM-CSF); ‡use of G-CSF at the discretion of the investigator; †based on blood cell counts taken on day 1 of the next cycle. B. Reported mean or median relative dose intensity in trials in ESBC, by chemotherapy regimen. The dotted line indicates an RDI of 85%.

FEC or CEF. The rates of grade 3 or 4 cytopenia reported with the FEC (5-fluorouracil, epirubicin, cyclophosphamide) regimen were, in general, lower than those reported with the CAF regimens, and were in the range of less than 5% to 30%. In contrast, an intensified CEF regimen was reported to have caused grade 3 or 4 granulocytopenia and leukocytopenia in 98% and 94% of patients, respectively.

Another commonly used anthracycline-containing regimen for ESBC is AC (doxorubicin and cyclophosphamide). The National Surgical Adjuvant Breast and Bowel Project (NSABP) tested the AC regimen in four large studies comprising more than 6,000 patients and eight treatment arms. The reported rates of leukopenia or granulocytopenia with AC in each of the eight treatment arms were less than 10%. However, the rates of granulocytopenia reported in NSABP studies B-22 and B-25 are probably understated, because these rates were based on blood cell counts obtained on day 1 of the next cycle.
Figure 3 Scatter plots of reported grades 3 and/or 4 myelotoxicity and relative dose intensity data from randomized clinical trials of chemotherapy in non-Hodgkin’s lymphoma. A. Rates of grades 3 and/or 4 myelotoxicity in randomized controlled trials of chemotherapy for NHL. The rates of grades 3 and 4 effects combined that were reported in the clinical trials are shown grouped by chemotherapy regimen. *Grade 4 only; †with prophylactic G-CSF or GM-CSF. B. Reported mean or median relative dose intensity in trials in NHL, by chemotherapy regimen. The dotted line indicates an RDI of 85%.

Chemotherapy Regimens

COP = cyclophosphamide, vincristine, prednisone; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone; CHVP = cyclophosphamide, doxorubicin, teniposide, prednisone; CTP = cyclophosphamide, teniposide, prednisone; CTVP = cyclophosphamide, pirarubicin, teniposide, prednisone; m-BACOD = bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, mechlorethamine, procarbazine, methotrexate; ProMACE-MOPP = cyclophosphamide, doxorubicin, etoposide, prednisone, vincristine, mechlorethamine, procarbazine, methotrexate; CHOPMtx = cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate; CHOEP = cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide; CAPOMEt = cyclophosphamide, doxorubicin, vincristine, prednisone, methotrexate, lomustine, etoposide; BACOP = bleomycin, doxorubicin, cyclophosphamide, vincristine, prednisone; ACVBP = doxorubicin or mitomycin, cyclophosphamide, vindesine, bleomycin, methotrexate, prednisone; MACOP-B = methotrexate, bleomycin, cyclophosphamide, doxorubicin, vincristine, prednisone; MECOP-B = methotrexate, bleomycin, cyclophosphamide, epirubicin, vincristine, prednisone, VACOP-B = etoposide, bleomycin, cyclophosphamide, doxorubicin, vincristine, prednisone; VICEP-B = etoposide, bleomycin, cyclophosphamide, idarubicin, vincristine, prednisone; VNCOP-B = mitoxantrone, cyclophosphamide, etoposide, vincristine, prednisone, bleomycin; F-MACHOP = 5-fluorouracil, methotrexate, doxorubicin, cyclophosphamide, cytarabine, vincristine, prednisone; PACEBOM = doxorubicin, cyclophosphamide, etoposide alternating with bleomycin, vincristine, methotrexate, prednisolone; ProMACE-CytaBOM = cyclophosphamide, doxorubicin, etoposide, prednisone, cytarabine, bleomycin, vincristine, methotrexate (*I* = doxorubicin replaced by idarubicin, “E” = doxorubicin replaced by epirubicin); COP-BLAM = cyclophosphamide, vincristine, procarbazine, bleomycin, doxorubicin, prednisone; CHOP-1EVP = cyclophosphamide, doxorubicin, vincristine, prednisone, ifosfamide, vindesine, etoposide, prednisolone; CEP-B/VIMB = cyclophosphamide, epirubicin, vincristine, prednisolone, bleomycin, etoposide, ifosfamide, mitoxantrone, bleomycin; CIOP = cyclophosphamide, idarubicin, vincristine, prednisone; VMP = etoposide, mitoxantrone, prednimustine.
Chemotherapy cycle, thus avoiding the neutrophil nadir. In addition, the reported rates of serious infection or sepsis in these trials ranged from 2.4% to 3.3%, suggesting that the actual incidence of severe neutropenia associated with this regimen is probably considerably higher.\textsuperscript{32,51,52}

A variety of other anthracycline-based regimens were evaluated, including some in combination with CMF, in either sequential or alternating protocols.\textsuperscript{22,32,37,53,54} These studies reported rates of grades 3 or 4 cytopenia that ranged from a 1% leukopenia rate with ACMF\textsuperscript{53} to 39% and 72% incidences of granulocytopenia and leukopenia, respectively, in patients given FAC with methotrexate (FAC-M).\textsuperscript{22}

Of 16 anthracycline-based ESBC study arms that reported dose intensity data, two treatment arms reported RDI of less than 85% (Fig. 2B). One study reported 83% RDI with a CAF regimen\textsuperscript{42} and another reported 77% RDI with the FEC regimen.\textsuperscript{40} The 14 remaining anthracycline-containing regimens reported RDI above 85%, including the eight AC treatment arms in which RDI was reported at or just below 100%.\textsuperscript{7,32,51,52}

Non-Hodgkin's Lymphoma

Chemotherapy for NHL has evolved from the early use of single agents and the combination of cyclophosphamide, vincristine, and prednisone (CVP) through the addition of doxorubicin (CHOP) in the 1970s to the second- and third-generation combination regimens that use additional non-cross-resistant agents. The data were organized into groups of related regimens, categorized as CHOP and modified CHOP, augmented CHOP and second-generation regimens, and third-generation regimens. The rates of grades 3 or 4 toxicities in trials in which they were reported are shown graphically in Figure 3.

**CHOP and Modified CHOP Regimens:** The CHOP regimen, composed by the addition of doxorubicin to the CVP regimen, has been reported to result in a complete response rate of between 55% and 60\textsuperscript{96} and long-term survival in some 30% of patients with NHL.\textsuperscript{97} Modified CHOP, augmented CHOP, and several second- and third-generation regimens initially appeared to improve the treatment of aggressive NHL. However, randomized trials comparing these regimens with CHOP found no difference in overall survival.\textsuperscript{98-100} Thus, CHOP remains the standard chemotherapy regimen for the treatment of NHL.

Eight of the randomized controlled trials in NHL that reported data on hematologic toxicity included a CHOP treatment arm, making it the most frequently tested regimen. The reported incidence of grade 3 or 4 cytopenia with standard-dose CHOP varied widely, from 34% to 73% of patients.\textsuperscript{98-105} Data on regimens that are modified forms of CHOP (with one agent omitted or substituted) are also shown in Figure 3A.\textsuperscript{101,106-108} The lowest rate of neutropenia reported with a modified CHOP regimen was with CHVP, in which vincristine was replaced by teniposide, and the rate of grade 3 or 4 neutropenia was 5%.\textsuperscript{108}

**Augmented CHOP and Second-Generation Regimens:** The CHOP regimen has been augmented by the addition of other agents in attempts to increase its effectiveness. Two widely adopted variations, known as second-generation regimens, are m-BACOD (bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone, methotrexate) and ProMACE-MOPP (cyclophosphamide, doxorubicin, etoposide, prednisone, vincristine, mechloretamine, procarbazine, methotrexate). Grades 3 and/or 4 cytopenias were, in general, higher with second-generation or augmented CHOP regimens than with standard CHOP treatment regimens (Fig. 3A). The rates of grades 3 and/or 4 cytopenia were all greater than 40%, ranging from 42% to 91%.\textsuperscript{98-100,103,110-116}

**Third-Generation Regimens:** The third-generation chemotherapy regimens for NHL introduced more-intense dosing schemes that use non-cross-resistant agents in alternating weeks. After CHOP, the second most commonly tested regimen analyzed here is MACOP-B (with methotrexate and bleomycin added to the CHOP elements).\textsuperscript{98,100,105,107-118} Other regimens include substitute agents in a similar alternate-week schedule.\textsuperscript{105,110-112} In common with the other regimen categories for NHL, the rates of grades 3 and/or 4 cytopenias with the third-generation regimens varied widely, with a range of 21% to 73% (Fig. 3A).\textsuperscript{98,100,103,110-112}

**Relative Dose Intensity in NHL Trials**

Patients in a significant portion of the NHL treatment arms received a median RDI of less than 85% of that of the planned (or reference) regimen. The mean or median RDI was less than 85% in 19 (42%) of 44 of treatment arms, displayed graphically by regimen in Figure 3B. Thirteen treatment arms reported RDI data for CHOP or modified-CHOP regimens.\textsuperscript{98,99,102,109,113-126} Although the majority of these regimens reported RDI at or above 90%, four (31%)
of 13 CHOP or modified CHOP treatment arms reported RDI at less than 85%. In three of these four arms, reduced RDI was identified as being the result of low patient performance status, elderly patient population, or concomitant use of interferon alfa. RDI was reported in six treatment arms categorized as augmented CHOP or second-generation regimens: four (67%) of six treatment arms reported RDI of less than 85%. Twenty-three treatment arms reported RDI associated with third-generation regimens; nine (39%) of 23 reported RDI less than 85%.

Interestingly, prophylactic treatment with hematopoietic growth factors allowed the maintenance of RDI at or above 85% in three NHL studies that compared treatment with or without the addition of growth factors. In addition, one study reported RDI data in relation to patient performance status. Not unexpectedly, higher RDI was reported in patients with a better performance status (0 or 1) than in those with a lower performance status (2 or 3).

**Discussion**

Giving less than the standard dose intensity of a particular chemotherapy regimen may compromise treatment outcome and overall survival of patients undergoing cancer therapy, because of the steep dose-response relationship. Therefore, it is important to understand the tolerability of a chemotherapy regimen and ability to deliver planned dose on time. Tolerability includes both the incidence of toxic effects and the dose intensity of the chemotherapy agents delivered.

The data summarized here are the most inclusive accounting to date of the overall incidence of neutropenia and dose intensity in recent major clinical trials of chemotherapy for ESBC and NHL. In this comprehensive survey of randomized trials, we have found that the incidence and severity of myelotoxic effects were not reported in a full 35% of articles assessed in this review. When provided, the data were inconsistently reported and had widely varying values for the same or similar chemotherapy regimens. Furthermore, most trial reports did not report data on delivered dose intensity or, when reported, provided low-level dose-intensity data. This makes the current literature base less useful for ascertaining the efficacy and tolerability of particular chemotherapy regimens.

The dose intensity of chemotherapeutic agents delivered is known to impact both the efficacy and the tolerability of a regimen. A delivered RDI of 85% has been reported as the threshold below which survival is compromised in ESBC. Of 26 ESBC study arms in which the RDI was provided, more than one quarter (27%) reported RDI of less than 85%. Of 46 NHL study arms in which RDI was provided, 41% reported RDI of less than 85%. If these percentages are representative of all clinical trials, including those that did not report data on dose intensity, then a significant number of trials may not have truly tested the regimens as described.

Several of the studies prescribed chemotherapy dose modifications (reductions or delays) for hematologic or other toxic effects. However, many of these studies did not provide data on the dose intensity that patients were given as a result of these modifications. Without knowing by how much dose intensity was reduced in a trial, we cannot accurately determine the true myelotoxic potential of the regimen, even when data on hematologic toxicity are provided.

Our results suggest that current practices for reporting the tolerability of chemotherapy treatments are inadequate for fully describing the risk of chemotherapy to patients or quantitatively assessing the risk of treatment alternatives. We recommend the development of standard procedures for documenting and reporting hematologic toxicity and dose intensity for the publication of randomized clinical trial results. To create a comprehensive record of the hematotoxicity and RDI of chemotherapy regimens, reports of clinical trials should document:

- The rates of all grades of leukopenia and neutropenia, according to the white blood cell and absolute neutrophil counts taken during the period of the expected nadir, preferably cycle-by-cycle as well as by overall cycles;
- The timing of the blood cell counts that were used to determine these rates;
- Protocols for the use of antibiotics and the actual use of antibiotics;
- Protocols for the use of hematopoietic growth factors and the actual use of growth factors;
- The rates of all infectious complications, including hospitalizations and bacteremias; and
- The dose intensities that were delivered in each arm of the trial relative to the planned intensities, preferably by cycle and across the entire planned course.

More-thorough reporting of hematologic toxicity and delivered dose intensity in trials of cancer
chemotherapy would lead to a more rational basis on which to judge the relative efficacy and safety of the regimens tested. The more information documented about the conditions surrounding the occurrence of the main dose-limiting toxicity in cancer chemotherapy, the more accurately we will be able to predict neutropenic complications. In the future, improved outcomes may be achieved with predictive models based on patient, disease, and treatment risk factors that can be used to target interventions, including prophylactic growth factors, in patients identified as being at high risk for complications.

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