Patterns of Chemotherapy Administration in Patients With Intermediate-Grade Non-Hodgkin’s Lymphoma

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Records from 653 patients treated between 1991 and 1998 in the Oncology Practice Patterns Study (OPPS) were analyzed to determine contemporary chemotherapy delivery patterns in patients with intermediate-grade non-

NHL is the seventh most common cancer in the United States, with approximately 56,200 new cases diagnosed each year.[1] Recent evidence shows that the mortality rate is increasing.[2] Although many patient- and disease-related factors such as age, performance status, comorbidities, stage, histology, laboratory values (eg, lactate dehydrogenase [LDH] level), and treatment affect survival, clinicians can only alter treatment. Among NHL patients, those with intermediate-grade disease are considered potentially curable, based on data from randomized clinical trials.[3-5]

Overview of Treatment

Selection of a chemotherapy regimen is a primary factor in the survival of intermediate-grade NHL patients. Common chemotherapy regimens used for NHL over the past 25 years have included CHOP (cyclophosphamide [Cytoxan, Neosar], doxorubicin HCl, vincristine [Oncovin], prednisone),[6-9] CNOP (cyclophosphamide, mitoxantrone [Novantrone], vincristine, prednisone),[10] and two different schedules of cyclophosphamide, vincristine, and prednisone (COP[11,12] and CVP[13,14]). Of these, however, only CHOP and CNOP are currently considered curative treatments for intermediate-grade NHL, along with newer regimens such as m-BACOD (methotrexate, leucovorin, bleomycin [Blenoxane], doxorubicin [Adriamycin], cyclophosphamide, vincristine, dexamethasone), ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, mitoxantrone, leucovorin), and MACOP-B (methotrexate, leucovorin, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin).[9] Additionally, two studies have suggested that the CHOP regimen is superior to the CNOP regimen in achieving a cure in these patients.[10,15] In addition to the choice of initial chemotherapy regimen, the planning and delivery of full-dose chemotherapy, both with respect to the total number of cycles administered and the dose intensity, are considered important factors in the outcome of patients with intermediate-grade NHL. Kwak et al have shown that intermediate-grade NHL patients who received less than 75% of their planned dose had worse 5-year survivals than those who received 75% to 100% of their planned dose.[16] Also, Epelbaum et al showed that intermediate-grade NHL patients who received less than 70% to 80% of their planned dose had a worse response and 5-year survival than did those who received their full planned dose.[17]

Unfortunately, retrospective studies cannot clearly differentiate the patients who were able to tolerate a higher dose of therapy and thus achieve a better survival from those who achieved better survival for other reasons. Few prospective randomized clinical trials have evaluated the effects of both total dose and dose intensity on survival in NHL.[8]

Dose-Limiting Factors

Delivery of standard-dose chemotherapy is often interrupted by the development of myelosuppression. The most common myelosuppressive dose-limiting phenomena is neutropenia. Neutropenia, defined as an absolute neutrophil count (ANC) less than 1,000 cells/µL, occurs frequently with the standard chemotherapy regimens used to treat NHL—in 78% to 91% of patients receiving CHOP[10,18,19]—and often leads to dose reductions or dose delays and sometimes to infection, hospitalization, and death.[20] Although dose reductions or delays may reduce the risk of neutropenia in subsequent cycles, they may also reduce the opportunity for prolonged survival and/or cure.
Variations in the treatment and outcomes of patients with NHL are largely undocumented in many therapeutic settings. For example, there are multiple reports on chemotherapy-related complication rates from randomized trials (often in academic settings); however, their effect on the delivery of chemotherapy in community practices is largely unknown.

The purpose of this article is to describe contemporary practices in the use of chemotherapy from a population-based perspective. In particular, we will consider (1) the choice of initial chemotherapy regimen, (2) the number of chemotherapy cycles administered, (3) variations in the planned and delivered doses of chemotherapy from referenced standards, (4) the incidence and management of chemotherapy-related neutropenia, and (5) the incidence and management of neutropenia-induced complications (including growth factor use). Herein are our findings from the ongoing Oncology Practice Pattern Study (OPPS) conducted at large managed-care, community, and academic practices.

**Methods**

**Study Design and Data Collection**

This study was conducted in nine large diverse practice settings across the United States, including health maintenance organizations, academic medical centers, integrated delivery systems, independent practice associations, and physician practice management associations. To be included, each study site needed the following two essential characteristics. First, there had to have been a minimum of 30 to 40 analyzable patients with intermediate-grade NHL who had been treated during the 3 years prior to the proposed study initiation date. The population of potentially eligible patients at each site was screened using existing databases such as tumor registry, billing, and pharmacy data. Second, each site needed to have documentation of the requisite information, as identified below. According to the institutional review board (IRB) guidelines for human subjects, 5 to 10 medical records were reviewed to ensure the completeness of the medical record relative to the case report form at each site.

Data collection started on the date the study was initiated, entailing the compilation of approximately 100 consecutive, eligible, and retrospective patient records (or data covering a 3-year span). Data were collected for patients who had been treated between 1991 and 1998 (with 98% from 1993 onward). Patients were eligible if they received their first course of chemotherapy for intermediate-grade NHL (stages I-IV) within 3 years of study initiation and were at least 18 years old. Patients were excluded if they had been entered into a clinical trial treatment protocol, had other primary invasive cancers, received another course of chemotherapy within 3 years before the treatment studied (ie, no relapses and no retreatments), or tested HIV positive.

The medical records were abstracted using uniform case report forms under the supervision of the site’s principal investigator. Information collected included (1) patient characteristics, ie, age, gender, race, comorbidity, size (height, weight, and body surface area for each cycle), stage, histology, number of extranodal sites involved, elevated LDH, and B symptoms (systemic symptoms); (2) the planned chemotherapy regimen (drugs, dose, route, length, and number of cycles); (3) the delivered chemotherapy regimen (drugs, dose, route, and the dates of delivery for each cycle); (4) all complete blood counts and differential information available; (5) growth factor and antibiotic use during the course of therapy, including drugs, dose, number of doses, and dates delivered; (6) prior and concurrent radiation therapy, including courses, total doses, and dates delivered; (7) characteristics of any surgical treatment; (8) short-term treatment complications, including presence of mucositis, febrile neutropenia, and hospitalizations, along with event dates, supporting documentation (pertinent notes from the medical record), and laboratory results; and (9) any medical record notation regarding chemotherapy dose modifications, complications, use of supportive-care agents, and early termination of chemotherapy.

**Data Processing**

The OPPS Data Coordinating Center within Pharmacoeconomics at Amgen Inc, Thousand Oaks, Calif, conducted quality assurance, data entry, and data analyses for this study. Staff included data entry personnel, statistical analysis software (SAS) programmers, and a multidisciplinary team of scientists including clinicians (oncologists, pharmacists, and oncology nurses), a biostatistician, an epidemiologist, a health economist, and a health services researcher.

Quality assurance and data analysis were coordinated and reviewed with the principal investigators and data collection coordinators at each site. An experienced oncology nurse reviewed all case report forms for completeness and consistency. Questions were returned to the study site for verification against the medical record. After forms were reviewed and corrected, data were double
entered to minimize data entry errors. Quality assurance checks were performed prior to data analyses, examining variables for appropriate ranges of values and for consistency across related fields.

**Methods for Calculating Dose Intensity**

In many published reports, the actual chemotherapy dose delivered is undocumented; thus, planned dose intensity is used as an approximation. In community practice studies, such an approximation may overestimate the actual delivered dose intensity because it does not reflect common dose modifications and/or the failure to complete the planned number of cycles. Other studies look at only one agent or the first few cycles, which would also overestimate the delivered dose intensity. Thus, dose intensities were examined using these definitions: Referenced dose is derived from the citations in Table 1; planned dose, from the medical record prior to the start of chemotherapy; and delivered dose is the actual chemotherapy delivered as indicated in the medical record.

Relative dose intensity was calculated in the following three ways: (1) planned dose relative to referenced dose; (2) delivered dose relative to planned dose; and (3) delivered dose relative to referenced dose. Because referenced dose intensity is based on doses reported in clinical trials, it is important to evaluate both the delivered dose intensity and planned dose intensity relative to the referenced dose intensity.

**Average Relative Dose Intensity**—The delivered dose intensity for each agent in a regimen was calculated by summing all the doses (mg/m²) delivered to a patient over the course of treatment and dividing that number by the total number of days taken to deliver them (ie, from the first day of the first cycle through the last day of the last cycle). Delivered dose intensities for individual agents were then converted to mg/m²/wk by multiplying by 7. Agent-specific relative dose intensity was calculated by taking the ratio of the delivered dose intensity for an agent (mg/m²/wk) to its corresponding referenced dose intensity (mg/m²/wk).

Average relative dose intensity was then calculated by averaging the agent-specific relative dose intensities delivered in each regimen. In this study, however, average relative dose intensity was determined for the CHOP regimen using mean calculations for cyclophosphamide and doxorubicin, and for the CNOP regimen using cyclophosphamide and mitoxantrone. Note that dose intensity, measured over the period of actual delivery, does capture dose reductions and delays but does not capture missed cycles of chemotherapy discontinued short of the referenced number of cycles.

**Definitions of Dose Delays and Dose Reductions**

Dose delays and reductions can be studied as discrete cycle-by-cycle events so as to note their timing during the course of chemotherapy and patterns of recurrence. For examples of how dose modifications affect outcomes, see the reports by Kwak and Epelbaum. Although dose delays and reductions of any magnitude influence dose intensity, our analysis considered only those that represented nontrivial alterations in the planned regimen.

A dose reduction was defined as a decrease of 20% or more from the planned dose of any primary chemotherapy agent (cyclophosphamide, doxorubicin, or mitoxantrone). For each cycle, a dose reduction was determined by calculating the total delivered dose of each agent per cycle (in mg) divided by the body surface area (m²), and comparing this result to the planned dose (mg/m²). A dose delay was defined as a suspension of 7 days or more in the planned start of chemotherapy (beginning with cycle 2) relative to the start of the previous cycle. The planned cycle schedule abstracted from the medical record was used to determine delays.

Neutropenia-Related Dose Delays and Dose Reductions—As in the study by Silber et al, to be considered neutropenia-related, the dose delay or reduction had to meet one of the following conditions: (1) the occurrence was associated with a specific comment in the medical record indicating neutropenia; or (2) when no comment was recorded in the medical record and the dose delay or dose reduction was preceded by an episode of neutropenia, an absolute neutrophil count (ANC) of 1,000 or less or white blood cell count (WBC) of 2,000 or less (cycle nadir), or an ANC of 1,500 or less or WBC of 3,000 or less (cycle baseline) was used.

**Results**

**OPPS Patient Records**

A total of 772 patient records were submitted into the OPPS survey for analysis. Of these, 54 patient records were deemed ineligible (40 records described patients with low-grade non-Hodgkin’s lymphomas, 7 concerned a recurrence of lymphoma, and 7 were duplicates), leaving 718 patient records eligible for further analysis. These records were abstracted, entered into a database, and checked for errors. An additional 65 patient records were then excluded from further analysis for the
following reasons: change in the chemotherapy regimen for unclear reasons (n = 37), missing chemotherapy dose or schedule information (n = 14), and radiation therapy administered prior to or concurrent with chemotherapy (n = 14). Thus, a total of 653 patient records were selected for analysis.

**Choice of Chemotherapy Regimen**

The 653 patients whose records were analyzable for choice of chemotherapy regimen had been treated between 1991 and 1998, with the majority (59.5%) treated between 1995 and 1998. Among these patients, 428 had received the CHOP regimen, and 64, the CNOP regimen (Table 1).[6,10] These regimens are referenced by dose, cycle length, and number of treatment cycles. Note that a 21-day cycle and a minimum of six cycles of chemotherapy were used for all referenced regimens. There was a trend toward increased use of the CHOP regimen during the time of the study, but this trend was not statistically significant (data not shown).

One hundred sixty-one patients received other chemotherapy regimens that were not referenced for dose or dose-intensity analysis (Table 1).[6,10] These patients can be grouped into those who received anthracycline-containing (71 patients; 44%) and non-anthracycline-containing (90 patients; 56%) regimens. These other regimens can also be grouped as CHOP-like, CHO-like, CH-like, C-like, and no-C schedules.

There were 42 CHOP-like regimens that added one or more of the following agents: methotrexate, L-asparaginase (Elspar), cytarabine, bleomycin, or etoposide. There were 13 CHO-like regimens adding one or more of the following agents: carmustine (BiCNU), procarbazine (Matulane), methotrexate, cytarabine, bleomycin, etoposide, mesna (Mesnex), or ifosfamide (Ifex). There were nine CH-like regimens adding one or more of the following agents: methotrexate, prednisone, cytarabine, vinblastine, etoposide, or leucovorin; and 79 C-like regimens adding one or more of the following agents: procarbazine, mitoxantrone, methotrexate, prednisone, cytarabine, bleomycin, dexamethasone, or etoposide.

There were 18 regimens containing no cyclophosphamide but including one or more of the following agents: etoposide, doxorubicin, bleomycin, prednisone, vinblastine, dacarbazine (DTIC-Dome), leucovorin, vincristine, mesna, methotrexate, mitoxantrone, ifosfamide, fludarabine (Fludara), dexamethasone, chlorambucil (Leukeran), or cisplatin (Platinol). Some of these patients, not referenced for dose or dose intensity, received newer-generation chemotherapy regimens for intermediate-grade lymphomas (eg, m-BACOD, ProMACE-CytaBOM, VACOP-B [etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin], or COP-BLAM [cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine]).

Of particular note, 14% (90/653) failed to receive regimens containing either doxorubicin or mitoxantrone, and thus would not have received a chemotherapy regimen considered potentially curative for intermediate-grade NHL according to current treatment guidelines.[4] Subsequent analysis focused primarily on the 492 patients (75%) who received CHOP or CNOP.

The basis for the choice of chemotherapy regimen by physicians participating in this study is not entirely clear. There was no significant difference between the number of patients aged 65 years or older receiving CHOP vs those receiving one of the other regimens except CNOP (as will subsequently be discussed). Also, when comparing Charlson scores (a severity index of comorbid conditions)[23] for patients receiving CHOP vs those receiving all the other regimens except CNOP (again, as will subsequently be discussed), there were no significant differences except that the other regimens were more often chosen for patients with comorbid cardiac conditions (data not shown).

**Characteristics of CHOP and CNOP Recipients**

The characteristics of patients receiving CHOP and CNOP in the OPPS sample are summarized in Table 2.[23] The majority of OPPS patients were white (92%), male and elderly (median age: 66.2 years; 54% were at least 65 years of age), and had no comorbidities (72%). Also, approximately one-half of OPPS patients had stage I/II NHL.

CHOP was used much more frequently that CNOP (87% vs 13%), even in patients 65 years of age or older (80% vs 20%). Race, gender, Charlson score, stage, histology, number of extranodal sites, presence of B symptoms, and elevated LDH were not significantly associated with selection of chemotherapy regimen. However, patients at least 65 years old were more likely to receive CNOP than CHOP (P = .0001), as were those with any major associated comorbid condition (P = .0322) or, more specifically, cardiac comorbidity (P = .0317). However, one cannot be sure that the choice of CNOP over CHOP was based strictly on a patient’s age and/or the presence of heart disease at the exclusion of patient-related or disease-related prognostic factors, including patient performance status.
Number of Chemotherapy Cycles Delivered
Per the literature, CHOP or CNOP therapy is to be delivered for a minimum of six cycles to patients continually responding to chemotherapy prior to discontinuation. Analysis of adherence to this standard by patients with stage I/II NHL is difficult to determine from the OPPS patients’ records due to the increasing use of abbreviated courses (ie, three or four cycles) of chemotherapy followed by involved-field radiation therapy. However, a sense of the degree of adherence to optimum cycle number can be gained by analyzing the number of cycles administered to stage III/IV patients who achieved complete or partial responses. Among 159 records describing such patients who received CHOP, 15% (24/159) failed to receive at least 6 cycles of treatment. A similar statistic of 18% (4/22) was found for patients receiving CNOP. Whether reductions in cycle number below the referenced standard for this patient group occurred due to patient refusal, chemotherapy toxicity, or physician decision cannot be further ascertained from the OPPS patient records at this time.

Average Relative Dose Intensity
Planned vs Referenced Chemotherapy Dose—In general, planned chemotherapy doses for patients receiving both CHOP and CNOP closely followed the referenced doses listed in Table 1 (see Table 3). Specifically, the mean of planned/referenced doses for CHOP and CNOP was 0.96 and 0.94, respectively. However, 12% (51/428) of patients receiving CHOP and 19% (12/64) of those receiving CNOP were planned for < 80% of the referenced dose level. The main prognostic factor considered when reducing the planned dose to < 80% of the referenced dose was for patients who were at least 65 years old (data not shown).

Delivered vs Planned Chemotherapy Dose—A comparison of the delivered chemotherapy dose to the planned dose showed that the mean of delivered/planned doses (over the delivered cycles only) for patients receiving CHOP and CNOP was 0.92 and 0.87, respectively (Table 3). Again, a significant number of patients received < 80% of the planned dosage—15% of CHOP recipients and 26% of CNOP recipients.

Delivered vs Referenced Chemotherapy Dose—The delivered average dose intensity computed as previously defined (again over the delivered cycles only) was also obtained (Table 4). Overall, 27.2% of CHOP and CNOP recipients (134/492) received an average relative dose intensity < 80%. An average relative dose intensity < 80% was more often seen among patients receiving CNOP (45.3%) than those receiving CHOP (24.5%). There was little difference between early-stage and advanced-stage patients in terms of the frequency with which they received an average relative dose intensity < 80% (22.6% vs 27.8%).

Considering the entire sample of 653 analyzable patient records, 90 patients failed to receive an anthracycline, and 64 received CNOP; 24 responding patients with advanced-stage disease who were receiving CHOP failed to receive a minimum of 6 cycles, and 105 additional CHOP patients received an average relative dose intensity < 80% (Table 4). Thus, 283/653 (43%) of the total patient group potentially received suboptimal chemotherapy, with respect to either choice of regimen or inferior delivery.

Dose Delays and Dose Reductions
A decrease in average relative dose intensity can occur either as a result of a delay in administration or a reduction in dose. A summary of the rate of dose delays and reductions for the OPPS sample by regimen (CHOP or CNOP) is presented in Table 5. Overall, 47.8% of OPPS patients had at least one dose reduction or dose delay during the course of therapy. There was no difference in dose delays between the two regimens, but the CNOP regimen was associated with a significantly higher incidence of dose reductions (P = .0007) than the CHOP regimen. The reasons for the dose delays and reductions (analyzed by cycle) in the OPPS sample varied (Table 6). Neutropenia was the primary cause of dose modifications, accounting for 56% of dose delays and 59% of dose reductions. Consequently, chemotherapy-induced neutropenia was the leading cause of low delivered dose intensity.

Growth Factor
Growth factor was used at least once in 53% (261/492) of patients (Table 7). It was used for primary prophylaxis (ie, starting on days 2 to 5) in 11% (53/492) and for secondary prophylaxis (ie, with a prior low ANC) in 39% (191/492). There was no statistical difference in the frequency of growth factor use between patients in the CHOP vs CNOP regimens (P = .5822, P = .1398, and P = .7509, respectively, for overall, primary, and secondary prophylaxis).

The occurrence and recurrence of treatment modifications were also examined (Table 8). Each patient was followed cycle-by-cycle and classified by the first treatment modification made. Treatment modification classifications included dose delay, dose reduction, growth factor use, and
no modification. After the first treatment modification, the patient was followed for subsequent cycles and similarly classified by the second treatment modification. The results indicate that these treatment modifications were most frequently of a repetitive nature—ie, the same type of modification was used repeatedly, most commonly in relation to neutropenia. Specifically, patients whose first experience was a dose delay had a 40.5% chance of experiencing a second dose delay, but only a 4.8% chance of experiencing a dose reduction, and a 2.4% chance of receiving a growth factor. Similarly, patients whose first experience was a dose reduction had a 68.4% chance of experiencing a second dose reduction, but only a 2.6% chance of experiencing a dose delay and a 2.6% chance of receiving a growth factor. Further analyses would be necessary to determine if this was a patient, physician, or institution effect, or whether this strategy for dealing with dose alteration is ideal.

**Neutropenia-Related Complications of Chemotherapy**

Treatment complications related to neutropenia were also analyzed according to chemotherapy regimen (Table 9). They included mucositis, febrile neutropenia, and hospitalizations associated with febrile neutropenia. Overall, the rates of these three complications were 20.3%, 31.3%, and 23.6%, respectively. There was no statistical difference in the complication rates between patients who received CHOP and those who received CNOP. However, an increased frequency of hospitalizations for febrile neutropenia occurred in patients with a planned average relative dose intensity of at least 80% and either a cardiac comorbidity (coronary artery disease, congestive heart failure, and/or cardiac arrhythmia) or an age of at least 65 years (Table 10). Furthermore, the prophylactic use of growth factor was associated with a significantly lower incidence of febrile neutropenic hospitalizations for both age 65 and over ($P = .0352$) and cardiac comorbidity ($P = .0230$). In fact, this association was found across all age groups and all comorbid conditions, using both the Charlson comorbidity index and individual comorbidity components ($P = .02$; data not shown).

**Discussion**

The purpose of the OPPS analysis was to obtain a population-based (as opposed to an institution- or protocol-based) description of contemporary chemotherapy administration for intermediate-grade NHL. The exclusion of patients from formal treatment protocols, however, introduces biases into the patient sample analyzed. Among these biases are (1) a potentially higher frequency of patient characteristics typically exclusionary for protocol enrollment, (2) a patient population less willing to enroll in clinical trials, (3) a diminished desire for both patients and physicians to use "state of the art" or "experimental" treatment methods, and (4) a potentially less detailed observation of clinical events during treatment.

Identifying the relatively high-volume NHL treatment centers centers that were a part of the OPPS—instiutions that often offered formal treatment protocols concurrent with the OPPS study—would tend to obviate some of these biases, at least in part. The exclusion of patients from a treatment protocol enabled this study to focus on clinical decision-making with respect to chemotherapy administration, presumably uninfluenced by factors other than the delivery of best patient care.

Analysis of treatment practices shows significant and perhaps surprising degrees of variation from established guidelines for the treatment of NHL.[4] Thirteen percent of patients failed to receive a treatment regimen with curative potential for NHL. An additional 10% received CNOP, which was found by two randomized trials to be inferior to CHOP in patients with intermediate-grade NHL.[10,11]

The optimum number of treatment cycles was not reached in 15% to 20% of cases—this reduction was seen even in responding patients receiving curative regimens, as witnessed by the data on number of cycles of chemotherapy administered to advanced-stage patients receiving CHOP or CNOP. Also, 27% of CHOP and CNOP patients received an average relative dose intensity < 80% over the number of administered chemotherapy cycles, either due to a reduction in the planned chemotherapy dose, a reduction in the delivered chemotherapy dose, or a delay in chemotherapy administration. Overall, compared to full-dose CHOP, 43% or nearly one-half of all patients in the OPPS analysis experienced a significant deviation from the ideal in delivered chemotherapy.

A variety of clinical developments in the treatment of NHL potentially influenced the choice of chemotherapy and its administration during the course of this analysis (1991-1998). Many of these developments would seem to have enhanced the optimum use of CHOP. Among these developments
were (1) the recognition of the equivalence of CHOP to newer chemotherapy regimens in large-cell lymphoma, (2) the recognition of the superiority of CHOP to CNOP in large-cell lymphoma, (3) the use of neutrophil growth factors to reduce neutropenic complications, and (4) the introduction of more effective antiemetics for chemotherapy-induced nausea. Despite these clinical advances, the use of CHOP as primary chemotherapy did not increase appreciably over the time of the study.

**Prognostic Factors**

The impact of the observed deviations in chemotherapy administration on the ultimate fate of patients in the OPPS study remains uncertain. A more comprehensive assessment of pretreatment prognostic factors and risk (eg, International Prognostic Index) would assist a comparison of treatment outcomes with other similarly treated populations with intermediate-grade lymphomas. Also, the confounding effect of other therapies, particularly radiation therapy, would have to be considered.

Most importantly, variations in the regimen, schedule, dose, and dose intensity need to be analyzed prospectively with respect to long-term disease-free and overall survival. The impact of these variations on overall outcome is unknown. Moreover, the question of the impact of dose intensity on the disease-free and overall survival of patients with intermediate-grade NHL, at least within the dose ranges that characterize the chemotherapy regimens referenced in this analysis, also requires active investigation.

The need to avoid the toxic consequences of chemotherapy while maintaining optimum dose intensity appears to be more established. Specifically, the delivery of an average relative dose intensity > 80% was frequently compromised by the neutropenic complications of treatment. In particular, mucositis, febrile neutropenia, and hospitalizations for febrile neutropenia each occurred in 20% to 30% of patients receiving CHOP or CNOP in this cohort. These complications occurred most commonly in patients receiving chemotherapy according to the referenced standard, who were either age 65 and over, or perhaps, more surprisingly, had evidence of cardiac comorbidity. Why patients with coronary artery disease, congestive heart failure, and/or cardiac arrhythmia would have a higher incidence of neutropenic complications is not intuitively obvious and requires further investigation.

**Advantages of Growth Factor Use**

Growth factor use was common and was indicated in slightly more than half of the patient records analyzed for this survey. Growth factors can assist in the timely delivery of full-dose chemotherapy. The potential benefits of optimizing the delivery of chemotherapy include improved response rates and improved disease-free and overall survival, while minimizing costly short-term complications such as hospitalization for febrile neutropenia. For example, consider the occurrence of febrile neutropenia in high-risk patients aged 65 years or older who had a planned average relative dose intensity > 80% and patients with cardiac comorbidities who had a planned average relative dose intensity > 80%. The incidence of hospitalization for febrile neutropenia in both of these groups was approximately 40% without the use of prophylactic growth factors, which is comparable to the rates cited in the 1994 and 1996 ASCO guidelines for growth factor usage.

The use of growth factors in this circumstance also relates potentially to the cost of therapy as per findings by Lyman et al. These investigators found that if a patient group has a 40% risk of hospitalization, prophylactic use of growth factors would completely offset a hospital cost of $1,000 per day. Note that this considers only direct medical costs—not indirect medical costs, nonmedical costs, or the impact on a patient’s health-related quality of life. Primary (prophylactic) use of growth factors in patients with intermediate-grade NHL merits additional consideration from physicians, particularly for high-risk patient subgroups.

**Factors in Chemotherapy Choice**

What decision-making process do physicians and their patients use to make decisions regarding chemotherapy administration? With respect to decisions about chemotherapy regimen (eg, CHOP vs CNOP) and planned dosage, patient age and disease comorbidity—particularly, cardiac comorbidity—seem to dominate physician consideration. Other patient- or disease-related prognostic factors, including performance status, appear to be of lesser influence.

With respect to issues of treatment alteration due to toxicity (primarily neutropenia-related), physicians seem willing to use dose delay, dose reduction, and growth factor as stratagems, but the logic behind why one is selected over another is unclear. What is clear is that once a stratagem is selected (eg, dose delay), it is generally used repeatedly if further dosing issues arise, rather than being discarded for another approach (eg, growth factor use).
Decisions concerning the type, dose, and modification of chemotherapy administered with curative intent are among the most important decisions made by medical oncologists. Further investigation regarding the actual vs appropriate impact of patient, disease, and physician factors on such decisions is of vital importance.

**Conclusions**

In summary, this population-based assessment of intermediate-grade NHL reveals significant variations in the administration of chemotherapy according to current standards of care. Careful attention to the choice of regimen, timely delivery of the full chemotherapy dose, and total number of cycles delivered may impact response rates as well as disease-free and overall survival of these patients. Strategies to optimize decision-making regarding the use of chemotherapy in the setting of neutropenic complications, such as when to use neutrophil growth factors to optimize chemotherapy delivery, require further investigation.

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