Chemotherapy dose intensity in non-Hodgkin’s lymphoma:
is dose intensity an emerging paradigm for better outcomes?

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Received 17 December 2004; revised 17 March 2005; accepted 23 March 2005

Background: Higher chemotherapy dose intensity has been studied as a way of improving the clinical outcomes in various malignancies, including non-Hodgkin’s lymphoma (NHL).

Methods: We reviewed clinical trials that have studied the relation between dose and response in cancer chemotherapy, the theory behind dose-intensive chemotherapy, and the clinical results with dose-escalated and dose-dense therapy in aggressive NHL.

Results: Myeloablative high-dose chemotherapy with stem cell transplantation produces higher 5-year survival rates than standard salvage chemotherapy in relapsed aggressive lymphoma, but its role as initial therapy is not yet clear. Nonmyeloablative dose-escalated chemotherapy is feasible with granulocyte colony-stimulating factor (G-CSF) support, but this approach does not improve outcomes. Dose-dense (14-day) CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with G-CSF support produces better results than 21-day CHOP in patients with previously untreated aggressive lymphoma, without additional toxicity. The addition of etoposide to dose-dense CHOP may provide further benefits in younger patients. The addition of rituximab to G-CSF-supported dose-dense CHOP is feasible. Preliminary data suggest the feasibility of dose-dense chemotherapy for NHL with the once-per-cycle G-CSF, pegfilgrastim.

Conclusion: Dose-dense chemotherapy with G-CSF support produced better clinical outcomes in both younger and older patients. Phase 3 trials of dose-dense CHOP plus rituximab with CSF support are warranted.

Key words: chemotherapy, colony-stimulating factor, filgrastim, neutropenia, non-Hodgkin’s lymphoma, pegfilgrastim

Introduction

The optimal therapy for aggressive non-Hodgkin’s lymphoma (NHL) remains to be determined. Patients with advanced-stage aggressive NHL are invariably treated with anthracycline-based chemotherapy, with or without radiotherapy. The best pharmacologic approach to curing the disease at present appears to be the standard regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), but the low cure rate (~40%) shows that there is a clear need for better therapies.

Since the introduction of the CHOP regimen by the Southwest Oncology Group in 1976 [1], clinical research has concentrated on testing new therapies for aggressive NHL. Some of the approaches have been adding novel agents, such as the monoclonal antibody rituximab, to existing effective regimens and modifying the dose or the schedule of the original CHOP regimen. These last approaches can increase the chemotherapy dose intensity (DI), which is a measure of the amount of drug delivered per unit of time (typically expressed as mg/m²/week). Retrospective analyses indicate that the DI is a strong predictor of the outcome in aggressive NHL [2–5]. Because maintaining a threshold DI has been shown to be important for survival [6], it is logical to then ask whether increasing the DI improves the outcomes. DI can be increased by increasing the amount of the drug given per cycle (dose escalation) or by reducing the time between the treatment cycles (dose density) (Figure 1) [7]. This review focuses on the rationale for dose-intensive chemotherapy in NHL and the clinical trials in which dose escalation and dose-dense therapy have been studied.

DI and clinical outcomes in NHL

Dose and schedule are important factors in cancer chemotherapy. In various in vivo tumor models with various...
chemotherapy agents, including cyclophosphamide and anthracyclines, there is a log-linear relationship between the size of the dose and the number of tumor cells killed [8]. The dose-response curve is steepest when the tumor is especially sensitive to the drug [8]. As a result, dose modifications markedly affect the number of tumor cells killed.

These preclinical findings indicate that substandard chemotherapy DI is less effective and leads to poorer outcomes than standard DI. Indeed, this hypothesis has been confirmed in retrospective analyses. Multivariate analysis of data from 95 patients with diffuse large-cell lymphoma (DLCL) found a strong association between the relative dose intensity (RDI; the ratio of the delivered DI to the planned DI) of a standard CHOP regimen and 5-year survival (Figure 2) [3]. The 5-year survival rate was 80% in patients treated with more than the median average RDI but only 32% in those treated with less than the median average RDI ($P < 0.001$). Similarly, analysis of the RDIs of three doxorubicin-based regimens (including CHOP) in 115 patients with DLCL found that the most important prognostic factor for survival was a doxorubicin RDI >75% (Figure 3) [2]. In another study the response and overall survival (OS) rates were significantly lower in patients with aggressive NHL who were treated with <70% of the planned DI of anthracycline-based therapy [4].

Another hypothesis is that not only is maintaining a minimum RDI important for outcomes, but also increasing the DI beyond that of the standard reference regimens may increase survival. The Goldie–Coldman hypothesis (Table 1) is based on a somatic mutation model of drug resistance. It posits that drug-resistant mutations arise spontaneously and at a measurable frequency and that these mutations are most likely to occur when the tumor burden is large [9]. The model predicts that the early use of the highest possible doses of all agents in a regimen would be the most effective in preventing the emergence of clones that are resistant to several agents and in eradicating the cancer. Another hypothesis, the Norton–Simon regression model (Table 2), is based on Gompertzian kinetics and postulates that small tumors grow faster than large tumors [7]. Thus, effective cytoreductive therapy paradoxically leads to higher rates of tumor regrowth between the cycles of treatment. Therefore, the interval between the chemotherapy cycles should be shortened to lessen tumor regrowth and provide the greatest opportunity to eradicate the disease.

Both the Goldie–Coldman and the Norton–Simon hypotheses indicate that there is a need to maximize tumor

**Table 1.** The Goldie–Coldman hypothesis

| Drug resistance will appear in tumors exposed to cytotoxic agents |
| Drug-resistant mutations arise spontaneously at a measurable frequency |
| The larger the tumor burden, the more likely a mutation will occur |
| Early, highest dose use of all agents is most likely to prevent multiply resistant clones and, thus, to effect a cure |

Data from Coldman and Goldie [9].

**Table 2.** The Norton–Simon hypothesis

| The growth rate decreases as the tumor approaches the limits of space, nutrient availability and blood supply |
| The fastest growth occurs when the tumor burden is reduced, i.e. after cytoreductive therapy |
| The proportion of cells killed per chemotherapy dose increases as the tumor shrinks, since more cells are mitotic |
| But regrowth between the cycles is faster at lower tumor burdens |
| Dose-dense chemotherapy with shorter cycles is most effective |

Data from Norton [7].
exposure to chemotherapy, but dose-intensive therapy has traditionally been limited by hematological toxicity, e.g. neutropenia and its complications (febrile neutropenia, infections, hospitalization) [10]. Efforts to overcome this limitation include the use of stem cell rescue after myeloablative chemotherapy and the use of colony-stimulating factors to ameliorate hematological toxicity.

Dose intensification by dose escalation

Myeloablative high-dose chemotherapy with transplantation

Myeloablative high-dose chemotherapy (HDT) with stem cell transplantation has been investigated in several trials, and it is the treatment of choice in young patients with relapsed aggressive lymphoma [11–13]. The benefits of HDT with stem cell rescue in relapsed aggressive lymphoma were clearly shown in the Parma trial, conducted in 215 patients <60 years old who were in first or second relapse. Patients who responded to the first two cycles of chemotherapy were randomized to four additional cycles of chemotherapy or to HDT with autologous bone marrow transplantation. The 5-year survival rate was 46% in the HDT arm and 12% in the standard salvage chemotherapy arm \((P = 0.001)\) [11]. OS was also higher in the HDT arm (53% versus 32%; \(P = 0.038\)).

A later study, LNH-93-RP, further defined the patient population in whom transplantation is appropriate. This prospective randomized trial found that late intensification with HDT and transplantation was superior to early intensification followed by transplantation [14]. Patients in first relapse were treated with salvage therapy and were then randomized to HDT with transplantation on day 30 or to two additional cycles of chemotherapy followed by HDT and transplantation on approximately day 90. OS was greater in patients who were treated with the additional two cycles of salvage therapy before HDT than in those who proceeded to HDT in untreated relapse (OS 38% with salvage therapy versus 21% with untreated relapse; \(P <0.001\)), suggesting that additional salvage chemotherapy may further decrease residual disease and thus lead to better outcomes with the transplantation [14].

Several studies have evaluated HDT as initial treatment for aggressive NHL, with less definitive results [15–20]. Retrospective analysis of the data in one of these studies found that HDT may confer a survival benefit in some patients with high-intermediate risk or high risk as defined by the International Prognostic Index [21]. Prospective trials of early HDT compared with conventional chemotherapy in patients with aggressive NHL have had conflicting results. One trial in 150 high-risk patients found no difference in the outcomes at 5 years [22]. Another randomized trial in 105 patients aged 60 years or younger with high-intermediate risk aggressive NHL, showed that, in contrast, 5-year event-free survival (EFS) (56% versus 28%; \(P = 0.003\)) and OS (74% versus 44%; \(P = 0.001\)) were significantly higher with first-line HDT than with CHOP [19]. Two other trials showed inferior outcomes with HDT [20, 23]. One of these studies, in 370 patients aged 60 years or younger, showed that conventional chemotherapy was superior to HDT [23]; another study, in 312 patients aged 60 years or younger, showed comparable survival with the two regimens, but there was earlier relapse and significantly poorer survival after the relapse in the HDT arm [20]. These conflicting results with early HDT can be accounted for, in part, by the different inclusion criteria and chemotherapy regimens used in the trials. The trial by Haioun and colleagues [21] used late consolidation in responders, and the trial by Gisselbrecht and colleagues [23] used early intensification with short therapy. Until further prospective trials have confirmed that early HDT is superior to standard chemotherapy [24], it may be prudent to reserve HDT for patients in whom the disease has relapsed [25].

Non-myeloablative HDT

Chemotherapy dose escalation with granulocyte colony-stimulating factor (G-CSF) support has been investigated in several studies, with mixed results. The use of G-CSF facilitates the delivery of higher than standard chemotherapy doses, but the resulting higher DI has not generally been associated with better outcomes. Rather, such therapy has resulted in greater toxicity, including neutropenia, in some trials. Two trials showed that the maximum tolerated dose (MTD) of cyclophosphamide in the CHOP regimen could be increased with G-CSF support. The cyclophosphamide MTD was increased from 1750 to 2750 mg/m\(^2\) in a trial in 87 patients with aggressive NHL [26] and from 1250 to 2250 mg/m\(^2\) in a trial in 33 patients [27]. In another study, 21 patients were given twice the usual doses of epirubicin (150 mg/m\(^2\)) and cyclophosphamide (1500 mg/m\(^2\)) with G-CSF support in a six-cycle regimen of CEOP (cyclophosphamide, epirubicin, vincristine and prednisolone) [28]. Neutropenia was common, but 19 of the 21 patients completed all cycles, including eight in whom dose reductions were not required. A similar dose-escalated regimen of CEOP with G-CSF support was compared with standard CEOP in a randomized trial in 250 patients with aggressive NHL [29]. Drug delivery was 78% higher in the dose-escalation group than in the standard-dose group, but there were no differences in complete response (CR) rates, 5-year disease-free survival (DFS) or OS. In addition, the rates of hematological and gastrointestinal toxicity were higher in the dose-escalation group, with febrile neutropenia in 70% of patients and four toxic deaths.

Dose-escalated CHOP plus etoposide (CHOEP) was studied in 227 patients with advanced aggressive NHL [30]. G-CSF support facilitated moderate dose escalations of both the cyclophosphamide (MTD increased from 1000 to 1300 mg/m\(^2\)) and the etoposide (MTD increased from 100 to 160 mg/m\(^2\)). The 5-year failure-free survival and OS rates in patients treated with dose-escalated CHOEP supported by G-CSF were 28% and 44%, but these outcomes were judged to be no better than those with standard CHOP therapy.

In a phase II trial in 74 patients with advanced aggressive NHL, CSFs were used to support a dose-escalated regimen of ProMACE-CytaBOM (cyclophosphamide 1300 mg/m\(^2\) day 1,
doxorubicin 50 mg/m² day 1, etoposide 240 mg/m² day 1, prednisone 60 mg/m² days 1–14, cytarabine 600 mg/m² day 8, bleomycin 5 mg/m² day 8, vincristine 1.4 mg/m² day 8, methotrexate 120 mg/m² day 8, and leucovorin 25 mg/m² every 6 h ×4 starting 24 h after the methotrexate) given every 21 days for eight cycles [31]. The CR rate was 69%, and 4-year DFS and OS were 71% and 73%, respectively. There were no toxic deaths, but myelosuppression was severe: grade 4 leukopenia in 97% of patients and grade 4 thrombocytopenia in 49%.

In a pilot trial of G-CSF-supported dose-escalated CHOP (cyclophosphamide 4000 mg/m², doxorubicin 70 mg/m², vincristine 2 mg and prednisone 100 mg/day for 5 days) in 30 patients with poor-prognosis aggressive NHL there was a CR in 19 (86%) of 22 patients treated at the MTD. There was one toxic death, however, and 65% of the cycles were complicated by febrile neutropenia and platelet transfusions were required in 84% of patients [32].

Thus, while dose-escalated chemotherapy with CSF support appears feasible in patients with aggressive NHL, clinical trials—albeit non-randomized and in small patient populations—have generally found greater myelotoxicity and no better clinical outcomes than those with standard-dose therapy. As a result of these negative findings, current research focuses more on dose-dense therapy as an alternative method of increasing the DI of chemotherapy for NHL.

Optimizing chemotherapy schedule by dose density

Potential benefits of dose-dense chemotherapy

On the basis of the Norton–Simon hypothesis, dose-dense chemotherapy has been investigated in several tumor types. The first support for the hypothesis came from a large randomized trial of adjuvant chemotherapy for early-stage breast cancer, in which the risk of relapse and death was significantly less with dose-dense therapy than with standard-dose therapy [33]. These results were viewed as proof of principle, and trials in other tumor types are underway.

Dose-dense chemotherapy has advantages other than the potential to improve clinical outcomes. By increasing the frequency of cycles, dose-dense chemotherapy results in a shorter treatment time. A generally well-tolerated dose-dense regimen could potentially lead to greater adherence and may be preferred by patients who appreciate the shorter time of treatment.

Dose-dense CHOP and CHOP-like regimens

The feasibility of dose-dense chemotherapy for NHL was first studied in several small trials (Table 3). An every-15-day and an every-10-day cycle of CHOP were compared with the standard 21-day cycle in a phase I study in 28 patients with aggressive NHL [34]. Dose-dense therapy was facilitated with G-CSF support, but non-hematological toxicity and infection were more common than with the standard regimen. A G-CSF-supported every-14-day CEOP regimen was given to 20 patients with aggressive NHL in a phase II study [35]. The regimen was generally well tolerated, and 18 patients (90%) were given the planned dose on time. There were eight CRs, and the median survival was 24 months. A G-CSF-supported every-14-day CHOP regimen with dose-escalated cyclophosphamide was tested in 61 patients in another trial [36]. There was a CR in 45 patients (74%), and 12-month freedom from progression and OS were 71% and 86%, respectively. Hospitalization for infection or febrile neutropenia was uncommon, occurring in only 10 of 189 cycles.

A larger, single-arm phase II trial of a G-CSF-supported every-14-day CHOP was conducted in 120 patients with advanced aggressive NHL (see Table 3) [37]. The CR rate was 43%, and the overall response rate was 89%, with comparable responses in older (≥60 years) and younger patients (Figure 4). Severe neutropenia was more common in the older patients, but the regimen was considered tolerable (Figure 5). Eighty-five per cent of the 720 cycles were given on schedule at full dose, and the median RDI of both the cyclophosphamide and the doxorubicin was 99%.

The Lymphoma Study Group of the Japan Clinical Oncology Group compared standard-dose 14-day CHOP with dose-escalated 14-day CHOP (cyclophosphamide 1500 mg/m² and doxorubicin 70 mg/m²) in a randomized trial in 70 patients with high-intermediate- or high-risk aggressive NHL [38]. Both regimens were given with G-CSF support. The CR rate and 3-year progression-free survival (PFS) were higher with the dose-escalated therapy (60% versus 51% and 43% versus 31%, respectively.) Toxicity was greater in the dose-escalated arm, with one toxic death, grade 4 neutropenia in 86% of patients, and grade 4 thrombocytopenia in 20%. On the basis of these results, the group is conducting a randomized phase III study to compare dose-dense 14-day CHOP with standard 21-day CHOP.

The Southwest Oncology Group reported similar findings in a single-arm phase II study of a dose-escalated and dose-dense CHOP regimen in aggressive NHL [39]. Eighty-eight patients with previously untreated aggressive NHL were treated with dose-escalated CHOP (cyclophosphamide 1600 mg/m², doxorubicin 65 mg/m², vincristine 1.4 mg/m², prednisone 100 mg on days 1–5) given every 14 days with G-CSF support for a maximum of six cycles. The estimated delivered DI of all drugs was 1.8 times that of standard CHOP. Five-year PFS and OS were 41% and 60%, respectively. As in previous dose-escalation studies, toxicity was greater, with three toxic deaths and 11 patients discontinuing treatment because of toxicity. Grade 3 or 4 granulocytopenia occurred in 90% of patients and grade 3 or 4 thrombocytopenia in 64%. The authors concluded that this regimen warrants further evaluation in randomized trials.

The largest trial of dose-dense chemotherapy in NHL to date, the NHL-B trial, was conducted by the German High-Grade Non-Hodgkin’s Lymphoma Study Group [40–42]. This randomized phase III trial compared 14- and 21-day CHOP (with or without etoposide) in more than 1500 patients with previously untreated aggressive NHL. Patients in
<table>
<thead>
<tr>
<th>Investigators (study phase)</th>
<th>No. of assessable patients</th>
<th>Age, years [median (range)]</th>
<th>Drug regimena</th>
<th>Dose intensity (mg/m²/week)b</th>
<th>Median follow-up (years)</th>
<th>Outcome</th>
<th>Safety</th>
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<tbody>
<tr>
<td>Smith et al. (1996) [34] (phase I)</td>
<td>28</td>
<td>56 (39–67)</td>
<td>CHOP: 21-, 15-, 10-day cycles; G-CSF 5 μg/kg</td>
<td>21-/15-/10-day: C: 250/350/525 H: 17/23/35 O: 0.7/0.9/1.4 P: 107/149/224</td>
<td>–</td>
<td>G-CSF facilitates cycle shortening</td>
<td>Dose-limiting toxicity: 21-day &lt;15-day &lt;10-day cycles</td>
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<tr>
<td>Pronzato et al. (1998) [35] (phase II)</td>
<td>20</td>
<td>66 (40–70)</td>
<td>CEOP: 6 × 14-day cycles; G-CSF 300 μg</td>
<td>C: 375 EP: 30 O: 0.7 P: 250</td>
<td>–</td>
<td>CR 40% OR 75% Median survival 24 months</td>
<td>Well tolerated; DI as planned = 90%</td>
</tr>
<tr>
<td>Balzarotti et al. (2002) [36] (phase I)</td>
<td>61c</td>
<td>48 (21–69)</td>
<td>CHOP: dose-escalated C and H; 3–6 × 14-day cycles, G-CSF 300 μg</td>
<td>C: 875 H: 38</td>
<td>1</td>
<td>CR 74% DFS 71% OS 86%</td>
<td>SN 56% FN 17%</td>
</tr>
<tr>
<td>Gregory et al. (2003) [37] (phase II)</td>
<td>120</td>
<td>54.5 (18–84)</td>
<td>CHOP: 6 × 14-day cycles; G-CSF 5 μg/kg</td>
<td>C: 375 H: 20 O: 0.7 P: 250</td>
<td>1.7</td>
<td>All: CR 43% DFS 52% OS 77% Elderly: CR 45% DFS 53% OS 74%</td>
<td>All: SN 52% FN 20% DI as planned = 85% Elderly: SN 70% FN 28% DI as planned = 80%</td>
</tr>
<tr>
<td>Itoh et al. (2000) [27] (phase II)</td>
<td>70</td>
<td>61 (33–69)</td>
<td>CHOP: dose-escalated C and H 8 × 21-day cycles; standard dose 8 × 14-day cycles; G-CSF 2 μg/kg</td>
<td>21-/14-day: C: 500/375 H: 23.3/25 O: 0.47/0.7 P: 250/250</td>
<td>3</td>
<td>CHOP-14 vs dose-escalated CHOP-21 CR: 60% vs 51% PFS: 43% vs 31%</td>
<td>CHOP-14 vs dose-escalated CHOP-21 Grade 4 neutropenia: 86% vs 50% Grade 4 thrombocytopenia: 20% vs 3%</td>
</tr>
<tr>
<td>Blayney et al. (2003) [39] (phase II)</td>
<td>88</td>
<td>53 (19–77)</td>
<td>CHOP: 6 × 14-day cycles; filgrastim 5 μg/kg/day</td>
<td>C: 800 H: 32.5 O: 0.7 P: 250</td>
<td>5.1</td>
<td>PFS 41% OS 60%</td>
<td>Grade 3 anemia: 57% Grade 3 or 4 neutropenia: 90% Grade 3 thrombocytopenia: 42% Grade 4 thrombocytopenia: 22%</td>
</tr>
<tr>
<td>Investigators (study phase)</td>
<td>No. of assessable patients</td>
<td>Age, years [median (range)]</td>
<td>Drug regimen*</td>
<td>Dose intensity (mg/m²/week)(^b)</td>
<td>Median follow-up (years)</td>
<td>Outcome</td>
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<td>Pfreundschuh et al. (2004) [40] (phase III)</td>
<td>689</td>
<td>NR (61–75)</td>
<td>CHOP ± e: 6 × 21-, 14-day cycles; G-CSF 5 μg/kg</td>
<td>21-/14-day: C: 250/375 H: 17/25 O: 0.5/0.7 P: 67/100 e: 100/150</td>
<td>4.8</td>
<td>EFS: CHOP-14 vs CHOP-21, 44% vs 33% (RR 0.66; (P = 0.003)) CHOEPE vs CHOEPE-21, 40% vs 41% (NS) OS: CHOP-14 vs CHOP-21, 53% vs 41% (RR 0.58; (P &lt; 0.001)) CHOEPE-14 vs CHOEPE-21, 50% vs 46% (NS)</td>
<td>Grade 3 or 4 leukopenia: CHOP-14: 70% CHOP-21: 72% CHOEPE-14: 92% CHOEPE-21: 94%</td>
</tr>
<tr>
<td>Pfreundschuh et al. (2004) [41] (phase III)</td>
<td>710</td>
<td>NR (18–60)</td>
<td>CHOP ± e: 6 × 21-, 14-day cycles; G-CSF 5 μg/kg</td>
<td>21-/14-day: C: 250/375 H: 17/25 O: 0.5/0.7 P: 67/100 e: 100/150</td>
<td>4.8</td>
<td>CR: CHOEPE vs CHOP, 88% vs 79% ((P = 0.003)) All 14-day vs all 21-day, 85% vs 83% (NS) EFS: CHOEPE vs CHOP, 69% vs 58% ((P = 0.004)) All 14-day vs all 21-day, 65% vs 62% (NS) OS: CHOEPE vs CHOP, 84% vs 80% (NS) All 14-day vs all 21-day, 85% vs 79% (RR 0.70; (P = 0.044))</td>
<td>Grade 3 or 4 leukopenia: CHOP-14: 34% CHOP-21: 34% CHOEPE-14: 73% CHOEPE-21: 74%</td>
</tr>
<tr>
<td>Moore et al. (2003) [45] (phase II)</td>
<td>29</td>
<td>52 (35–78)</td>
<td>CHOP-R: 6–8 × 14-day cycles; pegfilgrastim 6 mg once per cycle</td>
<td>C: 375 H: 25 O: 0.7 P: 100 R: 188</td>
<td>–</td>
<td>CR 69% PR 24%</td>
<td>No unexpected toxicities Cycles administered on time = 93% Full dose delivered = 79%</td>
</tr>
</tbody>
</table>

*Intravenous administration unless stated otherwise; details of radiotherapy or other therapy omitted.

\(^b\)Standard CHOP given every 21 days has the following DIs (mg/m²/week): C, 250; H, 17; O, 0.5; P, 67.

\*Some patients with low-grade NHL; 62 patients assessed for survival.

C, cyclophosphamide; CHOP, standard doses of CHOP unless otherwise stated; CR, complete response; DFS, disease-free survival; DI, dose intensity; E, epirubicin; EP, epidoxorubicin; e, etoposide; EFS, event-free survival; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; H, doxorubicin; NHL, non-Hodgkin’s lymphoma; NR, not reported; NS, non-significant; O, vincristine; OR, overall response; OS, overall survival; P, prednisone; PFS, progression-free survival; R, rituximab; RR, relative risk; SN, severe neutropenia.
The dose-dense groups were given G-CSF on days 4–13 of each cycle. One analysis (NHL-B1) was conducted in patients ≤60 years old with a good prognosis (normal lactate dehydrogenase level) and another (NHL-B2) in patients aged 61–75 years. Interim data from the first 503 patients to complete the therapy in the NHL-B1 trial showed that the median RDI was >99% for cyclophosphamide, doxorubicin and etoposide [42]. Only 5% of patients were given an RDI below 80% of that planned [42]. Thus, both 2-week regimens (CHOP-14 and CHOEP-14) could be delivered with few dose attenuations or treatment delays in patients ≤60 years of age. Dose adherence was also excellent in older patients (NHL-B2) who were treated with CHOP (median RDI >96%). In the CHOEP arms, however, 31% of elderly patients terminated treatment early because of toxicity. Substantial dose erosion was also observed with 17% of patients in the 21-day arm and 27% of patients in the 14-day arm being given etoposide at <80% of the planned dose. The authors concluded that dose-dense CHOP and CHOEP had RDIs equivalent to those of the standard regimens in patients up to 60 years old but that dose-dense CHOEP was not tolerated as well as dose-dense CHOP in elderly patients.

The final efficacy results in the NHL-B1 and -B2 trials provide the most compelling evidence for better outcomes with dose-dense therapy in aggressive NHL (see Table 3) [40, 41]. In the NHL-B1 trial the CR rate and 5-year EFS were better with CHOEP than with CHOP alone (CR 88% versus 79%, \( P = 0.003 \); 5-year EFS 69% versus 58%, \( P = 0.004 \)) (see Table 3) [41]. In multivariate analysis OS was significantly higher and disease progression was significantly lower with a 14-day regimen than with a 21-day regimen (relative risk 0.70, \( P = 0.044 \), and relative risk 0.50, \( P = 0.032 \), respectively). In NHL-B2 the CR rates were 76% [95% confidence interval (CI) 69% to 82%] versus 60% (95% CI 52% to 67%) with 14- and 21-day CHOP, respectively, and 72% (95% CI 64% to 78%) versus 70% (95% CI 63% to 77%) with 14- and 21-day CHOEP, respectively (Figure 6). After a median follow-up of 58 months, 5-year EFS (Figure 7A) and 5-year OS (Figure 7B) were significantly greater with 14-day than with 21-day CHOP (relative risk 0.66, \( P = 0.003 \), and relative risk 0.58, \( P < 0.001 \), respectively). There was no significant difference in efficacy between 14- and 21-day CHOEP in the elderly, which may be related to the fact that up to 27% of the patients who were treated in 14-day cycles were given <80% of the planned dose.

In summary, the results of these studies show that G-CSF support facilitates shortening the cycles of CHOP to 14 days in both younger and older patients. Adding etoposide may further improve the outcomes in younger patients. Dose-dense therapy has clear therapeutic benefits in patients of all ages and should now be considered an appropriate treatment for aggressive NHL.
Dose-dense CHOP and immunotherapy

Rituximab, a chimeric IgG1 monoclonal antibody that targets CD20, has been studied in combination with the CHOP regimen (CHOP-R) in several clinical trials. The first trial to show the superiority of CHOP-R over CHOP was conducted by the Groupe d’Etude des Lymphomes de l’Adulte (GELA) in elderly patients with previously untreated aggressive disease [43]. A total of 399 patients aged 60–80 years with advanced DLCL were randomized to CHOP-R or standard CHOP every 21 days for eight cycles. The CR rate was significantly higher (76% versus 63%; \( P = 0.005 \)) with CHOP-R, as were the EFS (57% versus 38%; \( P < 0.001 \)) and OS (70% versus 57%; \( P = 0.007 \)) at a median follow-up of 2 years. The addition of rituximab to the regimen was not associated with clinically significant toxicity. Manageable and reversible events that were related to the infusions of rituximab were reported, but no patients discontinued the study for this reason. Of note, however, the development of an unusual late-onset neutropenia after rituximab therapy has recently been reported [44]. The authors postulated that the neutropenia that developed in eight of 53 patients at 1–4 months after the rituximab might be due to a treatment-induced immune dyscrasia. It may be prudent to monitor patients for delayed-onset hematological toxicity after treatment with rituximab, either alone or in combination with chemotherapy.

The feasibility of dose-dense CHOP-R with G-CSF support has been studied in a single-arm phase II trial (see Table 3) [45]. Pegfilgrastim was chosen as the G-CSF rather than filgrastim because of its longer duration of action and simple once-per-cycle dosing schedule. Comparative trials have shown that a single dose of pegfilgrastim provides benefits comparable to those with 10 or 11 daily injections of filgrastim [46–48]. With pegfilgrastim support, 29 patients with intermediate-grade NHL were treated with 189 cycles of dose-dense CHOP-R, with 93% of the cycles delivered on time [45]. The chemotherapy was given on schedule in 62% of patients and at full dose in 79%. There were no cases of febrile neutropenia, and the treatment was generally well tolerated [45].

Two ongoing randomized clinical trials are evaluating the efficacy of dose-dense CHOP-R. One pivotal trial, by GELA, is comparing eight cycles of 21-day CHOP-R and eight cycles of 14-day CHOP-R. The second trial, by the German High-Grade Non-Hodgkin’s Lymphoma Study Group, is using a 2×2 factorial design to compare 14-day CHOP-R (six and eight cycles) and 14-day CHOP (six and eight cycles). The results of these trials are eagerly awaited.

Optimal timing and duration of supportive care

The use of G-CSFs helps facilitate dose-dense therapy, and it should be considered an integral part of the regimen. The efficacy of G-CSF therapy is affected by when it is initiated as well as by the duration of its use; for these reasons it is essential to adhere to the appropriate dose and schedule. The NHL-B studies showed that giving G-CSF from day 4 through day 13 provides effective hematopoietic support for dose-dense regimens [42]. In the ongoing RICOVER-60 trial in NHL, which is comparing dose-dense CHOP and dose-dense CHOP-R, the authors found in a planned interim analysis that delaying the start of G-CSF until day 6 (resulting in 7 days of G-CSF use) was associated with similar chemotherapy DIs but compromised leukocyte recovery (Figure 8). Indeed, leukopenia and infections may be more common with this approach (e.g., grade 3 or 4 infections in 20.6% of patients in RICOVER-60 but in only 10.7% of patients in NHL-B2) [49]. These preliminary findings have led the authors to recommend using G-CSF for at least 10 days, starting on day 4, with the 14-day CHOP regimen [49].
The duration of G-CSF therapy also affects the outcomes. In a retrospective analysis of data on 170 patients with intermediate-grade NHL who were treated with CHOP with filgrastim support, Scott et al. [50] showed that the risk of febrile neutropenia was lower in patients who were given filgrastim for at least 7 days. In addition, an open-label study in 780 patients with nonmyeloid malignancies (102 patients with NHL) showed that when filgrastim is administered as indicated (starting 24 h after the chemotherapy and continuing to a post-nadir absolute neutrophil count of at least $10 \times 10^9/l$) the mean duration of grade 4 neutropenia was only 0.4 days [51]. Furthermore, it was possible to give the next cycle of chemotherapy on schedule in >90% of the patients who were treated with full-duration filgrastim.

As discussed previously, preliminary data suggest that once-per-cycle pegfilgrastim instead of daily filgrastim is safe and effective with dose-dense therapy for NHL [45]. These data are further corroborated by the results of a phase II trial of CHOP-14 with pegfilgrastim support in patients >60 years old, in which the overall response rate was 77%, with a CR in 43% of patients. Of the 110 cycles of chemotherapy, 88% were delivered at full dose and on schedule. There were no unexpected toxicities, leading the authors to conclude that dose-dense regimens are feasible with once-per-cycle pegfilgrastim [52].

Moreover, pharmacokinetic analyses support the safety of pegfilgrastim with dose-dense therapy. A retrospective analysis of pharmacokinetic data from six clinical trials in patients with various nonmyeloid malignancies treated with myelosuppressive chemotherapy evaluated the serum concentrations of pegfilgrastim at different times after its administration. The results of this analysis showed that only 0.2% of patients had a serum pegfilgrastim concentration >2 ng/ml, the EC20 value that is considered the lowest concentration of pegfilgrastim that can produce meaningful granulopoiesis [53]. These data indicate that it is very unlikely that pegfilgrastim will overstimulate the production of neutrophils in the days before the next cycle of dose-dense therapy. Other data support this conclusion [54]. Seventeen patients with Hodgkin’s disease were given pegfilgrastim 6 mg 24 h after ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy. Of 170 cycles of ABVD chemotherapy planned, 165 (97%) cycles were administered on time. There was no febrile neutropenia and no cumulative effect on stem cells [54].

In summary, improvements in the standard 21-day CHOP regimen have been made. A 14-day cycle of CHOP with G-CSF support is well tolerated and has produced better outcomes in patients with aggressive NHL. The timing and duration of G-CSF therapy are important, and early initiation of G-CSF (e.g. 1 day after the chemotherapy) and daily use until 24 h before the next cycle produces optimal results. Preliminary data suggest that once-per-cycle pegfilgrastim can be used instead of daily filgrastim without compromising efficacy. Indeed, the use of a once-per-cycle agent may provide further benefits, such as simplifying the treatment regimen [48].

**Special populations: DI in elderly patients**

Elderly patients are a large proportion of those with NHL. The outcomes in elderly patients can be similar to those in younger patients [55], but older patients are less likely to be treated with full-dose chemotherapy. In a study in 195 patients with DLCL who were treated with doxorubicin-based chemotherapy 5-year survival was lower in older patients (>60 years) than in younger patients (30% versus 57%; P<0.001) when RDI was not taken into account [5]. The DI of doxorubicin was found in multivariate regression analysis to be a significant prognostic factor (P=0.039). Indeed, 5-year survival in the 25 older patients who were given doxorubicin at comparable DIs of 10 mg/m²/week or greater was similar to that in younger patients (52% in both older and younger patients). In contrast, the 20 elderly patients who were treated with a low doxorubicin DI were given the low DI intentionally, despite their having a good performance status and no comorbidities. These intentional dose reductions based solely on age resulted in poorer treatment outcomes, with 5-year survival of 36% [5].

Such dose reductions based on age are common in clinical practice. In a large practice pattern survey of 4522 patients who had been treated with CHOP or CHOP-like chemotherapy for aggressive NHL, older patients (>60 years) were consistently given lower DI than younger patients across all cycles. In multivariate analysis, age >60 years was a significant predictor of RDI <85% of the reference standard (adjusted odds ratio 2.28) [56]. A similar study in 577 patients with intermediate-grade NHL found that the planned and delivered doses of CHOP were significantly lower in elderly patients [57]. These results suggest that elderly patients are at risk of poor outcomes because of the relation between DI and survival and emphasize the importance of adhering to the full DI even in otherwise-fit elderly patients with curative tumors.
Because the elderly are at higher risk for myelosuppression, initiating G-CSF in the first cycle of chemotherapy should be considered. Jacobson et al. [58] treated 20 elderly patients who had aggressive NHL with standard CHOP given every 21 days for six cycles, with G-CSF started in each cycle on day 3 and continued until the absolute neutrophil count was $>10^9/l$. The average RDI of both the doxorubicin and the cyclophosphamide over six cycles was 97%, and the average cycle length was 22 days. There were no treatment-related deaths. Grade 4 leukopenia occurred in 12% of patients, and only 7% of the cycles were affected by hospitalizations for febrile neutropenia. Two-year PFS and OS were 42% and 66%, respectively. In a larger, randomized trial, Osby et al. [59] treated 455 elderly patients (>$60$ years) with aggressive NHL with CHOP or CNOP (mitoxantrone 10 mg/m$^2$ instead of doxorubicin) every 21 days for eight cycles with or without daily G-CSF (given on day 2 through days 10–14). CHOP was more effective than CNOP in terms of CR, time to treatment failure and OS at 3 years. The use of G-CSF was associated with a significantly lower incidence of granulocytopenia ($P<0.001$), granulocytopenic infections ($P<0.001$), and hospitalizations for granulocytopenic fever ($P<0.001$). Analysis of the results in the CHOP arms found that eight cycles of the chemotherapy and at least 90% of the planned dose were delivered in 50% of the patients who were given G-CSF but in only 36% of those who were not ($P<0.05$). Overall survival at 3 years was also significantly higher with CHOP plus G-CSF than with CHOP alone (60% versus 45%; $P=0.045$).

Similarly, Doorduijn et al. [60] compared standard CHOP with CHOP plus filgrastim in 389 elderly patients with aggressive NHL (median age 72 years; range 65–90). The RDI was significantly higher in the G-CSF arm, but the RDI was unexpectedly high in the control arm (96% versus 94% for cyclophosphamide; $P=0.01$; 95% versus 93% for doxorubicin; $P=0.04$). The CR rate was not different between the arms (52% with CHOP plus G-CSF and 55% with CHOP alone; $P=0.63$), nor was 5-year actuarial survival (24% with CHOP plus G-CSF and 22% with CHOP alone; $P=0.76$). The surprisingly high RDI in the control group and the low 5-year OS in this study are at odds with the results in other trials, which uniformly report significantly higher delivered RDI with the addition of G-CSF to the chemotherapy. In addition, the interpretation of these results is difficult because many of the patients were given possibly suboptimal doses of G-CSF, which was administered at a fixed dose of 300 μg/day on days 2–11 rather than at 5 μg/kg/day.

Conclusions

The delivery of dose-intense chemotherapy in patients with NHL is facilitated by the use of prophylactic CSFs. Two strategies have been used: dose escalation and dose density. Clinical trials of dose-escalated, but non-myeloablative, regimens have shown that these regimens are more toxic than standard regimens such as CHOP and do not improve the outcomes. Myeloablative high-dose chemotherapy with stem cell transplantation is effective in relapsed aggressive lymphoma, but its usefulness as initial therapy may be limited to certain high-risk patients as defined by the International Prognostic Index or adverse pathology.

Dose-dense (14-day) CHOP supported by G-CSF in all cycles has been well tolerated by patients, including the elderly. In addition, the clinical outcomes appear to be better with dose-dense than with standard CHOP, with convincing results in both older and younger patients. The outcomes with standard-schedule CHOP-R are superior to those with standard CHOP, and the efficacy of dose-dense CHOP-R with G-CSF support is being evaluated in ongoing clinical trials. In addition to producing better outcomes, dose-dense therapy may simplify the administration of chemotherapy and may be preferred by patients because of the shorter course of treatment.

References

13. Hahn T, Wolff SN, Czuczman MS et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse


