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Managing the myelotoxicity of CHOP chemotherapy

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ABSTRACT

The development of variations of the cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) chemotherapy standard regimen has led in recent years to significant improvements in the outcome of patients with lymphoma. Such regimens include the combination of the CD20-targeted monoclonal antibody, rituximab, with CHOP administered every 14 days (R-CHOP-14). These newer regimens have increased relative dose intensities compared with their predecessors and, as a consequence, adverse events – particularly myelotoxicity – are augmented. Myelosuppression is often the cause of chemotherapy dose reduction, while granulocyte colony-stimulating factor (G-CSF) support enables the timely administration of the planned dose of chemotherapy. The latest available G-CSF, pegfilgrastim, has a once-per-chemotherapy-cycle dosing schedule, which displays similar granulocytopoiesis-stimulating properties and tolerability to its parent protein, filgrastim. This article explores the use of G-CSFs, including pegfilgrastim to manage the myelotoxicities associated with R-CHOP-14 in patients with lymphoma, including the elderly.

1. Introduction

It is well established that the dose-dense regimen CHOP-14 (cyclophosphamide, vincristine, doxorubicin and prednisone administered every 14 days) provides longer overall survival (OS) than the standard 21-day regimen (CHOP-21) for non-Hodgkin's lymphoma (NHL), irrespective of the age of the patient. In two studies by the German High-Grade Non-Hodgkin's Lymphoma Study Group, both young patients (aged 18–60 years) and elderly individuals (>60 years) with aggressive NHL experienced significant benefits from CHOP-14 therapy compared with CHOP-21.[1,2] While an improvement in OS was seen with CHOP-14 in the younger group (5-year OS = 85.0% [95% confidence interval [CI] 79.3, 90.6] versus 74.9% [CI 67.8, 81.9] with CHOP-21; $P = 0.05$), elderly patients benefited from both significantly improved 5-year event-free survival (EFS) (43.8% [CI 35.4, 52.1] with CHOP-14 versus 32.5% [CI 24.7, 40.3] with CHOP-21; relative risk 0.66; $P = 0.003$) and OS (53.3% [CI 44.6, 62.1] versus 40.6% [CI 32.5, 48.6]; relative risk 0.58; $P < 0.001$) with CHOP-14 compared with CHOP-21.

Furthermore, the addition of the CD20-targeted monoclonal antibody, rituximab to CHOP-21 or CHOP-like regimens (R-CHOP) produces superior outcomes compared with CHOP-21 alone in both young patients with low-risk diffuse large B-cell lymphoma (DLBCL)[3] and elderly patients with predominantly high-grade disease,[4] without additional haematological toxicity.[3,4]

Additional improvements in the outcome have been achieved by combining CHOP-14 with rituximab (R-CHOP-14). Reports from two large studies of R-CHOP-14 in patients with lymphoma revealed a statistically significant improvement in time to treatment failure ($P < 0.005$)[5] and benefits in terms of disease-free survival and OS[6] compared with CHOP-14 alone. Results are eagerly awaited from ongoing phase III studies by the Groupe d'Etude des Lymphomes de l'Adulte and by the Cancer Research Network in the UK to compare the efficacy of R-CHOP-14 with R-CHOP-21 in patients with NHL. These studies are expected to shed light on the definitive regimen available for lymphoma.

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Administration of CHOP-14 improves outcomes in patients with lymphoma; however, it is associated with a greater myelotoxicity than CHOP-21 and requires granulocyte colony-stimulating factor (G-CSF) support to enable the timely administration of the planned dose. Results from studies of R-CHOP-14 revealed comparable toxicity rates to those observed with CHOP-14; these toxicities tended to be of a similar nature with both regimens.[7,8] This article will explore the management of myelotoxicities associated with R-CHOP-14 in patients with lymphoma, including the elderly.

2. G-CSF in patients with lymphoma

The majority of toxicities reported with dose-dense regimens in the lymphoma setting, including CHOP-14 and R-CHOP-14, are related to myelosuppression.[9] Chemotherapy-induced febrile neutropenia (FN) is a serious adverse effect of treatment, not only predisposing patients to serious and life-threatening infections,[10] but also placing a substantial burden on resources and associated healthcare costs. The risk of developing FN in patients with lymphoma varies greatly between chemotherapy regimens (Table 1). However, G-CSF support enables the use of intensified CHOP and CHOP-14 (incidence of FN 17% and 20%, respectively),[13,19] allowing the administration of maximal relative dose intensities (RDIs) of chemotherapy.

Advanced age (≥65 years) is the risk factor most consistently associated with an increased incidence of FN and as such, should be a consideration when contemplating the use of prophylactic G-CSF.[10] Fig. 1 highlights the incidence of FN in a number of placebo-controlled studies of G-CSF in elderly patients with NHL receiving CHOP or CHOP-like regimens.

In a study of 455 patients aged >60 years with aggressive NHL who received CHOP-21 or the CHOP-like CNOP (cyclophosphamide, vincristine, mitoxantrone, prednisone) regimen, the incidence of granulocytopenic fever requiring hospitalisation was significantly lower in patients who received G-CSF support from the first cycle compared with those who did not (33% versus 50%; $P < 0.001$).[12] In addition, prophylactic administration of G-CSF from the first cycle of CHOP-21 in elderly patients with aggressive NHL resulted in a low incidence of neutropenia and fever requiring hospitalisation (7.1% of 112 cycles).[23]

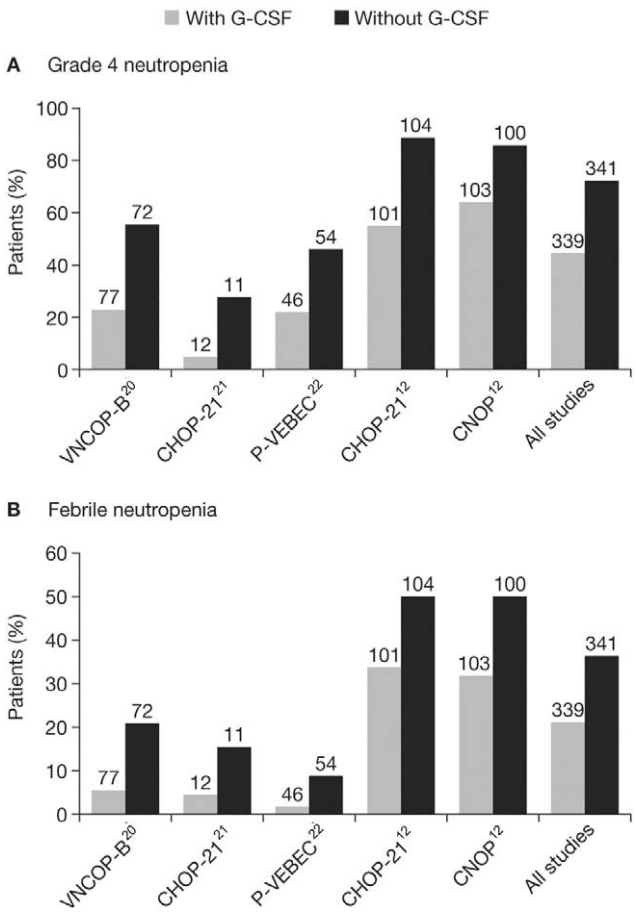

Fig. 1 – Incidence of (A) grade 4 neutropenia and (B) febrile neutropenia in controlled studies of G-CSF in elderly patients with non-Hodgkin lymphoma after CHOP or CHOP-like chemotherapy. The values shown above each bar are the number of patients.[12,20–22] *Abbreviations:* G-CSF, granulocyte colony-stimulating factor; CHOP, cyclophosphamide, vincristine, doxorubicin and prednisone; VNCOP-B, etoposide, mitoxantrone, cyclophosphamide, vincristine, predonisolone and bleomycin; P-VEBEC, epirubicin, cyclophosphamide, etoposide, vinblastine, bleomycin and prednisone; CNOP, cyclophosphamide, vincristine, mitoxantrone and prednisone.

Table 1 – Risk of febrile neutropenia (FN) with chemotherapy regimens for the treatment of lymphoma

Regimen	FN risk (%)	Reference
CHOP-21	17–50	Lyman and Delgado;[11] Ösby et al.[12]
CHOP-14	20	Gregory et al.[13]
FM	11	NCCN[14]
DHAP	48	NCCN;[14] Smith et al.;[15] Velasquez et al.[16]
ESHAP	30–64	NCCN;[14] Smith et al.[15]
VAPEC-B	44	Pettengell et al.;[17] NCCN;[14] Smith et al.[15]
ACVBP	52–78	NCCN;[14] Gisselbrecht et al.[18]

Abbreviations: CHOP-21, cyclophosphamide, vincristine, doxorubicin and prednisone administered every 21 days; CHOP-14, cyclophosphamide, vincristine, doxorubicin and prednisone administered every 14 days; FM, fludarabine and mitoxantrone; DHAP, dexamethasone, cytarabine and cisplatin; ESHAP, etoposide, methylprednisolone, cytarabine and cisplatin; VAPEC-B, vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide and bleomycin; ACVBP, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone.

Myelosuppression causes the majority of chemotherapy dose reductions in patients with aggressive lymphoma, and G-CSF can help to ensure the delivery of appropriate RDIs of chemotherapy. In the NHL-B1 study of young patients with good-prognosis (normal lactate dehydrogenase) aggressive lymphomas, the median RDI for cyclophosphamide and doxorubicin in the dose-dense CHOP-14 regimen with G-CSF support was 97%, which was similar to that with CHOP-21 (98%, with or without G-CSF support).[1] Similarly, when etoposide was added to this regimen (CHOEP), the G-CSF-supported CHOEP-14 regimen and CHOEP-21, with or without G-CSF, displayed comparable median RDIs for cyclophosphamide, doxorubicin and etoposide (95% versus 97%, respectively). In these young patients, although CHOEP-21 was associated with a higher rate of myelosuppression than CHOP-14, it achieved superior outcomes (complete remission and 5-year EFS). CHOEP-14 achieved significantly improved results (OS) only in younger patients with good-prognosis aggressive NHL. Of particular interest, the myelosuppressive toxicity of either dose-dense regimen was adequately supported by G-CSF administration thereby allowing a high RDI to be delivered.

An equivalent study in elderly patients found that the mean RDIs were 97% for CHOP-21, 93% for CHOP-14, 96% for CHOEP-21 and 83% for CHOEP-14.[2] Results for the CHOP-14 and CHOP-21 regimens in this patient population have been discussed earlier in this article; the CHOP-14 regimen achieved superior outcomes in terms of EFS and OS, while G-CSF support ensured the optimal administration of CHOP-14 by ameliorating the increased toxicity of the regimen. Grades 3 and 4 leukocytopenia and infections did not occur substantially more frequently in the CHOP-14 arm than in the CHOP-21 arm, although grades 3 and 4 anaemia and mucositis had a much higher incidence in the dose-dense arm.

There is clear evidence that the use of G-CSF reduces the risk of FN when the rate is approximately 20%; primary prophylactic G-CSF is indicated when the risk of FN is ≥20%,[10,15] and is appropriate as a supportive measure for most lymphoma regimens, including CHOP-21 and CHOP-14.

3. Pegfilgrastim

Pegfilgrastim is a polyethylene glycol-conjugated form of filgrastim, which displays similar granulocytopoiesis-stimulating properties and tolerability to filgrastim, but requires only once-per-cycle dosing, owing to its decreased clearance rate compared with the parent protein. Unlike filgrastim, which undergoes renal clearance from the body, pegfilgrastim is eliminated almost entirely via neutrophil receptor-mediated clearance.[24] As with daily administration of filgrastim, a single dose of pegfilgrastim induces a rapid increase in the absolute neutrophil count (ANC), followed by ANC nadir. Post-nadir neutrophil recovery is complete by around day 10 and, thus, ANC is sustained even when serum levels of pegfilgrastim have diminished (Fig. 2).[24] A review of studies comparing a single dose of pegfilgrastim per cycle of chemotherapy with daily infusions of filgrastim reported a similar efficacy in reducing the duration of severe

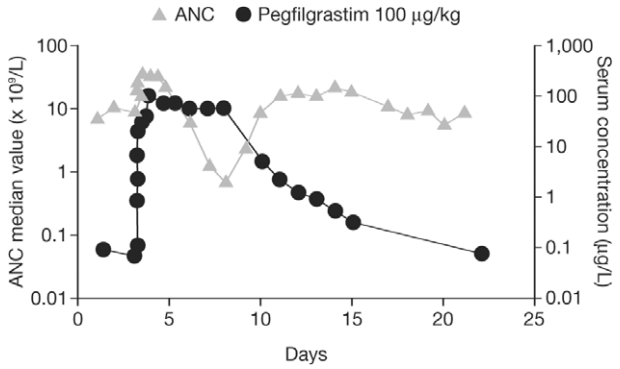

Fig. 2 – Effects of a single dose of pegfilgrastim on absolute neutrophil count (ANC). Adapted from Johnston et al.[24]

neutropenia for both G-CSFs.[25,26] The incidence of FN, use of antibiotics and hospitalisation rates were also comparable between pegfilgrastim and filgrastim.

A single dose of pegfilgrastim per cycle of chemotherapy has been used as support to facilitate the administration of maximal RDIs of chemotherapy regimens, including CHOP-14. A recent study investigated pegfilgrastim as support for up to six cycles of CHOP-14 in elderly patients (≥60 years of age) with previously untreated aggressive NHL.[27] Almost half the patients enrolled were able to receive their planned CHOP-14 dose at the scheduled time for all six cycles. Of the 159 cycles of CHOP-14 administered, chemotherapy was delayed on 15 occasions (due to FN on six occasions) and reduced on 17 occasions (none for FN).

Furthermore, pegfilgrastim does not appear to differ from filgrastim in its ability to support R-CHOP-14 administration, as demonstrated in a phase II study of patients with aggressive B-cell NHL in which the proportion of individuals reporting severe or life threatening adverse events (AEs) were comparable.[28] Of the R-CHOP-14 cycles administered, 94% (137/145) in the filgrastim arm and 93% (175/188) in the pegfilgrastim arm were administered at the planned dose and time.

The feasibility and toxicity of R-CHOP-14 supported by pegfilgrastim was investigated further in a phase II study (HOST trial) of patients (n = 50) with untreated DLBCL.[7] A single dose of pegfilgrastim per cycle of R-CHOP-14 enabled chemotherapy to be administered on time in 92% of cycles at an optimal average dose intensity (mean RDI was 95% for doxorubicin and cyclophosphamide and 91% for vincristine). Only 3% of cycles were delayed because of severe neutropenia and only 4% of cycles resulted in FN. The patients in this study had a median age of 55 years (range: 22–70 years) and included stage II–IV disease, with a performance status of 0–2 according to the Eastern Cooperative Oncology Group scale. Sixty-two per cent had an International Prognostic Index score >1, 52% stage IV disease and 40% bulky disease (mediastinal mass exceeding one-third of the maximum intrathoracic diameter or a nodal mass larger than 10 cm). A complete blood count was performed on days 1, 3, 6, 8, 10 and 13 of each cycle, and the median ANC values were cumulatively plotted for a given day (all patients and all cycles considered) and according to the cycle of therapy.

Table 2 – Haematological toxicity with R-CHOP-14 and pegfilgrastim in 269 evaluable cycles of therapy[7]

Event and duration	Incidence
Grade 3 neutropenia, *n* (%)	92 (34)
Median duration, days (range)	1 (1–3)
Grade 4 neutropenia, *n* (%)	51 (19)
Median duration, days (range)	2 (1–6)
Grade 3 thrombocytopenia, *n* (%)	11 (4)
Grade 4 thrombocytopenia	8 (3)
Grade 3 anaemia *n* (%)	19 (7)
Grade 4 anaemia	2 (0.7)

Abbreviations: R-CHOP-14, cyclophosphamide, vincristine, doxorubicin and prednisone administered every 14 days.

The incidence of World Health Organization grade 3 or 4 (severe) neutropenia was 34% and 19%, respectively, across all courses of therapy (calculated over 277 cycles) (Table 2). Neutropenia was short-lived, with grade 3 neutropenia lasting a median of 1 day, while grade 4 neutropenia lasted a median of 2 days. Patients younger than 60 years of age displayed a significantly lower incidence of grade 4 neutropenia than older individuals (16% versus 26%, respectively; $P = 0.01$). In total, 48% of patients reported at least one episode of grade 3 or 4 neutropenia, with the rate rising to 63% in those older than 60 years of age. Over 90% of cycles were delivered on time and at the planned dose, with haematological toxicity accounting for about 3% of dose delays (Table 3). Severe AEs (SAEs) were defined by the occurrence of a documented infection, and/or by organ or system toxicity requiring hospitalisation. Such events were reported in 12 out of 269 cycles (4.5%), involved 11 patients (22% of total), and prompted discontinuation of therapy in four patients. The SAE consisted of interstitial pneumonia in seven cases, septic shock in two, bacterial pneumonia and gastro-intestinal haemorrhage in one case, each. *Pneumocystis carinii* was demonstrated with bronchoalveolar lavage in three of seven cases of interstitial pneumonia and the high incidence of pneumonia caused by this micro-organism makes mandatory the use of cotrimoxazole prophylaxis during the R-CHOP-14 regimen. As illustrated in the study patient's flow chart (Fig. 3), ten patients (20% of total) did not complete the programme: six were withdrawn for toxicity and four for disease progression during therapy (two patients died before cycle 4). As of December 2006, (median follow up: 36 months), 34 patients are alive in complete remission and 13 have died (9 of disease progression, 3 of relapse and one of toxicity).

Table 3 – Feasibility results with R-CHOP-14 supported by pegfilgrastim[7]

Feasibility criteria over a total of 227 cycles	Frequency *n* (%)
Cycles delivered on time	208 (91.6)
Cycles delayed for haematological toxicity	6 (2.7)
Cycles delayed for non-haematological toxicity	13 (5.7)
Mean RDI	%
Cyclophosphamide	95
Doxorubicin	95
Vincristine	91

Abbreviations: R-CHOP-14, rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone administered every 14 days; RDI, relative dose intensities.

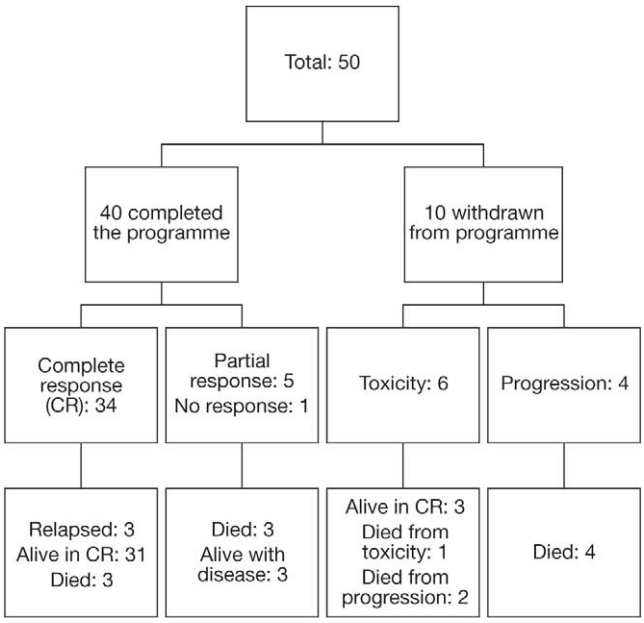

Fig. 3 – Flow of patients in the HOST (Hematology/Oncology Studies and Trials) trial.[7]

Pegfilgrastim has also been used to support the delivery of regimens other than CHOP, including hyper-CVAD (hyperfractionated cyclophosphamide, doxorubicin, vincristine and dexamethasone in one cycle and high-dose methotrexate and cytarabine in the other),[29] BEACOPP-14 (adriamycin, cyclophosphamide, etoposide, procarbazine, prednisone, bleomycin, vincristine every 14 days)[30] and standard ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine).[31]

4. Conclusions

Support with G-CSF (filgrastim, pegfilgrastim or lenograstim) is important in enabling the delivery of CHOP-14, with or without rituximab. These dose-dense regimens provide an optimal outcome for patients with aggressive lymphoma. G-CSF may also be indicated for the delivery of CHOP-21, as the risk of FN can be higher than 20%.[10] The efficacy of pegfilgrastim to support the administration of dose-dense R-CHOP-14 has been demonstrated and provides a convenient and well tolerated option due to its once-per-cycle dosing. Indeed, this simplified dosing schedule may have advantages by reducing patient burden and possibly improving compliance.

5. Conflict of interest statement

Ercole Brusamolino has no potential conflict of interest to declare.

6. Acknowledgement

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