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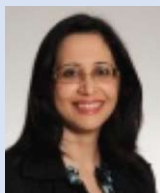
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This publication is a summary of presentations by Dr Ruth Pettengell, Senior Lecturer in Haematology and Honorary Consultant in Oncology at St George's University of London, and Dr Samar Issa, Consultant Haematologist and Clinical Head of the Lymphoma Service at Middlemore Hospital, Auckland. Drs Pettengell and Issa spoke throughout New Zealand in March 2011 about the prevention of chemotherapy-induced neutropenia.

Preventing chemotherapy-induced neutropenia: Why, who and when?

Presented by Dr Ruth Pettengell

Febrile neutropenia (FN) is a potentially life-threatening complication of myelosuppressive chemotherapy. Haematologists and oncologists deal with chemotherapy-induced neutropenia (CIN) and neutropenic sepsis in every day practice, and there is a tendency to become blasé about the condition, forgetting the impact and outcome that it has on patients.

The clinical impact of CIN

The overt manifestation of CIN is FN, with some patients presenting late and with complicated life-threatening infections. Such cases have a worse prognosis, require prolonged hospitalisation and are costly. Evidence suggests an in-hospital mortality rate of 9-10% in cancer patients who present with FN.[1] The more covert way in which neutropenia leads to decreased survival rates is due to the way in which chemotherapy is modified in patients presenting with the condition. Frequently, these patients are managed by delaying or reducing their chemotherapy dose, thereby decreasing the relative dose intensity (RDI) and ultimately reducing survival rates in patients being treated with curative intent.[2] **Figure 1** gives an explanation of dose intensity and RDI. In elderly patients with CIN, the management strategy is sometimes to withdraw chemotherapy altogether. A study by Barron et al involving 5176 patients with non-Hodgkin's lymphoma (NHL) who were receiving chemotherapy and were hospitalised with FN, revealed that patients with FN had double the risk of dying compared with matched controls (crude incidence rates for overall mortality: 7.2 vs 3.3 per 1000 person-months; p < 0.005).[3] Furthermore, a study by Dr Pettengell and colleagues involving patients with NHL revealed that the minimum RDI level required to treat patients in order to not impact on survival was 90%.[4] Dr Pettengell says that she was surprised by these findings and had expected the RDI threshold be lower. She emphasises that we only need to reduce the RDI by as little as 5-10% before we significantly impact on patient survival in patients with NHL, HL, adjuvant and neoadjuvant breast cancer.[4]

Not surprisingly, patients with comorbidities are more likely to have more complicated infections and die as a result of these. A US study involving 55,000 patients investigated the inpatient mortality rates in cancer patients hospitalised with FN, and showed that the chance of dying as a result of FN complications increased significantly with the number of comorbidities (overall rate 9.5%; no major comorbidity 2.6%; one major comorbidity 10.3%; more than one major comorbidity ≥21.4%).[1] In the study, comorbidities included heart, lung, liver, renal, cerebrovascular and peripheral vascular diseases, pulmonary embolism, deep-vein thrombosis (DVT), anaemia and transfusion requirement.[1] Pulmonary embolism, DVT, anaemia and transfusion requirements are commonly seen in patients presenting with cancer and advanced lymphoproliferative disease. Another significant risk factor for death from FN in cancer patients is age. A study by Pettengell and Schwenkglenks using data from Europe revealed that the relative risk (RR) of dying from an FN event for those aged >70 years was 10.9 (95% CI 2.4-49.4) compared with an RR of 1.7 (95% CI 0.2–8.6) for those aged ≤70 years.[5] Another study by Dr Pettengell and colleagues investigating RDIs in patients receiving rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP14 or R-CHOP21) regimens revealed that while 71-76% of patients without FN received an RDI of ≥90%, only 37% of patients with FN on R-CHOP14 and 62% of patients with FN on R-CHOP21 received RDIs above this threshold.[6]

A study by Picozzi et al revealed that 47.8% of patients with NHL receiving CHOP or cyclophosphamide, mitoxantrone, prednisone and vincristine (CNOP) experienced dose reductions of ≥20% or dose delays of ≥7 days, and that this was largely due to neutropenia.[7]

$$\frac{\text{Total dose delivered}}{\text{Time to complete therapy}} = \text{Dose intensity}$$

$$\downarrow\frac{\text{Dose}}{\text{Time}} \quad or \quad \uparrow\frac{\text{Dose}}{\text{Time}} = \downarrow\text{Dose intensity}$$

$$\text{RDI (\%)} = \frac{\text{Delivered dose intensity}}{\text{Standard dose intensity}} \times 100$$

Figure 1: Chemotherapy dose reductions, delays and relative dose intensity (RDI)

Available options for reducing the risk of FN

When a patient develops FN, several options exist:

- Reduce dose intensity
- Dose reduction
  - Treatment delay
  - Less intensive regimen
  - Discontinue therapy
- Prophylactic antibiotics
- Prophylactic granulocyte-colony stimulating factors (G-CSFs)

The importance of chemotherapy dose intensity

Prospective randomised studies in breast cancer have shown the importance of dose intensity. One such study, involving 1550 patients with early-stage breast cancer receiving adjuvant cyclophosphamide, doxorubicin and 5-fluorouracil (CAF), revealed that at a median follow-up of 9 years, those who received full-dose intensity or moderate-dose intensity (67% of full-dose intensity) had a significantly (p < 0.01) higher disease-free and overall survival (OS) than patients receiving low-dose intensity (50% of full-dose intensity) therapy.[8] Similar findings were seen in a study investigating the efficacy of 5-fluorouracil, cyclophosphamide and epirubicin (FEC)-100 and FEC-50 (epirubicin 100 mg/m^2 or 50 mg/m^2), with FEC-100 recipients having a significantly (p < 0.05) higher OS at 10 years than those receiving the FEC-50 regimen.[9] Consistent with the findings of Dr Pettengell and colleagues regarding threshold RDI levels,[4] a retrospective analysis of 793 breast cancer patients receiving adjuvant anthracycline-based non-taxane chemotherapy regimens revealed that those who received a reduced RDI of <85% had a significantly lower probability of survival without disease recurrence at 10 years than those who had received an RDI of ≥85%.[10] A Belgian study involving 210 patients with NHL receiving CHOP21 showed an RDI threshold of 90%, below which patients had a significantly (p = 0.002) lower OS than those receiving an RDI ≥90%.[11]

Dr Pettengell points out that it doesn't take much to get to the 90% RDI threshold. Simply reducing the dose by 10% or delaying treatment by 1 week will reduce the RDI to approximately 90%.[12]

Predicting chemotherapy-related neutropenic complications

Evidence shows that patients receiving chemotherapy are at highest risk of developing FN during their first cycle, and this appears to be true for a variety of cancer types. An analysis of data from 577 patients with NHL receiving CHOP, revealed that 160 patients developed FN and that in 50% of cases, FN developed within 14 days of the first cycle of therapy.[13] Additionally, it was evident that both a first episode of FN or a recurrence of FN may occur at any cycle of chemotherapy. It is therefore essential that any treatment for FN should be continued for the entire course of chemotherapy.

Lyman et al developed a model for predicting which patients may be at higher risk of FN during chemotherapy.[14] They collected data from 3638 patients initiating a new chemotherapy regimen for a variety of different cancer types in the US, and for whom data was available on neutropenic events. Endpoints were severe neutropenia (SN; ANC <0.5 x 10^9/L) and FN (fever/infection and ANC <1 x 10^9/L). They used two-thirds of the population for model derivation and one-third for model validation. Independent risk factors were previous chemotherapy, concomitant immunosuppressive therapy and renal or hepatic dysfunction. High- and low-risk groups were defined on the basis of median predicted risk using patient and treatment characteristics identified by the model, and the cumulative risk of SN and FN for these groups over the first 120 days of treatment was estimated by the method of Kaplan and Meier. In both the derivation and validation populations, the risk of FN over 100 days was found to be 20% in the high-risk group and 5% in the low-risk group (p < 0.0001). Furthermore, primary G-CSF prophylaxis was found to significantly reduce the risk of SN and FN. This model had an estimated sensitivity of 85% and a specificity of 58.7%.

G-CSF therapy

Under normal conditions, neutrophils develop over several stages (proliferation, differentiation and maturation) each taking several days. With the administration of G-CSF therapy, cell maturation is both amplified and occurs more quickly (1 day instead of 4-5 days).[15] Furthermore, cells released following G-CSF therapy show function equal to or greater than that of cells released as a result of neutrophil development without G-CSF treatment.[16]

Evidence of efficacy

The impact of primary prophylaxis (PP) with G-CSF on FN and mortality in cancer patients receiving chemotherapy was evaluated in a systematic review and meta-analysis by Kuderer and colleagues.[17] Their analysis included 17 randomised-controlled trials (RCTs) comparing PP G-CSF with placebo or untreated controls and involved a total of 3493 adult patients with solid tumours (65%) or NHL (35%); G-CSF recipients were required to have started G-CSF therapy within 1-3 days of chemotherapy. Ten studies used filgrastim, six used lenograstim and one used pegfilgrastim. The analysis showed a significantly lower incidence of FN in patients who had received PP with G-CSF compared with untreated patients or placebo controls, with a combined RR of 0.54 (95% CI 0.43-0.67). The RR reduction was numerically greatest in the pegfilgrastim subgroup (RR 0.08; 95% CI 0.03-0.17). In addition to the 46% overall reduction in risk seen with the use of G-CSF in this analysis, overall, the use of G-CSF was found to significantly reduce the risk of infection-related mortality (RR 0.55; 95% CI 0.33-0.90) and early mortality (RR 0.60; 95% CI 0.43-0.83). The study also showed that G-CSF prophylaxis enabled the delivery of more chemotherapy to patients, with all G-CSF arms of the trials having an RDI of >90% and the control arms having a broader range of RDIs (in 4 studies, controls had RDIs ≤85%).

It appears that the benefits of PP G-CSF occur irrespective of tumour type. This was seen in a meta-analysis by Lyman et al.[18] Their analysis of 25 trials showed that all-cause mortality was reduced in G-CSF recipients compared with controls, for breast cancer, endometrial cancer, germ cell cancer, Hodgkin's disease, NHL, non-small cell lung cancer and urothelial cancer. Further analysis separating the trials into intended chemotherapy dose intensity, revealed that G-CSF use was beneficial with regard to all-cause mortality irrespective of intended dose intensity, but that the largest benefit was seen in trials with a dose-intensive or dose-escalation schedule.

Prophylactic antibiotics and G-CSF

A recent cohort study by von Minckwitz et al investigated the efficacy of four regimens for FN prophylaxis in breast cancer patients receiving 6-8 cycles of neoadjuvant TAC (docetaxel, doxorubicin, cyclophosphamide).[19] The four prophylactic regimens were: oral ciprofloxacin 500mg twice daily on days 5-14 (n = 253); filgrastim 5 µg/kg/day or lenograstim 150 µg/m^2/day on days 5-10 (daily G-CSF; n = 377); pegfilgrastim 6mg on day 2 (n = 305); pegfilgrastim 6mg on day 2 plus ciprofloxacin twice daily (n = 321). The study revealed that pegfilgrastim and pegfilgrastim plus ciprofloxacin were significantly (p < 0.001) more effective than daily G-CSF or ciprofloxacin alone in preventing FN. This finding was evident when the data was analysed for all cycles and for just the first cycle of chemotherapy. Over all cycles, the incidence of FN was only 5-7% in pegfilgrastim ± ciprofloxacin recipients, compared with 22% for ciprofloxacin alone recipients and 18% for daily G-CSF recipients. During the first cycle of chemotherapy, there were no cases of FN in the pegfilgrastim plus ciprofloxacin group and only 2 cases in the pegfilgrastim group. Furthermore, pegfilgrastim ± ciprofloxacin was significantly (p < 0.001) more effective than ciprofloxacin alone or daily G-CSF in reducing the risk of hospitalisation due to FN (hospitalisations per cycle: 6-7% vs 19-21%).

Dr Pettengell points out that in clinical practice, due to concerns about antibiotic resistance, antibiotics would not normally be chosen for FN PP. However, they may be an option particularly during the first cycle of chemotherapy where there is infection beyond a gastrointestinal obstruction or ongoing infection.

Guidelines for the use of G-CSF

The latest European guidelines for the use of G-CSF to reduce the incidence of chemotherapy-induced FN in adult patients with lymphoproliferative disorders and solid tumours, recommend that patients with an FN risk of ≥20% receive prophylactic G-CSF and state that there is no clear indication for using G-CSF prophylaxis in patients with an overall FN risk of <20%.[20] The guidelines provide a patient assessment algorithm designed to aid in decision making regarding prophylactic G-CSF use (see **Figure 2**). The initial step involves determining the FN risk associated with the particular planned chemotherapy regimen. For those patients receiving a regimen with an FN risk of <10%, Dr Pettengell suggests reassessment at each cycle and the adoption of secondary G-CSF prophylaxis if necessary. If the associated risk of FN with the chemotherapy regimen falls into the 10-20% risk range, then the patient needs to be assessed for factors that increase their risk of FN (such factors are outlined in **Figure 2**). The most important risk factor is age,

and Dr Pettengell says that any patient over the age of 65 years being treated with curative intent will benefit from G-CSF prophylaxis as this puts them into a greater than 20% risk group.

These guidelines emphasise that it is not sufficient to just start a patient on a course of chemotherapy and assume that they will be fine. The patient needs to be carefully monitored and reassessed at each cycle to determine their risk of FN.
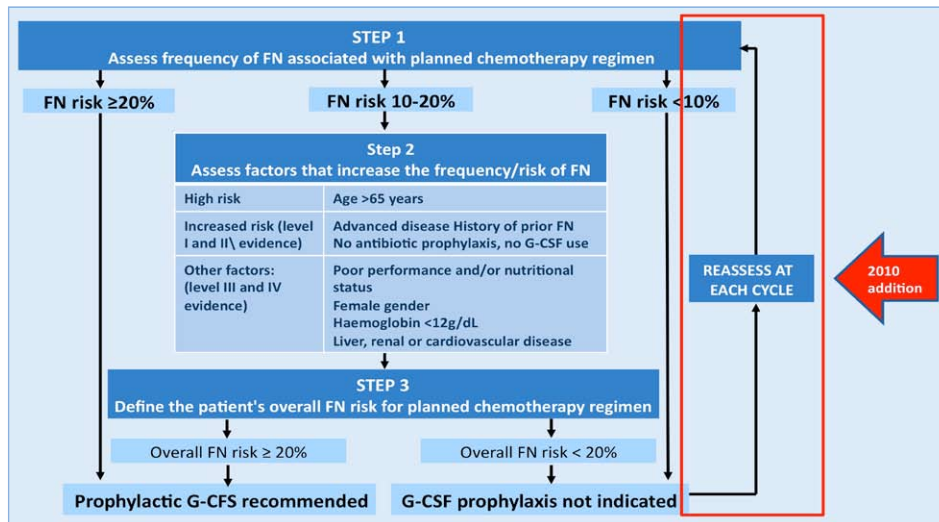

Figure 2: Patient assessment algorithm for determining the need for prophylactic G-CSF usage in cancer patients receiving chemotherapy. (Adapted from Aapro et al 2010[20]).
FN = febrile neutropenia; G-CSF = granulocyte-colony stimulating factor.

How good are clinicians at treating patients at risk of FN?

Salar and colleagues looked at physician-assessed FN risk, G-CSF use and the incidence of FN in patients treated with R-CHOP21 and R-CHOP14.[21] Their multicentre retrospective and prospective study involved 14 European countries and Australia. Analysis of data from 1136 patients with diffuse large B-cell lymphoma revealed that 18% of patients receiving R-CHOP21 who were deemed to be low risk for FN still received PP with G-CSF, and only 47% of those who were deemed to be high risk for FN received PP with G-CSF. Also, only 84% of R-CHOP14 recipients received PP with G-CSF, and this is surprising since it is well known that this regimen cannot be given at full dose on time without G-CSF PP.

High-risk chemotherapy regimens

The following chemotherapy regimens are some of those carrying an intermediate (10-20%) or high risk (>20%) of FN;[20]

- **Breast cancer regimens:**
  TAC
  Doxorubicin/cyclophosphamide (AC)
  Docetaxel ⟶ AC
  FEC-100

- **Non-small cell lung cancer regimens:**
  Cisplatin/vinorelbine/cetuximab

- **Metastatic gastric cancer regimens:**
  Leucovorin-primed fluorouracil (LVFU)
  LVFU-cisplatin
  LVFU-irinotecan
  Docetaxel/cisplatin/fluorouracil
  Docetaxel/cyclophosphamide/fluorouracil
  Epirubicin/cisplatin/fluorouracil

- **NHL/chronic lymphocytic leukaemia (CLL) regimens:**
  Rituximab/etoposide/methylprednisolone/cytarabine/cisplatin salvage post rituximab
  Hyper cyclophosphamide/vincristine/adriamycin/dexamethasone + rituximab (Burkitt's lymphoma)
  Mustard/doxorubicin/vinblastine/vincristine/bleomycin/etoposide/prednisolone (Stanford V)
  Mechlorethamine/vincristine/procarbazin/prednisone/etoposide/bleomycin–vincristine/cyclophosphamide/adriamycin/dexamethasone
  Fludarabine/cyclophosphamide
  Fludarabine/cyclophosphamide/rituximab (FCR)

Dr Pettengell points out that patients with CLL treated with FCR as first-line therapy have a particularly high risk of FN and that currently studies are looking at the best management of these patients (primary or secondary prophylaxis).

Factors predicting cycle 1 FN

The model developed by Lyman et al for predicting risk of FN was devised using data from patients with a variety of cancer types, and while the sensitivity of the model was good (85%), the specificity was lower than desired (58.7%).[14] Dr Pettengell and colleagues recently devised a lymphoproliferative risk model for FN occurrence during the first cycle of chemotherapy, based on data from 240 patients with NHL, who were scheduled to receive a new myelosuppressive chemotherapy regimen with at least four cycles.[22] Their model had a sensitivity of 82%, a specificity of 81% and a negative predictive value of 98%. Multivariate analysis once again revealed age as a significant risk factor (per additional 10 years of age: OR 2.2; 95% CI 1.21-4.01). Other significant risk factors were previous chemotherapy (OR 6.39; 95% CI 1.72-23.68), nutritional status (baseline albumin <35 g/dL: OR 4.76; 95% CI 1.35-16.71) and recent infection (OR 3.07; 95% CI 0.99-9.52). With the advent of electronic patient prescribing, models accurately predicting individual patient risk can be simply incorporated into a computer programme and will be very useful.

Proactive vs reactive use of pegfilgrastim

Balducci et al assessed the incidence of FN and related events in elderly (≥65 years; median age 72 years) cancer patients with NHL (n = 146) or solid tumours (n = 686) receiving pegfilgrastim beginning in cycle 1 (proactive) or after cycle 1 at the physicians discretion (reactive).[23] Patients were scheduled to receive ≤6 21-day cycles of a standard chemotherapy regimen. Analysis of all cycles revealed that for both solid tumours and NHL, proactive pegfilgrastim use resulted in a significantly (p ≤ 0.004) lower incidence of FN compared with reactive use (4% vs 10% and 15% vs 37%, respectively). Furthermore, there was a reduced incidence of chemotherapy-induced complications with proactive versus reactive use of pegfilgrastim; (data from patients with solid tumours) grade 3 or 4 neutropenia (30% vs 80%), dose delay (16% vs 28%), dose reduction (7% vs 14%), hospitalisation (5% vs 9%), antibiotic use (10% vs 28%).

Several studies have investigated the effects of pegfilgrastim on FN and related events in patients receiving CHOP-21 ± rituximab. A 2005 RCT, by Ershler and colleagues, involving 146 elderly patients (median age 73 years) with NHL who received pegfilgrastim in cycle 1 and subsequent cycles of R-CHOP or CHOP-like regimens or who did not receive pegfilgrastim in cycle 1, but received the agent in subsequent cycles at the physicians discretion, demonstrated the efficacy of first-cycle use of pegfilgrastim.[24] Patients receiving pegfilgrastim in cycle 1 of chemotherapy had a significantly reduced overall incidence of FN, compared with those who did not receive the agent in cycle 1 (15% vs 37%; p = 0.0043); the incidence of first-cycle FN and hospitalisations due to FN or neutropenia-related events was also lower for cycle 1 pegfilgrastim recipients (7% vs 25% and 17% vs 37%, respectively).

Dr Pettengell undertook an integrated analysis of data from three prospective studies of CHOP or CHOP-like regimens with once-per-cycle PP with pegfilgrastim, with or without rituximab in 275 patients with NHL.[25] Their findings revealed FN incidence rates identical

to those seen in Ershler et al's study (first cycle FN 7%; FN over all cycles 15%). A prospective study by Ozer et al involving 325 patients with cancer other than leukaemia or myelodysplastic syndrome showed similar findings.[26]

R-CHOP14 vs R-CHOP21

A recent UK phase III study undertaken by Cunningham et al compared the toxicity and survival outcomes of R-CHOP14 with those of R-CHOP21 in diffuse large B-cell non-Hodgkin's lymphoma.[27] Patients (n = 1080) were randomly assigned to either eight cycles of standard R-CHOP21 or six cycles of R-CHOP14 (+ G-CSF) with two additional cycles of single agent rituximab. The rates of grade 3/4 toxicities were similar between the R-CHOP14 and R-CHOP21 groups; neutropenia 31 vs 58%, thrombocytopenia 9 vs 4%, FN 5 vs 13% (deaths 0 vs 2) and infection 18 vs 21% (deaths 2 vs 1). Dr Pettengell points out that the toxicity rates were similar between the two studies because of the use of G-CSF. She says that these regimens are comparable and that it is a matter of clinician and patient choice whether to use the R-CHOP14 or R-CHOP21 regimen.

Current practice vs pegfilgrastim PP in breast cancer

The Neulastim vs Current neutropenia management Practice (NeuCuP) study is an integrated analysis of 11 clinical studies involving 2282 patients with breast cancer receiving chemotherapy regimens with ≥15% FN risk.[28] Current neutropenia management included any neutropenia management not dictating PP by protocol (no G-CSF, pegfilgrastim in any cycle or daily G-CSF). The use of PP pegfilgrastim resulted in a significantly lower incidence of FN than current neutropenia management (5 vs 29%), and significantly reduced the odds for FN (OR 0.124: 95% CI 0.08-0.194). The analysis also showed that PP pegfilgrastim significantly reduced overall and cycle 1 hospitalisations compared with current practice (4 vs 10% and 3 vs 6%, respectively).[29] PP pegfilgrastim recipients were also found to have a lower incidence of requirement for dose reduction ≥15% than those treated with current practice (9 vs 24%).[29]

Filgrastim and pegfilgrastim

Filgrastim is a recombinant growth factor that regulates the number of circulating neutrophils. The agent is cleared by both neutrophils and by the kidneys. Pegfilgrastim is formed by the addition of a polyethylene glycol (PEG) group to the N-terminus of filgrastim. Pegfilgrastim appears to have mainly neutrophil-mediated clearance as the larger molecule is prevented from being cleared by the kidneys. This results in pegfilgrastim staying around longer in the blood until neutrophils have recovered. As the absolute neutrophil count (ANC) recovers to within the normal range, the clearance of pegfilgrastim increases. Thus, the elimination mechanism of pegfilgrastim is self-regulating. This phenomenon was demonstrated by Green et al in a randomised double-blind multicentre phase III study of pegfilgrastim in patients receiving myelosuppressive chemotherapy.[30] In fact, their study demonstrated that a single 6mg SC injection of pegfilgrastim per chemotherapy cycle maintains a clinically effective serum concentration for as long as it takes to achieve neutrophil recovery, and is as effective as multiple daily injections of filgrastim. Furthermore, Brugger et al have shown that pegfilgrastim promoted ANC recovery compared with no growth factor support in elderly patients with breast cancer who were receiving anthracycline-containing chemotherapy.[31] On average, the depth and duration of ANC nadir was reduced in the pegfilgrastim group compared with the non G-CSF group, therefore reducing the period of risk for FN and complications due to grade 3/4 neutropenia.

Dr Pettengell says that the area under the ANC curve will change depending on the intensity of the chemotherapy regime, but generally the use of pegfilgrastim will significantly reduce the area under the curve.

Pegfilgrastim vs daily G-CSF –cohort studies

In their retrospective cohort study involving data from 99 US community based oncology practices, Hershman et al analysed the impact of G-CSF PP on FN in cancer patients (n = 3123) initiating chemotherapy (≥21-day cycle length) with filgrastim, pegfilgrastim or no G-CSF support.[32] The analysis revealed that PP with filgrastim did not significantly reduce the odds of FN compared with no G-CSF, or delayed administration (filgrastim or pegfilgrastim initiated >3 days after the first cycle of chemotherapy), but that PP with pegfilgrastim did significantly reduce the likelihood of FN compared with no G-CSF or delayed G-CSF (OR 0.46; 95% CI 0.31-0.68). It appears that delayed G-CSF is almost as ineffective as using no G-CSF.

Weycker et al showed similar findings in their retrospective cohort study involving cancer patients who received filgrastim or pegfilgrastim prophylaxis, with the risk of hospitalisation due to neutropenic complications being significantly lower for the latter group (ORs 0.64-0.73; p < 0.05).[33]

Timing and duration of G-CSF administration

The importance of the timing of G-CSF administration was demonstrated by Koumakis et al in their sequential cohort study investigating the impact of daily G-CSF (filgrastim) on the incidence of FN following high-dose cyclophosphamide chemotherapy.[34] The study revealed that patients who received G-CSF late (>96 hours after chemotherapy) or not at all, had a significantly (p < 0.05) higher incidence of FN than patients who received the agent earlier (24, 48 or 72 hours after chemotherapy). In addition, more total G-CSF injections were given to treat FN, and as secondary prophylaxis, compared to patients who received primary prophylaxis.

A large retrospective study by Weycker et al examined the relationship between the number of days of filgrastim prophylaxis and the risk of hospitalisation in patients receiving chemotherapy for NHL (n = 133), breast (n = 205) or lung cancer (n = 260).[35] In all cases, patients had been started on filgrastim on or before chemotherapy cycle day 5. The study revealed risk reductions with each additional day of prophylaxis of 15-19% for NHL patients, 17-23% for breast cancer patients and 8-9% for those with lung cancer.

Pegfilgrastim vs filgrastim – meta-analysis

A meta-analysis of five RCTs comparing the efficacy and safety of a single dose of pegfilgrastim (100 μg/kg or a fixed dose of 6mg) with that of daily dose filgrastim (5 μg/kg/day; median duration 10-14 days) in patients (n = 617) with breast cancer or NHL undergoing myelosuppressive chemotherapy, was undertaken by Pinto et al. Their analysis revealed significantly favourable results for pegfilgrastim over filgrastim for FN incidence reductions (RR 0.64; 95% CI 0.43-0.97).[36] Dr Pettengell points out that although the inappropriate use of G-CSF (i.e. delayed start and short duration) accounts in clinical practice for a substantial amount of the reduced efficacy of daily G-CSF, in RCTs where daily G-CSF has been used as per licence, we still see a benefit in favour of pegfilgrastim. In fact, this meta-analysis showed a 36% improvement with pegfilgrastim compared with filgrastim.

Impact of pegfilgrastim on early all-cause mortality

A large community-based, prospective observational study by Lyman et al investigated the effects of pegfilgrastim therapy on the time to FN and on progression-free survival (PFS) and OS in 4458 consecutive adults patients initiating chemotherapy at 115 US practice sites.[37] Pegfilgrastim recipients (n = 1209; 620 patients received PP starting in cycle 1) exhibited significant improvements in early OS and PFS compared with those who had not received such therapy, with a 59% and 45% reduction in risk, respectively. Furthermore, patients with a planned RDI ≥85%, Eastern Cooperative Oncology Group (ECOG) performance status ≥1, lung cancer or liver dysfunction all exhibited significant (p ≤ 0.04) improvements in OS with the use of pegfilgrastim.

Take-home messages

CIN and its complications are associated with considerable morbidity and mortality[1]

CIN represents an important dose-limiting toxicity, potentially compromising long-term outcome[2,9]

G-CSF primary prophylaxis reduces the depth and duration of neutropenia. Compared with placebo or untreated controls this leads to:[17]

Reduced risk of FN

Reduced risk of infection-related mortality

Reduced risk of early mortality

Increased RDI

Pegfilgrastim, which can be administered once per cycle, has been associated with:

Lower risk of FN, hospitalisation and IV antibiotic use vs daily G-CSF[17,19]

Improved delivery of planned chemotherapy vs current practice neutropenia management[29]

Improvements in early PFS and OS vs no pegfilgrastim use[37] (further evaluation of this effect is warranted).

References

1. Kuderer NM et al. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer 2006;106(10):2258-66.
2. Bosly A et al. Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. Ann Hematol. 2008;87(4):277-83.
3. Barron R et al. Risk of mortality in patients with cancer experiencing febrile neutropenia. ASCO meeting 2009. Abstract 9561. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=34841. (Accessed April 2011).
4. Pettengell R et al. Association of reduced relative dose intensity and survival in lymphoma patients receiving CHOP-21 chemotherapy. Ann Hematol 2008;87(5):429-30.
5. Pettengell R and Schwenkglenks M. Incidence of neutropenia, chemotherapy delivery, and use of colony-stimulating factor in patients with non-Hodgkin lymphoma of different age groups. Leuk Lymphoma 2011. [Epub ahead of print].
6. Pettengell R et al. Impact of febrile neutropenia on RCHOP chemotherapy delivery and hospitalizations: results from an international observational study in patients with non-Hodgkin lymphoma (IMPACT NHL). Haematologica 2010;95(suppl. 2):365, Abstract 0877.
7. Picozzi VJ et al. Patterns of chemotherapy administration in patients with intermediate-grade non-Hodgkin's lymphoma. Oncology 2001;15(10):1296-306.
8. Budman DR et al. Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. J Natl Cancer Inst. 1998;90(16):1205-11.
9. Bonneterre J et al. Epirubicin increases long-term survival in adjuvant chemotherapy of patients with poor-prognosis, node-positive, early breast cancer: 10-year follow-up results of the French Adjuvant Study Group 05 randomized trial. J Clin Oncol. 2005;23(12):2686-93.
10. Chirivella I et al. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. Breast Cancer Res Treat. 2009;114:479-84.
11. Bosly A et al. Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. Ann Hematol. 2008;87(4):277-83.
12. Lyman GH. Guidelines of the National Comprehensive Cancer Network on the use of myeloid growth factors with cancer chemotherapy: a review of the evidence. J Natl Compr Canc Netw. 2005;3(4):557-71.
13. Lyman GH et al. Risk of febrile neutropenia among patients with intermediate-grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. Leuk Lymphoma 2003;44(12):2069-76.
14. Lyman GH et al. Final risk prediction model for neutropenic complications in patients receiving cancer chemotherapy. ASH meeting 2008. Abstract 1312. Available from: http://ash.confex.com/ash/2008/webprogram/Paper10915.html (Accessed April 2011).
15. Kim SK et al. Chemotherapy and neutropenia. Hematol Oncol Clin North Am. 1996;10(2):377-95.
16. Dexter TM. Granulocyte colony stimulating factor: from laboratory bench to clinical use. Eur J Cancer 1994;30A(Suppl 3):S15-9.
17. Kuderer NM et al. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol. 2007;25(21):3158-67.
18. Lyman GH et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: a systematic review. J Clin Oncol. 2010;28(17):2914-24.
19. von Minckwitz G et al. Pegfilgrastim +/- ciprofloxacin for primary prophylaxis with TAC (docetaxel/doxorubicin/cyclophosphamide) chemotherapy for breast cancer. Results from the GEPARTRIO study. Ann Oncol. 2008;19(2):292-8.
20. Aapro MS et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47(1):8-32.
21. Salar A et al. Febrile neutropenia risk assessment and granulocyte-colony stimulating factor support in patients with diffuse large B cell lymphoma receiving R-CHOP regimens. ASH meeting 2009. Abstract 107. Available from: http://ash.confex.com/ash/2009/webprogram/Paper16696.html (Accessed April 2011).
22. Pettengell R et al. Multivariate analysis of febrile neutropenia occurrence in patients with non-Hodgkin lymphoma: data from the INC-EU Prospective Observational European Neutropenia Study. Br J Haematol. 2009;144(5):677-85.
23. Balducci L et al. Elderly cancer patients receiving chemotherapy benefit from first-cycle pegfilgrastim. Oncologist 2007;12(12):1416-24.
24. Ershler W et al. First-cycle pegfilgrastim reduces chemotherapy-induced febrile neutropenia among older patients with NHL treated in community practice: results from a large, randomized, controlled trial. Blood (ASH Annual Meeting Abstracts) 2005;106:Abstract 4286.
25. Pettengell R et al. Pegfilgrastim provides effective primary prophylaxis against febrile neutropenia in patients with NHL undergoing chemotherapy: initial results from an integrated analysis – The Neulasta versus current neutropenia management practice (Neucup) project. Blood (ASH Annual Meeting Abstracts) 2006;108:Abstract 1150.
26. Ozer H et al. Neutropenic events in community practices reduced by first and subsequent cycle pegfilgrastim use. Oncologist 2007;12(4):484-94.
27. Cunningham D et al. A phase III trial comparing R-CHOP 14 and R-CHOP 21 for the treatment of patients with newly diagnosed diffuse large B-cell non-Hodgkin's lymphoma. J Clin Oncol. 2009;27(N0 15S):Abstract 8506.
28. von Minckwitz G. Incidence of febrile neutropenia in breast cancer patients receiving pegfilgrastim as primary prophylaxis compared with current practice neutropenia management: results from an integrated analysis. ASCO Breast Cancer Symposium 2007. Abstract 267. Available from: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=52&abstractID=40297 (Accessed April 2011).
29. Aapro M et al. Improved chemotherapy delivery in breast cancer patients receiving pegfilgrastim primary prophylaxis compared with current practice neutropenia management – results from an integrated analysis (NeuCuP). ECCO 14. 2007:Abstract 0#2033.
30. Green MD et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003;14(1):29-35.
31. Brugger W et al. Pegfilgrastim promotes neutrophil recovery in elderly breast cancer patients following anthracycline-containing chemotherapy. 30th Annual San Antonio Breast Cancer Symposium (SABCS) 2007:Abstract 1089.
32. Hershman D et al. Impact of primary prophylaxis on febrile neutropenia within community practices in the US. J Med Econ. 2009;12(3):203-10.
33. Weycker D et al. Risk of hospitalization for neutropenic complications of chemotherapy in patients with primary solid tumors receiving pegfilgrastim or filgrastim prophylaxis: a retrospective cohort study. Clin Ther. 2009;31(5):1069-81.
34. Koumakis G et al. Optimal timing (preemptive versus supportive) of granulocyte colony-stimulating factor administration following high-dose cyclophosphamide. Oncology 1999;56(1):28-35.
35. Weycker D et al. Are shorter courses of filgrastim prophylaxis associated with increased risk of hospitalization? Ann Pharmacother. 2006;40(3):402-7.
36. Pinto L et al. Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. Curr Med Res Opin. 2007;23(9):2283-95.
37. Lyman GH et al. Impact of pegfilgrastim on early all-cause mortality in patients receiving cancer chemotherapy. J Clin Oncol 2008;26 (May 20 suppl):Abstract 6552.

The curse of neutropenia

Presented by Dr Samar Issa

Neutropenia is defined as an ANC <1.5 x 10^9/L, and is further classified into the following grades;

Grade 4: ANC <0.5 x10^9/L

Grade 3: ANC 0.5-1.0 x10^9/L

Grade 2: ANC 1.0-1.5 x10^9/L

Neutropenia in patients with cancer carries an overall mortality rate as high as 30%, and the risk of infection correlates directly with the grade of neutropenia.[1] The elderly and patients with co-morbidities such as heart disease, renal disease and baseline Hb <12 g/dL, are at an increased risk of developing FN. FN can potentially become a major problem for a patient and clinician, and often requires prolonged hospitalisation. FN is expensive, and European data suggest that costs including hospitalisation, drugs and tests add up to around €4000 per patient.[2]

Role of growth factors in NHL

An increasing number of patients are presenting with NHL. One of the challenges in treating this disease is that many patients are elderly. Older patients are more susceptible to developing FN, and these patients often receive more aggressive chemotherapy regimens. FN can be a major dose-limiting factor for chemotherapy and neutropenia has been shown to be the most frequent cause of both dose reductions and dose delays in patients with NHL.[3]

Cost-benefit analysis of PP G-CSF in NHL

Dr Issa and colleagues recently undertook a cost-benefit analysis of PP with G-CSF in reducing hospital admissions with FN in patients undergoing chemotherapy for NHL.* A G-CSF prophylaxis protocol was implemented at the Haematology Department at Middlemore Hospital in Dec 2007. Primary G-CSF prophylaxis was given to patients aged >65 yrs undergoing high-dose chemotherapy for NHL. Secondary G-CSF prophylaxis was given to patients <65yrs following a previous episode of FN. R-CHOP-14 was already routinely given with G-CSF support. Initially, all patients received daily filgrastim [Neupogen®], but now pegfilgrastim [Neulastim®] is increasingly used.

The aims of the retrospective cohort study were to assess the impact of G-CSF on the incidence of FN, to determine its cost-effectiveness, to establish its treatment outcomes and to determine the treatment-related all-cause mortality during the study period. In total, 65 consecutive paitents who received CHOP-14 or CHOP-21 ± rituximab for NHL were recruited between December 2006 and May 2009. A total of 40 patients received primary G-CSF prophylaxis and 25 received no such therapy. Cost-benefit analysis was carried out using the actual cost of hospital admissions and numbers needed to treat (NNT). Patient characteristics are presented in **Table 1**.

*These data are in abstract form, but the final results are currently being written up for submission for publication.

	All patients (n=65)	G-CSF prophylaxis (n=40)	No G-CSF prophylaxis (n=25)
Median age (years)	61 (range 20-85)	62 (range 20-85)	56 (range 36-76)
Gender Male	33	22	16
Female	28	18	9
Diagnoses:			
Diffuse large B cell lymphoma	52	33	20
Follicular lymphoma	5	3	2
T cell lymphoma	4	4	0
B-acute lymphoblastic lymphoma	1	1	0
Mantle cell lymphoma	1	1	0
Waldenstrom's macroglobulinaemia	1	0	1
Advanced stage (III-IV)	40(63%)	27(68%)	13(52%)

Table 1: Characteristics of patient included in the cost-benefit analysis or G-CSF primary prophylaxis in reducing hospital admissions with FN in patients undergoing chemotherapy for NHL at Middlemore Hospital

Analysis of results revealed a significantly (p < 0.0001) lower incidence of FN in patients who received G-CSF prophylaxis compared to those who did not (5% vs 60%; absolute risk reduction 55% [95% CI 34-64%], with a NNT of 1.8 [95% CI 1.6-2.9]). When CHOP-21 recipients alone were compared to non-G-CSF patients, risk reduction and NNT were also 5% vs 60% and 1.8, respectively. Subgroup analysis of CHOP-21 recipients who did and did not receive G-CSF revealed the following FN incidence rates with regard to age: >65 years 9% vs 63%; ≤65 years 0% vs 59%, respectively (p ≤ 0.01). **Figure 3** provides a graphical representation of the findings of the study with regard to the incidence of FN in G-CSF and non-G-CSF recipients.
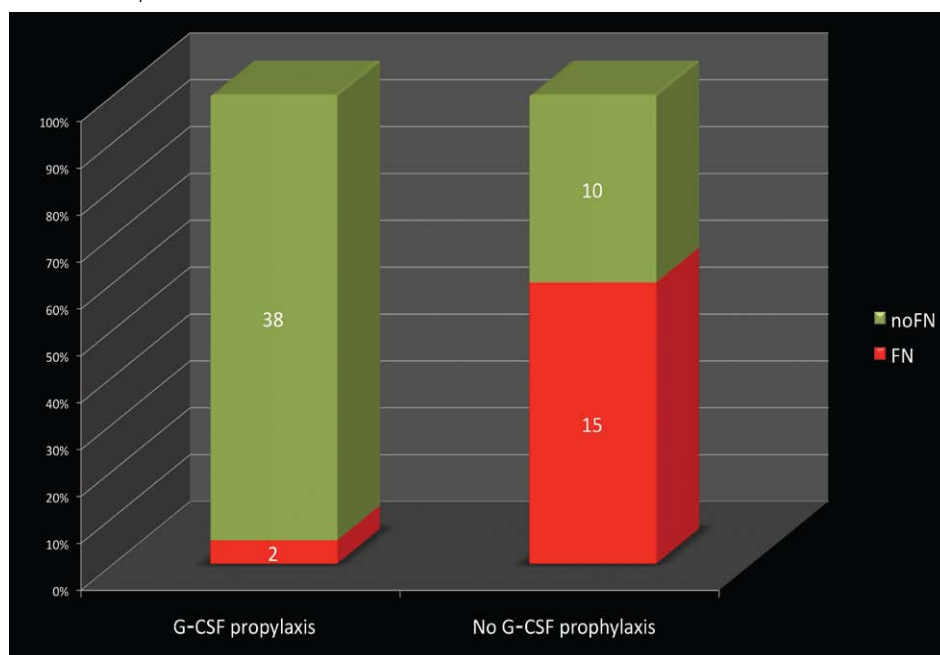

Figure 3: Difference in incidence of febrile neutropenia between patients with or without primary G-CSF prophylaxis.

FN =febrile neutropenia; G-CSF = granulocyte-colony stimulating factor

There were no significant differences in response rates (complete or partial remission) to chemotherapy between the two groups, and no difference in mortality (either from disease or all cause combined). The average cost of hospital admission due to FN was calculated to be NZ$6753.31. Dr Issa points out that Pharmac estimates the average cost of each hospitalisation due to FN to be NZ$4500. The average length of hospital stay was 5.25 days (median 4 days).

Per cycle cost analysis for the use of pegfilgrastim versus the cost of an episode of FN based on a NNT of 1.8, revealed that primary G-CSF appeared to be cost effective with an estimated cost saving of NZ$2431.66 per patient. Furthermore, when this analysis was performed with primary G-CSF administered for a complete 6-cycle course of chemotherapy vs one FN episode plus the cost of secondary prophylaxis, G-CSF prophylaxis was still deemed to be cost effective.

Dr Issa says that on purely financial terms, it costs merely NZ$280 more to give PP G-CSF per patient and that when we compare this with the indirect costs of FN, such as loss of productivity, reduced quality of life, caregiver time, pressure on hospital beds and staff, the small financial cost of G-CSF therapy is more than offset.

Take-home messages

- Primary G-CSF prophylaxis is effective in preventing FN in patients undergoing high-dose chemotherapy
- This study is the first to show that primary G-CSF prophylaxis is also cost-effective
- Primary G-CSF prophylaxis is recommended in this patient group
- The Middlemore group are currently investigating the effects of PP G-CSF on quality of life.

References:

1. Hsieh MM et al. Prevalence of neutropenia in the U.S. population: age, sex, smoking status, and ethnic differences. Ann Intern Med. 2007;146(7):486-92.

2. Moeremans K et al. Economic aspects and drivers of febrile neutropenia in cancer – a multicentre retrospective analysis in Belgium. Value Health 2005;8(6):Abstract PCN23.

3. Picozzi VJ et al. Patterns of chemotherapy administration in patients with intermediate-grade non-Hodgkin's lymphoma. Oncology 2001;15(10): 1296-306.

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