Neutropenia in cancer patients: risk factors and management

Neutropenia – low levels of neutrophils – poses a serious threat to patients on chemotherapy. It exposes them to the risk of infection – including potentially fatal infections – and also leads to delays in treatment and reductions in dose intensity, which can compromise the chance of a favourable outcome. Awareness of risk factors and prompt action are essential.

Severe neutropenia places patients at high risk of serious infection. The lower limit of normal blood neutrophil count is approximately 2000/mm^3. Counts below this are classified as neutropenia, and graded according to severity. Counts below 500 cells/mm^3 are categorised as grade 4, between 500 and 1000 as grade 3, between 1000 and 1500 grade 2, and the least severe – between 1500 and 2000 cells/mm^3 – grade 1.

Neutropenia increases susceptibility to infection, particularly in cancer patients. We have known since the early 1960s that both duration and severity of neutropenia are factors that lead to febrile neutropenia – fever and infection – in cancer patients. The duration of neutropenia is particularly important in terms of the risk of infections.

Some key lessons in the management of febrile neutropenia in cancer patients have been learned since the 1960s. We have learned to anticipate the problem, and to see and evaluate our patients promptly when any sign of an infection occurs. We have learned

European School of Oncology
e-grandround

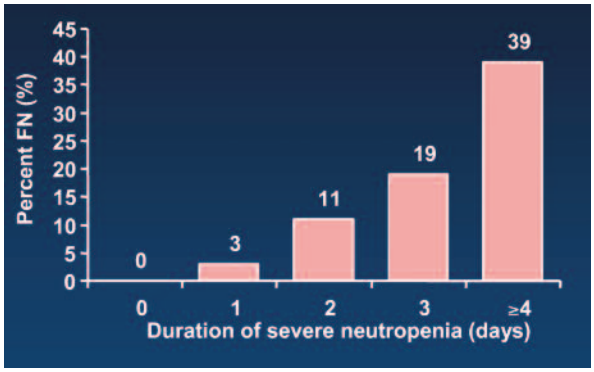
The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading experts in the field. One of these will be selected for publication in each issue of *Cancer World*.

In this issue, David Dale, of the University of Washington, in Seattle, USA, reviews the risk factors associated with neutropenia in cancer patients treated with chemotherapy, together with management strategies to reduce adverse outcomes.

Jeffrey Crawford, of the Duke University Medical Center, in Durham, North Carolina, USA, poses questions that explore the issue further. The presentation is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do

PROMPT TREATMENT IS KEY



The risk of febrile neutropenia (FN) rises steeply in cancer patients the longer severe neutropenia persists unchecked

Source: Adapted from Luiz Meza et al. *Proc Am Soc Clin Oncol* 2002; 21: abstract 2640

where to examine the patient, looking particularly at the skin, the mouth, the area around the anus, and the abdomen for signs of infection. A complete blood count should be taken, including white blood cell count (WBC), WBC differential, haemoglobin, haematocrit and platelet count. If there is fever and severe neutropenia, it is essential to start antibiotics promptly. These basic clinical practices are extremely important for the welfare of our patients.

For the past few years, I have been working with my colleagues in the ANC (Awareness of Neutropenia in Chemotherapy) study group towards defining as precisely as possible the risk factors associated with infection, fever, reduction in chemotherapy and unfavourable outcomes in cancer treatment. Or, looked at from another perspective, we have been working to identify the factors that lead to a favourable outcome.

Risk factors

Most clinicians who have been in practice for a long time will have had experiences of patients doing unexpectedly poorly or dying early in cancer treatment. This risk heightens concern about providing good care and emphasises the need to know the landmarks along the way to avoid this very unfavourable outcome.

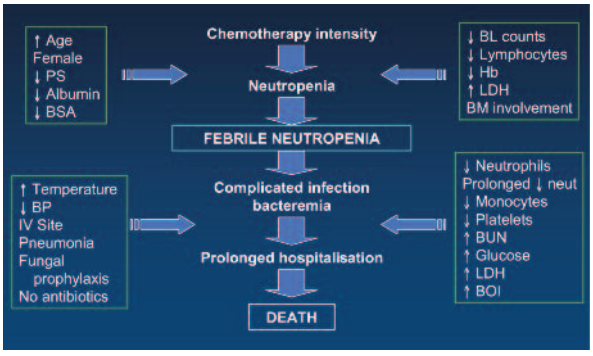
The figure below outlines the factors that are associated with neutropenia in cancer patients as well as the prognostic factors or risk factors for unfavourable outcomes in patients receiving chemotherapy.

One of the most important findings made by the ANC study group a few years ago is that the greatest risk of febrile neutropenia in a patient receiving a course of chemotherapy is with the first cycle. The figure opposite (*top*) shows the hazard ratio or risk of febrile neutropenia in patients with non-Hodgkin's lymphoma receiving standard-dose CHOP (cyclophosphamide, adriamycin, vincrinstine and prednisolone) or equivalent chemotherapy. There is a major peak of febrile neutropenia occurring about 10 days into treatment – at the time of maximum neutropenia with these standard drugs. Later cycles tend to be associated with less severe risk of febrile neutropenia.

Many factors may account for this observation, including dose reductions and adaptation of the haematopoietic system after an episode of neutropenia. It is important to realise that neutropenia is a predictable result of exposing the haematopoietic system to standard myelotoxic chemotherapy drugs. This pattern of febrile neutropenia peaking in the first cycle of treatment is observed across a wide spectrum of different types of cancer, indicating that it is a general pattern and that great vigilance is required with the first cycle of treatment with myelotoxic agents in all types of cancer.

In the course of our research, we looked at risk factors for neutropenia. The figure opposite (*bottom*) shows important and common risk factors, identified using a risk model based on 1246 patients with non-Hodgkin's lymphoma who were receiving CHOP. The easily identified risk factors, shown here for patients with lymphoma but more generally applicable, are: age, albumin (as a proxy for nutritional status), the intensity of chemotherapy, the starting white blood cell or neutrophil count, and the presence of hepatic disease. The more risk factors, the greater the risk. Being aware of

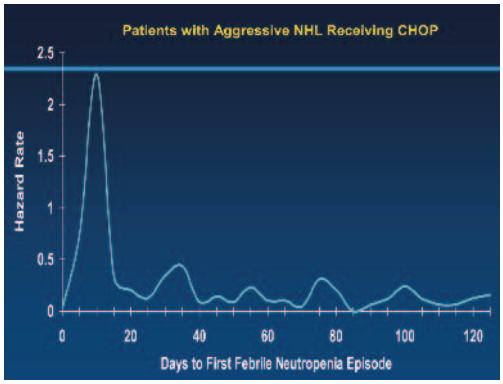
RISK FACTORS AND COMPLICATIONS



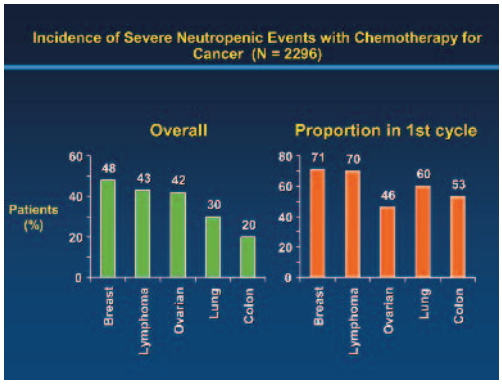
Knowing what to look out for is key to avoiding the worst outcomes

PS, performance status; BSA, body surface area; BP, blood pressure; BL counts, blood leukocyte counts; Hb, haemoglobin; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; BOI, burden of illness; *Source:* GH Lyman *The Oncologist* 2005; 10:427-437. Reproduced with permission of ALPHAMED PRESS

THE FIRST CYCLE CARRIES THE HIGHEST RISK



The greatest risk for febrile neutropenia comes 10 days after the start of chemotherapy in patients with aggressive non-Hodgkin's disease



In patients with the five most common cancers, the majority of severe neutropenic episodes (between 53% and 71%) occur with the first cycle

Source (left): Lyman GH, Morrison VA, Dale DC et al. Risk of febrile neutropenia among patients with intermediate grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. *Leukemia and Lymphoma* 2003, reprinted by permission of the publisher (Taylor & Francis Group, http://www.informaworld.ocm)

Source (right): Adapted from J Crawford et al. *J Natl Compr Canc Netw* 2008; 6:109–118

these risk factors helps health professionals to anticipate the problem of febrile neutropenia.

Multivariate analysis shows that age is a very important risk factor, and all older cancer patients need to be aware that they are at greater risk of febrile neutropenia when starting chemotherapy, usually not just because of their age but also because of the comorbidities that accompany the ageing process.

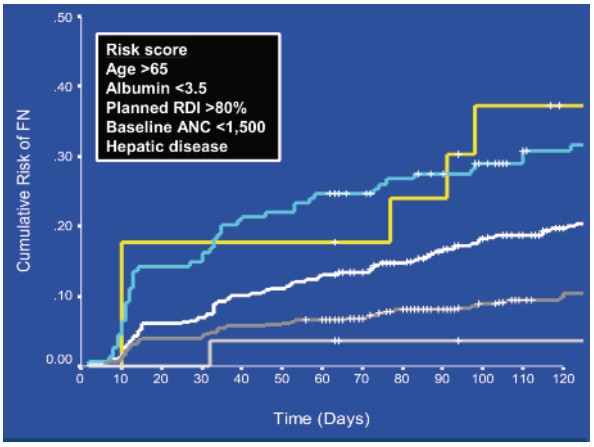
MORTALITY, MORBIDITY AND COSTS

Patients who have febrile neutropenia that makes them sick enough to be admitted to hospital have a high risk of an unfavourable outcome. A study by Kuderer et al, which looked at more than 40,000 adult cancer patients treated in large US hospitals, found a mortality rate of 9.5% (*Cancer* 2006, 106:2258). This increased to 21.4% in those with more than one comorbidity. Other risk factors for mortality were fungal infections, sepsis and pneumonia. Mortality is obviously a severe concern, but hospitalisation and prolonged illness also carry major healthcare costs.

Myelosuppressive chemotherapy-induced neutropenia causes a range of problems, including febrile neutropenia and increased risk of severe infection. It also leads to delays in chemotherapy doses and dose reductions. The dose may be reduced either by giving a smaller amount of drug, or by extending the time over which it is given, resulting in a reduction in dose intensity. Both can lead to reduced survival.

There are reasonably good data to indicate that dose intensity is very important. The strongest data come from studies in early-stage breast cancer. A retrospective study carried out by Bonadonna et al, following up patients for at least 20 years, showed that relapse-free survival and overall survival decreased in line with chemotherapy dose intensity (*NEJM* 1995, 332:901–906). Survival in a study by Pfreundschuh and colleagues of patients with non-Hodgkin's lymphoma (another chemotherapy-sensitive cancer) showed similar results (*Blood* 2004, 104:634–641). There may be some cancers where chemotherapy is less

CUMULATIVE RISK FACTORS



Five significant risk factors for febrile neutropenia have been identified – the more risk factors a patient has, the higher their risk of febrile neutropenia

RDI relative dose intensity, ANC absolute neutrophil count
Source: Personal communication, Lyman et al, ANC study group, Duke University, USA

MULTIVARIATE ANALYSIS OF RISK

Covariate	Adjusted odds ratio* (95% CI) All patients 6 cycles (n = 4,522)
Age > 60 years	2.28 (1.96-2.67)
Stage >III	1.18 (1.01–1.39)
ECOG performance status >2	1.28 (1.01–1.64)
Albumin <3.5 g/dL	1.26 (0.98–1.62)
Prophylactic G-CSF	0.70 (0.55–0.89)

An analysis of risk factors in patients whose treatment was reduced to less than 85% of recommended dose intensity showed that being aged over 60 was the biggest single risk factor

*Adjusted for year of treatment, planned duration of treatment and practice site

Source: GL Lyman et al. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkins's lymphoma: A nationwide study. *JCO* 2004; 22:4302-4311

effective, but overall it is clear that giving full-dose, or standard-dose, chemotherapy is the way to achieve the best outcome for patients.

It is very important to be aware that relative dose intensity (a measure of the delivered dose intensity as a proportion of the standard dose intensity) is often underreported in randomised controlled trials and long-term outcomes are also not reported. However, when data are available, we have found that dose reductions are very common. The strongest data suggest that a reduction in the dose to less than 85% of what would be predicted to be optimal therapy is quite common in many cancers (Dale et al, *JNCCN* 2003; 1:440-454).

A study of breast cancer adjuvant chemotherapy for a large US population showed that around 50% of patients received less than full-dose chemotherapy. This is a concern, and we should aim to optimise therapy by finding ways to give treatment at the dose that has been shown to be effective in randomised trials.

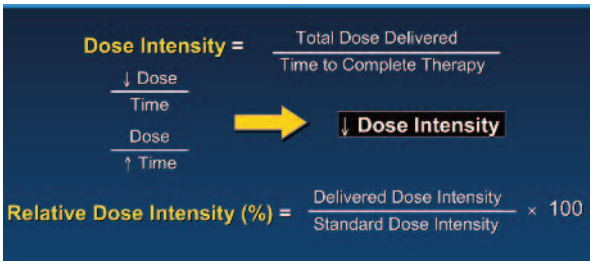
Management strategies

To reduce the risk of neutropenic events, including infections, and to avoid dose reductions in the course of giving cancer chemotherapy, our focus has been on prevention. Treatment of patients with febrile neutropenia admitted to hospital has improved modestly over the years, with better supportive care and better antibiotics, but problems remain, and prevention is the most important strategy to reduce the risk of undertreating or infections in the course of giving cancer chemotherapy.

There are three approaches:

- delay or reduce the drugs
- administer prophylactic antibiotics
- give haematopoietic growth factors or myeloid growth factors in a prophylactic strategy.

DOSE REDUCTIONS



Dose reduction

There is little or no evidence that using a dose below 85% of that recommended is favourable for any patient group, although it is a common strategy in palliative care to try to maintain a patient's quality of life and days that they have to live.

Prophylactic antibiotics

A large randomised trial conducted by Cullen et al., comparing the quinolone antibiotic levofloxacin with placebo in preventing infection associated with cancer chemotherapy in a large and diverse group of patients, mostly with solid tumours, showed that the antibiotic reduced the occurrence of febrile neutropenia. However, it did not reduce deaths (*NEJM* 2005, 353:988-998).

There are several issues associated with this approach, including that the risk of giving prophylactic antibiotics to the large numbers of patients undergoing treatment with cancer chemotherapy may result in the development of resistant organisms that might cause infections later in cancer treatment.

A second international study with levofloxacin in patients with cancer and neutropenia, carried out by Bucaneve and co-workers, also showed that it was effective in reducing febrile episodes (relative risk 76%), but there was no significant effect on infectious deaths or overall deaths (*NEJM* 2005, 353:977–987). The results show the benefits of antibiotics in reducing the number of bacteria in the short term. However, based on clinical experience, this is only a short-term effect, because the body surface is a rich place for bacteria and fungi to grow, and suppressing some organisms enables others to rapidly emerge.

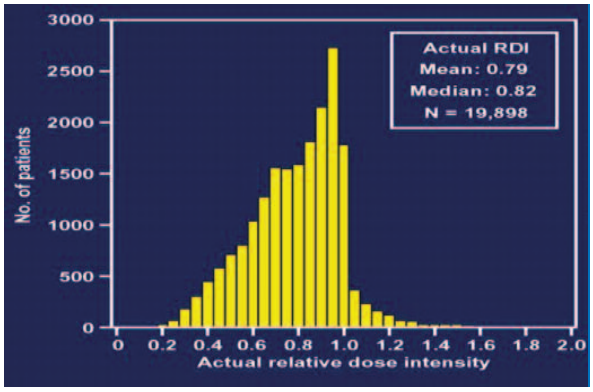
Haematopoietic growth factors

Haematopoietic growth factors have been a research interest of mine for a long time, both at basic and clinical levels. Colony stimulating factors, or

myeloid growth factors, were discovered in the 1960s, utilising a simple Petri dish culture system. Discovering how to grow blood cells *in vitro* was a dramatic event – very important in the history of haematology and in the development of modern medical oncology.

Probably the most important finding in this research was the discovery of the specific factors that regulate haematopoiesis. Out of this work came the drug we call G-CSF – granulocyte colony stimulating factor – which is a relatively small glycoprotein produced in many cell types in the body, in response to a range of stimuli including injury or infection. Over time, it was learned that the levels of G-CSF in the body regulate the production of neutrophils.

REDUCED DOSE INTENSITY IS COMMON



The number of breast cancer patients found to be on a reduced dose intensity is a cause for concern, given what is known about the impact of reductions in dose intensity on survival

Source: GL Lyman et al. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices. *JCO* 2003; 21:4523–4531. Reprinted with permission. © 2008 ASCO. All rights reserved.

We now know that levels of G-CSF increase abruptly when a patient develops an infection. However, becoming gradually neutropenic – as occurs with cancer chemotherapy – does not usually cause G-CSF levels to rise until neutrophils have reached a very low level. The problem with the onset of neutropenia after cancer chemotherapy is that the signal to recover neutrophils occurs late, and gradual recovery occurs if you wait for this natural response.

This understanding led to the development of an important clinical use of G-CSF as a drug to accelerate neutrophil recovery after chemotherapy. G-CSF has often been compared to GM-CSF – granulocyte-macrophage colony stimulating factor – because it had similar effects in the early studies in the Petri dish model. However, GM-CSF is a distinctly different molecule and is produced by different cells, particularly T-cells and monocytes. Experimental studies have shown that deficiencies of G-CSF cause neutropenia, but deficiencies of GM-CSF do not. GM-CSF is a very different agent biologically, with different clinical effects.

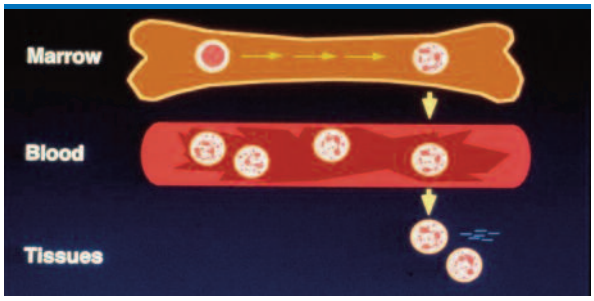
G-CSF/FILGRASTIM

G-CSF, or filgrastim (a G-CSF analogue), has a helical structure, which gives the molecule its three-dimensional shape, which is key for interacting with its receptor on myeloid cells. G-CSF acts specifically on myeloid cells that have a receptor for the molecule. G-CSF stimulates neutrophil proliferation and accelerates the delivery of neutrophils from the bone marrow into the blood. Normal neutrophil development and deployment occurs at three levels. In the marrow, cells develop from stem cells to mature neutrophils. In the blood, neutrophils flow along with the red cells, but they stick at sites of inflammation. In the tissues, they migrate to fulfil their function in the containment and killing of bacteria and in mounting a response to infection.

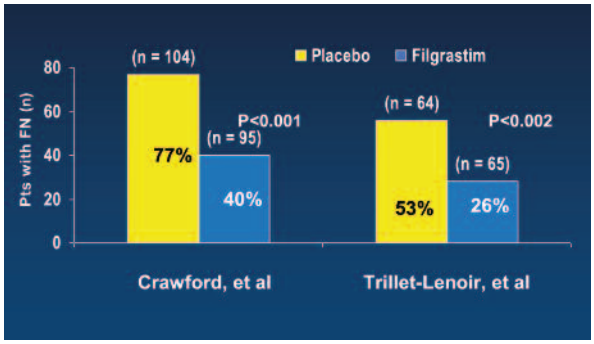
In studies to understand the role of G-CSF, we gave these agents to healthy young and elderly volunteers. We were interested in the ageing process and whether older people would respond less well. The studies showed that age does not block the response to G-CSF. The bottom line is that a wide range of patients with different comorbidities and varying in many other factors, including age, all respond to G-CSF quite well, if they have haematopoietic cells in their marrow that are capable of responding.

An important point in terms of oncology practice is the effect of G-CSF and GM-CSF on marrow transit time. In our studies we looked at how these agents stimulate the flow of cells through the bone marrow. With no drug, the time for production of a neutrophil, from the last stage of dividing cells to a mature neutrophil in the marrow and its entry

NORMAL NEUTROPHIL KINETICS



BENEFIT OF G-CSF/FILGRASTIM



G-CSF/filgrastim has been shown to result in a significant reduction in cases of febrile neutropenia among cancer patients receiving chemotherapy

Source: Adapted from J Crawford et al. *NEJM* 1991; 325:164–170; V Trillet-Lenoir et al. *Eur J Cancer* 1993; 29A:319-324

into the blood, was about six days. Giving G-CSF accelerates the time for maturation of neutrophils and their entry into the blood. We showed that G-CSF can reduce the time for maturation and deployment of neutrophils by about 50%, reducing the time for cells to transit through the marrow to the blood from approximately six to three days. By stimulating neutrophil production and entry into the blood, G-CSF helps to increase the accumulation of these cells at sites of infection and inflammation.

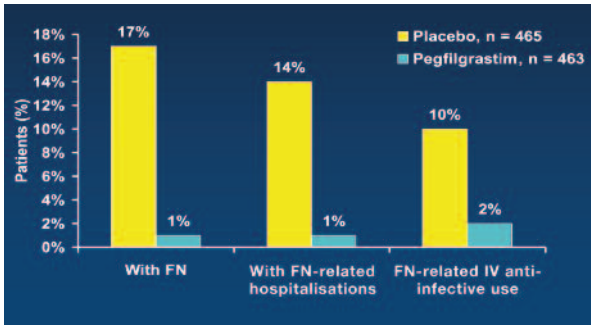
Crawford and Trillet-Lenoir and their co-workers were early investigators of G-CSF in cancer chemotherapy; their work emphasises the principles mentioned above. Their reports were the first to demonstrate a reduction in the occurrence of febrile neutropenia in randomised controlled trials (*NEJM* 1991, 325: 164-170; *EJC* 1993, 29A:319-324). Their studies showed that G-CSF accelerates neutrophil recovery after chemotherapy; the return of blood neutrophils was much faster in the G-CSF treated patients.

In subsequent clinical trials, Timmer-Bonte and others demonstrated the same effects of G-CSF use to prevent febrile neutropenia with less myelotoxic chemotherapy regimens. For example, in the trial by Crawford et al, there was approximately a 60% risk of febrile neutropenia. In the Timmer-Bonte trial, patients had approximately a 30% risk of febrile neutropenia, and G-CSF treatment also reduced this risk by about 50% (*Proc ASCO* 2004, 23:726).

This is such an important development that there have been many efforts to improve on it over the years. The most valuable was the development of the pegylated molecule (pegfilgrastim), adding polyethylene glycol, making the G-CSF molecule bigger and thereby reducing its renal clearance.

A clinical trial carried out by Vogel and co-workers showed that using pegfilgrastim in patients who were treated with less intensive chemotherapy and whose risk of febrile neutropenia was only approximately 20% virtually eliminated the risk of febrile neutropenia (*JCO* 2005, 23:1178-1184).

BENEFIT OF CSF/PEGFILGRASTIM



Pegfilgrastim virtually eliminated febrile neutropenia in cancer patients at 20% risk of developing the condition

Source: Vogel et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study. *JCO* 2005; 23:1178–1184

Issues in the use of G-CSF

Although these data are very sound and we can rely on them to set the guidelines in cancer practice, many questions remain. These include whether the dose of G-CSF can be reduced, whether there is a difference between G-CSF and pegylated G-CSF, the place of GM-CSF versus G-CSF, and the use of G-CSF with other drugs such as corticosteroids, which also raise neutrophil counts. There are also questions about timing – should we give G-CSF early, late, or for a few days? Many of these questions have general answers, although most have not been subjected to large randomised trials.

Because the myeloid growth factors G-CSF and GM-CSF can stimulate proliferation of both the normal and leukaemic cells, researchers and physicians have been concerned about the potential risks associated with their use. Recently the ANC study group performed a meta-analysis to investigate the risk of myelodysplasia and leukaemia associated with the use of G-CSF as part of supportive care for patients

receiving cancer chemotherapy. A systematic review of randomised trials compared the outcomes for cancer patients receiving either chemotherapy alone or chemotherapy plus G-CSF. The study showed a small but statistically significant increase in the occurrence of leukaemia in patients who were randomised to receive G-CSF. On the other hand, overall mortality rates were lower in the patients treated with G-CSF. The G-CSF treated patients also receive more chemotherapy – a finding that complicates the interpretation of these data, because many commonly used myelotoxic drugs can cause leukaemia. There are also other limitations that make these data and similar studies difficult to interpret. The trials were obviously not conducted to see whether treatment causes leukaemia; it is only observed as an adverse effect. There were also variations between trials in the way adverse effects were described and how long the patients were followed before the results of the trial were reported. Some of the 'control' patients may also have been given G-CSF, if they seemed to need it. This study was presented and discussed at the American Society of Hematology meeting in December 2009.

Nevertheless, the increase in leukaemia with G-CSF treatment was about 0.4% and supportive care with G-CSF is associated with an absolute reduction in all-cause mortality of about 3%–4%.

ASCO guidelines on the use of white blood cell growth factors recommend that G-CSF should be used when there is a risk of febrile neutropenia of greater than 20%, unless the treatment is symptomatic or palliative, when dose reduction is usually appropriate. The guidelines also say that primary prophylaxis – the use of CSFs for prevention in the first cycle of treatment – should always be considered for older patients, or where the patient's medical history or other disease characteristics suggest that there is substantial risk of febrile neutropenia.

The National Comprehensive Cancer Network (NCCN) CSF guidelines recommend focusing on three aspects of each patient when determining risk for febrile neutropenia:

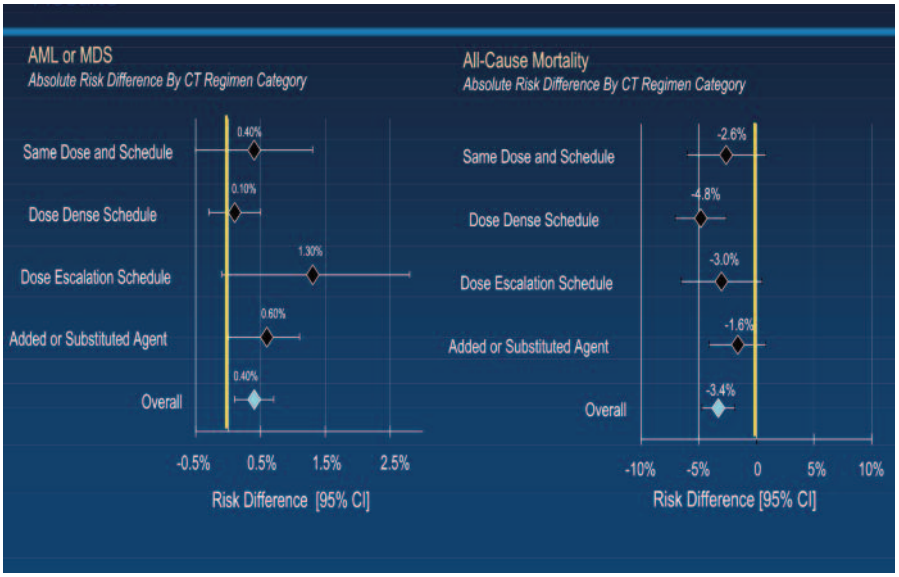
- Patient-related aspects: age, gender, performance and nutritional status, comorbidities,
- Treatment-related aspects: neutropenia, drugs – anthracyclines, relative dose intensity,
- Cancer-related aspects: some cancers, including haematological malignancies and lung cancer, and all cancers at advanced stage, predispose patients to infections.

The NCCN growth factor algorithm for prophylaxis with growth factors addresses whether chemotherapy is curative, intended to prolong survival or to help with symptom management, or palliative. For cases with a >20% risk of febrile neutropenia with chemotherapy, the CSFs have a benefit that should be considered. CSFs should not be used where the estimated risk is less. In summary:

- Use G-CSF if there is a high risk of febrile neutropenia (>20%) with curative intent, to prolong survival, to improve quality of life.
- Consider G-CSF if risk of febrile neutropenia is 10%–20%.
- Do not use G-CSF if risk of febrile neutropenia is <10%.

Each patient should be assessed for their risk of febrile neutropenia, and decisions on whether to give CSFs should be based on this risk.

BENEFITS OUTWEIGH RISKS



A review of randomised controlled trials showed a small but significant rise in leukaemia among cancer patients receiving G-CSF as supportive care, but this was far outweighed by the fall in mortality

Source: American Society of Hematology Meeting, December 2009

Jeffrey Crawford (JC), of the Duke University Medical Center, in Durham, North Carolina, USA, explored some of the issues further with David Dale (DD).

JC: *Can we generalise that the standard dose of chemotherapy is standard for all patients, or do we need to think about differences in patients in terms of tolerance to chemotherapy?*
DD: It is important to see the differences between patients and patient groups. Age is a critical differentiating factor: it bundles together comorbidities and many other factors. Patients over the age of 65, or certainly over age 70, should always be considered at risk and therefore potential candidates for some prophylactic strategy.
A second differentiating factor is the patient's blood cell counts. Patients who have evidence of previous haemotoxicity from drugs or disease are at greater risk, particularly if they have a low white cell count or low neutrophil count. The general physical examination and basis blood count also help us to easily identify patients at greater risk of febrile neutropenia and other complications.
Another differentiating factor is the specific drug to be given in the planned chemotherapy regimen. This is a complicated area, because there are so many drugs and combinations. The NCCN guidelines (readily available at nccn.org) provide the best information available about relative risk of neutropenia and severe neutropenia with different drugs.
JC: *Should there be differences in dosing based on different ethnic populations?*
DD: There are probably ethnic differences, but we do not know very much about them. For example, the African/American population tends to have somewhat lower baseline white blood cell and neutrophil counts than other groups, but seems to tolerate chemotherapy equally well.
JC: *How should one calculate the dose of chemotherapy for an obese patient?*
DD: This is another confusing area. We generally use the body surface area or ideal body weight instead of body mass, as the index for dosing, but there is a point at which there is considerable uncertainty.
JC: Larger patients tend to be underdosed if you use the ideal body weight rather than the actual body weight when delivering standard chemotherapy doses. Even though they are getting larger total doses, the body surface area corrects for most of that. One of the concerns about the poor outcomes for obese women with adjuvant breast cancer may be that they are relatively underdosed. Some data suggest that they have less neutropenia, so you should at least use the standard of total body weight and surface area in your calculations.
There is also literature around about the importance of neutropenia as a surrogate endpoint for chemotherapy effectiveness. There are data on lymphoma and other settings that patients who develop some degree of neutropenia have a better outcome than those who do not. The same has been shown in advanced-stage lung cancer. This gets back to the question, if we could individualise therapy, what would be the right dose? Presumably what is happening is that there is enough pharmacogenomic variation in how individuals handle drugs that one dose probably does not fit all. But knowing the dose that achieves cytotoxic effect on the patient and that treats their tumour requires further study.
JC: *Can you comment on the functional effects of G-CSF and GM-CSF? You spoke about neutrophil numbers, but what are the functional effects when these cytokines are active in our bodies?*
DD: This is a very interesting area. G-CSF has many effects beyond stimulating neutrophil production. It also activates many processes in the cell. For example, it stimulates the formation of the enzymes that go into the granules of neutrophils, particularly the primary granules that are involved with the killing of organisms. G-CSF also 'primes' neutrophils, so that they have a greater metabolic burst and greater oxygen and glucose consumption when they are exposed to bacteria or other foreign particles. All of these changes can be seen as part of the host response to infection to enhance the body's capacity to deal with an infection.

Conclusions

Neutropenia, febrile neutropenia and reductions in chemotherapy dosing remain serious problems in medical oncology. Delivering chemotherapy at standard doses and on schedule is important in optimising outcomes. There is good physiological and clinical evidence for the use of G-CSF to prevent febrile neutropenia and ameliorate the myelotoxicities of cancer chemotherapy. Evidence-based medicine and clinical guidelines support the use of G-CSF to prevent chemotherapy-induced neutropenia. Prophylactic antibiotics are alternatives to the CSFs. Treatment of febrile neutropenia, when it occurs, requires very careful attention to the patient, prompt antibiotic therapy and good hospital care.