The clinical use of granulocyte-colony stimulating factor

Introduction

Chemotherapy-induced neutropenia is a major risk factor for infection-related morbidity and mortality as well as a significant dose-limiting toxicity in cancer treatment (reviewed in Welsh and Strauss, 2012a). Febrile neutropenia is a relatively frequent event in cancer patients treated with chemotherapy, and is defined as a rise in axillary temperature to >38.0°C for a duration of >1 hour, or >38.5°C on one occasion, while having an absolute neutrophil count of <1.0x10^9/litre.

The incidence of febrile episodes after intensive myelosuppressive chemotherapy for haematological malignancy lies in the range of 70–100% depending on the intensiveness of therapy (Martin et al, 2003; Danai et al, 2006; Moerer and Quintel, 2009). Approximately 40% of these patients developed severe sepsis and septic shock. Patients developing severe neutropenia (grade 3/4, i.e. <1.0 x10^9/litre) or febrile neutropenia during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy. Such changes in planned chemotherapy may have serious impacts on the outcome of treatment, particularly when the intention of treatment is either curative or to prolong survival (Aapro et al, 2011).

To enable oncologists and haemato-oncologists to avoid potentially life-threatening treatment-related toxicity while maintaining the correct dose of chemotherapy and relative dose intensity or density, granulocyte-colony stimulating factor may be used as an adjunct to chemotherapy. The term primary prophylaxis is used when granulocyte-colony stimulating factor is given prospectively to support dose-dense and dose-intense chemotherapy regimens with the aim of reducing the risk of patients developing neutropenia caused by chemotherapy.

Granulocyte-colony stimulating factor can also be administered after an episode of neutropenic sepsis, i.e. with subsequent cycles of chemotherapy, to maintain dose intensity, which is known as secondary prophylaxis. Additionally, granulocyte-colony stimulating factor can be used therapeutically to aid recovery of the bone marrow during an episode of neutropenia, and is also used to mobilize peripheral stem cells for harvesting, e.g. for use in autologous or allogeneic stem cell transplants. These uses are discussed in greater detail later in this review.

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Granulocyte colony-stimulating factor

Granulocyte colony-stimulating factor is a cytokine that normally acts in the bone marrow microenvironment to stimulate blood cell formation. It selectively promotes growth and maturation of neutrophil progenitor cells. The administration of granulocyte-colony stimulating factor to humans results in a dose-dependent increase in circulating neutrophils mainly because it has a reduced transit time from stem cell to mature neutrophil (Griffin, 2001).

Granulocyte-colony stimulating factor receptors are present on precursor cells in the bone marrow. By binding to these receptors, granulocyte-colony stimulating factor initiates proliferation and differentiation into mature granulocytes, and also stimulates bone marrow cell release into the circulation. In addition to growth promotion, granulocyte-colony stimulating factor also effects phagocytosis, motility, bactericidal activity and surface molecule expression of neutrophils and monocytes (Carulli, 1997; Fazzi et al, 2007). Therefore, granulocyte-colony stimulating factor can be used to treat neutropenia as a result of not only shortening a neutropenic episode but also by increasing the anti-infectious capacity of myeloid blood cells.

This article explains the appropriate use of granulocyte-colony stimulating factor (focussing on oncology and haemato-oncology patients) and provides an understanding of when granulocyte-colony stimulating factor use should be considered. However, granulocyte-colony stimulating factor should only be used following specialist advice from either a specialist registrar or consultant.

Commercially available granulocyte-colony stimulating factor products

Several types of granulocyte-colony stimulating factor are available commercially. Evidence suggests that filgrastim, lenograstim and pegfilgrastim have equal clinical efficacy and can be used to prevent febrile neutropenia and febrile neutropenia-related complications (Aapro et al, 2011). *Table 1* lists important proper-

Table 1. Commercially available granulocyte-colony stimulating factors

Type of G-CSF	Timing of initiation for prophylactic use	Dose	Duration	Cost*
Filgrastim	24–72 hours post chemotherapy	5 μg/kg/day subcutaneously	Until neutrophil counts have recovered	300 μg = £52.71
				960 μg =£84.06
Lenograstim	24 hours post chemotherapy	Body surface area <1.8 m^2 = 263 μg subcutaneously	Until neutrophil counts have recovered	263 μg = £62.54
		Body surface area 1.9–2.4 m^2 = 368 μg subcutaneously		368 μg = £102.65
Pegfilgrastim (pegylated G-CSF)	24 hours post chemotherapy	6 mg subcutaneously	Single dose in each cycle	6 mg = £686.38

GCSF = granulocyte-colony stimulating factor. * according to the British National Formulary, January 2014 (www.bnf.org)

ties of each of these agents. Filgrastim biosimilars are also approved for use in Europe and may be recommended by individual hospital guidelines.

Most forms of granulocyte-colony stimulating factor, including biosimilars, are administered by a course of daily subcutaneous injections. Pegfilgrastim is prepared by coupling a 20 kDa polyethylene glycol (PEG) molecule to the N-terminus of the filgrastim protein. This increases its half-life to 15–80 hours, which is significantly longer than the parent filgrastim, whose half-life is 3–4 hours (Ho and Gibaldi, 2003). Thus, pegfilgrastim need only be administered once per chemotherapy cycle. This patient benefit has to be weighed against significant higher cost with the pegylated agent. Choice of formulation remains a matter for individual clinical judgement and varies between hospitals according to local prescribing guidelines. However, evidence from multiple low level studies derived from audit data and clinical practice suggests that some patients receive suboptimal treatment when using daily granulocyte-colony stimulating factors (as a result of missed doses), therefore the use of pegfilgrastim may avoid this problem.

Indications for the use of granulocyte-colony stimulating factor

Several examples suggest that higher dose chemotherapy given over a shorter time period (so-called dose-dense chemotherapy) is associated with survival benefits over standard regimens. A meta-analysis has been performed combining data from 17 clinical trials involving 3493 adult cancer patients who were being treated with chemotherapy (Kuderer et al, 2007). In all the trials, patients were assigned randomly to receive granulocyte-colony stimulating factor, placebo, or no additional treatment. Febrile neutropenia occurred one or more times in 22.4% patients treated with granulocyte-colony stimulating factor, compared with 39.5% patients who received a placebo or no granulocyte-colony stimulating factor treatment. Granulocyte-colony stimulating factor reduced the risk of febrile neutropenia regardless of the type of cancer or the type of granulocyte-colony stimulating factor the patient received. Importantly, fewer patients treated with granulocyte-colony stimulating factor died while receiving chemotherapy (3.5% *vs* 5.7%) or died specifically from infection (1.5% *vs* 2.8%).

Although the use of granulocyte-colony stimulating factor with chemotherapy reduces the incidence of febrile neutropenia and its related morbidity and mortality for a high proportion of patients receiving chemotherapy, the risk or neutropenia is low so routine use of granulocyte-colony stimulating factor is confined to those patients at high risk of febrile neutropenia or neutropenic complications. This is discussed in more detail below. Several sets of international endorsed guidelines (including the American Society of Clinical Oncology, European Organization for Research and Treatment of Cancer and European Society of Medical Oncology guidelines) are available which enable the physician to identify patients who will be benefit from the use of granulocyte-colony stimulating factor.

Primary prophylaxis

The current guidelines produced by the British Committee for Standards in Haematology (Pagliuca et al, 2003) indicate that the febrile neutropenic risk has to be 40% or greater to be regarded as 'high'. However, the updated American Society of Clinical Oncology and European Organization for Research and Treatment of Cancer guidelines (Smith et al, 2006; Aapro et al, 2011) recommend consideration of granulocyte-colony stimulating factor where the risk of febrile neutropenia is 20% or higher, which has been adopted as the trigger for granulocyte-colony stimulating factor use by most hospitals in the UK. Granulocyte-colony stimulating factor is generally not indicated when risk of febrile neutropenia is less than 10%. In between these risk groups (10–20% risk), primary prophylaxis may be considered where appropriate by the oncologist or haemato-oncologist prescribing the chemotherapy.

The risk of febrile neutropenia is defined in terms of patient-related factors (*Table 2*) or chemotherapy-related factors (examples of which are described below). Individual patient risk needs to be considered using these guidelines and granulocyte-colony stimulating factor should only be prescribed after discussion with a specialist oncology or haematology doctor.

Commonly used chemotherapy regimens with an overall risk of febrile neutropenia of >20% include anthracycline- and taxane-containing regimens such as those used for treatment of breast cancer (e.g. T-FEC which combines fluorouracil, epirubicin, cyclophosphamide and docetaxel). Other examples include CHOP chemotherapy (combining cyclophosphamide, doxorubicin, vincristine and prednisone) which is used for treatment of non-Hodgkin's lymphoma (Aapro et al, 2011) in addition to the docetaxel, cisplatin and 5-fluorouracil (DCF/TPF) regimen used for treatment of gastric (Ajani, 2008) and head and neck cancer (Vermorken et al, 2007; Posner and Vermorken, 2008).

However, it should be noted that the routine use of granulocyte-colony stimulating factor with such regimens does not entirely eliminate the risk of neutropenia in these patients. Therefore it is advised that caution is used if such patients present to medical professionals with symptoms of infection or sepsis, and local protocols for the treatment of neutropenic sepsis should be immediately instigated without waiting to measure the neutrophil count. The recognition, diagnosis and management of neutropenic sepsis has been reviewed (Welsh and Strauss, 2012a, b) and should involve local acute oncology services. It is important to note that both national and international guidelines stipulate that if a

Table 2. Patient-related risk factors which increase the risk of febrile neutropenia

Age >65 years
Poor performance status
Previous episode of febrile neutropenia
Extensive prior treatment (with either chemotherapy, or radiotherapy – particularly to areas containing large amounts of bone marrow, e.g. pelvis)
Pre-existing neutropenia (e.g. as a result of bone marrow involvement by tumour)
Poor nutritional status
The presence of open wound and active infection
More advanced cancer
Other medical comorbidities which may increase the risk (or consequences) of sepsis

patient has suspected neutropenic sepsis he/she must receive appropriate antibiotics within 1 hour of presentation.

The recommendations for prescribing granulocyte-colony stimulating factor as primary prophylaxis (according to most guidelines in the UK) are:

For risk of febrile neutropenia >20%:

- Prescribe daily granulocyte-colony stimulating factor for 7 days

For risk of febrile neutropenia 10–20%:

- If considered appropriate, prescribe daily granulocyte-colony stimulating factor for 7 days

Generally:

- Dose the patient on daily granulocyte-colony stimulating factor according to patient weight
- Consider long-acting granulocyte-colony stimulating factor (pegfilgrastim) in psychosocial situations that make daily granulocyte-colony stimulating factor difficult or impractical (additionally pegfilgrastim is often given in teenage and young adult patients receiving chemotherapy).

Secondary prophylaxis

Secondary prophylaxis is used following an episode of neutropenic sepsis to avoid repeated episodes, maintain dose intensity and/or to prevent treatment delays. This may be important, particularly in treatment of lymphoma, adjuvant treatment of breast cancer, germ cell cancer, and also in some sarcomas (particularly in teenage and young adolescents) where intensive programmes of chemotherapy are used, usually where treatment is being given with curative intent, and where reduction of intensity has been shown to have a negative impact on outcome. However, in most patients undergoing palliative chemotherapy, there is little evidence that maintaining dose intensity has any impact on survival and dose reductions are considered following episodes of febrile neutropenia or prolonged neutropenia with previous cycles in order to manage patient safety in preference to use of growth factors in most cases.

In principle, secondary prophylaxis is usually considered in patients with curable cancers and when dose reduction is believed to alter disease-free survival or treatment outcome. However, despite the above guidelines, it is noted that clinical practice may be changing. For example, approximately 40% of patients receiving FOLFIRINOX chemotherapy (5-fluorouracil, irinotecan and oxaliplatin) for palliative treatment of metastatic pancreatic adenocarcinoma now receive granulocyte-colony stimulating factor (Conroy et al, 2011). Studies have also shown that myelosuppressive chemotherapy regimens, including taxane-containing (neo-) adjuvant regimens, can be safely delivered with the addition of granulocyte-colony stimulating factor in elderly patients who often previously have not been considered as candidates for full-dose aggressive chemotherapy (Balducci et al, 2007; Loibl et al, 2008).

Therapeutic use of granulocyte-colony stimulating factor

Granulocyte-colony stimulating factor is not routinely used in patients who become neutropenic and are afebrile, or to treat uncomplicated febrile neutropenia as an adjunct to antibiotic therapy, unless they have profound or protracted neutropenia (absolute neutrophil count <0.1x10^9/litre). However, it is recommended for patients with febrile neutropenia who are at high risk of infection-induced complications and likely to have poor clinical outcome. *Table 3* summarizes prognostic factors predictive of poor outcome when granulocyte-colony stimulating factor use may be considered.

Side effects of granulocyte-colony stimulating factor

Granulocyte-colony stimulating factor can be associated with drug-induced side effects. They include bone pain, gastrointestinal disturbances, anorexia, headache, asthenia, fever, musculoskeletal pain, rash, alopecia, injection site reactions and leucocytosis. Less frequent side effects include chest pain, hypersensitivity reactions and arthralgia. There have been reports of pulmonary infiltrates leading to acute respiratory distress syndrome (Karlin et al, 2005), so treatment should be discontinued if patients develop signs of pulmonary infiltration on chest X-ray. As with all patients on chemotherapy, it is advised that full blood counts, including differential white cell and platelet counts, should be monitored throughout treatment including granulocyte-colony stimulating factor. No specific guidelines exist for how regularly full blood counts should be measured as the frequency will be determined by the indication for use of granulocyte-colony stimulating factor.

Recombinant human growth factors are to be used with caution in patients with premalignant or malignant myeloid conditions and advice should be sought from a haematologist if granulocyte-colony stimulating factor is being considered.

Table 3. Prognostic factors that are predictive of poor outcome in febrile neutropenic patients

Profound (<0.1x10^9/litre) neutropenia
Age >65 years
Uncontrolled primary disease
Pneumonia
Hypotension
Multi-organ failure
Invasive fungal infection
Being hospitalized at the time of development of fever

KEY POINTS

- Febrile neutropenia is defined as a rise in axillary temperature to >38.0°C for >1 hour, or over 38.5°C on one occasion, in a patient with an absolute neutrophil count of <1.0 x 10^9/litre.
- Febrile neutropenia is one of the most common side effects of cytotoxic chemotherapy.
- Appropriate use of granulocyte-colony stimulating factor prevents febrile neutropenia and febrile neutropenia-related complications.
- Primary prophylaxis refers to granulocyte-colony stimulating factor given prospectively to support dose-dense and dose-intense chemotherapy regimens with the aim of reducing the risk of patients developing neutropenia during or following chemotherapy.
- Secondary prophylaxis refers to granulocyte-colony stimulating factor administered after an episode of neutropenic sepsis, i.e. with subsequent cycles of chemotherapy, to avoid repeated episodes and maintain dose intensity.

Additionally, it should be noted that, on the basis of retrospective data, it has been suggested that the use of granulocyte-colony stimulating factor might lead to a small increase in the risk of secondary malignancies. For example, 1.77% of patients with breast cancer who were treated with adjuvant chemotherapy with granulocyte-colony stimulating factor support developed acute myeloid leukaemia or myelodysplastic syndrome, compared to 1.04% of those who had not received granulocyte-colony stimulating factor (hazard ratio 2.14, 95% confidence interval 1.12–4.08) (Hershman_ et al, 2007). However, these data are difficult to interpret as anthracyclines and cyclophosphamide chemotherapy is also known to increase the risk of second malignancies in a dose-related manner and granulocyte-colony stimulating factor may have allowed higher chemotherapy doses to be delivered, thereby confounding the analysis (Praga et al, 2005).

Conclusions

Febrile neutropenia is a frequent event in cancer patients receiving chemotherapy. It is also the most common life-threatening and dose-limiting side effect of cytotoxic chemotherapy. Granulocyte-colony stimulating factor is efficacious in both preventing and treating chemotherapy-induced neutropenia. Prophylaxis (primary and secondary) with granulocyte-colony stimulating factor reduces the duration and severity of chemotherapy-induced neutropenia, enabling regimens to be delivered at optimal intensity and density, while avoiding toxicity.

It is recommended that the decision to use granulocyte-colony stimulating factor complies with international and local hospital guidelines. Particular attention should be given to patient-related risk factors which increase the risk of febrile neutropenia, therapeutic regimens which increase the risk of febrile neutropenia and patient prognostic factors predictive of poor outcome from febrile neutropenia. It is also important to recognize that the prophylactic use of granulocyte-colony stimulating factor does not guarantee that patients do not become neutropenic and until neutropenic sepsis is ruled out, at-risk patients should automatically be treated according to local acute oncology guidelines, aiming for antibiotic administration 'door-to-needle time' of less than 1 hour in patients with neutropenic sepsis. **BJHM**

Conflict of interest: none.

TOP TIPS

- Febrile neutropenia is one of the most commonly encountered complications in patients receiving chemotherapy.
- Granulocyte-colony stimulating factor is a cytokine that normally acts in the bone marrow microenvironment to stimulate blood cell formation to selectively promote growth and maturation of neutrophil progenitor cells.
- Granulocyte-colony stimulating factor is widely used in oncology and haematology practice as primary and secondary prophylaxis to enable physicians to maintain the correct dose and relative dose intensity of chemotherapy.
- Several types of granulocyte-colony stimulating factors are available. Its use should be considered only after obtaining specialist advice.
- Common side effects of granulocyte-colony stimulating factor are bone pain, gastrointestinal disturbance, leucocytosis, fever, anorexia, and reactions at the injection site.

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