Management of Chemotherapy-induced Neutropoenia

a report by

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During the past several years, a number of novel targeted anticancer drugs have been integrated into clinical practice. Despite the efficacy and variety of new agents, traditional myelosuppressive chemotherapy remains the backbone of cancer treatment. In addition, the new biologicals often increase myelotoxicity when added to standard chemotherapy regimens. Therefore, myelosuppression remains the most common toxicity encountered in the oncology clinic today and this complication is likely to remain a serious problem indefinitely. Chemotherapy-induced neutropoenia (CIN) is defined clinically as an absolute neutrophil count (ANC) of $<1.0x10^9$/l, at which point the risk of infection begins to rise. This risk is related both to the depth and duration of neutropoenia.[1] An ANC below $0.5x10^9$/l is therefore considered severe neutropoenia (SN) and febrile neutropoenia (FN) is defined as a temperature >38.2°C on two determinations with an ANC $<0.5x10^9$/l, which indicates a high likelihood of a localised or systemic infection. FN requires prompt intervention with broad spectrum antibiotics until endogenous recovery of the bone marrow occurs. During FN, patients are at risk of overwhelming infection in the absence of neutrophils and anti-infectives.

Despite the availability of broad-spectrum antibiotics, FN continues to have significant consequences including increased morbidity, hospitalisation, mortality and excessive cost. Even in recent years, mortality from FN has remained high when patients have co-morbidities. Reviews of hospitalised patients have clearly documented risk factors for complications of FN.[2,3] CIN and FN occur across a wide spectrum of patients who harbour heterogeneous disease and co-morbid conditions. Clearly, some patients are at low risk of developing serious complications from FN and perhaps can be spared intensive therapy. The Multinational Association for Supportive Care in Cancer (MASCC) risk index was developed in 2000 to be a validated, clinically useful tool to help sort patients into low- and high-risk groups.[4] Risk factors including symptom burden, chronic obstructive pulmonary disease (COPD), hypotension, solid tumoir histology, outpatient status, dehydration and age <60 years were defined as significant in a derivation set of several hundred patients. The MASCC score can distinguish patients at low versus high risk with a high positive predictive value.

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Subsequent evaluation of the MASCC index has validated the prognostic accuracy of the score in other patient populations.[5] The tool has proven clinical utility in allowing patients at low risk to be treated successfully with oral antibiotics and be followed as outpatients.[6,7] Attempts to incorporate blood inflammatory marker analysis into the clinical scale did not add to the predictive value of the MASCC score.[8] A risk-adapted strategy utilising the MASCC index allows a significant fraction of low-risk patients to be treated in the outpatient setting when follow-up is careful and adherence to medical care is high.[9] Nonetheless, the majority of patients with FN do require at least some inpatient observation and treatment with intravenous antibiotics. The costs associated with FN and its treatment are substantial and are not limited to the direct cost of hospitalisations. It is likely that even separating out low-risk patients for outpatient treatment will not have a great impact on costs, which are driven mostly by the fraction of patients who have severe complications.[10] Health systems may therefore be obligated to expend increased resources caring for patients with FN.

Risk of SN and FN from chemotherapy depends on several factors, most importantly the myelosuppressive intensity of the chemotherapy regimen utilised. One way to reduce the risk of CIN is to reduce the drug dosage delivered. However, substantial direct and retrospective evidence suggests that reduction in relative dose intensity is deleterious in terms of disease-free outcome and overall survival in the curative and perhaps life-prolonging indications for chemotherapy.[11,12] CIN is a common cause of chemotherapy dose delay and dose reduction,[13] and prolonged recovery from FN may compromise subsequent cycle delivery of full dose on schedule.

Colony-stimulating Factors for Chemotherapy-induced Neutropoenia

An alternative to reducing dose is supportive care utilising granulocyte colony-stimulating factor (G-CSF) to stimulate the proliferation, differentiation, survival and functionability of myeloid cells, resulting in an increase in circulating neutrophils. Recombinant G-CSF has been available since the early 1990s and has transformed the approach to CIN. Recombinant human G-CSF is marketed as filgrastim (Neupogen), an *Escherichia coli*-derived non-glycosylated protein, and lenograstim (Granocyte), a glycosylated version derived from Chinese hamster ovary cells. Regulatory approval of filgrastim occurred after a US multicentre double-blind placebo-controlled study demonstrated a reduction in FN from 77 to 40% in small-cell lung cancer patients receiving G-CSF after intensive myelosuppressive chemotherapy.[14] In addition, the incidence and duration of SN, days in hospital and days of antibiotics, and documented infection were also reduced significantly. These results were confirmed in a European study with a similar proportional benefit.[10] Multiple other trials in a variety of disease settings and with base FN rates of 30–50% without growth factor support show similar reduction in FN rates and other markers of CIN when filgrastim was utilised after myelosuppressive chemotherapy.[16–18]

A long-acting form of filgrastim was developed by adding a polyethylene glycol molecule to the N-terminus of the G-CSF protein, which greatly increases the hydrodynamic size of the molecule, preventing renal clearance while preserving activity. Pegfilgrastim (Neulasta) given once per cycle was compared with daily filgrastim in two randomised double-blind placebo-controlled studies in breast cancer patients receiving doxorubicin and docetaxel.[19,20] The control arm consisted of daily injections of filgrastim continued until an ANC recovery of >10x10^9/l. Both trials demonstrated non-inferiority of a single dose of pegfilgrastim given the day after chemotherapy compared with an average of 11 doses of daily filgrastim. A combined analysis of the two studies suggested clinical superiority for pegfilgrastim based on a reduction in FN to 11% versus 19% for filgrastim with a risk ratio (RR) of 0.56.[21] Pegfilgrastim was further studied against placebo in a multicentre randomised trial of patients receiving a less myelosuppressive regimen consisting of single-agent docetaxel 100mg/m^2.[22] The incidence of FN was markedly reduced from 17% in the control group to 1% (p<0.001) and the incidence of hospitalisation was likewise markedly reduced from 14 to 1% (p<0.001). No differences in toxicity between filgrastim and pegfilgrastim have been observed. A meta-analysis comparing the efficacy of pegfilgrastim with filgrastim in five randomised clinical trials showed a significant difference in FN favouring pegfilgrastim, with an RR of 0.64 (95% confidence interval (CI), 0.43–0.97).[23]

Primary Prophylaxis Against Chemotherapy-induced Neutropoenia with Growth Factors

The use of G-CSF support after the first and subsequent cycles of myelosuppressive chemotherapy to prevent FN is recommended by various organisational guidelines. Clinical trial data supports the use of primary prophylaxis when the risk of FN is in the range of 20% or greater. Myelosuppression and FN risk are dependent upon many factors including the chemotherapy regimen, patient age, prior chemotherapy or radiotherapy, bone marrow involvement by tumour, and other co-morbidities. Risk models that can be used to define the probability of FN have been developed and are clinically useful.[24] In addition, many of the same co-morbidities and risk factors also predict for prolonged hospitalisation and risk of mortality following the development of FN.[25] These factors should all be taken into account when making a decision about utilisation of G-CSF for primary prophylaxis after chemotherapy.

The risk of FN from any given regimen appears to be highest after the first cycle of chemotherapy. Prospective studies in breast cancer and retrospective analyses of non-Hodgkin's lymphoma (NHL indicate that 50–65% of FN events occur in the first cycle.[22,26] Recently, a prospective nationwide study of community practices in the US examining a large number of patients and tumour types demonstrated 58.9% of FN events occurred in cycle 1.[27] Including SN, the incidence in cycle 1 was 68.8%. Patients who had first-cycle FN were twice as likely to undergo planned dose reductions in cycle 2 (11.1% versus 5.9%, p=0.0033) and also exhibited significantly increased dose delays (22.2% versus 13.0%). This resulted in an unplanned relative dose intensity of <85% in over one-third of patients.

The impact of primary prophylaxis on patient outcome was subject to a recently reported systemic review of 17 randomised controlled studies of growth factors in 3,491 patients receiving conventional chemotherapy.[28] Infection-related mortality had an RR of 0.552 (95% CI, 0.338–0.902; p=0.018) with G-CSF and early mortality was significantly reduced as well; RR=0.599 (95% CI, 0.433–0.833; p=0.002). The risk of FN with G-CSF was reduced with a summary RR of 0.54 (95% CI, 0.43–0.67; p<0.0001). These findings were observed across a broad array of tumour types, regimens and baseline risk of FN.

A meta-analysis of 12 randomised clinical trials in 1,823 patients with NHL and Hodgkin's disease determined that prophylactic CSF significantly reduced FN (RR=0.74; 95% CI, 0.62–0.89), severe neutropoenia (RR=0.67; 95% CI, 0.60–0.73) and infection (RR=0.74; 95% CI, 0.64–0.85).[29] Based on these analyses, it is clear that when the *a priori* risk of FN is approximately 20% or greater, the use of prophylactic G-CSF improves outcome.

Secondary Prophylaxis Against Chemotherapy-induced Neutropoenia with Growth Factors

The use of CSF is recommended after a patient experiences CIN and complications arise during a previous cycle of chemotherapy, assuming that maintenance of dose intensity is important. A randomised trial utilising a conditional model based on first-cycle ANC <0.5x10^9/l demonstrated a lower risk of FN and FN-related complications and greater preservation of dose intensity when G-CSF was used in subsequent cycles.[30] Once a patient experiences FN, the risk of recurrent FN remains substantial in subsequent cycles and measures to reduce this risk, including growth factor support, are indicated.

Treatment of Chemotherapy-induced Neutropoenia with Growth Factors

There is no evidence that patients who develop SN and no associated co-morbidity benefited from the addition of CSF. Whether or not planned dose on schedule could be maintained with this approach has not been tested. Studies have been conducted evaluating the worth of G-CSF begun when patients experience FN. One prospective trial from Spain randomising FN patients receiving intravenous antibiotics to G-CSF or not showed a reduction in the duration of FN, length of hospitalisation, and duration of antibiotic therapy in the G-CSF arm.[31] A Cochrane meta-analysis including 1,518 patients from 13 trials evaluated the use of CSF in the treatment of FN.[32] This systematic review showed less prolonged neutropoenia, less hospitalisation, less infection-related mortality but no significant difference in overall mortality. Based on these findings, prophylaxis against the development of FN is much preferred to growth factor treatment started at the time of FN.

Dosing of Granulocyte Colony-stimulating Factor for Prophylaxis of Chemotherapy-induced Neutropoenia

The recommended schedule and dose of G-CSF is to begin administration of the agent 24–72 hours after myelosuppressive therapy and to continue until count recovery after nadir, typically for 10–12 days. The G-CSF label calls for dosing at 5µg/kg/day given subcutaneously. Pegfilgrastim is given subcutaneously 24 hours after myelosuppressive chemotherapy at a fixed dose of 6mg. Previous studies demonstrated no difference in outcome between weight-based and fixed dosage of pegfilgrastim, resulting in the single fixed dosage being commercially available for adults.[19] Evaluation of pegfilgrastim in the paediatric population has been limited, and pegfilgrastim is not currently indicated for paediatric use. One small study showed safety and efficacy of pegfilgrastim at 100µg/kg in repetitive cycles of myelosuppressive chemotherapy in 28 children.[33]

Less frequent dosing of daily G-CSF through a cycle has been studied in the setting of patients receiving relatively lower myelosuppressive chemotherapy, consisting of an anthracycline and cytoxan for breast cancer.[34] Intermittent schedules were not significantly worse in daily dosing.

However, this study has several serious design issues including being a retrospective review, underpowered due to small sample groups and using only a moderately myelosuppressive regimen with a baseline FN risk of 7%. A retrospective claims database consisting of patients with NHL, breast cancer or lung cancer was analysed by days of prophylactic G-CSF administration. The risk of hospitalisation for neutropoenia or infection declined with each additional day of filgrastim prophylaxis.[35] Thus, discontinuation of growth factor before neutrophil recovery appears to be less effective under conditions of more myelosuppressive regimens and is not recommended.

Clearance of filgrastim occurs mainly through renal mechanisms while pegfilgrastim appears to be metabolised by cellular endocytosis after binding of G-CSF to its receptor on newly formed myeloid progenitors. This self-regulating mechanism explains the long action of the drug pegfilgrastim is generally not administered less than 13 days before the next cycle of chemotherapy. A study in Hodgkin's disease patients tested pegfilgrastim after each cycle of bi-weekly adriamycin (doxorubicin), bleomycin, vinblastine and dacarbazine (ABVD) and demonstrated efficacy and safety of once per cycle dosing.[36]

The toxicities of G-CSF are generally mild and self limited. Neutrophilia is occasionally seen on day 1 of subsequent cycles of chemotherapy after administration of G-CSF. This finding is typically of no clinical significance. Splenic enlargement and splenic rupture occur rarely. The most commonly reported toxicity of filgrastim, lenograstim and pegfilgrastim is bone pain.[23] This occurred at any severity in 25–50% of patients in clinical trials, while severe bone pain occurred in fewer than 10% of patients. Pain typically starts one to three days after initiation of G-CSF and appears to be worse in the first cycle of therapy.[37] Bone pain may be exacerbated by certain chemotherapeutics such as taxanes. Most patients require acetaminophen or other non-narcotic analgesics to control the pain. Reports of discontinuation of G-CSF for toxicity are rare. Pre-treatment education of patients about this potential side effect in the author's experience reduces the intensity and impact of bone pain on activities of daily living.

Antiobiotic Usage in Chemotherapy-induced Neutropoenia

Primary antibiotic prophylaxis with or without growth factors has been evaluated in a variety of oncologic settings. A randomised trial of 760 patients receiving high-dose chemotherapy for solid tumours or treatment for leukaemia or lymphoma showed a significant reduction in FN with daily oral levofloxacin compared with placebo.[38] However, the rates of fever were high in both groups: 65% for the antibiotic group versus 85% in the placebo group.

A meta-analysis published in 2005 reviewed prophylactic antibiotic use in 95 studies involving 9,283 patients with neutropoenia.[39] Most studies were conducted with in-patients with haematological cancers. Antibiotics, particularly quinolones, showed efficacy with an RR of 0.67 (95% CI, 0.55–0.81) for all-cause mortality and RR of 0.38 (95% CI, 0.21–0.69) for fluoroquinolones versus no antibiotics in infection-related mortality. Nonetheless, in more myelosuppressive regimens antibiotic prophylaxis alone is not sufficient to prevent FN, as seen in two trials comparing taxotere, adriamycin (doxorubicin) and cyclophosphamide (TAC) with fluorouracil, adriamycin (doxorubicin) and cyclophosphamide (FAC) in breast cancer patients.[40,41] In this setting, the addition of prophylactic G-CSF to antibiotic therapy markedly reduced the FN rate. Recently, a study evaluating a variety of approaches to the prevention of FN was evaluated in sequential cohorts of patients receiving neoadjuvant TAC chemotherapy during a large clinical trial.[42] Cohorts included ciprofloxacin alone, daily G-CSF from days five to 10 of each cycle, pegfilgrastim once per cycle or the combination of pegfilgrastim and ciprofloxacin. The pegfilgrastim arms were superior to the antibiotic or abbreviated G-CSF arms, with 22% experiencing FN with ciprofloxacin, 18% with daily G-CSF for six days, 7% with pegfilgrastim once per cycle and 5% with pegfilgrastim + ciprofloxacin ($p<0.01$). Hospitalisation was significantly lower in the growth factor groups and pegfilgrastim lowered hospitalisation rates compared with filgrastim. These results highlight the importance of growth factor support as the primary prophylactic strategy against FN when myelosuppressive chemotherapy is given.

Current Guidelines

Several organisations have periodically released guidelines regarding the use of G-CSF to reduce complications of CIN based on updated reviews of the literature. In general, the American Society of Clinical Oncology (ASCO),[43] National Comprehensive Cancer Network (NCCN)[44] and the European Organisation for Research and Treatment of Cancer (EORTC)[45] guidelines are very similar in their recommendations. All recommend primary prophylaxis with G-CSF when the risk of FN is approximately 20% or greater based on a careful consideration of both patient risk factors and chemotherapy regimens. All three groups recommend considerations of growth factor prophylaxis when the risk of FN falls in the 10–20% range, depending upon the intent of treatment – curative or life-prolonging versus palliative – desire to maintain dose intensity, and patient risk factors. The EORTC and ASCO guidelines emphasise the importance of age >65 as a critical consideration for use of growth factor support. A prospective trial of G-CSF prophylaxis in elderly patients supports this concept.[46]

The use of pegfilgrastim once per cycle given 24 hours after chemotherapy simplifies treatment. Many clinicians would like to provide chemotherapy and supportive care on the same day, particularly in the US where self-injectables are often not reimbursed. There are potential safety issues arising from earlier administration of G-CSF; these include efficacy concerns as well as the theoretical risk of exposing mitotically stimulated myeloid precursors to genotoxic chemotherapy. A study in breast cancer patients receiving TAC demonstrated a three-fold increase in FN from 7% to 22% in patients receiving pegfilgrastim the same day as chemotherapy compared with the next day.[47] Trials in other tumour types are awaiting publication, but at this time patients receiving myelosuppressive chemotherapy and prophylactic growth factors should continue to initiate G-CSF 24 hours after chemotherapy, as indicated in current guidelines.

Cost-effectiveness of Prophylaxis with Growth Factors

Growth factor support adds to the overall cost of treatment, but the cost of FN, direct hospital costs, out-patient costs and indirect costs to patients and care-givers can be enormous. Cost and cost utility analyses have demonstrated that utilising G-CSF in the appropriate primary prophylactic setting is cost-effective compared with US and European costs for inpatient care,[48,49] and could be cost saving when indirect costs and out-of-pocket costs are included.[50,51] When a more effective, but more myelosuppressive, regimen is appropriate the use of this regimen with growth factor support appears cost effective as well.[52] Another recent analysis of cost-effectiveness utilising the payer's perspective in Europe has concluded that secondary prophylaxis with antibiotics is more cost-effective than a combined strategy of antibiotics and G-CSF.[53]

Conclusion

CIN remains the most common serious toxicity of current chemotherapeutic regimens for cancer and is frequently responsible for dose reductions and delays, which may compromise outcome. Febrile neutropoenia continues to have serious sequelae in a fraction of patients receiving myelosuppressive treatment. Both chemotherapy regimens and patient- and disease-specific factors should be taken into account when considering the risk of developing CIN. The use of growth factor support prophylactically in first and subsequent cycles with myelosuppressive chemotherapy markedly reduces the risk of FN and is uniformly recommended by current guidelines. Pegfilgrastim, a long-acting form of G-CSF given once per cycle, is more convenient for the patient and the healthcare system and is at least as or more effective as daily dosing of G-CSF. ■

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