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Filgrastim in Patients with Neutropenia
Potential Effects on Quality of Life

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Abstract

Treatment- and disease-related neutropenia are associated with a number of negative clinical effects such as febrile neutropenia, documented infection, hospitalisation for infection-related morbidity, infection-related mortality, and decreased ability to administer the planned chemotherapy dose on schedule. Reductions or delays in dosage have the ability to jeopardise the effectiveness of treatment by lowering response rates. Not only are clinical outcomes adversely affected, but these complications can have a negative influence on patient quality of life. Filgrastim is a haematopoietic growth factor that primarily acts to stimulate the proliferation and differentiation of neutrophil progenitor cells. Filgrastim is capable of reducing the incidence and severity of neutropenia and the complications that accompany it in patients with cancer or HIV infection. Although there are few data evaluating the effect of treatment with granulocyte colony-stimulating factor on quality of life, it is assumed that the benefits would be seen through both the reduction of treatment-related complications and the enhanced potential for long-term disease control. A new, longer-acting form of filgrastim is now available that has the potential to simplify the management of neutropenia and further improve patient quality of life by decreasing the number of necessary injections. Additional prospective controlled trials that contain quality-of-life issues as endpoints are needed .

1. Introduction

Neutropenia and its consequent infectious complications are the most common dose-limiting toxicities associated with cytotoxic cancer chemotherapy.[1] Patients infected with HIV often experience neutropenia, most commonly in those who have progressed to AIDS.[2,3] In fact, the myelosuppression associated with cancer chemotherapy and the effects of HIV infection and its treatment represent the most common causes of neutropenia found in major healthcare institutions today. Treatment- and disease-related neutropenia are associated with a number of adverse clinical outcomes, such as febrile neutropenia requiring hospitalisation, documented infection, infection-related mortality, and a reduced ability to deliver the planned chemotherapy dose on time. Dose reductions or delays have the potential to compromise the efficacy of treatment by reducing response rates as well as disease-free survival. In addition to the observed adverse effect on clinical outcomes, these complications can have an adverse effect on patient quality of life (QOL).

Filgrastim is a recombinant human granulocyte colony-stimulating factor (G-CSF) that has biological activity identical to that of the endogenous molecule.[4] The drug is widely used for the pre-

vention of chemotherapy- and HIV infection-induced neutropenia. Although few specific studies have been performed, filgrastim produces a number of effects that have the potential to improve patient QOL. This article provides an overview of the effect of filgrastim on improving patient outcomes, with special emphasis on QOL.

2. The Challenge of Quality-of-Life (QOL) Studies

QOL assessment is used to evaluate disease outcome or the effectiveness of treatment; to guide clinical decision-making; and to assess population health as well as health policy formulation. The fundamentals used to evaluate and select QOL measures are as follows: reliability (reproducibility); internal and external validity (no bias); and precision (sensitivity). Two primary types of instruments are used to assess patient QOL: health profile measurements derived from psychosocial theories, which assess the important physical, emotional and social domains associated with QOL; and utility measures derived from economic and decision theory, which assess patient preferences for various health states.[5]

2.1 Health Profile Measures

Health profile measures may be either generic to multiple health states, or specific to a certain health state, condition, symptom or treatment. They attempt to measure the important dimensions of QOL and allow broad comparisons between populations, although they may be unresponsive to changes in specific conditions. There are both global and specific scales. The former are generalisable measures, which permit comparison with other populations and conditions, while the latter are most sensitive to the aspects of QOL commonly altered by a specific condition or intervention. Although each is designed to measure objective functional status (physical or mental) or subjective well-being, there are advantages and disadvantages to each assessment method.[6]

Health profiles may provide considerable information about the various dimensions of QOL and are generally designed for self-administration, making them useful for implementation in large-scale controlled clinical trials. Generic and disease-specific instruments assess patient-, disease- and treatment-related problems along a number of dimensions, including physical concerns (symptoms); functional ability; family well-being; emotional well-being; treatment satisfaction; sexuality/intimacy; and social functions, among others.[7]

2.2 Patient Preferences

Patient preferences or utilities, on the other hand, measure the net effect on QOL as a single number along a continuum from death (0) to full health (1). Scores reflect health status and its value, which can be used to combine time and QOL in a cost-utility analysis. This may be assessed through either a standard reference gamble such as willingness to pay to achieve a certain outcome, or through a time trade-off method allowing the combined assessment of quality and duration.[8] Such measures are difficult to assess, labour intensive and costly, generally require personal interviews, and cannot examine the various dimensions of QOL. No matter which QOL instrument is selected for use in a particular clinical situation, it is important that it be adequately validated prior to its application.[9] This requires a comparison with a currently accepted preference measure to validate its precision and reliability.[9]

2.3 Design and Analysis Challenges

There are several challenges associated with the design and analysis of QOL studies. QOL measures are often considered secondary outcomes with no *a priori* hypotheses defined. They may also suffer from small sample sizes with poor definition of the magnitude of clinically important differences; high variability with skewed measurement distributions; frequently missing data; and important analysis issues, including multiple outcomes and repeated measures over time, as well as their consideration in subgroup analyses.[10]

Studies that are specifically designed to address QOL issues are often of small size, resulting in low

power to detect clinically meaningful differences between treatment groups.[11] In addition, there is often noncompliance in completing or submitting the QOL questionnaires, resulting in missing forms, late forms and incomplete forms, which produces imprecise and biased results.[12] Differences in methodology between studies and the problems associated with conducting QOL evaluations mean that the results of studies must be interpreted with caution.

3. The Impact of Cancer and HIV on Patient QOL

3.1 Patients with Cancer

Combination cytotoxic chemotherapy regimens are often associated with significant toxicity, which includes myelosuppression, mucositis and opportunistic infections, among others.[1] Chemotherapy-induced neutropenia is associated with a variety of negative clinical effects, including febrile neutropenia, documented infection, hospitalisation for infection-related morbidity, infection-related mortality, and a diminished ability to deliver the planned chemotherapy dose on schedule. The severity and duration of neutropenia and febrile neutropenia produced by combination chemotherapy are primarily dependent on the specific regimen and dose intensity administered (i.e. the amount of drug delivered over a specified time period). The type and stage of cancer and patient-specific comorbidities also play a role. The risk of infection and subsequent complication is predominantly related to the severity and duration of neutropenia.[13] Episodes of febrile neutropenia require empirical antibiotic support and a variety of diagnostic procedures to assess the type and location of infection where possible. In addition to the direct effect of the illness, systemic cancer chemotherapy may have an adverse effect on patient QOL, with significant impairment in social, physical and global functionality.[12,14-16] The incidence, duration and severity of adverse events experienced by stage II-IV breast cancer patients, including dehydration, anorexia, asthenia and vomiting, have been shown to be several-fold greater during periods in which febrile neutropenia occurred.[17] However, after the completion of chemotherapy, QOL scores generally returned to baseline values relatively quickly.[12,15] In addition to the measured effects on patient QOL, treatment-related adverse effects can compromise treatment response. Since response is often correlated with dose intensity, dose reductions and delays have the potential to adversely affect clinical outcome. The potential benefit of filgrastim on patient QOL arises from the reduction in treatment-related toxicity, including hospitalisation as well as sustained dose intensity and improved potential for disease control.

Bone marrow reserves decline with increasing age, making chemotherapy toxicity more common in elderly patients.[18] The incidence and severity of neutropenic complications, including febrile neutropenia, are greater in elderly patients receiving cancer chemotherapy.[5] Nevertheless, the haematopoietic growth factors appear to be as effective at reducing the risk and severity of neutropenic complications among elderly cancer patients as among younger patients.[19] Therefore, while the effect of successful cancer therapy on life expectancy is less among the elderly, the potential favourable effect of filgrastim on QOL may, in fact, be greater.[20] The National Comprehensive Cancer Network currently recommends the routine prophylactic use of the colony-stimulating factors (CSFs) in elderly patients receiving cancer chemotherapy with a dose intensity equivalent of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).[21]

3.2 Patients with HIV Infection

Neutropenia is a common complication in HIV-infected individuals, occurring most frequently among patients who have progressed to AIDS.[2] The incidence of neutropenia has been estimated to vary from 10 to 20% in patients with AIDS-related complex, and from 35 to 75% of patients with AIDS.[2] The presence of neutropenia in HIV-infected patients is a signifi-

cant risk factor for the development of bacteraemia.[22]

The development of neutropenia appears to be related, in part, to a disturbance in the production of G-CSF among HIV-infected individuals.[3] Other factors that contribute to HIV-associated neutropenia include concomitant opportunistic diseases or the presence of malignancy requiring treatment with cytotoxic chemotherapy.[2] In addition, many drugs used in the treatment of HIV and its complications are myelosuppressive. These include antiretroviral agents (e.g. zidovudine, dideoxycytidine, dideoxyinosine), ganciclovir, interferon-α, antifungal agents, sulphonamides and antineoplastic agents.[2]

Not only are there decreased numbers of neutrophils in HIV-infected patients, but the remaining neutrophils have multiple functional abnormalities,[2,23] such as impairments in chemotaxis and phagocytosis, as well as reduced expression of cellular adhesion molecules.[23] Since neutrophils are a major part of the host defence system, HIV-related neutropenia is associated with an increased rate of infection with opportunistic pathogens. A correlation between the absolute neutrophil count and the risk of hospitalisation for bacterial infection among HIV-infected patients has been demonstrated.[2,24] The risk of hospitalisation for bacterial infection is highly associated with the severity and the duration of the neutropenia.[24]

Febrile neutropenia appears to decrease QOL for patients with AIDS in the same manner as it does for cancer patients. Among HIV-infected patients with non-Hodgkin's lymphoma receiving oral combination chemotherapy, a decrease in QOL scores has been reported for those who experienced febrile neutropenia, but not for those who did not develop febrile neutropenia.[25] The deterioration in QOL scores reflected primarily a decline in functional capacity among those who developed febrile neutropenia.[25]

4. QOL Benefits of Filgrastim

Filgrastim is a haematopoietic growth factor that primarily acts to stimulate the proliferation and differentiation of neutrophil progenitor cells.[4] The drug may also increase the activity of mature neutrophils by enhancing chemotaxis and phagocytosis.[4] Filgrastim is capable of reducing the incidence and severity of neutropenia and neutropenic complications, including febrile neutropenia, hospitalisation and documented infection in patients with cancer and HIV. On the basis of these properties, filgrastim has the potential to improve patient QOL (table I). The following sections overview the capacity of filgrastim to improve QOL among patients with either chemotherapy- or HIV-related neutropenia.

4.1 Effect on Neutropenia and its Complications

Currently, there is no disease- or symptom-specific QOL instrument for determining the effect of neutropenia and its complications on QOL. Thus, there are few data evaluating the effect of treatment with G-CSF on patient QOL. A neutropenia-specific subscale of the Functional Assessment of Cancer Treatment (FACT) QOL instrument is currently under development (FACT-N). Promising results have been reported thus far with a larger-scale validation study, which is ongoing to further assess its psychometric properties and clinical usefulness.[26] The availability of the FACT-N may facilitate an increase in the number of studies evaluating the effects of treatment on QOL in patients with neutropenia. In addition to questions addressing physical, social/family, emotional and functional well-being, a number of additional concerns are addressed, including worry over infections, getting sick from low blood counts, and fear

Table I. Potential quality-of-life–related benefits of filgrastim

Decreased incidence of febrile neutropenia requiring hospitalisation
Decreased duration of hospitalisation for febrile neutropenia
Decreased rate of documented infection
Decreased use of antibiotics
Decreased nonmyeloid toxicity (e.g. mucositis)
Enhanced efficacy of antibiotics
Ability to increase dose intensity, thereby improving clinical outcome without compromising quality of life

of public places, etc. This scale is like all QOL measures in that it will face the challenges of defining clinically important differences in measured effects, and of missing or incomplete data due to death/disability, delays in treatment, loss to follow-up or simple noncompliance. As mentioned above, treatment-associated neutropenia also has the potential for limiting treatment intensity and effectiveness. The benefit of filgrastim on patient QOL, therefore, arises both from the reduction in treatment-related toxicity including hospitalisation for febrile neutropenia and from improving the potential for long-term disease control.

4.2 Effect on Non-Haematological Toxicity

Mucositis is a common dose-limiting effect of chemotherapy often associated with neutropenia that can have an adverse effect on patient QOL. Patients who experience mucositis have a decreased ability to eat, which in some cases may result in the need for parenteral nutrition. Chemotherapy-induced mucositis can also result in treatment delays and/or dose reductions of potentially curative therapy. Several studies have shown that filgrastim decreases the incidence of mucositis in patients receiving chemotherapy.[27-30] Filgrastim has even been shown to decrease the incidence of mucositis in patients receiving dose-intensified chemotherapy compared with those receiving standard-dose chemotherapy.[29] In this study, patients receiving filgrastim were also less likely to discontinue one or more of the antineoplastic agents in the chemotherapy regimen than were patients receiving standard-dose chemotherapy without haematopoietic growth factor support.[29] A recent retrospective analysis of stage II-IV breast cancer patients reported a strong temporal relationship between febrile neutropenia and the incidence and/or severity and/or duration of abdominal pain, anorexia, asthenia, dehydration, fatigue, rigors and vomiting.[17] The authors suggest that the use of prophylactic growth factors may decrease the effect that these toxicities have on patient QOL.

5. Filgrastim in Patients with Cancer

Filgrastim has benefits in a number of clinical situations in patients with cancer that potentially translate into improvement in QOL. These include use as primary prophylaxis, i.e. given with the first cycle of chemotherapy prior to the onset of febrile neutropenia; secondary prophylaxis, i.e. given after a prior episode of febrile neutropenia; treatment of patients with established febrile neutropenia to reduce the consequences of infection or length of hospital stay; use in patients with myeloid malignancies (e.g. acute myeloid leukaemia; AML); as an adjunct to progenitor-cell transplantation; to increase chemotherapy dose intensity; and to prevent chemotherapy-induced toxicities. The effect of filgrastim in these clinical situations is described in more detail in following sections.

5.1 Primary Prophylaxis

Filgrastim decreases the risk of febrile neutropenia by approximately 50% in patients receiving myelosuppressive chemotherapy administered on a variety of schedules for a number of malignancies.[31] This includes myelosuppressive chemotherapy for small-cell lung cancer[32,33] and non-Hodgkin's lymphoma.[34,35] Overall, filgrastim therapy produces a dose-dependent decrease in the duration of neutropenia and an increase in neutrophil counts at the nadir. Several studies have demonstrated that the reduction in severity and duration of neutropenia is associated with a decrease in febrile neutropenia requiring hospitalisation, as well as a decrease in documented infections and the use of intravenous antibiotics.[32,33,35] In two large, multicentre, phase III trials conducted in the US and Europe, filgrastim produced reductions of approximately 50% in the incidence of febrile neutropenia and the use of intravenous antibiotics.[32,33] Similarly, the incidence of culture-confirmed infections was decreased by nearly 50% in these studies.[32,33] A recent meta-analysis of the eight published randomised, controlled trials of prophylactic G-CSF in patients receiving systemic chemotherapy confirms its efficacy across a vari-

ety of disease entities and treatment regimens.[36] While a definite effect on disease-free and overall survival for filgrastim has not yet been established in this patient population, hospitalisation and treatment of febrile neutropenia should have a clear effect on overall patient QOL.[13,31]

5.2 Patients with Afebrile Neutropenia

There is little evidence to support the use of filgrastim in the treatment of patients with afebrile neutropenia.[13] Although filgrastim administration produces a faster time to neutrophil recovery in these patients, this has not been associated with significant reductions in the need for hospitalisation, the number of days in hospital, the number of days of intravenous antibiotic therapy, or the number of culture-positive infections.[37] While filgrastim appears to provide limited benefit in patients with afebrile neutropenia within the present cycle, several risk models have been validated to support the secondary administration of filgrastim in subsequent cycles based on nadir absolute neutrophil counts (ANC) <500/μl.

5.3 Patients with Febrile Neutropenia

In contrast to the results in afebrile patients, there is substantial evidence to support the use of filgrastim in the treatment of high-risk patients with fever and neutropenia.[13] Patients who develop severe and prolonged neutropenia are at increased risk of developing febrile neutropenia, which generally requires hospitalisation for empirical broad-spectrum antibiotics. In addition, patients hospitalised with febrile neutropenia are at risk of prolonged hospitalisation, medical complications and even death. Clearly, these factors have a negative effect on patient QOL.

Several randomised trials in patients with established chemotherapy-induced febrile neutropenia have demonstrated that the addition of filgrastim to antibiotic therapy decreases the duration of neutropenia;[38-41] decreases the proportion of patients experiencing prolonged hospitalisation;[38-41] decreases the use of antibiotics;[40,41] and decreases the duration of fever.[40,41] In a recent randomised study of broad-spectrum antibiotic therapy with or without filgrastim in patients with solid tumours and high-risk febrile neutropenia, patients receiving filgrastim had a significantly shorter median duration of grade IV neutropenia (2 *vs* 3 days), antibiotic therapy (5 *vs* 6 days), and hospital stay (5 *vs* 7 days) than those in the control arm.[41] Patients at greatest risk of serious medical consequences of febrile neutropenia, and therefore appropriate candidates for filgrastim treatment, include those with profound neutropenia, uncontrolled primary disease, pneumonia, hypotension, multiorgan dysfunction (i.e. sepsis syndrome) and invasive fungal infection.[13]

The addition of filgrastim to antimicrobial therapy has the potential to improve response rates by accelerating neutrophil regeneration and by potentiating the antimicrobial activity of the neutrophils already present. As noted previously, CSFs are believed to play a major role in the host defence mechanism against fungi and bacteria, primarily by enhancing phagocytic activity and chemotaxis.[4] Results from several small studies and case reports suggest that the addition of G-CSF to antifungal combination therapy may improve response in patients with chemotherapy-induced neutropenia and difficult-to-treat fungal infections.[42-46]

5.4 Patients with Acute Leukaemia

Febrile neutropenia requiring intravenous antibiotics is very common in patients receiving induction and consolidation chemotherapy for acute leukaemia.[13] Infectious complications are a major source of morbidity and mortality limiting remission induction and the associated duration of remission.

Randomised, controlled trials in patients with AML demonstrate that filgrastim, administered after induction therapy, decreases the duration of neutropenia[47-49] and modestly decreases the use of antibiotics, the rates of severe infection, and hospitalisation. Filgrastim appears to have similar benefits in patients with AML when the drug is administered after consolidation therapy.[49]

Filgrastim has also demonstrated benefit in patients with acute lymphocytic leukaemia, after the initial induction chemotherapy. In these patients, filgrastim consistently decreased the duration of neutropenia[50-54] and, at least in some studies, filgrastim was associated with statistically significant decreases in the incidence of febrile neutropenia,[54] documented infection,[51,53,54] and hospitalisation.[50,51]

5.5 Dose Intensification in Solid Tumours

A number of studies have suggested that filgrastim may allow for increases in dose intensity in non-myeloablative chemotherapy regimens in a variety of cancers (e.g. breast, ovarian, small-cell lung, urothelial tract, head and neck tumours, and non-Hodgkin's lymphoma).[13,29,55-61] The addition of filgrastim has permitted higher doses of chemotherapy to be delivered on time with fewer dose delays. Several of these studies have shown that dose-intensified chemotherapy is associated with improvements in response rates and locoregional control compared with standard regimens. Two trials have also demonstrated that this approach results in improvement in progression-free survival in patients with urothelial tract cancer[29] or improved overall survival in patients with small-cell lung cancer.[56] In addition, Sternberg et al.[29] and Budd et al. [61] reported a reduction in the number of days of neutropenia experienced by patients during dose-intensive chemotherapy while receiving filgrastim. The use of filgrastim to maintain standard-dose chemotherapy in patients with potentially curable tumours (i.e. breast cancer, non-Hodgkin's lymphoma) has also been demonstrated.[15,33-35]

Recent studies have demonstrated that filgrastim is effective in allowing increases in chemotherapy dose intensity while maintaining QOL in patients with breast or small-cell lung cancer.[12,56,62] Thatcher and colleagues[56] randomised 403 patients with small-cell lung cancer to receive six cycles of doxorubicin/cyclophosphamide/etoposide chemotherapy every 3 weeks, or to the same regimen every 2 weeks with filgrastim. Patients receiving filgrastim had, on average, a 34% increase in dose intensification compared with those in the control group. This resulted in a significantly higher complete response rate (40 *vs* 28%, $p = 0.01$) and improved survival ($p = 0.04$) for those receiving the dose-intensified regimen. This dose intensification was achieved without an associated increase in symptoms of toxicity or an excess in deaths attributable to drug toxicity. Both treatment groups produced similar palliation of symptoms of psychological distress, and neither group experienced interference in the activities of daily living.

In the High-dose Chemotherapy for Breast Cancer Study Group trial, previously untreated patients with inflammatory breast cancer received high-dose cyclophosphamide, doxorubicin, and fluorouracil plus filgrastim and blood stem-cell transplantation.[12] QOL was measured using the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) and an ad hoc adverse effect questionnaire. Patients experienced only transient decreases in QOL after receiving highly cytotoxic chemotherapy plus filgrastim. The reductions in QOL during treatment primarily affected the physical, working and social capabilities of patients. However, after the completion of treatment, all QOL parameters except physical functioning returned to baseline. Notably, 1 year after inclusion in the study, some parameters, including emotional functioning and global QOL, were significantly improved over baseline.

In another trial that has only been published in an abstract, the comparative effect of treatment with standard fluorouracil, epirubicin and cyclophosphamide versus dose-intensified epirubicin/cyclophosphamide plus filgrastim was evaluated in patients with locally advanced breast cancer.[62] Although the dose-intensified regimen had significantly lower QOL scores during the first 3 months of treatment, these patients achieved an earlier return to baseline QOL scores than the standard chemotherapy group. There was no significant

difference in QOL between the two treatment groups over the first year of follow-up.

5.6 Adjunct to Bone Marrow and Progenitor-Cell Transplantation

The G-CSFs have been administered after autologous or allogeneic bone marrow transplantation with the goal of decreasing the time to neutrophil recovery and severity of infectious complications, thereby reducing the duration of hospitalisation, decreasing costs, and potentially improving QOL.[13] The G-CSFs are also used to mobilise peripheral blood progenitor cells (PBPCs) prior to harvesting, in an effort to enhance neutrophil and platelet recovery following reinfusion after myeloablative or myelosuppressive chemotherapy.[13,63] Several studies have demonstrated that filgrastim decreases the number of episodes of febrile neutropenia and the number of platelet transfusions required, and shortens the duration of hospital stay in patients receiving mobilised PBPCs.[13,63-66] Transplantation of filgrastim-mobilised PBPCs has produced earlier haematopoietic recovery than that seen after transplantation of sargramostim-mobilised PBPCs[67] or after autologous bone marrow transplantation.[68] Thus, mobilised PBPCs have largely replaced bone marrow-derived cells for use in autologous transplantation.[13,63,65] The efficacy of filgrastim after high-dose chemotherapy and PBPC transplantation has also been demonstrated.[66]

6. Filgrastim in Patients with HIV Infection

The ability of filgrastim to decrease HIV-related neutropenia is well established.[69-73] In one study, filgrastim increased the median ANC from $<1.5 \times 10^3/\mu l$ to $>4 \times 10^3/\mu l$ among 200 patients with AIDS-related neutropenia.[73] Ninety-eight percent of these patients had a reversal of neutropenia (ANC $\geq 2 \times 10^3/\mu l$). Filgrastim has also been shown to increase CD4+ cell counts in HIV-infected patients, in association with increasing the number and differentiation of myeloid progenitors.[74]

Filgrastim has also been shown to decrease morbidity associated with neutropenia in HIV patients.[69,72] In a randomised trial, Kuritzkes and colleagues[72] demonstrated that filgrastim, titrated to maintain ANC $\geq 2 \times 10^3/\mu l$, decreased the incidence and duration of bacterial infection, the incidence of severe bacterial infection, the duration of hospitalisation for infection, and the number of days of intravenous antibiotic usage. There was also a trend towards decreased use of intravenous antibacterial medications and increased use of potentially myelosuppressive agents.

The risk of neutropenia in patients with HIV is aggravated by the myelosuppressive effects of some agents used in the treatment of HIV, such as zidovudine, ganciclovir, and cotrimoxazole. Drug-induced neutropenia is a frequent cause of dose reduction or discontinuation of these agents. Filgrastim reduces the neutropenia associated with myelosuppressive agents and increases tolerance to these agents.[70,73,75] This has enabled patients in this population to resume full therapeutic doses of antiretroviral medications.[71,75] In one study, treatment with filgrastim enabled more than 80% of patients to increase or maintain the dose levels of myelosuppressive drugs or allowed these drugs to be added to their treatment regimen.[73]

HIV-infected patients with disseminated *Mycobacterium avium* complex (DMAC) have a relatively high incidence of neutropenia.[76] One retrospective study of 91 patients with DMAC found that the addition of filgrastim to clarithromycin and ethambutol prolonged survival.[76]

6.1 QOL Studies in HIV Patients

QOL is an important factor for patients with cancer or HIV infection. In patients with cancer, baseline QOL parameters have been shown to be independently predictive of overall survival.[77] However, there has been minimal investigation of QOL in patients experiencing febrile neutropenia. As noted previously, febrile neutropenia has been reported to decrease QOL among patients with

Table II. Summary of quality-of-life (QOL) studies involving filgrastim

Study	Design	No. of patients	QOL scale	Outcome
Chronic neutropenia				
Jones et al.[78]	nr, nb	21	NHP	↑ QOL subscales (energy, emotional reactions, social isolation, job/work, social life, hobbies and vacation) and self-assessed satisfaction and health status *vs* baseline
Fazio & Glaspy[79]	nr, nb	10	F&P QOL Index	↑ In 4/4 QOL subscales (health and functioning, socioeconomic, psychological/spiritual and family) *vs* baseline
Dose intensification				
Thatcher et al.[56]	r, nb	403	Unspecified QOL questionnaire	↑ In complete response rate and survival with no adverse effect on QOL compared with standard chemotherapy
Macquart-Moulin et al.[12]	nr, nb	95	EORTC QLQ-C30	Dose intensity accomplished with only transient ↓ in QOL
Therasse et al.[62]	r, nb	448		Greater ↓ in QOL at 3 months than standard chemotherapy, but quicker return to baseline QOL status
AIDS-related non-Hodgkin's lymphoma				
Remick et al.[25]	nr, nb	38	FLIC, BSI	No significant functional or psychological deterioration during therapy except for patients experiencing FN. G-CSF decreased the frequency of hospitalisation for FN

BSI = Brief Symptom Inventory; **EORTC QLQ-C30** = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30; **FLIC** = Functional Living Index – Cancer; **FN** = febrile neutropenia; **F&P QOL Index** = Ferrand & Powers Quality of Life Index; **G-CSF** = granulocyte colony-stimulating factor; **nb** = nonblind; **NHP** = Nottingham Health Profile; **nr** = nonrandomised; **r** = randomised.

cancer and/or HIV infection.[12,15,25] Unfortunately, there are only a limited number of studies evaluating the effect of filgrastim on patient QOL. Thus, there is a great need for studies that incorporate QOL endpoints. The available QOL data for the use of filgrastim are summarised in table II and reviewed in the following sections.

7. Filgrastim in Patients with Severe Chronic Neutropenia

Jones and colleagues[78] evaluated 21 patients aged 4 to 68 years with congenital, cyclic or idiopathic neutropenia who were treated with filgrastim (0.3 to 24 μg/kg/day). QOL was measured by use of the Nottingham Health Profile and by patient-assessed health satisfaction questionnaires. The long-term use of filgrastim was associated with statistically significant improvements in several subscales within this QOL instrument, including energy, emotional reactions, social isolation, job/work, social life, hobbies and vacation. In addition, patient-assessed satisfaction with health improved from 14 to 87% ($p < 0.01$) after the initiation of filgrastim. Similarly, there was a significant improvement in the percentage of patients who assessed their health status as excellent or good during treatment compared with pretreatment (86% *vs* 24%, $p < 0.0$).[78]

Similar results were reported by Fazio and Glaspy,[79] who evaluated ten paediatric patients with congenital neutropenia (7 patients), cyclic neutropenia (2) or idiopathic neutropenia (1), who were receiving long-term treatment with filgrastim. QOL was assessed using the Ferrand & Powers Quality of Life Index, which is designed to

determine patient-assessed satisfaction with a number of factors that are grouped into four subscales (health and functioning, socioeconomic, psychological/spiritual, and family). Assessments after 4 and 10 months of treatment demonstrated statistically significant improvements in all four subscales, with the greatest increases occurring in the health and functioning and the socioeconomic subscales.[79]

8. QOL Impact of Longer-Acting Forms: Pegfilgrastim

The half-life of filgrastim of approximately 3 hours necessitates repeated injections, often daily, to maintain effective serum concentrations. Since parenteral administration (subcutaneously or intravenously) is required, frequent repeated injections are needed during each treatment cycle to achieve the desired effect. Extensive efforts have been undertaken to develop longer-acting formulations of the haematopoietic growth factors erythropoietin and filgrastim. The attachment of a 20kD polyethylene glycol moiety to the N-terminus of the filgrastim molecule has provided an agent (pegylated filgrastim) with a considerably longer half-life, allowing dose administration on a once-per-cycle schedule. Pegylated filgrastim has recently been approved by the US Food and Drug Administration for prophylaxis of neutropenic complications in patients receiving systemic chemotherapy. Approval was based on a series of phase I/II studies in healthy volunteers and patients with lung cancer, breast cancer and non-Hodgkin's lymphoma, as well as two pivotal phase III studies in women with breast cancer. Efficacy and safety comparable to those of standard filgrastim daily administration have been demonstrated for a single injection using a weight-based regimen at 100 μg/kg or a fixed dose of 6mg of the pegylated formulation. Safety concerns have been largely allayed by the agent's apparent self-regulatory feature.[80] After saturation of neutrophil-binding sites, serum concentrations rise after a single injection in proportion to dose and are sustained throughout the period of neutropenia as a result of decreased clearance. On recovery of neutrophil counts and reappearance of receptor-binding sites, the agent is rapidly cleared prior to the next cycle of chemotherapy. The two pivotal phase III studies in breast cancer were designed to demonstrate (i) noninferiority for as little as a single day difference in the duration of severe neutropenia and, (ii) a decrease in the proportion of patients experiencing febrile neutropenia compared with a median of ten daily injections of standard filgrastim, while at the same time maintaining the same high safety profile.[81,82] The potential to simplify the administration of G-CSF through a reduced need for multiple injections and repeated clinic visits based on a once-per-cycle regimen, as well as the use of fixed-dose schedules, provides the opportunity for greater patient compliance as well as the potential to improve patient QOL.

9. Conclusions

The effect of cancer, cancer treatment and supportive care measures on patient QOL has not been adequately investigated. QOL instruments are designed to measure the functional, emotional, social and other subjective outcomes resulting from a disease and its treatment, such as pain, anxiety, depression, restricted mobility, and inability to engage in work, family and recreational activities. Nevertheless, the effect of cancer and cancer treatment on patient QOL has been investigated in a variety of settings. Nowhere is this more dramatically demonstrated than in the elderly population with cancer who may have various comorbidities, including limited bone marrow reserves.

Filgrastim has a favourable effect on many clinical outcomes such as incidence, severity and duration of neutropenia, documented infection, and duration of hospitalisation, in many patients with either cancer- or HIV-related neutropenia. Filgrastim has also been shown to decrease some nonmyelosuppressive adverse events of cancer chemotherapy. The benefit of filgrastim on the incidence and severity of neutropenic complications in the elderly has been clearly demonstrated and incorporated into clinical practice guidelines.

Furthermore, studies have demonstrated that the addition of filgrastim to antimicrobial regimens may improve response rates through a synergistic enhanced end cell activation of neutrophils. Although QOL measures have not been included in most clinical trials of filgrastim conducted to date, the remarkable clinical benefits demonstrated by filgrastim in clinical trials have the potential to improve patient QOL. In small studies in patients with chronic neutropenia, filgrastim has been found to improve QOL compared with that in the pretreatment period.

Filgrastim also has potential QOL effects in patients with cancer receiving highly toxic chemotherapy. A major barrier to the application of high-dose chemotherapy is that dose-intensification regimens are often associated with substantial toxicity and physical and psychological distress. Such effects can limit the feasibility and acceptability of these chemotherapy regimens. The use of filgrastim permits the delivery of dose-dense regimens with the potential to improve response rate and long-term outcome in these patients. Large studies have demonstrated that filgrastim is effective in permitting dose intensification with only transient impairments in QOL.

The available data, although limited, suggest a positive effect of filgrastim on patient QOL, both in patients with cancer and those with HIV. Further prospective, controlled trials of filgrastim support in a variety of clinical settings are needed, using validated and reliable QOL measures. The use of QOL endpoints should also be included in studies evaluating new formulations of filgrastim, such as longer-acting pegylated forms of filgrastim. These agents have the potential to simplify the management of chemotherapy and further increase patient QOL by decreasing the number of required injections and clinic visits as well as the use of fixed-dose schedules.[80]

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