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Lenograstim

An Update of its Pharmacological Properties and Use in Chemotherapy-Induced Neutropenia and Related Clinical Settings

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Data Selection

Sources: Medical literature published in any language since 1995 on Lenograstim, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand) and Medline. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search term was 'Lenograstim'. Medline search term was 'Lenograstim'. Searches were last updated 28.2.2000.

Selection: Studies in patients with neutropenia who received lenograstim. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Lenograstim, recombinant human granulocyte colony stimulating factor, rHuG-CSF, cancer, chemotherapy, bone marrow transplantation, peripheral blood stem cell transplantation, leukaemia, aplastic anaemia, congenital neutropenia, AIDS, pharmacodynamics, pharmacokinetics, therapeutic use, pharmacoeconomics, tolerability, dosage and administration.

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Summary

Abstract

Lenograstim is the glycosylated recombinant form of human granulocyte colony stimulating factor. The drug is used to reduce the risk of life-threatening infection in patients with neutropenia, particularly after cytotoxic chemotherapy.

Lenograstim accelerates neutrophil recovery significantly after chemotherapy, with beneficial effects on clinical end-points such as incidence of laboratory-confirmed infection and length of hospital stay. Chemotherapy dose intensity has also been increased in patients receiving lenograstim, notably those with breast or small cell lung cancer, although improvements in tumour response and survival have not been demonstrated.

Lenograstim also assists neutrophil recovery in patients undergoing bone marrow transplantation, and stimulates the production of peripheral blood stem cells (PBSCs) for autologous transfusion after aggressive chemotherapy. Lenograstim also mobilises CD34+ cells more efficiently in unit dose terms than filgrastim and has been used successfully to mobilise PBSCs from healthy donors for allogeneic transplantation.

Randomised trials have shown increases in rates of disease remission after lenograstim therapy in patients with acute myeloid leukaemia, with no evidence of stimulation of malignant blasts. The drug has also shown potential in the mobilisation of nonmalignant PBSCs for autotransplantation in patients with chronic myeloid leukaemia. Other studies show efficacy of lenograstim in patients with acute lymphoblastic leukaemia, aplastic anaemia, in children with severe chronic neutropenia and in the reversal of neutropenia related to antiviral therapy in patients with AIDS, although data are not extensive.

Cost analyses of lenograstim have been carried out from a hospital perspective, although results have been inconclusive. Cost-effectiveness or cost-benefit data are lacking at present.

Lenograstim is well tolerated, with bone pain and injection site reactions being reported most frequently in clinical trials.

Conclusions: Lenograstim has been confirmed as a valuable adjunct to minimise the haematological toxicity of myelosuppressive chemotherapy in patients with malignant disease. The drug also enhances neutrophil recovery in patients undergoing stem cell rescue, and assists PBSC mobilisation. Data indicate clinical benefit with lenograstim in myeloid disorders, with no evidence of malignant blast cell proliferation. Further studies are required to assess more fully the pharmacoeconomic implications of the use of lenograstim and other recombinant growth factors, to provide more data on the efficacy of the drug in the management

of disease-related neutropenia, and to clarify fully its position relative to filgrastim.

Pharmacological Properties

Lenograstim is the glycosylated recombinant form of human granulocyte colony stimulating factor (rHuG-CSF). The drug supports the differentiation of neutrophil-committed colony-forming cells and increases absolute neutrophil counts (ANC) in a dose-dependent manner.

Postulated functional effects of lenograstim on neutrophils include increased phagocytic activity, activation, recruitment and adhesion. These effects appear to be mediated by changes in a variety of neutrophil surface proteins. Current data suggest that rHuG-CSFs do not stimulate the proliferation of leukaemic blasts *in vivo*, although the safety of these agents in patients with myeloid conditions remains to be fully confirmed.

Lenograstim exhibits dose-dependent pharmacokinetic characteristics, with peak serum levels being proportional to the injected dose. There is no evidence of accumulation after repeated administration. Absolute bioavailability after subcutaneous doses of 2 to 5 μg/kg is approximately 30%, and the apparent volume of distribution is approximately 1 L/kg. Serum elimination half-lives after subcutaneous or intravenous injection are approximately 3 or 1 to 1.5 hours, respectively. Routes of metabolism and excretion have not been fully ascertained, but a very small proportion only of each dose is excreted unchanged in urine.

Therapeutic Use

Standard Dose Chemotherapy. A phase II randomised placebo-controlled study in 64 patients showed significant reductions ($p < 0.05$) in the median duration of neutropenia after chemotherapy with 14-day courses of subcutaneous lenograstim 0.5, 2, 5 or 10 μg/kg/day, and the authors recommended the 5 μg/kg/day dosage for future use.

Results from 2 randomised placebo-controlled phase III trials showed significant reductions in median duration of neutropenia ($<1.0 \times 10^9$/L) after 8- to 10-day courses of lenograstim 5 μg/kg/day subcutaneously between chemotherapy cycles in patients with inflammatory breast cancer or non-Hodgkin's lymphoma (NHL). Effects persisted throughout all 4 treatment cycles in both studies, and there were significant reductions in incidence of laboratory-confirmed infection, duration of hospital stay for treatment of infection and use of antibiotics. Increases in dose intensity made possible by treatment with lenograstim did not translate into improvements in tumour response or 3-year survival, however.

Similar efficacy in terms of rate of hospitalisation for febrile leucopenia has been shown for subcutaneous lenograstim 263 μg/day compared with oral ciprofloxacin 500 mg/day plus amphotericin B 2 g/day in a nonblind randomised comparison in 40 patients with breast cancer. The incidence of leucopenia ($<1.0 \times 10^9$/L) after chemotherapy was significantly lower, but that of febrile leucopenia significantly higher, with lenograstim.

Chemotherapy Dose Intensification. The use of subcutaneous lenograstim 5 μg/kg/day on day 2 to day 14 of treatment cycles based on fluorouracil, epirubicin and cyclophosphamide in patients with breast cancer resulted in a reduction in cycle time from 3 to 2 weeks. Encouraging tumour response rates have been reported in anthracycline-resistant or heavily pretreated patients receiving lenograstim with docetaxel or paclitaxel. Preliminary reports from phase III studies in patients with breast cancer also show increases in relative dose intensity in patients receiving lenograstim, although subsequent effects on tumour response and survival are not clear.

Reductions in cycle length have also been achieved with the addition of lenograstim in patients with small cell lung cancer (SCLC) undergoing cisplatin- or anthracycline-based chemotherapy. Phase III data from 280 patients with SCLC have shown the addition of lenograstim 150 μg/m^2/day subcutaneously to each of 6 cycles of doxorubicin, cyclophosphamide and etoposide to be associated with a significantly decreased requirement for chemotherapy dose reduction (≥1 reduction in 17.3 *vs* 27.7% of patients receiving chemotherapy alone; $p = 0.037$), although there was no significant increase in median survival time in patients who received lenograstim. Intensification of chemotherapy regimens has also been achieved with lenograstim in patients with soft tissue sarcoma, NHL or ovarian cancer, although clinical benefit in terms of improved tumour response and survival requires further investigation.

High Dose Chemotherapy with Stem Cell Rescue. After significantly accelerated neutrophil recovery was observed in patients undergoing bone marrow transplantation (BMT) who received lenograstim in a phase II trial, a phase III randomised, double-blind and placebo-controlled study has shown 30 and 41% reductions, respectively, in median times to achieve ANC ≥0.5 and 1.0×10^9/L (both $p < 0.001$ *vs* placebo) with lenograstim 5 μg/kg/day intravenously after BMT. In this study of 298 evaluable patients with lymphoma, myeloma, acute lymphoblastic leukaemia or other malignancies, there were also significant reductions relative to placebo in median durations of hospitalisation, antibiotic use, total parenteral nutrition (TPN; intravenous hyperalimentation), infection and febrile neutropenia, although there were no significant effects of lenograstim on the actuarial risk of disease relapse or the 1-year survival rate.

As well as assisting neutrophil recovery after BMT, lenograstim has been used to stimulate the production of peripheral blood stem cells for autologous transfusion after aggressive chemotherapy. Two studies in 141 previously treated patients with lymphoma showed median times to achieve ANC $\geq 0.5 \times 10^9$/L of 11 to 12 days after chemotherapy followed by lenograstim-assisted autologous PBSC transplantation (PBSCs collected after mobilisation with lenograstim 263 μg/day subcutaneously after cyclophosphamide 1.5 g/m^2 on day 1). Approximately half the patients enrolled received filgrastim 10 μg/kg/day in 1 study; although results were presented collectively, stem cell mobilisation effects were stated to be similar between agents.

Similar median neutrophil recovery times (13 to 15 days to ANC $> 0.5 \times 10^9$/L) were shown with PBSC transplantation after subcutaneous lenograstim 5, 7.5 or 10 μg/kg/day with cyclophosphamide for mobilisation in 29 children with solid tumours treated with high dose melphalan in a double-blind dose-finding study.

Data from a randomised nonblind comparison in 61 patients receiving stem cell support from matched sibling donors indicate similar efficacy of lenograstim and filgrastim (median dosages 4 and 10.3 μg/kg/day, respectively) when either drug was given after stem cell transplantation.

The feasibility of using lenograstim to mobilise PBSCs from healthy donors for allogeneic transplantation has been demonstrated in Japanese and European trials, and reflects a trend towards allogeneic PBSC transplantation since the early 1990s. In dose-response terms, lenograstim mobilises CD34+ cells (the number of which affects the probability of successful engraftment) more efficiently than filgrastim in healthy volunteers. In a pilot study, 54 patients with leukaemia or myelodysplasia received PBSCs obtained from sibling donors who had received

a priming regimen of lenograstim 10 μg/kg/day subcutaneously for 5 days. After initial myeloablation with high intensity chemo- and/or radiotherapy, 51 patients achieved an ANC of 0.5×10^9/L within 15 days. The rate of survival was 50% after a median 25-month follow-up.

Myeloid Leukaemias. Although the use of rHuG-CSF in patients with myeloid conditions is controversial because of fears of stimulation of leukaemic blast cells, clinical studies of lenograstim have been carried out in this setting.

Randomised placebo-controlled trials carried out in Japan have shown accelerated neutrophil recovery and evidence of infection-related clinical benefit with lenograstim 5 μg/kg/day intravenously for 14 days after consolidation chemotherapy in patients with acute myeloid leukaemia (AML). In addition, European placebo-controlled trials have shown significant improvements in neutrophil recovery times, together with increased rates of complete remission of disease, with lenograstim after induction chemotherapy in patients with AML. Increases over placebo in complete haematological remission in 2 of these studies were 49 and 38% with lenograstim, although the reason for this effect has not been determined: high rates of complete remission of AML have also been reported after treatment with idarubicin-based protocols with and without addition of lenograstim. Integrated European data show reductions against placebo in incidence and duration of infection in lenograstim recipients aged 55 years and over.

Data are also available to indicate a potential role for lenograstim in the mobilisation of PBSCs for autotransplantation as an alternative to autologous BMT in patients with AML.

Studies conducted recently show that lenograstim might be used for the mobilisation of Philadelphia chromosome (Ph)-negative (i.e. nonmalignant) PBSCs for autotransplantation in patients with chronic myeloid leukaemia (CML) who are not eligible for conventional allogeneic BMT. Administration of lenograstim 150 μg/m^2/day subcutaneously or intravenously as part of a cytarabine-based mobilisation protocol resulted in complete cytogenetic remission in the leucapheretic product in 21% of 29 patients in 1 study; the same dosage of lenograstim was associated with a Ph-positive cell content of less than 35% in 91% of 47 evaluable leucaphereses from 20 patients in a second trial.

Increases from baseline in leucocyte counts have been achieved after 7 to 14 days' lenograstim therapy (5 μg/kg/day or 263 μg/day) in 2 small studies in patients with myelodysplasia, with no evidence of progression to AML.

Acute Lymphoblastic Leukaemia. Augmentation of neutrophil recovery, but no effect on patterns of infection or antibiotic use, was shown with intravenous or subcutaneous lenograstim in 2 randomised studies in patients with acute lymphoblastic leukaemia (ALL) or acute undifferentiated leukaemia (AUL).

Increased chemotherapy dose intensities with decreased duration of fever, hospitalisation and intravenous antibiotic treatment were achieved in children with ALL receiving lenograstim 5 μg/kg/day, but there was no improvement in 3-year disease-free survival.

Aplastic Anaemia. Addition of lenograstim 5 μg/kg/day subcutaneously to immunosuppressive therapy with antilymphocyte globulin, methylprednisolone and cyclosporin in 40 patients with severe aplastic anaemia (SAA) resulted in trilineage-complete responses and transfusion independence in 82% of participants, with actuarial survival of 92% after median follow-up of 428 days. Phase III data have shown addition of subcutaneous lenograstim 5 μg/kg/day in 53 of

102 patients undergoing immunosuppressive therapy with cyclosporin and antithymocyte globulin to increase the proportion of patients with complete ANC response ($\geq 1.5 \times 10^9$/L) significantly after 112 days (83 *vs* 44.9% without lenograstim; $p = 0.001$). There was no apparent effect of lenograstim on long term haematopoietic recovery or survival after a median follow-up of 23 months.

Other Neutropenic Conditions. Rates of infection and hospitalisation were reduced significantly relative to figures obtained before lenograstim treatment in a phase II study in 19 children with severe chronic neutropenia who received subcutaneous therapy with lenograstim. An induction dosage of 5 μg/kg/day was sufficient to obtain a neutrophil response in 15 patients. Clinical improvement has also been noted in children with glycogen storage disease Ib who received subcutaneous lenograstim at a median initial dosage of 5 μg/kg/day.

Encouraging results have been obtained with lenograstim therapy in a small number of patients with Felty's syndrome, and subcutaneous treatment has been used successfully to manage immunosuppressant-induced leucopenia after renal transplantation. In addition, preliminary data from a randomised single-blind phase II study have indicated lenograstim 50 μg/m^2/day subcutaneously to be suitable for the management of ganciclovir-induced neutropenia in patients with AIDS.

Pharmacoeconomic Considerations

Pharmacoeconomic studies of lenograstim have to date focused on cost issues from a hospital perspective. Attempts have not been made to assign values to health outcomes such as improvements in quality of life or years of life gained.

Pharmacoeconomic evaluations of lenograstim in 3 phase III studies showed lenograstim therapy to be associated with reductions in hospitalisation and total direct costs in patients with breast cancer or NHL, and reduced cost of antibiotic therapy in patients with breast cancer, NHL or SCLC. Intensification of chemotherapy in patients who received lenograstim to assist neutrophil recovery resulted in an increase in chemotherapy drug costs. Increasing interest in allogeneic PBSC transplantation in preference to BMT has led to a case control study (n = 17) in which the direct medical costs associated with transplantation of lenograstim-mobilised PBSCs were shown to be substantially (29%; $p = 0.006$) lower than those in a historical control group of 17 patients undergoing allogeneic BMT.

Results are available from a well designed and robust cost analysis in which children with NHL were randomised to receive 2 courses of intensive induction chemotherapy with (n = 75) or without (n = 72) lenograstim 5 μg/kg/day subcutaneously for 6 to 15 days. The total cost from a hospital perspective of lenograstim-assisted induction therapy was $US29 765 per patient; without lenograstim, the cost was $US30 774 (1996 values). Overall, the acquisition cost of lenograstim was balanced by 2 additional days in hospital in patients who did not receive the drug.

A saving of approximately $US1800 (1997 values) per course of chemotherapy from a hospital perspective was indicated when lenograstim 150 μg/m^2/day rather than filgrastim 10 μg/kg/day was used after autologous BMT in a series of 36 patients (55 chemotherapy courses) with solid tumours undergoing intensive chemotherapy. This saving was attributed to a difference in acquisition cost between the 2 growth factors.

Tolerability

Data from clinical studies indicate overall adverse reaction rates with lenograstim therapy to be similar with those seen with placebo. Bone pain and injection site

reactions were the most commonly reported events in patients receiving lenograstim for chemotherapy-induced neutropenia, and were more frequent than with placebo. A database of pooled adverse reaction reports from 1495 patients shows incidences of adverse events attributed to lenograstim as follows: fever 1.2%; lumbar pain 1.1%; increased blast cell counts in patients with AML 0.9%; hepatic disturbances 0.5%; bone pain 0.4%; eruptions/rashes 0.4%.

No association has been found between clonal cytogenetic abnormalities and dysplasia of bone marrow in patients receiving lenograstim, but all rHuG-CSFs have been linked to isolated episodes of interstitial pneumonia and respiratory distress syndrome. There are no tolerability data relevant to the use of lenograstim in pregnant or nursing women, the elderly, infants or patients with hepatic or renal dysfunction.

Dosage and Administration

There are variations between Western countries and Japan in the recommended dosages and licensed indications for lenograstim. International dosage and administration guidelines for Western patients recommend a dosage of 150 μg/m^2/day (equivalent to 5 μg/kg/day as used in clinical trials) to reduce the duration of chemotherapy-induced neutropenia and to assist PBSC mobilisation. Subcutaneous administration is recommended, except after BMT where a 30-minute intravenous infusion should be used to assist recovery from neutropenia.

Lenograstim should not be given at the same time as cytotoxic chemotherapy, and the drug is not recommended in patients with severe hepatic or renal insufficiency, or in nursing mothers. There are no dosage recommendations for the elderly, infants or pregnant women.

1. The Immune System and Growth Regulatory Factors

Normal immune function in humans involves the proliferation and differentiation of leucocytes in myeloid bone marrow tissue. This results in a rapid and sustained rise in the leucocyte count in the plasma of patients with active infection. Leucocytes are divided into 2 types:

- mononuclear cells (monocytes and lymphocytes), responsible for the mounting of the immune response
- granulocytes (neutrophils, eosinophils and basophils), responsible for the inactivation by phagocytosis of invading micro-organisms, and involved in the acute inflammatory response.

The name granulocyte arises from the granular appearance of the cytoplasm of these cells under microscopic examination; the neutrophils are by far the most abundant of this group.[1] The various cell types and their lineages are shown in figure 1.

The colony stimulating factors are a series of cytokines (or growth factors) that act on various stages of blood cell proliferation and differentiation. Granulocyte colony stimulating factor (G-CSF) is a haematopoietic growth factor that regulates chiefly the formation and development of neutrophils within the bone marrow and their release into the peripheral circulation (fig. 1). It also increases the expression of chemotactic receptors on mature neutrophils, thereby enhancing chemotaxis and promoting phagocytosis and antimicrobial activity at sites of infection (reviewed by Hollingshead and Goa[2]). Other such regulatory cytokines that have been identified and molecularly cloned include granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage colony stimulating factor (M-CSF).

Human G-CSF is produced *in vivo* in only very small quantities. However, developments in gene technology have permitted the isolation and cloning of this and other haematopoietic growth factors. Lenograstim is the international non-proprietary name for the glycosylated recombinant form

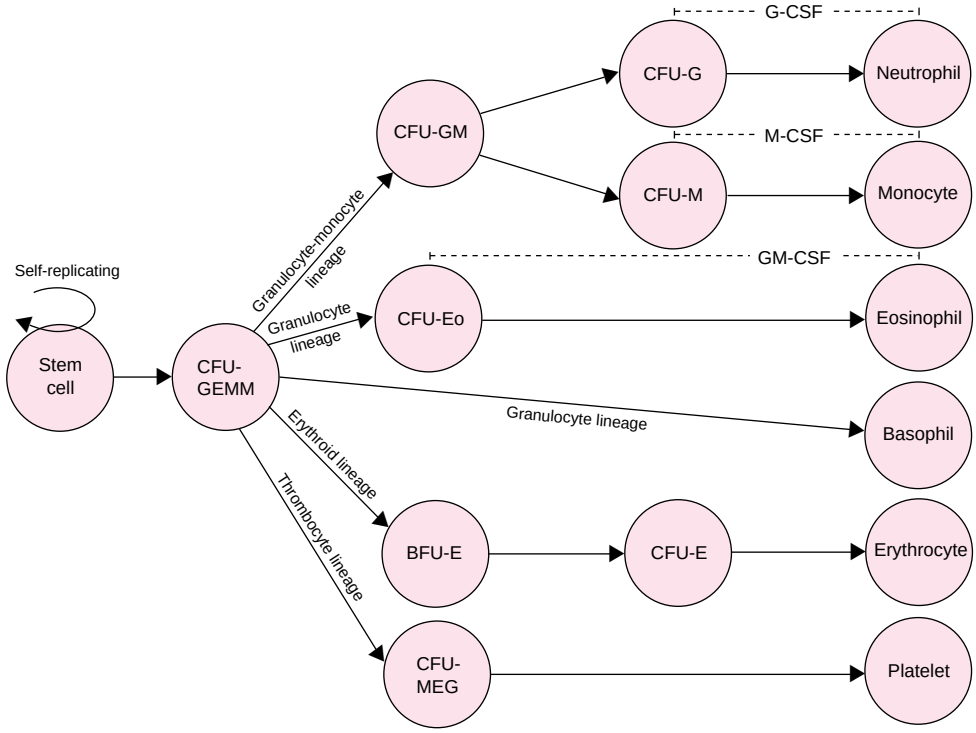

Fig. 1. Simplified representation of haematopoiesis. Sites of action are shown for granulocyte (G-CSF), granulocyte-macrophage (GM-CSF) and macrophage (M-CSF) colony stimulating factors.[2] **BFU** = burst-forming unit; **CFU** = colony-forming unit; **E** = erythroid; **Eo** = eosinophil; **G** = granulocyte; **GEMM** = granulocyte-erythrocyte-megakaryocyte-monocyte; **GM** = granulocyte-monocyte; **M** = monocyte; **MEG** = megakaryocyte.

of human G-CSF (rHuG-CSF). This compound, which has 174 amino acids and a mass of approximately 20kD, is expressed as a glycoprotein in a Chinese hamster ovary cell line and has biological activity indistinguishable from that of endogenous human G-CSF (fig. 2).[3,4] Both are glycosylated at threonine 133, unlike the other rHuG-CSF, filgrastim, which is produced in *Escherichia coli* cells and carries an extra methionine residue at the N-terminal.[4] Glycosylation increases the *in vitro* stability of G-CSF in the presence of alterations in pH and temperature, and increases the resistance of the compound to degradation by proteases in serum.[6-9]

The availability of recombinant forms of G-CSF has resulted in intense interest in the use of these compounds to reduce the risk of life-threatening infections in patients with neutropenia, particularly that caused by the administration of cytotoxic chemotherapy. The use of lenograstim in patients undergoing chemotherapy for nonmyeloid malignancies [including myeloablative therapy with stem

cell rescue provided by bone marrow transplantation (BMT) or peripheral blood stem cell (PBSC) infusion] and several other neutropenic conditions is well documented and has been reviewed previously in *Drugs*.[5] Since then, further data relevant to lenograstim in patients receiving cytotoxic chemotherapy have become available in addition to information on the use of the drug in other conditions including PBSC mobilisation in patients and healthy donors, leukaemia, myelodysplasia or chronic severe neutropenia, and in neutropenia in patients with AIDS.

2. Summary of Pharmacological Properties

2.1 Pharmacodynamic Properties

Lenograstim increases absolute neutrophil counts (ANC; i.e. polymorphonuclear cells plus band forms) in a dose-dependent manner in non-neutropenic and neutropenic patients with cancer (reviewed by Frampton et al.[5]). The drug supports the differentiation of neutrophil-committed colony-forming cells *in vitro* and the early stages of eosinophil differentiation,[10] shortens significantly the duration of chemotherapy-induced neutropenia (section 3.1.1) and accelerates recovery of neutrophil counts in patients undergoing BMT (section 3.2.1). Lenograstim also increases PBSC counts (section 3.2.2), with maximum counts being achieved after 4 to 7 days.[11]

Although the precise function of the sugar chain, which accounts for approximately 4% of the molecular weight of lenograstim, is not fully understood, bioassay data indicate that glycosylation increases the biological potency of lenograstim over that of filgrastim.[12] Results of nuclear magnetic resonance studies indicate that glycosylation confers molecular rigidity and improved receptor affinity;[13] Scatchard analysis has indicated that the affinity of lenograstim for G-CSF receptor sites is approximately 3 times that of filgrastim.[14] Studies of neutrophil colony formation have indicated glycosylation to confer potency advantages

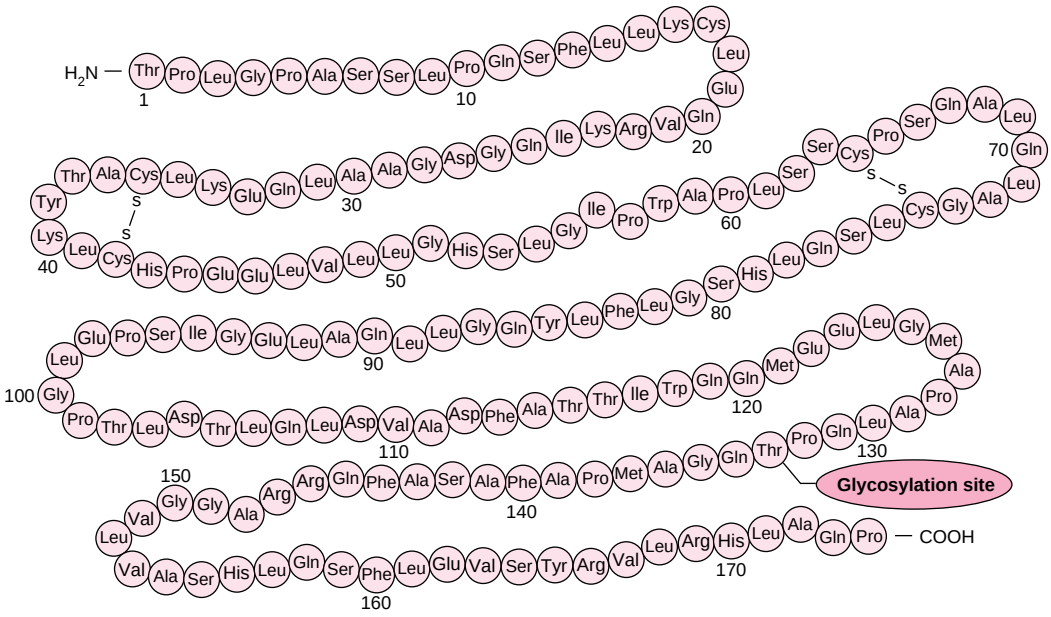

Fig. 2. Primary amino acid sequence as determined for lenograstim and natural human granulocyte colony stimulating factor (G-CSF). The glycosylation site at amino acid 133 (threonine, Thr) is the same for both natural human G-CSF and lenograstim. The alternative recombinant human G-CSF filgrastim carries an extra methionine (Met) moiety at the N-terminal.[5]

Table I. Postulated effects of recombinant human granulocyte colony stimulating factor (rHuG-CSF) on human neutrophils

Effect	References
Enhanced capacity for adhesion (to nylon fibres and physiological substrates)	21,22
Increased phagocytic activity	21,23,24
Increased expression of neutrophil surface antigens CD11b, CD13, CD14, CD18, CD35, CD32, CD45, CD54, CD64, CD66b and CD67, and reduced expression of CD62L (L-selectin) and CD16 (all changes indicate effects on functional responses including activation, maturation, recruitment, migration and adhesion)	21,23,25-28
Unchanged lucigenin-enhanced chemiluminescence (suggests no effect of rHuG-CSF on peroxide-producing enzyme complexes of respiratory bursts)	21
Increased luminol-enhanced chemiluminescence (suggests increased availability of myeloperoxidase in presence of rHuG-CSF)	21
Increased superoxide anion production in response to N-formylmethionylleucylphenylalanine (FMLP)	23
Improved neutrophil survival	29
Activation of neutrophil degranulation with mobilisation of secretory vesicles	26,30
Reduced chemotaxis towards zymosan-activated serum, FMLP and interleukin-8	21

upon lenograstim *in vitro* when compared with non-glycosylated forms of rHuG-CSF (including filgrastim):[15] lenograstim stimulated colony formation at concentrations 16 times lower that those required for 2 non-glycosylated rHuG-CSFs. It is therefore important to ensure that comparisons between the 2 types of rHuG-CSF are carried out with bioequivalent doses, as shown by effects on PBSC progenitor formation.

Other *in vitro* data show unaltered morphology of polymorphonuclear neutrophils exposed to lenograstim (unlike those exposed to filgrastim),[16] and enhanced priming associated with glycosylation of the rHuG-CSF molecule of superoxide production by human neutrophils.[17]

Approximately 100 antigen groups (known as clusters of differentiation or CDs) have been identified on the surface of haematopoietic cells,[18] and CD34 antigen expression is commonly used to measure progenitor cell yields. Similar mobilisation of CD34+, CD34+/38- and CD34+/DR- cell subsets was reported in 30 patients with breast cancer with bioequivalent dosages of lenograstim [mean dosage 6.4 μg/kg/day (0.82 MU/kg/day)] and filgrastim [mean dosage 8.4 μg/kg/day (0.84 MU/kg/day)].[19] On the other hand, mobilisation of progenitor cells was greater with lenograstim 10 μg/kg/day for 5 days than with the same (i.e. non-bioequivalent) dosage of filgrastim administered subcutaneously in healthy volunteers.[20]

Table I shows a summary of the postulated functional effects on human neutrophils of rHuG-CSF (lenograstim or filgrastim). Overall, available data show increased phagocytic activity and effects on expression of surface proteins indicative of neutrophil activation, recruitment and adhesion in healthy volunteers receiving either the glycosylated or non-glycosylated form (table I). Studies published since the previous review in *Drugs* have shown further evidence of enhancement of functional responses of neutrophils to stimulation by physiological agonists in healthy volunteers treated with lenograstim specifically, including enhanced capacity for adhesion after dosages of 2.5 to 7.5 μg/kg/day for 5 to 6 days.[21,22] This effect may be mediated by an increase in functional capacity of cell surface antigens CD11b and CD18,[22] but requires further investigation (table I).

Fears that recombinant human growth factors may stimulate the growth of leukaemic blast cells *in vivo* do not appear to have been borne out in pharmacodynamic or clinical studies.

2.2 Pharmacokinetic Properties

The pharmacokinetics of lenograstim have been evaluated in patients with nonmyeloid malignancies (reviewed by Frampton et al.[5]) and in healthy volunteers,[31-33] and are similar in both populations. Major parameters assessed after subcutaneous administration of single doses in healthy volunteers are summarised in table II.

Overall, lenograstim exhibits dose-dependent pharmacokinetic characteristics, with peak serum concentrations after repeated subcutaneous or intravenous doses being proportional to the injected dose.[34] There is no evidence of accumulation after repeated administration, and no sequence effects were observed in a crossover study.[33]

The absolute bioavailability after subcutaneous administration of doses of 2 to 5 μg/kg is approximately 30% (table II), and the apparent volume of distribution is approximately 1 L/kg.[34] ANCs increase in a dose-dependent manner after intravenous or subcutaneous administration of lenograstim,[34] but more prolonged rises with higher peaks have been reported with the subcutaneous route.[33]

The serum elimination half-life after subcutaneous administration is approximately 3 hours (table II), but is shorter after repeated intravenous infusion (1 to 1.5 hours).[31,33] Routes of metabolism and excretion remain to be clarified, but lenograstim is thought to be metabolised to its constituent peptides.[34] A very small proportion of each dose is excreted unchanged in the urine.[33]

3. Therapeutic Use

3.1 Patients with Nonmyeloid Malignancies

Myelosuppression is one of the major dose-limiting toxicities associated with cytotoxic chemotherapy in patients with cancer. The success of chemotherapy depends on the achievement of the correct balance between the delivery of doses sufficient to maximise antitumour effects and the avoidance of unacceptable levels of toxicity. Bone marrow suppression, manifested particularly as neutropenia, may result in severe and possibly life-threatening infection in patients undergoing cytotoxic chemotherapy. It was first reported over 30 years ago that there is a dramatic increase in the incidence of serious infections when granulocyte counts fall below 0.5×10^9/L in patients with leukaemia, and that the risk of infection increases with the duration of neutropenia.[35]

Table II. Mean pharmacokinetic characteristics of subcutaneously administered first doses of lenograstim in healthy volunteers[31-33]

Parameter	Dose (μg/kg)		
	2	5	10
C_{max} (mg/L)	2.7	10.3-11.9	30.0
t_{max} (h)	5.3	6.0	8.7
AUC_{24} (mg/L • h)	24.3	89.8-102.3	319.3
$t_{½β}$ (h)	3.1-3.3	2.3-3.0	NR
CL_R (L/h)	<0.03 for all doses		
F (%)	33.9	30.2	25.7

AUC_{24} = area under the serum drug concentration versus time curve from zero to 24h; **C_{max}** = peak serum concentration; **CL_R** = renal clearance; **F** = bioavailability; **NR** = not reported; **$t_{½β}$** = serum elimination half-life; **t_{max}** = time to C_{max}.

In addition to limiting or interrupting chemotherapy, neutropenia in patients with cancer often results in hospitalisation for treatment with intravenous antibacterial agents. Infectious disease is the most common cause of mortality in patients receiving cytotoxic chemotherapy and accounts for 40% of treatment-related deaths in patients with solid tumours and 65% of such deaths in patients with lymphoma (reviewed by Faulds et al.[36] and Goa & Bryson[37]).

Observations from clinical practice over the last 30 years have led to a general consensus that patients with an ANC of 0.5×10^9/L or less should be considered neutropenic. From a practical viewpoint, patients whose ANC is between 0.5 and 1 $\times 10^9$/L but is falling rapidly because of recent antineoplastic therapy should also be considered to have neutropenia.[38] The definition of a febrile patient is somewhat more arbitrary, but consensus guidelines define fever as a single temperature of 38.5°C or more, or 3 readings of at least 38°C taken at least 4 hours apart within a single 24-hour period.[38] More recent guidelines from the US National Comprehensive Cancer Network define febrile neutropenia as a single oral temperature of 38°C with an ANC below 0.5×10^9/L, or below 1 $\times 10^9$/L with a predicted decline to less than 0.5×10^9/L over the next 48 hours.[39]

3.1.1 Standard Dose Chemotherapy

The primary use of lenograstim has been in the alleviation of chemotherapy-induced neutropenia, and studies have focused on reductions due to lenograstim in the duration and intensity of neu-

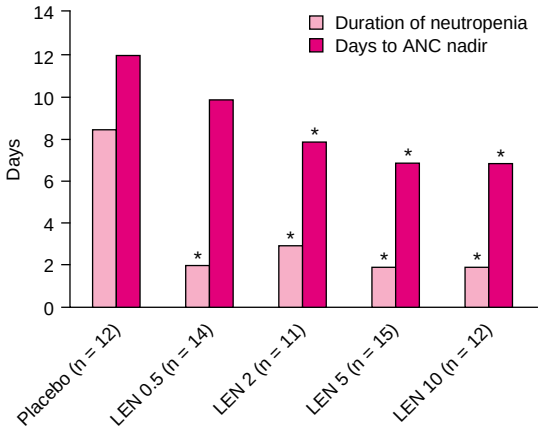

Fig. 3. Neutrophil responses after 4 subcutaneous dosages of lenograstim (LEN) given prophylactically after standard dose chemotherapy. 64 patients were evaluated in this randomised and placebo-controlled trial. Dosages are in μg/kg/day, and all values are medians. Malignancies included breast, lung, ovarian and gastric cancer and lymphoma. 27% of patients received epirubicin alone; the others received combination chemotherapy (not specified).[41] **ANC** = absolute neutrophil count; * $p < 0.05$ *vs* placebo.

tropenia. Clinical end-points such as incidence of febrile neutropenia and confirmed infection, rates of hospitalisation and use of antibiotics have also been measured in some studies. Prophylactic administration of lenograstim has been shown to be more effective than a therapeutic regimen (i.e. started after the onset of neutropenia).[40] In the studies reviewed here, lenograstim was administered prophylactically after chemotherapy and before the onset of neutropenia.

Phase II data from a randomised vehicle (placebo)-controlled study showed significant ($p < 0.05$) reductions in the median duration of neutropenia ($<1.0 \times 10^9$/L) with 14-day courses of lenograstim 0.5, 2, 5 or 10 μg/kg/day subcutaneously, started the day after completion of chemotherapy, in 64 evaluable patients with solid tumours or lymphoma.[41] Mean neutrophil counts recovered to more than 1.0×10^9/L by day 13 in the placebo group, compared with days 11, 10, 8 and 7 in the 0.5, 2, 5 and 10 μg/kg/day lenograstim groups, respectively. In addition to having a similar effect to 0.5 and 2 μg/kg/day relative to placebo on the median duration of neutropenia (fig. 3), time to ANC nadir (fig. 3) and area under the curve of ANC versus time, the 5 μg/kg/day dosage also decreased the total area indicative of neutropenia on the curve of ANC versus time. No additional benefit was obtained with lenograstim 10 μg/kg/day, and the authors concluded that a dosage of 5 μg/kg/day should be used in future studies, although Japanese and Australian investigators have assessed lower dosages in adult patients with lymphoma or small cell lung (SCLC), breast, gastric, testicular, ovarian or urothelial cancer, and in children with malignant disease.[42-47]

Two randomised and placebo-controlled phase III clinical studies showed significant reductions in median duration of neutropenia ($<1.0 \times 10^9$/L) with subcutaneous lenograstim 5 μg/kg/day for 8 to 10 days between chemotherapy cycles in patients with inflammatory breast cancer[48] or non-Hodgkin's lymphoma (NHL)[49] [table III]. The median ANC nadir was also significantly higher in lenograstim recipients with inflammatory breast cancer than in those who received placebo (table III). Effects persisted throughout all 4 treatment cycles in both studies, and a similar pattern was observed when neutropenia was defined as ANC less than 0.5×10^9/L. Lenograstim treatment was also associated with significant reductions in incidence of laboratory-confirmed infection during neutropenia, shorter duration of hospitalisation for treatment of infection and reduced use of antibacterial agents (table III).

Retreatment with chemotherapy after the first cycle was possible on the planned date at cycles 2, 3 and 4, respectively, in 84, 85 and 84% of patients with inflammatory breast cancer who received lenograstim.[48] Corresponding percentages of patients in the placebo group were 81, 63 and 74. In the study in patients with NHL, the mean relative dose intensity was significantly increased in patients receiving lenograstim (93.3 *vs* 80.1%; $p = 0.0001$).[49] No effects of lenograstim treatment on tumour response or 3-year survival were evident in either study.

Decreased incidence and severity of neutropenia have also been reported in an ongoing randomised multicentre study in 423 patients with advanced colorectal cancer receiving camptothecin 350 mg/m^2 every 21 days with or without lenograstim 150 μg/m^2 (route not stated) from day 2 to day 10 of each cycle.[50] Preliminary data indicate febrile (not defined) neutropenia in 3% of 195 patients (0.8% of 887 cycles) who have received lenograstim and 2% of 101 (0.4% of 489 cycles) who have not. Grade 3 to 4 neutropenia has been reported in 19.5% of lenograstim recipients and 44% of those who have not received the drug (7 *vs* 16.3% of cycles).

Similar efficacy between treatments has been shown in a study comparing lenograstim with antimicrobial prophylaxis using ciprofloxacin and amphotericin B.[51] In this trial, 40 patients with breast cancer received 3 cycles of cyclophosphamide 1.5 g/m^2, epirubicin 80 mg/m^2 and fluorouracil 1 g/m^2 followed by 3 cycles of cyclophosphamide 1 g/m^2 with fluorouracil 600 mg/m^2 (day 1) and methotrexate 1.5 g/m^2 (day 2). Chemotherapy was scheduled for administration every 21 days, and patients were randomised in a nonblind fashion to prophylaxis with lenograstim 263 μg/day subcutaneously from day 3 to day 12 (n = 18) or oral ciprofloxacin 500 mg/day with oral amphotericin B 2 g/day from day 3 to day 17 (n = 22) of each cycle.

As might be expected, the incidence of leucopenia (leucocyte count $<1.0 \times 10^9$/L) was significantly lower in patients receiving lenograstim (fig. 4). However, febrile leucopenia (temperature >38.5°C) was more frequent in these patients (fig. 4), and there was no difference between groups in the rate of hospitalisation for this end-point. Of patients receiving lenograstim, 39% required hospitalisation after 10 of 108 cycles, whereas 32%

Table III. Summary of randomised, double-blind, placebo (PL)-controlled phase III trials of lenograstim (LEN) in patients (pts) with nonmyeloid malignancies. All doses (in μg/kg/day) were given subcutaneously for the periods indicated starting 24 hours after chemotherapy for 4 cycles. All cytotoxic drugs were given intravenously unless stated otherwise

Reference	Malignancy and chemotherapy	Regimen (no. of evaluable pts at C1)	Median duration of neutropenia (d) [ANC < 1.0 × 10^9/L]		Median ANC nadir (× 10^9/L)		Incidence of microbiologically confirmed infection during neutropenia (%)	Mean duration of hospitalisation for infection (d)	Mean duration of antibiotic therapy (d)
			C1	C4	C1	C4			
Chevallier et al.[48]	Inflammatory breast cancer. FEC-HD induction protocol every 21d	LEN 5 d6–15 (59)	3***	4***	0.16**	0.28***	8.2*	3.7**	8.7**
		PL d6–15 (61)	8	8	0.09	0.1	22.0	8.3	15.4
Gisselbrecht et al.[49]	NHL. LNH-84 induction protocol every 14d	LEN 5 d6–13 (80)	2***	1***	NR	NR	18.5*	5.3*	6.0**
		PL d6–13 (80)	6	5	NR	NR	34.0	10.0	11.8

ANC = absolute neutrophil count; **C** = cycle; **d** = day(s); **FEC-HD** = fluorouracil 750 mg/m^2 continuous infusion d1–4, epirubicin 35 mg/m^2 d2–4, cyclophosphamide 400 mg/m^2 d2–4; **LNH-84** = doxorubicin 75 mg/m^2 or mitoxantrone 12 mg/m^2 d1, cyclophosphamide 1.2 g/m^2 d1, vindesine 2 mg/m^2 d1 & 5, prednisone 60 mg/m^2 orally d1–5, methotrexate 15 mg intrathecally d1; **NHL** = non-Hodgkin's lymphoma; **NR** = not reported; * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ *vs* PL.

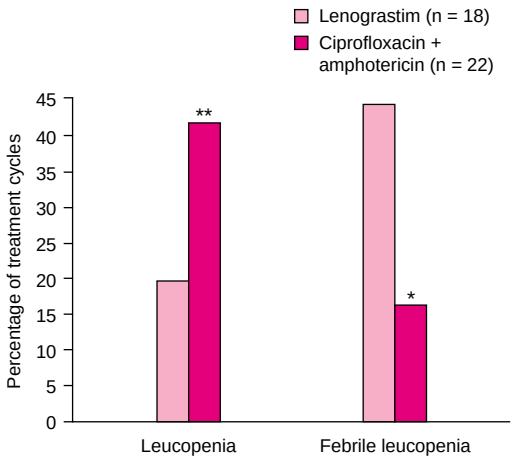

Fig. 4. Incidence of leucopenia (leucocyte count <1.0 × 10^9/L) and febrile leucopenia (temperature >38.5°C) in a randomised study comparing lenograstim with ciprofloxacin plus amphotericin B. Patients with breast cancer undergoing chemotherapy (6 cycles) were randomised to subcutaneous lenograstim 263 μg/day (days 3–12) or oral ciprofloxacin 500 mg/day with amphotericin B 2 g/day (days 3–17). Incidences of leucopenia were calculated as percentages of all treatment cycles, whereas incidences of febrile leucopenia were calculated as percentages of cycles in which leucopenia was reported.[51] * $p < 0.025$, ** $p < 0.0025$ *vs* lenograstim.

(7 of 98 cycles) of those receiving ciprofloxacin with amphotericin B did so.

3.1.2 Chemotherapy Dose Intensification

Accumulating evidence has shown that intensity of cytotoxic chemotherapy is an important determinant of outcome in patients with chemosensitive tumours.[52] Models of cytotoxic drug resistance indicate that aggressive treatment reduces the risk of relapse, and much interest has therefore resulted in the use of human growth factors to ameliorate the haematological toxicity associated with increased dose intensity of standard regimens. As well as being given prophylactically after conventional myelosuppressive chemotherapy to reduce the depth and duration of neutropenia (section 3.1.1) and to facilitate the delivery of planned doses on time, rHuG-CSF has also been used to support increased doses or accelerated administration of chemotherapy in attempts to improve rates of response to treatment. Examples of patients in whom such an approach has been evaluated include those with SCLC, in whom response rates to initial chemotherapy are high but relapse is common,[53] and those with breast cancer.[54]

Breast Cancer

A 50% increase in chemotherapy dose intensity was achieved with the use of subcutaneous lenograstim 5 μg/kg/day on day 2 to day 14 of each treatment cycle in a phase I study in patients with breast cancer.[54] The interval between administration of fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 was reduced from 3 to 2 weeks in this study in 14 patients with stage II to IV disease, although further dose intensification was precluded by excessive toxicity. Encouraging overall tumour response rates have also been obtained in phase II studies in anthracycline-resistant heavily pretreated patients receiving docetaxel (44%)[55] or paclitaxel (30%)[56] in conjunction with lenograstim.

Preliminary reports from subsequent phase III trials also show increases in dose intensity with the addition of lenograstim 263μg or 150 μg/m^2 daily to regimens based on fluorouracil and cyclophosphamide with one other cytotoxic agent (table IV). However, the effects of the drug on response rates and survival remain unclear: 1 study[58] has shown greater toxicity with no response advantage with lenograstim-assisted dose intensification, although interim results from another trial indicate a trend towards increased response rates with dose intensification[57] (table IV).

Lung Cancer

Previously reviewed studies[5] showed reductions in cycle length for cisplatin-based chemotherapy[59,60] and a regimen of doxorubicin, cyclophosphamide and etoposide in patients with SCLC.[61] In addition, data from 65 patients with SCLC showed significantly higher dose intensities in patients who received lenograstim 5 μg/kg/day subcutaneously from day 4 until 48 hours before the next chemotherapy cycle than in those who did not.[53] Six cycles of VICE chemotherapy (vincristine, ifosfamide plus mesna, carboplatin and

etoposide) were given in this study, and the greatest difference in relative dose intensity was seen in the first 3 cycles (1.34 *vs* 1.17; $p < 0.001$). Overall tumour response rates and median survival times were similar between groups.

Preliminary results from a larger phase III study in which 280 patients with SCLC were randomised have shown no significant effect of subcutaneous lenograstim on overall tumour response rates or event-free survival.[62] The addition of lenograstim 150 μg/m^2/day (starting on day 4 of each cycle) to 6 cycles of ACE chemotherapy (doxorubicin 45 mg/m^2, cyclophosphamide 1 g/m^2 and etoposide 100 mg/m^2 on day 1 plus further etoposide on days 2 and 3) resulted in improvements in the rate of neutrophil recovery by day 14 (95.8 to 100% *vs* 14.3 to 24.1% across cycles) and reduced incidence of infection (≥1 infectious episode in 36.7 *vs* 54% of patients; $p = 0.004$). Use of lenograstim also resulted in a significantly decreased requirement for chemotherapy dose reduction (≥1 reduction in 17.3 *vs* 27.7% of patients; $p = 0.037$) and a trend towards less chemotherapy delay (≥1 delay in 51.8 *vs* 56.2% of patients). The median overall survival time in the lenograstim group was longer, but not significantly so, than in the group receiving chemotherapy alone (11.2 *vs* 9.8 months).

Other Malignancies

Intensification of chemotherapy regimens has been achieved with the addition of lenograstim in patients with several other types of malignancy, including soft tissue sarcoma, NHL and ovarian cancer. The clinical significance in terms of re-

Table IV. Summary of randomised, multicentre phase III trials of lenograstim (LEN)-assisted chemotherapy dose intensification in patients (pts) with breast cancer. LEN was given subcutaneously for the periods indicated. All cytotoxic drugs were given intravenously on day 1 of each cycle. Both study reports are abstracts

Reference	Treatment regimen (chemotherapy doses in mg/m^2)	No. of pts + treatment cycles	Median interval between cycles (d)	Incidence of WHO grade 3-4 leucopenia	Incidence of febrile[a] neutropenia (% of pts)	Overall (complete + partial) tumour response rate (%)
Bonadonna et al.[57] (interim report of CSF-001 study)	Fluorouracil 600, mitoxantrone 10 + cyclophosphamide 600 every 21d	42 pts evaluated; total of 204 cycles	NR	53% of cycles	8	35
	Fluorouracil 800, mitoxantrone 14 + cyclophosphamide 800 + LEN 150 μg/m^2/d × 10d every 21d	52 pts evaluated; total of 252 cycles	NR	42.5% of cycles	6	55
	Fluorouracil 600, mitoxantrone 10 + cyclophosphamide 600 + LEN 150 μg/m^2/d × 10d every 14d	52 pts evaluated; total of 315 cycles	NR	29.2% of cycles	3	50
Garrone et al.[58] (GONOMIG-3 study)	Fluorouracil 600, epirubicin 60 + cyclophosphamide 600 every 21d	151 pts recruited; median 8 cycles each	22	4% of pts	NR	49
	Fluorouracil 600, epirubicin 80 + cyclophosphamide 1000 + LEN 263 μg/d d4-11 every 14d		15	23% of pts	NR	51

a Not defined.

d = day(s); **NR** = not reported; **WHO** = World Health Organization.

sponse and survival rates of these increased dose intensities requires further investigation, however.

Intensification of the MAID (doxorubicin 20 mg/m^2, ifosfamide 2.5 g/m^2, mesna 3 g/m^2 and dacarbazine 300 mg/m^2 daily on day 1 to day 3 of each 21-day cycle) chemotherapy protocol was achieved with the addition of lenograstim in 16 patients with soft tissue sarcoma (a malignancy characterised by its local aggressiveness and high metastatic potential).[63] These patients were recruited from an earlier trial in which a relative dose intensity of at least 0.95 was reported across 6 cycles with lenograstim (5 μg/kg/day subcutaneously from day 4 to 13 of each cycle) added to the MAID regimen in 28 patients.[64] An overall 25% increase in dose intensity was achieved with the addition of subcutaneous lenograstim 5 or 10 μg/kg/day from day 4 to day 14 of each cycle. Further increases were precluded by excessive toxicity. Median survival duration was 15.2 months in 15 evaluable patients; no survival comparison with the standard MAID regimen is available to date.

Lenograstim has also been assessed in the reduction of chemotherapy cycle times in Japanese patients with NHL,[65] although at a lower dosage than used elsewhere.

In a phase I study in 29 patients with ovarian cancer, the use of lenograstim 150 μg/m^2/day subcutaneously was associated with an increase in the maximum tolerated dose of carboplatin from 200 to 250 mg/m^2 in a 3-weekly regimen consisting of carboplatin with cisplatin 60 mg/m^2 and cyclophosphamide 600 mg/m^2.[66] Further studies are required to assess any clinical benefit associated with intensification of this regimen.

3.2 High Dose Chemotherapy with Stem Cell Rescue

Allogeneic stem cell transplantation is an established treatment in patients with dysfunctional or neoplastic myeloid tissue [e.g. aplastic anaemia, chronic myeloid leukaemia (CML) and acute leukaemia with high risk features]. The recognition of the importance of dose escalation in the management of patients with more common malignancies (such as breast and ovarian cancer) has resulted in increased use of high dose (or myeloablative) chemotherapy with stem cell transplantation (allogeneic or autologous) to overcome the profound pancytopenia that persists until the bone marrow cavity is repopulated with sufficient stem cells.[67]

Traditionally, the major source of haematological stem cells has been the bone marrow, as it was originally thought that only this tissue contained these progenitors. However, the identification of haematological progenitors in adult peripheral blood and the development of mobilisation protocols (including the use of rHuG-CSF) to maximise progenitor yields has resulted in a significant shift away from the use of this source towards the use of PBSCs,[68] which are easier to collect than bone marrow progenitors and are associated with more rapid neutrophil and platelet engraftment and recovery.[69-73]

Donated bone marrow is collected under general or regional anaesthesia by needle aspiration; PBSC collection eliminates the need for anaesthesia, but requires pharmacological manipulation of the donor.[67] Mobilisation schemes (which have made possible the routine use of PBSCs) vary, but are based on the observation that chemotherapy-induced myelosuppression followed by administration of rHuG-CSF promotes the mobilisation of stem cells. The chemotherapy can be part of the standard treatment protocol or can be specific to mobilisation. The progenitor cells required are separated from the donated blood by leucapheresis, an automated process carried out in sterile cell separators.[67]

In most available studies in patients undergoing PBSC transplantation, lenograstim has been administered with chemotherapy for mobilisation in order to maximise progenitor cell yield, although the drug has also been used alone for this purpose. Lenograstim has also been used after PBSC transplantation (as is the practice in patients undergoing BMT) in an attempt to accelerate neutrophil and platelet recovery.

Many of the studies published since the previous review[5] have been carried out in patients

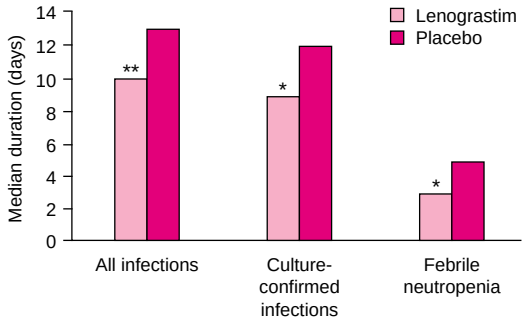

Fig. 5. Effect of intravenous lenograstim 5 μg/kg/day on duration of infection and fever after bone marrow transplantation. Patients received lenograstim to accelerate neutrophil recovery (n = 152) or placebo (n = 146) after intensive chemo- and/or radiotherapy. Febrile neutropenia was defined as temperature ≥38.5°C with neutrophil count <1.0 × 10^9/L.[77] * $p < 0.05$, ** $p < 0.01$ *vs* placebo.

with lymphoma undergoing autologous PBSC transplantation and have confirmed the mobilising effect of lenograstim, although trials have tended to be of limited size. Notably, however, results of comparisons with filgrastim are now becoming available for both bone marrow and PBSC transplantation. Some investigators have also attempted to measure clinical end-points such as length of hospital stay and antibiotic use, although results have been variable.

3.2.1 Bone Marrow Transplantation

Early studies carried out in Japanese patients undergoing autologous or allogeneic BMT showed an intravenous dosage of lenograstim 5 μg/kg/day for 21 days to shorten the period of neutropenia after transplantation by about 2 weeks compared with that seen in patients who did not receive the drug.[74,75] Lenograstim had no significant effect on the incidence of infection, but there was a decrease associated with lenograstim in the number of days with fever during the first month after transplantation.

A phase II placebo-controlled trial in 121 European patients, all of whom underwent BMT (102 autologous) with intravenous lenograstim support after intensive chemo- and/or radiotherapy, showed significantly accelerated neutrophil recovery (to ANC ≥1.0 × 10^9/L) with lenograstim dosages of 2, 5, 10 or 20 μg/kg/day (14 to 19 days *vs* 26 days with placebo; $p < 0.001$).[76] The most rapid recovery was seen with dosages of 5 μg/kg/day or above. Assessment of antibiotic use was made difficult in this study by the administration of prophylactic broad spectrum agents in approximately 33% of patients, however.

A subsequent phase III double-blind placebo-controlled study by the same group of investigators showed significant reductions in neutrophil recovery time in patients with lymphoma, myeloma, acute lymphoblastic leukaemia (ALL) or other unspecified malignancies.[77] The addition of intravenous lenograstim 5 μg/kg/day to allogeneic or autologous BMT after intensive chemo- and/or radiotherapy resulted in 30 and 41% reductions ($p < 0.001$) relative to placebo in median times to achieve ANCs of at least 0.5 and 1.0 × 10^9/L, respectively (table V). In this, the largest study carried out to date in patients (298 evaluable) receiving stem cell support with lenograstim, significant reductions relative to placebo were also noted in median time in hospital (14%; $p = 0.02$), duration of antibiotic use (21%; $p < 0.001$) and duration of total parenteral nutrition (TPN; intravenous hyperalimentation) [33%; $p < 0.001$] {table V}. Although the incidences of infection, febrile neutropenia and septicaemia were similar between treatment groups, there were significant reductions in median durations of infection and febrile neutropenia with lenograstim (fig. 5). Lenograstim treatment had no effect on the actuarial risk of disease relapse or survival after 1 year, however.

Delay of lenograstim treatment from the first day after allogeneic BMT to the sixth had no significant effect on neutrophil recovery in a randomised study in 38 patients with haematological malignancies.[82]

3.2.2 Peripheral Blood Stem Cell Transplantation

As stated earlier, lenograstim has been assessed primarily as a means of priming (promoting the proliferation and release into the circulation of) progenitor cells for harvesting, although the drug

Table V. Randomised comparative studies of lenograstim (LEN) in patients (pts) undergoing bone marrow (BMT) or peripheral blood stem cell transplantation (PBSCT). LEN and filgrastim (FIL) were administered subcutaneously and chemotherapy intravenously unless stated otherwise, with 1 to 3 mobilisation courses and leucapheresis being used for PBSC harvest. Autologous transplantation took place unless stated otherwise

Reference (design)	Mobilisation regimen	Treatment regimen [no. of evaluable pts (where stated)]	Median time after treatment to ANC recovery (d)		Other clinical end-points (median duration in days)			Comments
			$\geq 0.5 \times 10^9$/L	$\geq 1.0 \times 10^9$/L	time in hospital	antibiotic use	TPN	
BMT								
Gisselbrecht et al.[77] (db)	NA	Intensive chemo-/radiotherapy + LEN 5 μg/kg/d IV × 28d or until ANC $\geq 1.0 \times 10^9$/L [152]	14***[a]	16***[a]	25*	15***	16***	Pts had HD, NHL, myeloma, ALL or other unspecified tumours. Autologous transplantation in 78%
		Intensive chemo-/radiotherapy + PL [146]	20	27	29[a]	19[a]	24[a]	
PBSCT								
Campilho et al.[78] (nb) [abstract]	NA	LEN 263 μg/d	12.5	13.5		14	7	Allogeneic transplantation from matched siblings. 61 pts evaluated. Disease not stated
		FIL 10 μg/kg/d (to nearest no. of vials)	12	13		14.5	6	
Kinsey et al.[79,80] (db) [abstract]	CYC 30 mg/kg d1; LEN 5 μg/kg/d d2-11	High dose MEL	15		28	19		Dose-finding study in 29 children with solid tumours
	CYC 30 mg/kg d1; LEN 7.5 μg/kg/d d2-11		13.5		20.5	10		
	CYC 30 mg/kg d1; LEN 10 μg/kg/d d2-11		13		21[b]	11.5*[c]		
Linch et al.[81] (nb)	CYC 1.5g d1; LEN 263 μg/d d2-10	BEAM + LEN 263 μg/d to ANC >0.5 $\times 10^9$/L × 3d or >1.0 $\times 10^9$/L × 1d [34]	9†		13***	7		Pts had relapsed or resistant lymphoma
		BEAM [28]	12.5		15.5	9		

a 149 and 141 pts in the LEN and PL groups, respectively, evaluated for these end-points.

b $p = 0.04$ *vs* LEN 5 μg/kg/d.

c Median durations of infection also reported: 24, 9 and 10.5d with LEN 5, 7.5 and 10 μg/kg/d, respectively. $p = 0.04$ for comparison of 5 and 10 μg/kg/d.

ALL = acute lymphoblastic leukaemia; **ANC** = absolute neutrophil count; **BEAM** = carmustine 300 mg/m^2 on d1, etoposide 200 mg/m^2 and cytarabine 400 mg/m^2 on d2-5, melphalan 140 mg/m^2 on d6; **CYC** = cyclophosphamide; **d** = day(s); **db** = double-blind; **HD** = Hodgkin's disease; **IV** = intravenously; **MEL** = melphalan; **NA** = not applicable; **nb** = nonblind; **NHL** = non-Hodgkin's lymphoma; **PL** = placebo; **TPN** = total parenteral nutrition (intravenous hyperalimentation); * $p < 0.05$, *** $p < 0.001$, † $p \leq 0.0001$ *vs* comparator(s).

has additionally been given after high intensity chemotherapy with PBSC support to accelerate neutrophil recovery.[80,81] It is noteworthy that peripheral blood is replacing bone marrow as a source of stem cells for allogeneic transplantation, and data from the annual survey on transplant activity

carried out by the European Group for Blood and Marrow Transplantation (EBMT) show marked shifts in clinical practice from 1991 to 1997.[83] During this period, proportions of bone marrow-derived transplants dropped from 100 to 70% for allogeneic stem cell recipients and from 90 to 7% for those receiving autologous stem cells.

Consistent neutrophil recovery times have been shown in patients with lymphoma receiving lenograstim-mobilised PBSC support after aggressive chemotherapy in noncomparative studies carried out since 1995. In 2 studies in a total of 141 previously treated patients with Hodgkin's disease or NHL, the median time to achieve an ANC of at least 0.5×10^9/L was 11 to 12 days after courses of BEAM chemotherapy (carmustine 300 mg/m^2 on day 1, etoposide 200 mg/m^2 and cytarabine 400 mg/m^2 on days 2 to 5 and melphalan 140 mg/m^2 on day 6) followed by autologous PBSC transplantation.[84,85] A mobilisation regimen of cyclophosphamide 1.5 g/m^2 intravenously on day 1 followed by lenograstim 263μg subcutaneously per day until either first leucapharesis or completion of PBSC harvesting was used in these studies. It should be noted that approximately half the patients enrolled received filgrastim 10 μg/kg/day subcutaneously in 1 trial and results were presented collectively;[84] the authors reported similar stem cell mobilisation effects with either type of rHuG-CSF at the dosages used. In addition, rHuG-CSF was given after BEAM chemotherapy and PBSC transplantation in 26 of 81 evaluable patients in this study, but this had no apparent overall effect on the median neutrophil recovery time.

A double-blind dose-finding study in 29 children with solid tumours (including rhabdomyosarcoma, neuroblastoma and Ewing's sarcoma) treated with high dose melphalan showed similar median neutrophil recovery times after PBSC transplantation (13 to 15 days to ANC $>0.5 \times 10^9$/L) when lenograstim 5, 7.5 or 10 μg/kg/day was used as part of a cyclophosphamide-based mobilisation regimen (table V).[79,80] Variation of lenograstim dosage had no significant effect on PBSC yields in this study, but patients who underwent priming with 7.5 or 10 μg/kg/day had shorter hospital stays and fewer days with antibiotic treatment (table V).

Lenograstim has been used after PBSC transplantation as well as during mobilisation in 1 study (table V).[81] In this randomised nonblind trial, patients with resistant or relapsed lymphoma received the same priming regimen as in the noncomparative studies described earlier,[84,85] but were then randomised to chemotherapy with the BEAM protocol plus PBSC transplantation with or without lenograstim 263 μg/day subcutaneously (table V). The median time to achieve an ANC of at least 0.5×10^9/L was reduced by 28% ($p = 0.0001$) and the time spent in hospital after PBSC transplantation by 16% ($p = 0.0002$) in patients who received BEAM plus lenograstim.

A randomised nonblind comparison of lenograstim with filgrastim has been carried out in 61 patients (details of diseases and treatment regimens not yet available) receiving stem cell support from matched sibling donors.[78] In this study, rHuG-CSF was not used for priming, but was given after stem cell transplantation only. Preliminary results show similar neutropenia recovery times and antibiotic and TPN duration after administration of either drug (actual median dosages used were 4 and 10.3 μg/kg/day for lenograstim and filgrastim, respectively) [table V]. Median platelet recovery times and durations of rHuG-CSF therapy were also similar between groups.

Allogeneic Stem Cells From Healthy Donors

The feasibility of using lenograstim to harvest PBSCs from healthy volunteers for allogeneic transplantation has been demonstrated in previously reviewed[5] Japanese[86] and European[87] trials. The results of the European study (12 participants) showed satisfactory harvests in 3 of 6 individuals who received lenograstim 5 μg/kg/day subcutaneously for 6 days. A subsequent dose-finding study in 29 healthy donors has shown attainment of target yields with a single leucapheresis after 4 days of subcutaneous lenograstim 15 μg/kg/day.[88] These studies reflect changes in clinical practice that have taken place since the early

1990s: EBMT data show that 28% of recorded transplants in 1991 were allogeneic and 72% were autologous; in 1997, the respective proportions were 44 and 56%.[83] The increasingly important issue of donor safety is addressed in section 5.

As reviewed in section 2.1, more efficient (in terms of dose administered) mobilisation of CD34+ cells by lenograstim than filgrastim has been demonstrated in healthy volunteers.[20] This is of interest in PBSC transplantation because data indicate that the probability of successful engraftment is related to the number of CD34+ cells infused or to the attainment of a 'threshold' level.[71,89] Clinical benefit of transfusion of PBSCs from healthy donors to patients with leukaemia or myelodysplasia has been shown in a pilot study in which 54 individuals received stem cells donated by human leucocyte antigen (HLA)-matched sibling donors.[89] The donors were primed with lenograstim 10 μg/kg/day subcutaneously for 5 days, after which a minimum of 2 cytaphereses were scheduled to collect at least 6×10^6 CD34+ cells/kg. The patients underwent initial myeloablation with chemo- and/or radiotherapy. Engraftment was not achieved in 4 patients (2 deaths and 2 graft failures), but 51 achieved an ANC of 0.5×10^9/L within 15 days. The overall relapse rate was 16% and the rate of survival 50% after a median follow-up of 25 months. Better outcomes were reported in patients aged under 45 years and those with early disease, in whom the rate of survival was 71%.

3.3 Myeloid Leukaemias

Leukaemias are clonal neoplastic proliferations of immature cells of the haematopoietic system that are characterised by aberrant or arrested differentiation (as opposed to the lymphomas, which arise in the reticuloendothelial and lymphatic systems). Leukaemia cells accumulate in the bone marrow cavity and ultimately replace much of the normal tissue; this causes the bone marrow failure and subsequent anaemia, haemorrhage and infection seen in patients with this group of diseases. The abnormal cells circulate into the bloodstream and are distributed to other tissues throughout the body, with the patterns characteristic of each particular type of leukaemia.[18]

The original basis for the classification of the leukaemias into acute and chronic forms was life expectancy, but this has been replaced by differentiation on the basis of cell maturity. Thus, acute leukaemias are characterised by predominantly undifferentiated cell populations and chronic leukaemias by more mature cell forms.[18]

Untreated acute myeloid leukaemia (AML) causes death within weeks or months. Standard induction therapy is based on cytarabine combined with an anthracycline, with postremission treatments consisting of variations of high dose chemotherapy regimens and/or BMT. In patients who are eligible, however, the best chance of a cure is provided by BMT.[18] CML is characterised by the presence of a chromosomal marker, the Philadelphia (Ph) chromosome, which results from a reciprocal translocation and is present on all cells of the neoplastic clone. The only curative treatment to date, allogeneic BMT, is generally restricted to patients aged 50 years or under with an HLA-identical donor, although treatment with interferon-α (IFNα) may significantly prolong survival in some patients.[90,91]

The use of human growth factors in patients with myeloid conditions remains controversial because of concerns over the potential stimulation of leukaemic blasts by these agents (section 2.1). Nevertheless, clinical studies of lenograstim in these disorders have been carried out and have focused on acceleration of neutrophil recovery after intensive chemotherapy and facilitation of autologous PBSC transplantation as an alternative to BMT in patients with AML, and mobilisation of Ph-negative PBSCs for potential autologous transplantation in those with CML.

3.3.1 Acute Myeloid Leukaemia

Study reports from the mid-1990s by the Japanese rG-CSF Clinical Study Group showed intravenous lenograstim at a dosage of 5 μg/kg/day to be associated with significant reductions in duration of neutropenia in patients with AML, although effects on other parameters were less clear.[92,93] In

Table VI. Summary of published randomised placebo (PL)-controlled double-blind studies of lenograstim (LEN) in patients (pts) undergoing chemotherapy for acute myeloid leukaemia (AML). LEN was administered as a short intravenous infusion in both trials

Reference	Pt characteristics	Induction therapy	Randomised therapy (no. of pts)	Time to neutrophil recovery (d)	CR rate (%)	Mortality at 8 wks (%)	Incidence of infection (%)
Dombret et al.[94]	Age >65y (median 71y); previously untreated	DAU 45 mg/m^2 × 4d + CYT 200 mg/m^2 × 7d, then salvage or consolidation as appropriate	LEN 5 μg/kg/d from d9 × 28d or until ANC >1.0 × 10^9/L or treatment failure (88)	21***[a]	70**	23	47.7[b]
			PL (85)	27[a]	47	27	48.2[b]
Link et al.[95,96]	Median age 52y	Various protocols	LEN 150 μg/m^2 from day after chemotherapy until ANC >0.5 × 10^9/L (93)	12.6***[c]	60.2*[d]		62.4[e]
			PL (94)	18.2[c]	43.6[d]		57.4[e]

a Median time to ANC >1.0 × 10^9/L in patients who achieved CR after 1 course of chemotherapy (LEN = 54; PL = 34).

b Severe and life-threatening infections in the first 7 weeks.

c Mean time to ANC >0.5 × 10^9/L after first course of chemotherapy.

d After 2 induction cycles.

e Within 50d of the first cycle of chemotherapy (severity not reported).

ANC = absolute neutrophil count; **CR** = complete response; **CYT** = cytarabine; **d** = day(s); **DAU** = daunorubicin; * p < 0.05, ** p < 0.01, *** p < 0.001 *vs* PL.

one of these trials,[92] patients were randomised in a double-blind manner to treatment with lenograstim (n = 57) or placebo (n = 64) for 14 days after completion of consolidation chemotherapy. A significant reduction in the duration of neutropenia (neutrophil count <1.0 × 10^9/L) with lenograstim was accompanied by significantly decreased incidences of fever and febrile neutropenia and reduced frequency of antibiotic use. Duration of neutropenia was also reduced in the other study, in which 90 patients were evaluable after randomisation to 14 days' lenograstim or placebo treatment after induction chemotherapy.[93] There were no differences between groups in incidence or duration of fever (≥38°C), however.

In addition to the above, significant improvements attributable to lenograstim therapy in neutrophil recovery times and complete remission rates have been reported by European groups who have conducted randomised placebo-controlled studies of lenograstim given after induction therapy for AML. Published results from 2 of these studies are shown in table VI.[94,95] Incidence of infection was not affected by the use of lenograstim in either of these trials (table VI).

The reason for the improvements in rates of complete haematological remission with lenograstim in these studies (49[94] and 38%[95] *vs* placebo) is unclear (particularly as overall survival and duration of response were not affected in the 1 study in which these end-points were reported[94]), although a direct antileukaemic effect of the drug has been postulated.[94] It should also be noted that an Australian group has reported high rates of complete remission of AML with 3 different idarubicin-based induction and consolidation protocols, only one of which included lenograstim.[97]

Two further randomised double-blind studies in a total intention-to-treat population of 501 patients (median age 48 years) with AML have been carried out by the Medical Research Council Working Party on Leukaemia in Adults.[98] After induction chemotherapy, patients received either lenograstim 263 μg/day or placebo subcutaneously for a maximum of 10 days or until attainment of ANC above 0.5 × 10^9/L. Median times to recovery from

grade 3 or 4 neutropenia were 24 and 29 days in patients receiving lenograstim and placebo, respectively (p = 0.0001). Rates of complete haematological remission and median duration of survival were similar between groups, although a higher proportion of high risk patients in the lenograstim than in the placebo group may have influenced these results.

Integrated overall results from the above European studies[94-96,98] showed significant improvements over placebo with lenograstim therapy in median time to recovery of the ANC to both 0.5×10^9/L (22 *vs* 26 days; p = 0.0001) and 1.0×10^9/L (23 *vs* 28 days; p = 0.0001) in patients aged 55 years and over. No infections were reported in 44.8% of patients in this age group who received lenograstim and 32.2% of placebo recipients (p = 0.009), and the median duration of infection was significantly lower in the lenograstim group (4 days *vs* 1 day; p = 0.04).

Encouraging results have also been reported by a group in the Netherlands to indicate potential for the use of lenograstim in the mobilisation of autologous PBSCs for transplantation as an alternative to autologous BMT in patients with AML in first remission.[99] The data from this feasibility study, in which 54 patients underwent leucapheresis after mobilisation with 1 of 4 dosages of lenograstim (150 to 600 μg/m^2/day), suggested that satisfactory PBSC yields for transplantation are obtainable with suitable lenograstim support after aggressive chemotherapy.

3.3.2 Chronic Myeloid Leukaemia

The majority of patients with CML are not eligible for conventional and potentially curative allogeneic BMT because they lack HLA-matched sibling donors or are aged over 50 years.[91,100] Autografting of PBSCs represents a possible alternative for these patients. Although there is no evidence to date that patients with CML may be cured by autotransplantation, survival can be prolonged.[101,102] Widespread use of autologous PBSCs has been hampered by the problems inherent in obtaining progenitor cell grafts that are predominantly or completely free of malignant (Ph-positive) precursors. Recently, however, intensive chemotherapy protocols resulting in successful mobilisation of Ph-negative PBSCs and restoration of normal haematopoiesis after autografting have been described.[103-105] Data are also now available to show satisfactory mobilisation of Ph-negative progenitor cells with lenograstim support in patients with CML.

In 1 study, despite the high risk characteristics of the patient population involved (chronic phase CML with poor cytogenetic response to IFNα therapy), successful mobilisation of PBSCs was achieved with lenograstim in over a quarter of patients.[100] Of the 29 patients who were evaluated, 21% had a Ph-negative leucapheretic product and 14% a major cytogenetic response (1 to 34% Ph-positive cells). Mobilisation was carried out with various intensive cytarabine-based protocols, with lenograstim 150 μg/m^2/day subcutaneously or intravenously started 24 hours after chemotherapy and continued until completion of leucaphereses.

The same dosage of lenograstim for a median 9 days was used to obtain satisfactory PBSC collections in 20 evaluable patients with CML who had responded (Ph-positive metaphases <35%) to previous treatment (median duration 17.2 months) with IFNα.[91] The median percentage of Ph-positive metaphases per leucapheresis was 0, and 91% of all 47 evaluable leucaphereses had a Ph-positive cell content of below 35% (53% were entirely negative). The mobilisation and collection of Ph-negative cells was not affected by the dosage of IFNα and the duration of therapy, or by the quality of the cytogenetic response.

Preliminary data from a further 23 patients have indicated that there are 2 distinct populations of individuals with newly diagnosed CML: a good prognosis group in which Ph-negative cells can be reliably mobilised with regimens of moderate intensity with rHuG-CSF, and a high risk group in which Ph-positive cells are likely to be mobilised regardless of prior haematological control.[106]

3.3.3 Myelodysplastic Syndromes

The myelodysplastic syndromes (MDS) are a group of clonal neoplastic haematological disor-

ders characterised by varying degrees of bone marrow failure, abnormal haematopoiesis and proliferation of myeloid blast cells. Disease subtypes with excess blasts have a high potential for malignant transformation. Complete remissions are difficult to achieve with chemotherapy, and the condition progresses to AML in one-fifth of patients (mainly those classified as high risk).[107]

Neutrophil counts were increased significantly from baseline by factors of 4 and 8, respectively, after 7 and 14 days of intravenous treatment with lenograstim 5 μg/kg/day in 18 Japanese patients with MDS.[108,109] None of the patients developed AML either during treatment or in the immediate follow-up period. In a similar study in 22 Greek patients with MDS and infection, lenograstim 263 μg/day for 7 days (with antibiotic treatment; route not stated) increased the total leucocyte count from baseline by a factor of more than 6 (whether mean or median counts not stated).[110]

In theory, the potential acceleration by rHuG-CSF of progression of MDS to AML is a major concern in these patients.[111] Maintenance therapy with these growth factors has not been evaluated in this respect, although there has been a report of conversion to AML (in a patient with aplastic anaemia) with short term lenograstim treatment.[112] Further studies will be needed to provide a definitive answer to the question of whether or not lenograstim therapy affects the progression of MDS to AML.

3.4 Acute Lymphoblastic Leukaemia

ALL is distinguished from lymphoma by more mature lymphoid cells and their presence in the lymph nodes, spleen and other extramedullary sites before they spread to the blood and bone marrow in the latter disease.[18] It is predominantly a childhood disease with a peak incidence at age 3 to 5 years, but is also seen in adolescents and, less commonly, in adults. Lenograstim has been evaluated as an adjunct to chemotherapy in 2 previously reviewed[5] randomised trials in which patients with ALL or acute undifferentiated leukaemia (AUL) were enrolled.[113,114] Both studies showed augmentation of neutrophil recovery with lenograstim, although there were no significant effects on patterns of infection or antibiotic use.

In 1 study,[113] 41 patients with ALL were randomised to treatment with lenograstim 2, 5 or 10 μg/kg/day intravenously after induction therapy with vincristine, cyclophosphamide, doxorubicin, mitoxantrone and asparaginase. The same dosages of lenograstim were compared with each other and with no growth factor treatment during 4 consolidation cycles. Most notably, there were no increases associated with lenograstim therapy in the number of leukaemic blasts in the bone marrow or blood of these patients. In the second study,[114] subcutaneous lenograstim 5 μg/kg/day as support for induction chemotherapy (2 cycles) was associated with significant reductions compared with chemotherapy alone in the duration of neutropenia in 73 patients with ALL or AUL.

Preliminary details from a study in children with ALL with poor prognosis have shown increased dose intensity with the addition of lenograstim 5 μg/kg/day subcutaneously to 6 courses of consolidation chemotherapy (until achievement of ANC $\geq 1.0 \times 10^9$/L).[115] The relative dose intensity was increased from 0.91 in 33 children who did not receive lenograstim to 1.05 in 34 who did ($p < 0.001$). Lenograstim was also associated with decreased duration of fever, hospitalisation and intravenous antibiotic treatment in 3 of the consolidation cycles, but there was no effect on 3-year disease-free survival.

3.5 Aplastic Anaemia

Aplastic anaemia (AA) is characterised by pancytopenia and bone marrow hypoplasia. The pathogenesis of the disease (which is usually idiopathic in origin or toxin-induced) is thought to involve the loss or dysfunction of haematopoietic stem cells, defects in bone marrow microenvironments and immune-mediated inhibition of haematopoiesis. Complications such as anaemia, infection and bleeding result in a poor prognosis.[116-118] BMT is curative,[119] but is limited by availability of donors and age of recipients. Antilymphocyte or

antithymocyte globulin combined with cyclosporin and corticosteroids are effective in many patients,[120-122] but supportive therapy with red blood cell and platelet transfusions (with the attendant risks of iron overload, infection and reaction to leucocyte antigens) may still be necessary.

Early data from Japan indicated that a dosage of lenograstim 5 μg/kg/day for at least 7 days was effective in the alleviation of neutropenia in patients with AA.[123] A subsequent pilot study carried out by the Severe Aplastic Anaemia (SAA) Working Party of the EBMT showed a low mortality rate after the addition of lenograstim 5 μg/kg/day subcutaneously to immunosuppressive therapy.[121] Forty patients with newly diagnosed SAA and a neutrophil count of 0.5×10^9/L or less received antilymphocyte globulin (15 mg/kg/day for 5 days) with methylprednisolone and cyclosporin (5 mg/kg/day from day 1 to 180). The median maximum neutrophil count during lenograstim treatment was 12×10^9/L and 82% of patients had a trilineage-complete response and became transfusion-independent. Actuarial survival was 92% at median follow-up of 428 days.

A multicentre randomised phase III study has also been carried out by the EBMT, preliminary results of which are emerging.[124] In this trial, lenograstim 5 μg/kg/day subcutaneously from day 1 to day 98 was added to therapy with cyclosporin and antithymocyte globulin in 53 of 102 patients with newly diagnosed SAA. The addition of lenograstim was associated with a significant increase in proportion of patients with complete ANC response ($\geq 1.5 \times 10^9$/L) after 112 days (83 *vs* 44.9% with no lenograstim; $p = 0.001$) and a significant reduction in time to ANC response ($p = 0.0001$). There was a trend towards reduction of incidence of severe (but not overall) infection with lenograstim therapy, but no apparent effect on long term haematopoietic recovery or survival (median follow-up of 23 months). Full details of the results of this study are awaited.

Clinical benefit has also been shown in patients with AA who received a combination of lenograstim and recombinant human erythropoietin (rHu-EPO).[125] The lenograstim dosage was adjusted in this study in each of 3 groups to maintain a neutrophil count of 1.0 to 5.0×10^9/L while the addition of different dosages of rHu-EPO was investigated.

3.6 Other Neutropenic Conditions

Lenograstim has also been evaluated for its role in the management of neutropenia in a variety of other conditions, including congenital neutropenia, Felty's syndrome, immunosuppressant-induced neutropenia after organ transplantation and myelosuppression associated with antiretroviral therapy in patients with AIDS.

3.6.1 Congenital Neutropenia

The term congenital neutropenia embraces a heterogeneous group of disorders that includes primitive neutropenia (e.g. Kostmann's syndrome, cyclic neutropenia, myelokathexis) and neutropenia associated with complex malformative syndromes (e.g. neutropenia with immune deficiencies, glycogen storage disease Ib). The underlying molecular causes of these syndromes are generally not known, although cyclic neutropenia appears to be associated with impairment of a gene localised at chromosome 19p13.3 that codes for neutrophil elastase,[126] and glycogen storage disease Ib (von Gierke disease) has been linked with a defect on chromosome 11q23 that affects microsomal glucose-6-phosphatase activity.[127]

Since 1991, small groups of patients with congenital neutropenia have been treated with lenograstim. In 1 study, neutrophil recovery (to ANC $>1.0 \times 10^9$/L) was reported in all 19 children with severe chronic neutropenia of childhood (a disorder associated with arrest of neutrophil precursor development and ANC $<0.5 \times 10^9$/L) who received subcutaneous lenograstim therapy in a phase II European study.[128] A starting dosage of 5 μg/kg/day was given for 2 weeks, increasing if necessary to a maximum of 20 μg/kg/day, with a further 3 weeks' maintenance therapy with dosage adjustment to maintain recovery. The median time to neutrophil recovery was 7 days, with attainment of normal marrow cytology in 10 of 19 patients.

Fifteen patients achieved neutrophil recovery at an induction dosage of 5 μg/kg/day. Relative to the period before treatment, the number of infectious events per 100 weeks was reduced by 60% ($p = 0.012$) after lenograstim therapy and the number of hospitalisations by 100%.[128] Quality-of-life questionnaires completed by parents or caregivers showed statistically significant improvements in perceived health and disease-related symptoms but no change in functional status. Not unexpectedly, quality of life was impaired by the need for regular injections.

Additional data from a case series of 7 children with glycogen storage disease Ib showed rapid clinical improvement with lenograstim at a median subcutaneous initial dosage of 5 μg/kg/day.[129] Acute inflammatory buccal lesions healed within 7 days and gingival hypertrophy was alleviated within 1 month in all patients. In 6 of the 7 children, ANC counts increased from 3.8 to 12.1 times baseline with lenograstim treatment, which was continued for a mean 20.8 months. After initial daily treatment to achieve ANC of at least 1.5×10^9/L, frequency of administration was reduced to alternate days or 2 or 3 times weekly in 6 patients, and was administered only during periods of infection in the remaining recipient.

3.6.2 Other Conditions

Felty's syndrome is a rare late complication of rheumatoid arthritis that is usually seen in severely affected patients with extra-articular symptoms and a long history (>10 years) of erosive joint disease. Splenomegaly and neutropenia with infectious complications are the major features of this condition.[130] A series of 6 patients who were stabilised on treatment with either lenograstim or filgrastim (starting dosages 263 and 300 μg/day, respectively, subcutaneously) achieved increased neutrophil counts (to 1 to 4.5×10^9/L) and reductions in incidence of severe infection (further details not given) over treatment periods ranging from 4 to 40 months.[131] Encouraging data have also been reported in Japanese patients receiving subcutaneous lenograstim for the alleviation of immunosuppressant-induced leucopenia after renal transplantation.[132,133]

Neutropenia is a dose-limiting adverse effect of antiretroviral and anti-infective agents used to manage patients with HIV infection or AIDS, and amelioration of the myelosuppressive effect of zidovudine was achieved with lenograstim therapy in 11 of a series of 12 patients with AIDS or AIDS-related complex.[134] Preliminary data from a phase II randomised single-blind study have indicated a dosage of lenograstim of 50 μg/m^2/day subcutaneously to be adequate for the management of neutropenia in patients with AIDS receiving ganciclovir 10 mg/kg/day.[135] Median ANC values ($\times 10^9$/L) at 3 weeks were as follows:

- lenograstim 150 μg/m^2/day: 6.0
- lenograstim 100 μg/m^2/day: 7.4
- lenograstim 50 μg/m^2/day: 4.5
- lenograstim 25 μg/m^2/day: 1.9
- placebo: 0.75 ($p \leq 0.05$ *vs* all lenograstim dosages).

Lenograstim was given for 10 to 21 days, and 68 patients were enrolled with a median duration of HIV infection of 64 months.

4. Pharmacoeconomic Considerations

Concern over costs associated with the use of lenograstim (as with all recombinant human growth factors) has led to discussion and investigation of means to ensure the most efficient use of the drug. Studies of the cost effectiveness, cost benefit or cost utility of the drug have not been conducted, however. Investigations to date have instead concentrated on containment or minimisation of costs associated with the use of adjunctive therapy with lenograstim in patients with cancer.

The previous review in *Drugs*[5] reported the findings of a series of pharmacoeconomic evaluations of 3 phase III randomised clinical trials in patients with inflammatory breast cancer,[48] NHL[49] or SCLC[53] which are discussed in section 3.1.[136] The addition of lenograstim to therapy was associated with reductions in the cost of antibiotic therapy in all 3 studies, and reduced hospitalisation costs in 2 (inflammatory breast cancer in German

and Italian patients[137] and NHL in French patients[138]). The cost of chemotherapy increased with lenograstim because patients receiving the growth factor were able to receive more intensive chemotherapy courses. Total direct healthcare costs were reported to be reduced in patients with inflammatory breast cancer and in those with NHL who received lenograstim, but not in those with SCLC.[139]

Although these studies illustrate institutional healthcare costs associated with the use of lenograstim, results obtained in different centres and countries are likely to be influenced by variations in cost sources (e.g. hospital billing arrangements, physician charges, etc.) and the actual costs accounted for. As yet, no attempts have been made to assign values to healthcare outcomes such as improved quality of life or years of life gained in patients who receive lenograstim, or to assess broader costs over periods beyond that of hospitalisation (e.g. costs incurred by community healthcare systems in the management of subsequent complications and indirect societal costs associated with loss of productivity).

Since the publication of the above data, several other economic assessments of lenograstim have been carried out, most notably in patients undergoing BMT. Accelerated ANC recovery times and subsequent reductions in costs associated with hospital treatment resulted in an overall cost saving of FF24 000 (French francs; year of costing not stated) per patient with lenograstim (5 μg/kg/day intravenously until recovery of total leucocyte count after BMT) in a study in 16 patients with lymphoma or solid tumours undergoing autologous BMT after chemotherapy.[140] However, there was no difference in overall hospital costs (1995 costs in British pounds) between patients who received rHuG-CSF and those who did not in a similar study carried out in the UK in 40 children undergoing allogeneic or autologous BMT.[141] It should be noted that 14 of 22 patients who received rHuG-CSF in this study received filgrastim, and that the acquisition cost of the recombinant growth factors used was not accounted for in either analysis.

Recently published findings in 38 patients undergoing allogeneic BMT for haematological malignancies have suggested that it may be possible to reduce substantially the cost of lenograstim treatment by delaying the first dose after BMT.[82] Administration of the first dose on day 6 rather than on day 1 shortened the duration of lenograstim treatment from 19 to 14 days and the cost of use of the drug by 26.3% with no apparent loss of any clinical benefit (see also section 3.2.1).

Despite the availability of the above data, allogeneic PBSC transplantation is increasing in prominence relative to BMT (see section 3.2.2), and economic data relevant to this type of stem cell rescue are therefore of considerable current interest. A case-control study in which 17 patients with leukaemia who received allogeneic PBSC transplantation after lenograstim mobilisation were compared with a historical control group of 17 patients who underwent allogeneic BMT has indicated a substantial cost advantage for the former procedure.[142] The 17 study donors were primed with lenograstim 10 μg/kg/day subcutaneously for 5 days, and the cost of mobilisation was included in the final analysis. All direct medical costs (including outpatient visits and hospital overheads) were recorded from patients' notes and were based on French monetary values for 1996 converted to $US. All patients underwent stem cell transplantation after receiving a chemotherapeutic conditioning regimen; 7 patients in the BMT (control) group and 1 in the PBSC group received lenograstim (300 μg/day by intravenous infusion) after transplantation. Patients in the PBSC transplantation group had neutrophil engraftment within a median 14 days, compared with 19 days in the control group ($p < 0.05$). The mean total cost per patient in the PBSC group was $US16 134 (29%) lower than that in the control group ($p = 0.006$).

The most rigorously controlled and robust pharmacoeconomic study of lenograstim to date was carried out in 147 evaluable children with NHL who were randomised to receive lenograstim 5

μg/kg/day [up to 263μg (1 vial)] subcutaneously for 6 to 15 days after each of 2 courses of intensive induction chemotherapy (n = 75) or to chemotherapy only (n = 72).[143] Costs were described clearly and included those associated with daily hospitalisation (staff salaries, housekeeping expenses, cost of office and medical supplies and overheads), the acquisition cost of lenograstim, other drugs and blood products used, and laboratory costs. The analysis covered the time spent in hospital only, with costs in French francs for 1996 converted into $US ($US1 = FF6). Sensitivity analyses involved variation of the cost of lenograstim and the daily hospital room cost, and the addition of cost of time spent in intensive care.

The primary clinical end-point, incidence of febrile neutropenia (ANC $<0.5 \times 10^9$/L with rectal temperature >38°C), did not differ significantly between groups. However, the median total duration of febrile neutropenia was 2 days shorter in patients who received lenograstim ($p < 0.01$). The total cost of induction chemotherapy with

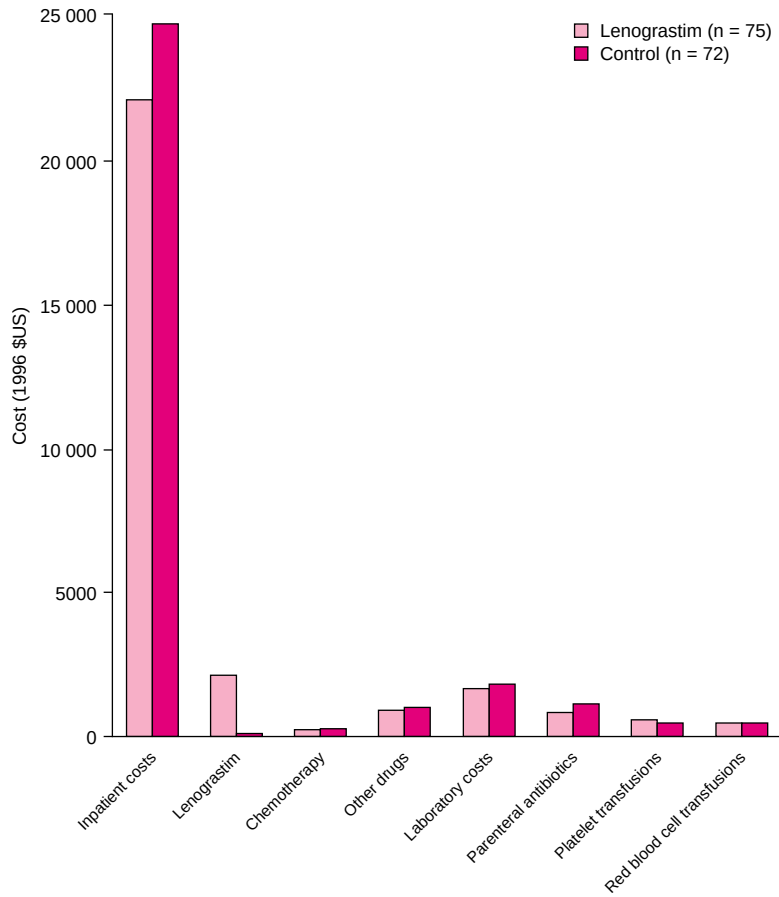

Fig. 6. Mean hospital costs per patient (1996 $US) of intensive induction chemotherapy with or without lenograstim. 147 children with non-Hodgkin's lymphoma received intensive chemotherapy with or without lenograstim 5 μg/kg/day for 6 to 15 days. Chemotherapy consisted of 2 courses of COPAD(M) (cyclophosphamide, vincristine, prednisone and doxorubicin, with or without methotrexate). Lenograstim was started the day after completion of chemotherapy.[43] 'Inpatient costs' included the daily staffing costs, expenses and overheads associated with a stay in a hospital room.

lenograstim was $US29 765 per patient, of which lenograstim represented 7%. In the control group, the total cost per patient was $US30 774, the majority of which was accounted for by a mean 33-day hospitalisation period (fig. 6). Overall, the acquisition cost of lenograstim was balanced by the cost of 2 additional days in hospital in the control group, and the sensitivity analyses indicated the findings to be robust. It should be noted that a small element of cost associated with lenograstim was recorded in the control group (fig. 6), but that this was not explained. The authors concluded that the addition of lenograstim to chemotherapy in patients with NHL did not affect the overall cost of treatment, but advised caution in the interpretation of their results because of doubts over the power of the study (the number of patients recruited was based on clinical and not economic criteria). Furthermore, as with other studies available to date, direct hospital costs only were considered, with no further follow-up.

A brief cost analysis attached to a clinical study carried out in the Netherlands in 40 patients with breast cancer (reviewed in section 3.1.1[51]), in which lenograstim therapy was compared with prophylaxis with ciprofloxacin plus amphotericin B showed a cost advantage for the latter treatment. Clinical outcomes were similar in each group. Direct hospital costs only (derived from a previous study[144]) were considered, with no further analysis. The higher overall cost per hospitalisation in patients who received lenograstim was accounted for by the wholesale acquisition cost per course of this agent ($US1085 *vs* $US164 for ciprofloxacin plus amphotericin B; year of costing and rate of conversion from Dutch guilders not stated).

The cost implications of the choice between lenograstim and filgrastim have been explored by some authors. An Australian audit carried out over 18 months in a public hospital estimated an annual saving of $A20 000 (costs for 1994–1995) when lenograstim was used in preference to filgrastim in a mean 45 patients per quarter.[145] This analysis, for which preliminary details only are available, appeared to focus on the acquisition costs of the growth factors and reimbursement arrangements unique to the Australian healthcare system. The applicability of these results to other healthcare systems is therefore likely to be limited.

Data from 36 consecutive French patients with solid tumours who underwent autologous BMT after intensive chemotherapy favoured lenograstim over filgrastim in terms of cost from a hospital perspective.[146] A total of 55 courses of chemotherapy were analysed, of which 26 were followed by lenograstim (150 μg/m^2/day) and 29 by filgrastim (10 μg/kg/day) until the ANC reached 0.5×10^9/L for at least 3 consecutive days. Costs associated with hospitalisation were calculated for each patient and expressed in $US for the year 1997. Clinical benefit was similar with lenograstim or filgrastim, but the cost of lenograstim was approximately half that of filgrastim ($p = 0.0001$), and represented an approximate $US1800 saving per course of chemotherapy. The authors suggested that the recommended dosage of filgrastim as used may have been unnecessarily high, or that the greater biological activity due to glycosylation of lenograstim may have been a contributing factor. It should be noted that hospital costs (other than those of rHuG-CSF) were similar between treatments in this retrospective case series from a single institution, duration of administration was similar for lenograstim and filgrastim, and that the difference was attributable solely to a difference in acquisition cost between the 2 types of rHuG-CSF.

5. Tolerability

Data from placebo-controlled clinical trials in patients with chemotherapy-induced neutropenia or those recovering from BMT have shown overall adverse reaction rates with lenograstim to be similar to those observed with placebo.[5] As with filgrastim, bone pain is the most commonly reported adverse event associated with lenograstim therapy in patients with chemotherapy-induced neutropenia and is more frequent than with placebo. In studies reviewed in section 3.1.1, bone pain was reported with lenograstim and placebo, respectively, by 22% and 5% of patients with

NHL[49] and in 49% and 8% of patients with breast cancer.[48] Injection site pain (39 *vs* 7%) and reactions (57 *vs* 17%) were more frequent with subcutaneous lenograstim than with placebo in 1 study,[48] but rates of injection site reaction were not appreciably different in the other trial (4 *vs* 0%).[49]

Previously reported data from 259 patients receiving BMT with lenograstim support showed no excess of clinical or laboratory adverse events with active growth factor treatment relative to placebo.[5] Interestingly, incidences of allergy, pain and bone pain were similar between groups, although the incidence of graft-versus-host disease (GVHD) was lower in patients who received lenograstim than in those who received placebo (46 *vs* 66%).[5] The effect of lenograstim on the incidence and severity of GVHD has not been clarified further, however.[34]

Pooled data that have become available since the last review of lenograstim in *Drugs* have shown adverse reactions in 89 of 1495 patients receiving the drug.[147] Most frequent events were fever (1.2%), lumbar pain (1.1%), increased blast cell counts (patients with AML) [0.9%], hepatic disturbances (0.5%), bone pain (0.4%) and eruptions or rashes (0.4%). These figures are much lower than those from individual clinical studies, and probably reflect the larger numbers of patients involved.

Concern over the acceleration by rHuG-CSF of progression of benign myeloid conditions to malignancy has led to a year-long study in 84 centres of individuals with aplastic anaemia to evaluate the effect of lenograstim on the incidence of clonal cytogenetic abnormalities and their progression to MDS or AML.[148] Clonal cytogenetic abnormalities were seen in 17.5% of 57 patients available for chromosome analysis, but no association was found between these changes and dysplasia of marrow cells.

Adverse reaction reports published since the previous review have linked all rHuG-CSFs, including lenograstim, to occasional cases of acute respiratory distress syndrome and interstitial pneumonia, and monitoring for these conditions is now recommended in some countries.[149,150] Patients should also be monitored for the onset of leucocytosis.[34] There have also been single isolated reports of splenic rupture,[151] Sweet's syndrome[152] and apparent reactivation of a red cell alloantibody[153] in patients receiving lenograstim, although the clinical significance of these reports remains unclear.

The increasing use of allogeneic stem cells mobilised from healthy donors with the assistance of rHuG-CSF has highlighted the issue of the tolerability of these agents in this group of individuals. No adverse events serious enough to stop administration of lenograstim were reported in 54 healthy PBSC donors who received the drug in a study reported in section 3.2.2;[89] of the 30 events reported in 19 donors, 17 were related to bone pain or myalgia. These symptoms were readily treated and resolved after PBSC priming had finished. Current consensus data indicate acceptable tolerability of rHuG-CSF overall in healthy PBSC donors, but stress the need for continuing monitoring and the possible creation of an international PBSC donor registry.[154] The incidence of moderate to severe acute GVHD in patients who received these allografts was 56%, which was stated to be comparable to rates seen after allogeneic BMT.[89]

The safety of lenograstim has not been established in pregnant women, although animal studies show no evidence of teratogenicity.[34] The drug is not recommended in nursing mothers, as it is not known whether excretion takes place in breast milk.[34] The tolerability of lenograstim in patients with hepatic or renal dysfunction, the elderly and infants has also not been defined.[34,147]

6. Dosage and Administration

The uses for which lenograstim is licensed and dosages and routes of administration recommended for the drug vary, most notably between Japan and Western countries. The following discussion focuses on international recommendations for patients in Western countries; differences pertinent to patients in Japan are highlighted where necessary.

To reduce the duration of neutropenia and incidence of associated complications in patients undergoing cytotoxic chemotherapy or BMT the recommended dosage of lenograstim is 150 μg/m^2/day (19.2 MU/m^2/day).[155] This is therapeutically equivalent to the 5 μg/kg/day dosage used in clinical studies. The same dosage for 4 to 6 days (with leucapheresis between days 5 and 7) is recommended in patients undergoing PBSC mobilisation with a chemotherapeutic priming regimen; in patients or healthy donors receiving lenograstim alone for this purpose, the recommended dosage is 10 μg/kg/day for 5 to 6 days.[155]

Subcutaneous administration is recommended to aid ANC recovery in patients undergoing myelosuppressive chemotherapy. Lenograstim should be started 24 hours after chemotherapy ends and should continue through the expected nadir until the ANC has returned to the normal range (usually 8 to 14 days; maximum of 28 days). A 30-minute intravenous infusion in normal saline, starting 24 hours after transplantation, is recommended in patients undergoing BMT.[155]

In patients undergoing PBSC mobilisation, lenograstim should be given subcutaneously and should be started the day after the end of chemotherapy. Leucapheresis should be carried out when the post-nadir ANC is rising, or after CD34+ assessment. The acceptable minimum yield for adequate haematological reconstitution is 2×10^6 CD34+ cells/kg.[155]

Leucocyte counts should be monitored regularly during lenograstim therapy, and treatment should cease immediately if the leucocyte count exceeds 50×10^9/L in patients receiving cytotoxic chemotherapy or BMT, or 70×10^9/L in patients undergoing PBSC mobilisation.[155]

Smaller dosages of lenograstim are given for some indications in Japanese patients than in Caucasians, and it should be noted that the drug is licensed for more conditions in Japan than in Western countries. Briefly, dosages of 2 or 5 μg/kg/day by subcutaneous or intravenous injection are recommended in Japanese patients (table VII). Intravenous infusion of 5 μg/kg/day is recommended for the acceleration of neutrophil recovery after BMT, with treatment to be started on either day 1 or day 5 after transplantation.[147] Dosages for a range of other conditions for which lenograstim is not recommended in the West are also shown in table VII. In general, Japanese labelling specifies extreme caution, with regular haematological and bone marrow monitoring, in patients with myeloid malignancy or myelodysplasia. Prompt discontin-

Table VII. Dosage recommendations for lenograstim: international and Japanese guidelines

Indication	Dosage	
	international (μg/m^2/day)[155]	Japanese (μg/kg/day)[147]
Chemotherapy-induced neutropenia	150 SC[a] from 24h after chemotherapy	5 IV or 2 SC or IV after completion of chemotherapy
Neutrophil recovery after BMT	150 IV from 24h after BMT	5 IV from day 1 or 5 after BMT
PBSC priming	150 SC[b] to CD34+ count ≥2×10^6/kg	
Acute lymphoblastic leukaemia	150 SC from 24h after chemotherapy	5 IV or 2 SC when ANC <1.0×10^9/L
Acute myeloid leukaemia	150 SC from 24h after chemotherapy	5 IV when ANC <1.0×10^9/L
Neutropenia in MDS		5 IV when ANC <1.0×10^9/L
Neutropenia in aplastic anaemia		5 IV or SC when ANC <1.0×10^9/L
Congenital or idiopathic neutropenia	150 SC (initial induction period of 7-14 days)[c]	2 IV or SC when ANC <1.0×10^9/L
Neutropenia precluding treatment for HIV		5 IV when ANC <1.0×10^9/L
Neutropenia after immunosuppression (renal transplantation)		2 SC when ANC <1.5×10^9/L (adults)

a Equivalent to the dosage used in clinical trials (5 μg/kg/day).

b If used in conjunction with a chemotherapeutic priming regimen. The dosage should be increased to 10 μg/kg/day if lenograstim is used alone.

c May be increased to 20 μg/kg/day if necessary. Recommendation from prescribing information for Australia and New Zealand.[157]

ANC = absolute neutrophil count; **BMT** = bone marrow transplantation; **h** = hours; **IV** = intravenous administration; **MDS** = myelodysplastic syndrome; **PBSC** = peripheral blood stem cell; **SC** = subcutaneous administration.

uation of lenograstim therapy is necessary if increases in blast cell counts are noted.

Two presentations are available: vials containing 263μg for patients with body surface area up to 1.8m^2, and 105μg for those with body surface area up to 0.7m^2.

Lenograstim should not be coadministered with chemotherapy, and the drug is not recommended in patients with severe hepatic or renal impairment or in nursing mothers.[34,147] There are no dosage recommendations for infants, the elderly or pregnant women.

7. Place of Lenograstim in the Management of Patients with Neutropenia

Since the publication of the last review of lenograstim in *Drugs*,[5] the role of lenograstim in minimising neutropenia and its related complications in patients undergoing chemotherapy or BMT, and its efficacy in mobilising PBSCs, has been confirmed. However, several issues require further clarification: these include any reduction by lenograstim of early mortality rates related to infectious complications, effects on survival that may be attributed to avoidance of neutropenia-induced delays in administration of chemotherapy cycles, and the pharmacoeconomic implications of the use of the drug.

The beneficial effect of prophylactic lenograstim on neutrophil recovery, with attendant reductions in rates of laboratory-confirmed infection, hospitalisation and antibiotic use in patients receiving standard dose chemotherapy, has been demonstrated (section 3.1.1). Evidence also shows that patients are more likely to receive chemotherapy cycles without delay when lenograstim is used to control neutropenia, and some studies have shown facilitation of dose intensification (although this practice is the subject of some discussion at present). The preferred end-point when considering optimisation or intensification of chemotherapy cycles is duration of survival, but such an advantage has not been shown with rHuG-CSF therapy to date.

No difference in the rate of hospitalisation for febrile neutropenia was shown between lenograstim and antibacterial/antifungal prophylaxis with ciprofloxacin and amphotericin B (section 3.1.1), despite the decreased incidence of leucopenia with lenograstim. Further studies will be required to elucidate fully the relative prophylactic efficacies of lenograstim and antibacterial/antifungal therapy, especially in the light of differing recommendations for antibacterial and antifungal prophylaxis between hospitals and countries.

The decision to use lenograstim prophylactically in patients undergoing myelosuppressive chemotherapy is likely to be based on several factors, including patient status, the aggressiveness of the chemotherapy regimen used (and the patient's reaction to any previous courses given), and the anticipated risk of infection and other complications. Guidelines from the American Society of Clinical Oncology (ASCO) suggest on the basis of experience in clinical trials that rHuG-CSF prophylaxis should be considered in situations in which the incidence of febrile neutropenia is expected to exceed 40%.[157]

Lenograstim clearly accelerates neutrophil recovery in patients undergoing autologous or allogeneic BMT, although effects on clinical endpoints are less certain. There is some evidence of reduced duration, but not of reduced overall incidence, of infection and fever (section 3.2.1). More data are needed to clarify these issues. Nevertheless, ASCO guidelines state that there is a clear and valuable role for lenograstim and other such growth factors in the reduction of neutropenia in patients receiving autologous BMT; the data reviewed in section 3.2.1 are in accordance with this view.[157]

Lenograstim also accelerates the mobilisation of PBSCs (either autologous or allogeneic) for transplantation when used as part of a priming regimen, and a role for this agent in assisting neutrophil recovery when it is given after PBSC transplantation (especially in patients experiencing delayed or inadequate engraftment[157]) is apparent (section 3.2.2). The limited data available suggest that leno-

grastim is similar in efficacy to filgrastim when therapeutically equivalent doses are used (section 3.2.2). Thus, higher doses in microgram terms of filgrastim are required, and this concurs with the more efficient mobilisation of CD34+ cells by lenograstim than by filgrastim in healthy volunteers (sections 2.1 and 3.2.2).

The use of growth factors in patients with myeloid conditions is a subject of debate, although clinical studies have shown reductions in neutrophil recovery times with lenograstim treatment after intensive chemotherapy in patients with AML (section 3.3.1). There is also evidence of improvements in rates of complete haematological remission, and integrated data from several European studies showed lenograstim therapy to be associated with reduced incidence and duration of infection in older patients (≥55 years).

Increased duration of response and improved rates of survival have not been associated with lenograstim therapy to date in patients with AML who receive lenograstim, but fears of stimulation of malignant blasts by rHuG-CSF in patients with leukaemia have not been borne out in clinical practice. No association has been shown between clonal cytogenetic abnormalities and dysplasia of marrow in patients receiving lenograstim (section 5).

Some success has been reported in the mobilisation of Ph-negative PBSCs for possible autotransplantation in patients with CML who are not eligible for allogeneic donor-matched BMT (section 3.3.2), and there is evidence of benefit with the drug in patients with ALL (section 3.4), although more studies are needed. Whether lenograstim can improve infection rates and survival in patients with SAA also remains unclear, and further details of a phase III trial are awaited (section 3.5).

Lenograstim also assisted neutrophil recovery and reduced infectious morbidity in children with severe chronic neutropenia (a condition for which there are few other therapeutic options), and alleviated leucopenia in patients undergoing immunosuppressant therapy after renal transplantation. The drug may also assist in the management of dose-limiting neutropenia associated with antiviral therapy in patients with AIDS (section 3.6). Studies are in progress to assess the clinical advantages of lenograstim use and any effect of the drug on survival in these settings.

The full economic implications of the widespread use of lenograstim (and other formulations of rHuG-CSF) remain uncertain: only direct costs associated with hospitalisation have been examined so far. There are no data available with which to relate the cost of therapy to quality of life or additional years of life gained, and no attempts have yet been made to measure medical and other costs (e.g. indirect or societal) incurred after discharge from hospital. The relationship between savings in terms of reduced hospital costs (e.g. duration of stay and antibiotic use, etc.) and the acquisition cost of lenograstim requires assessment in more and larger studies in a variety of different clinical settings. The increased potency of lenograstim on a weight-to-weight basis over filgrastim may have positive cost implications for the use of lenograstim (section 4),[158] but well designed and robust pharmacoeconomic comparisons of the 2 agents are as yet unavailable.

Overall, lenograstim is well tolerated, with the most common adverse effects in clinical trials (bone pain and injection site reactions) being related to its mode of action and route of administration. There is no evidence to show an association between clonal cytogenetic abnormalities and progression to MDS or AML in patients receiving lenograstim, but monitoring has been recommended for a small number of rare idiosyncratic reactions (section 5). Current data show acceptable tolerability of lenograstim in healthy donors of PBSCs for allogeneic transplantation. Continued monitoring of these donors, with the creation of an international donor registry, has been called for[154] (section 5).

In conclusion, lenograstim has been confirmed as a valuable adjunct to minimise the haematological toxicity of myelosuppressive chemotherapy in patients with malignant disease. The drug also enhances neutrophil recovery in patients undergoing stem cell rescue, and assists PBSC mobilisation.

Data indicate clinical benefit with lenograstim in myeloid disorders, with no evidence of malignant blast cell proliferation. Further studies are required to assess more fully the pharmacoeconomic implications of the use of lenograstim and other recombinant growth factors, to provide more data on the efficacy of the drug in the management of disease-related neutropenia, and to clarify fully its position relative to filgrastim.

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