Comparative Efficacy of Reduced or Standard Doses of Lenograstim for Peripheral Blood Stem Cell Mobilisation and Transplantation – A Review

Mustafa Öztürk[1] and Fikret Arpaci[2]

1. Assistant Professor; 2. Chief, Department of Medical Oncology, Gulhane Military Medical Academy

DOI: 10.17925/EOH.2010.06.1.76

Abstract

Recombinant human granulocyte colony-stimulating factors (G-CSFs) are used for mobilisation of peripheral blood stem cells (PBSCs) and their subsequent infusion. Lenograstim is the glycosylated recombinant form of human G-CSF. Compared with filgrastim, lenograstim has a greater capacity to stimulate the colony growth *in vitro* of both purified CD34 and unmanipulated PBSCs. Due to the increased potency of lenograstim, several clinical studies were carried out to show the comparative efficacy of reduced or standard doses of lenograstim for PBSC mobilisation and transplantation. *In vivo* prospective randomised studies indicate that lenograstim is more potent than filgrastim. Short-course low-dose lenograstim was found to be as effective as the standard dose in reducing neutrophil engraftment time following high-dose chemotherapy and PBSC recovery. Lenograstim at a 25% lower dose does not negatively affect the number of CD34+ stem cells harvested or the engraftment results.

Keywords

Granulocyte colony-stimulating factor, aphaeresis, lenograstim, filgrastim, peripheral blood stem cell mobilisation, transplantation

Disclosure: The authors have no conflicts of interest to declare.
Received: 3 October 2009 **Accepted:** 26 February 2010 **Citation:** *European Oncology*, 2010;6(1):76–9
Correspondence: Mustafa Öztürk, Gulhane Medical Academy, Department of Medical Oncology, General Tevfik Saglam Caddesi, 06018 Etlik/Ankara, Turkey.
E: drmustafaozturk@yahoo.com

Recombinant human granulocyte colony-stimulating factors (G-CSFs) are the only currently available agents that are used for mobilisation of peripheral blood stem cells (PBSCs) and their subsequent infusion. Lenograstim is the glycosylated recombinant form of human G-CSF. Compared with filgrastim, lenograstim has a greater capacity to stimulate the colony growth *in vitro* of both purified CD34 and unmanipulated PBSCs.[1] Other *in vitro* studies indicate that lenograstim is more potent than filgrastim on a weight-for-weight basis.[2–4] It has been shown that 1µg of filgrastim was equivalent to 100,000 units of activity, whereas 1µg of lenograstim was equivalent to 127,750 units of activity, demonstrating that lenograstim is 27% more potent than filgrastim *in vitro*.[5,6] 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.[7] However, both products are recommended at the same dosage of 10µg/kg for PBSC mobilisation if used without chemotherapy.[8] Due to the increased potency of lenograstim, several clinical studies were performed to show the comparative efficacy of reduced or standard doses of lenograstim for PBSC mobilisation and transplantation. In this review, data were collected to show the comparative efficacy of reduced or standard doses of lenograstim for PBSC mobilisation and transplantation.

Methodology

Computerised literature searches of MEDLINE, PreMEDLINE and PubMed were undertaken to identify reports of relevant clinical studies. The studies were required to be published in the English language between 31 December 1993 and 30 August 2009. Studies with reduced- and standard-dose lenograstim were examined involving adults >18 years of age. Details of this search, which included data published to date on the use of lenograstim for autologous and allogeneic stem cell transplantation, can be found in *Tables 1* and *2*.

Results and Discussion

Studies with Lenograstim on Peripheral Blood Stem Cell Mobilisation in Autologous Transplantation

Prospective randomised clinical trials were carried out to find the optimal dosage of lenograstim in autologous stem cell transplantation (ASCT) patients. Some studies compared different GCSFs; others compared reduced doses of lenograstim with standard doses in terms of mobilisation and engraftmant kinetics.

De Arriba et al. conducted an *in vivo* prospective randomised study in 30 patients and compared the efficacy of bioequivalent doses in terms of biological activity of lenograstim and filgrastim for mobilisation of PBSCs (0.82MU/kg/day lenograstim or 0.84MU/kg/day filgrastim for four days or until completion of leukapheresis). When they compared the effect of the administration of the same number of IU of each product, they saw that 31% more filgrastim was needed to achieve the same result (8.4 versus 6.4µg/kg/day).[9]

Ria et al. compared the efficiency of lenograstim and filgrastim in mobilising PBSCs in a total of 86 patients who were consecutively enrolled for mobilisation with cyclophosphamide plus either lenograstim or filgrastim, and underwent leukapheresis. Lenograstim mobilised more CD34+ cells than did filgrastim in terms of reaching a

Table 1: Data Published to Date on the Use of Lenograstim for Autologous Stem Cell Transplantation

Author, Reference, Type of Study	n	Mb	PT	Lenograstism Dose (µg/kg/day)	Control Group (µg/kg/day)	Number of CD34+ Cells, Engraftment Parameters	Other Information
De Arriba et al.,[9] prospective, randomised	30	+	–	Lenograstism 6.4	Filgrastim 8.4	To achieve the same number of CD34+ cells	*31% more filgrastim was needed to achieve the same result
Ria et al.,[10] prospective, randomised	86	+	–	Cy + lenograstim 5	Cy + filgrastim 5	>3x10^6 CD34+/kg (in two LPs)	*Lenograstim mobilised more CD34+ cells
Ataergin et al.,[11] prospective, randomised	40	+	+	Lenograstim 7.5	Filgrastim 10	Successful mobilisation in first LP 46% versus 50% patients	NS
Öztürk et al.,[12] prospective, randomised	49	+	+	Lenograstim 7.5	Lenograstim 10	Successful mobilisation in first LP 42% versus 56% patients	NS
Kopf et al.,[13] prospective, randomised	103	+	–	Disease-specific regimen CT plus lenograstim	Disease-specific regimen CT plus filgrastim and disease-specific regimen CT plus molgramostim	CD34+ cells 5.8x10^6/kg lenograstim versus 8.4x10^6/kg filgrastim versus 4.0x10^6/kg molgramostim	NS
Karanth et al.,[14] prospective, randomised	79	+	–	Cy (2g/m^2) + prospective lenograstim 5	Lenograstim alone at 10	Successful mobilisation in 56.4% versus 70%	NS
Lefrère et al.,[15] retrospective	126	+	–	Lenograstim 10	Filgrastim 10	Difference to obtain a minimal number of 3x10^6 CD34+ cells/kg between groups	NS
Linch et al.,[20] prospective, randomised	90	+	+	Lenograstim 263µg/day SC	Placebo	Neutrophil engraftment 9 days lenograstim versus 12.5 days placebo	*p=0.0001
Brice et al.,[21] prospective, randomised	16	–	+	Lenograstim 150µg/day SC	Placebo	Less frequent hospitalisation in lenograstim-treated group	*
Schmitz et al.,[22] double-blind, randomised	192	–	+	Lenograstim 5	Placebo	Improved neutrophil recovery 11 days versus 15 days	*p<0.001
Suh et al.,[23] prospective, randomised	33	–	+	Lenograstim 100µg/day SC	Lenograstim 250µg/day SC	For both lenograstim doses, neutrophil engraftment was 9 days and PLT engraftment was 11 days	NS
Nolan et al.,[24] double-blind, placebo-controlled, randomised	61	–	+	Lenograstim 105µg/day SC (Short-course, low-dose)	Lenograstim 263µg/day and placebo	Neutrophil engraftment 10 days versus 11 days versus 14 days (*p<0.001 compared with placebo)	Short-course low-dose lenograstim is as effective as standard dose in reducing neutrophil engraftment
Jang et al.,[25] prospective randomised	40	–	+	Lenograstim 5 (single dose)	Lenograstim 2.5 twice daily (split dose)	Neutrophil engraftment 10 days for both groups, PLT engraftment 11 days for the single-dose group versus 14 days for the the split-dose group	NS

**Difference significant; CT = chemotherapy; Cy = cyclophosphamide; LP = leukapheresis; Mb = mobilisation; N = number of patients; NS = not significant; PT = post-transplant; PLT = platelet.*

collection level of >3x10^6 CD34+/kg bodyweight in two leukaphereses.[10] Ataergin et al. showed in a randomised study that filgrastim 10µg/kg/day and lenograstim 7.5µg/kg/day resulted in successful mobilisation of CD34+ cells in patients undergoing high-dose chemotherapy (HDC) and PBSC transplantation. Successful mobilisation with the first apheresis was achieved in 10 of 20 patients (50%) in the filgrastim group versus nine of 20 patients (46%) in the lenograstim group. No significant difference was seen in the median number of CD34+ cells mobilised, the median number of aphereses, the median volume of apheresis, the percentage of CD34+ cells or CD34+ cell number. This study showed that lenograstim at a 25% lower dose does not negatively affect the number of CD34+ stem cells harvested.[11]

Table 2: Data Published to Date on the Use of Lenograstim for Allogeneic Stem Cell Transplantation

Author, Reference, Type of Study	N	Mb	PT	Lenograstism Dose (µg/kg/day)	Control Group (µg/kg/day)	Number of CD34+ Cells information	Other
Ho'glund et al.,[16] prospective	32	+	–	Lenograstism 3	Lenograstim 5, 7.5 and 10, filgrastim 10	Lenograstim 10 (103.6 cells/µl) versus filgrastim 10 (82.2 cells/µl) CD34+ cells	*An additional 27% more CD34+ cells in lenograstim group
Watts et al.,[17] prospective	20	+	–	Lenograstim 5	Filgrastim 5	Average CD34+ cell count on days 5, 6 and 7	*The average CD34+ cell count on days 5, 6 and 7 was 28% higher
Ings et al.,[18] retrospective	400	+	–	Lenograstim 5	Filgrastim 5		*A greater number of GM-CFC were harvested using lenograstim compared with filgrastim
Heuft et al.,[19] prospective, randomised	52	+	–	Lenograstim 3.1 + dexametazone 8mg/day	Lenograstim 11.8 alone (single SC injection)	Average CD34+ cell count	NS
Ocheni et al.,[26] prospective, randomised	44	–	+	Lenograstim 263µg/day	6mg pegfilgrastim on day +5	Neutrophil engraftment faster in the pegfilgrastim group (p=0.006), NS difference in PLT engraftment	*

**Difference significant; GM-CFC = granulocyte–macrophage colony-forming cells; Mb = mobilisation; N = number of patients; NS = not significant; PLT = platelet; PT = post-transplant; SC = subcutaneous.*

Another prospective randomised study conducted by Öztürk et al. compared 49 patients undergoing autologous peripheral stem cell transplantation (APSCT) and mobilisation. This study compared patients with a low dose (7.5µg/kg/day) or a standard dose (10µg/kg/day) of lenograstim. Successful mobilisation with the first apheresis was achieved in 10 of 24 patients (42%) in the low-dose group versus 14 of 25 patients (56%) in the standard-dose group. No significant difference was seen in the median number of CD34+ cells mobilised, the median number of aphereses, the median volume of apheresis, the percentage of CD34+ cells or CD34+ cell number.[12]

A prospective, randomised clinical trial was conducted by Kopf et al. to assess the mobilising efficacy of filgrastim, lenograstim and molgramostim. Following a disease-specific chemotherapy regimen, randomisation to filgrastim, lenograstim or molgramostim at 5µg/kg/day was performed. The median number of CD34+ cells obtained after mobilisation was $8.4x10^6$/kg in the filgrastim arm versus $5.8x10^6$/kg in the lenograstim arm versus $4.0x10^6$/kg in the molgramostim arm (p=0.1). All three growth factors were efficacious in mobilising peripheral stem cells, with no statistically significant difference.[13]

Another prospective randomised study, by Karanth et al., compared the efficiency of PBSC mobilisation using either cyclophosphamide (2g/m²) and lenograstim at 5µg/kg (n=39) or lenograstim alone at 10µg/kg (n=40). Successful mobilisation was achieved in 28 of 40 (70%) in the G-CSF group versus 22 of 39 (56.4%) in the cyclophosphamide–G-CSF group (p=0.21). There was no significant difference in the median number of mobilised CD34+ cells. However, nausea, vomiting and total time spent in the hospital during mobilisation were significantly increased after cyclophosphamide–lenograstim (p<0.05). Lenograstim at 10µg/kg was as efficient at mobilising stem cells as the combination of cyclophosphamide and lenograstim at 5µg/kg but with reduced hospitalisation and fewer side effects.[14]

Despite several prospective studies showing that lenograstim is more effective on a weight-for-weight basis, a retrospective study in 126 patients by Lefrère et al. showed that there is no statistically significant difference between lenograstim and filgrastim groups in terms of number of leukaphereses necessary to obtain a minimal number of $3x10^6$ CD34+ cells/kg.[15]

Studies with Lenograstim on Peripheral Blood Stem Cell Mobilisation in Allogeneic Transplantation

Ho'glund et al. showed in a dose-finding trial in healthy volunteers that lenograstim 10µg/kg/day for six days mobilises PBSCs more efficiently than 3.5 and 7.5µg/kg/day, and the average CD34+ cell number was higher with lenograstim administration than with filgrastim. Lenograstim produced 103.6 cells/µg versus 82.2 cells/µg with filgrastim, meaning that an additional 27% CD34+ cells were produced with lenograstim.[16] *In vitro* studies indicate that lenograstim is more potent than filgrastim on a weight-for-weight basis.

Höglund et al. showed in 32 healthy male volunteers that lenograstim 10µg/kg/day mobilises PBSCs more efficiently than the identical dose of filgrastim, indicating a difference in *in vivo* potency between the two G-CSFs.[7] In a similar cross-over study by Watts et al., filgrastim and lenograstim was administered at a dose of 5µg/kg/day subcutaneously for six days. The blood peak level of white blood cells and granulocyte monocyte colony-forming units (CFU-GM) was significantly higher with lenograstim than with filgrastim.[17] A study by Ings et al. showed similar results to these.[18]

A prospective study with unrelated volunteers conducted by Heuft et al. showed that lenograstim at 3.1µg/kg plus dexamethasone 8mg orally (n=29) was as effective as lenograstim 11.8µg/kg without dexamethasone (n=23) in terms of stem cell mobilisation and collection.[19] This study showed that the combination of lenograstim – even at 3.1µg/kg concentration – with dexamethasone can be

beneficial for stem cell transplantation patients, and further studies should be carried out.

Studies with Lenograstim on Post-transplant Engraftment for Autologous Transplantation

A randomised trial conducted by Linch et al. showed that G-CSF after PBSC transplantation in lymphoma patients significantly accelerated neutrophil recovery and shortened time in hospital.[20] In another study, Brice et al. showed that the duration of neutropenia and hospitalisation were both lower in patients who received lenograstim (150µg/m^2/day) compared with those who received no treatment. Savings were largely attributable to decreased expenditure on hospitalisation in the lenograstim-treated group.[21] Schmitz et al. showed, in a double-blind, randomised trial, that the administration of lenograstim after high-dose therapy (HDT) and ASCT significantly reduced the incidence of infections until neutrophil recovery and also led to less use of antibiotics and earlier discharge from hospital.[22]

A prospective randomised study was performed by Suh et al. on 33 patients undergoing ASCT. Patients were randomly administered 100 or 250µg lenograstim daily starting after stem cell reinfusion. There were no significant differences in neutrophil and platelet engraftment, episodes of clinically documented infections or red blood cell or platelet transfusion. This study showed that administration of lower doses of lenograstim was as effective as standard doses of lenograstim in terms of neutrophil engraftment after ASCT.[23]

A double-blind, placebo-controlled, randomised trial was performed by Nolan et al. to determine whether short-course low-dose or standard-dose lenograstim would influence recovery of haematopoiesis following HDT and PBSC recovery. Sixty-one patients were randomised to receive standard-dose lenograstim (263µg/day), low-dose lenograstim (105µg/day) or placebo injections. Short-course low-dose lenograstim was found to be as effective as standard-dose lenograstim in reducing neutrophil engraftment time following HDT and PBSC recovery.[24]

A prospective, randomised trial conducted by Jang et al. showed that administration of split doses of lenograstim was not associated with superior clinical efficacy compared with conventional daily single-dose administration for haematopoietic recovery after ASCT.[25]

Ataergin et al. showed in a randomised study that filgrastim 10µg/kg/day and lenograstim 7.5µg/kg/day resulted in successful mobilisation of CD34+ cells in patients undergoing HDC and PBSC transplantation. In the post-transplant period, lenograstim was given at 5µg/kg/day for both groups until leukocyte engraftment. Leukocyte and platelet engraftments, the number of days requiring G-CSF and parenteral antibiotics and the number of transfusions were similar in both groups in the post-transplant period.[11]

Another prospective randomised study, conducted by Öztürk et al., compared patients undergoing APSCT and mobilisation with a low dose (7.5µg/kg/day) or a standard dose (10µg/kg/day) of lenograstim. In the post-transplant period, lenograstim was given at 5µg/kg/day for both groups until leukocyte engraftment. Leukocyte and platelet engraftments, parenteral antibiotics and the number of transfusions were similar in both groups in the post-transplant period.[12]

Studies with Lenograstim on Post-transplant Engraftment for Allogeneic Transplantation

Ocheni et al. compared a single, subcutaneous, fixed dose of 6mg pegfilgrastim on day +5 with daily lenograstim 263µg from day +5 and continued until neutrophil engraftment after allogeneic PBSC transplantation. Neutrophil engraftment was significantly faster (p=0.006) in the pegfilgrastim compared with the lenograstim group. No significant difference was seen in terms of platelet engraftment.[26]

Conclusion

In vitro studies indicate that lenograstim is more potent than filgrastim on a weight-for-weight basis. Short-course, low-dose lenograstim was found to be as effective as the standard dose in reducing neutrophil engraftment time following HDT and PBSC recovery. Lenograstim at a 25% lower dose does not negatively affect the number of CD34+ stem cells harvested or engraftment results. ■

Mustafa Öztürk is an Assistant Professor in the Department of Medical Oncology at Gulhane Military Medical Academy, Ankara. He is interested in high-dose chemotherapy and stem cell transplantation. He is a member of the International Bone Marrow Transplant Registry (IBMTR), the Multinational Association of Supportive Care in Cancer (MASCC), the Turkish Oncology Group and the Turkish Oncology Association. Dr Öztürk attended medical school at Gulhane Military Medical Academy, graduating in 1994. He completed a fellowship in internal medicine between 1997 and 2001 at the same institution.

Fikret Arpaci is Chief of the Department of Medical Oncology at Gulhane Military Medical Academy. He is particularly interested in high-dose treatment and stem cell transplantation. He is a member of the International Bone Marrow Transplant Registry (IBMTR), European Bone Marrow Transplant (EBMT), the European Society for Medical Oncology (ESMO), the Turkish Oncology Group and the Turkish Oncology Association. Dr Arpaci graduated from medical school at Istanbul University Faculty of Medicine in 1983. He completed his fellowship in internal medicine in 1991 at Ankara Gulhane Military Medical Academy and his medical oncology residency in 1994. He then worked for one year as a research fellow on T-cell depletion and immunomagnetic purging at the Center for Cancer Treatment and Research in Columbia, South Carolina.

1. Pedrazzoli P, et al., *Anticancer Res*, 1996;16:1781–5.
2. Decleva E, et al., *Int J Tissue React*, 1995;17:191–8.
3. Mire-Sluis AR, et al., *J Immunol Methods*, 1995;179:117–26.
4. Nissen C, et al., *Drug Invest*, 1994;7:346–52.
5. Decleva E, et al., *Int J Tissue React*, 1995;17:191–8.
6. Höglund M, *Med Oncol*, 1998;15(4):229–33.
7. Höglund M, et al., *Eur J Haematol*, 1997;59(3):177–83.
8. Martin-Christin F, *Anticancer Drugs*, 2001;12:185–91.
9. De Arriba F, et al., *Br J Haematol*, 1997;96:418–20.
10. Ria R, et al., *Bone Marrow Transplant*, 2010; 45:277–81.
11. Ataergin S, et al., *Am J Hematol*, 2008;83(8):644–8.
12. Ozturk M, et al., *J Clin Oncol*, 2009;27(15):380s.
13. Kopf B, et al., *Bone Marrow Transplant*, 2006;38(6):407–12.
14. Karanth M, et al., *Bone Marrow Transplant*, 2004;34(5): 399–403.
15. Lefrère F, et al., *Leuk Lymphoma*, 1999;35(5–6):501–5.
16. Ho'glund M, et al., *Bone Marrow Transplant*, 1996;18:19–27.
17. Watts MJ, et al., *Br J Haematol*, 1997;98:474–9.
18. Ings SJ, et al., *Br J Haematol*, 2006;134:517–25.
19. Heuft HG, et al., *Transfusion*, 2002;42(7):928–34.
20. Linch DC, et al., *Br J Haematol*, 1997;99(4):933–8.
21. Brice P, et al., *Pharmacoeconomics*, 1995;7(3):238–41.
22. Schmitz N, et al., *Bone Marrow Transplant*, 2004;34(11):955–62.
23. Suh C, et al., *Transfusion*, 2004;44(4):533–8.
24. Nolan L, et al., *Br J Haematol*, 2007;137(5):436–42.
25. Jang G, et al., *Transfusion*, 2008;48(4):640–46.
26. Ocheni S, et al., *Leuk Lymphoma*, 2009;50(4):612–18.