European Journal of Cancer (2012) **48**, 713–720

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

A randomised phase II study of the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study)

C. Sebban [a,*], A. Lefranc [b], L. Perrier [c,d], P. Moreau [e], D. Espinouse [f], A. Schmidt [g], L. Kammoun [h], H. Ghesquieres [a], C. Ferlay [b], J.O. Bay [i], S. Lissandre [j], D. Pérol [b], M. Michallet [k], P. Quittet [l]

[a] *Hematology Department, Cancer Centre Léon Bérard, Lyon, France*
[b] *Biostatistics unit, Cancer Centre Léon Bérard, Lyon, France*
[c] *Gate-UMR5824 CNRS, University of Lyon, Lyon, France*
[d] *Department Cancer and Environment and health economics, Cancer Centre Léon Bérard, Lyon, France*
[e] *Hematology Department, University Hospital, Nantes, France*
[f] *Hematology Department, University Hospital Lyon Sud, Pierre Bénite Lyon, France*
[g] *Hematology Department, University Hospital, Angers, France*
[h] *Hematology Department, Cancer Centre Henri Becquerel, Rouen, France*
[i] *Hematology Department, University Hospital, Clermont-Ferrand, France*
[j] *Hematology Department, University Hospital, Tours, France*
[k] *Hematology Department, University Hospital Edouard Herriot, Lyon, France*
[l] *Hematology Department, University Hospital Saint Eloi, Montpellier, France*

Available online 14 January 2012

KEYWORDS
Chemotherapy; Cost effectiveness analysis
Lymphoma
Myeloma
Pegfilgrastim
Filgrastim
Transplantation
Clinical trial

Abstract *Aim:* To evaluate in a multicentre randomised study the effect on duration of febrile neutropenia (FN), the safety and cost-effectiveness of a single subcutaneous pegfilgrastim injection compared with daily injections of filgrastim after peripheral blood stem cell transplantation in patients receiving high dose chemotherapy for myeloma and lymphoma.
Methods: Patients were randomly assigned to a single dose of pegfilgrastim at day 5 (D5) or daily filgrastim from D5 to the recovery of absolute neutrophil count (ANC) to 0.5 G/L. Duration of FN, of neutrophil and platelet recovery, transfusion and antibiotic requirements were the main end-points of the study. Costs were calculated from D0 until transplant unit discharge. The incremental cost-effectiveness ratio was expressed as the cost per day of FN prevented. Probabilistic sensitivity analysis was performed by non-parametric bootstrap methods.

* *Corresponding author:* Address: Centre Léon Bérard, 28 rue Laënnec, 69373 Lyon Cedex 08, France. Tel.: +33 (4) 78 78 27 37; fax: +33 (4) 78 78 27 16.
E-mail address: catherine.sebban@lyon.unicancer.fr (C. Sebban).

doi:10.1016/j.ejca.2011.12.016

Results: Between October 2008 and September 2009, 10 centres enrolled 151 patients: 80 patients with lymphoma and 71 patients with myeloma. The mean duration of FN was 3.07 days (standard deviation (SD) 1.96) in the pegfilgrastin arm and 3.29 (SD 2.54) in the filgrastim one. Mean total costs were 23,256 and 25,448 euros for pegfilgrastim and filgrastim patients, respectively. There was a 62% probability that pegfilgrastim strictly dominates filgrastim.

Concluding statement: Pegfilgrastim after PBSC transplantation in myeloma and lymphoma is safe, effective when compared with filgrastim and could represent a cost-effective alternative in this setting.

1. Introduction

High-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (HDC-SCT) is an established treatment that improves outcome in certain patients with lymphoma and multiple myeloma.[1–4] Post-transplant Granulocyte Colony-Stimulating Factor (G-CSF) such as filgrastim accelerates neutrophil engraftment and reduces duration of hospitalisation and medical costs. It has been approved in Europe in accordance with the American Society of Clinical Oncology (ASCO) and the European Organisation for Research and Treatment of Cancer (EORTC) guidelines[5,6] for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

Pegylation of filgrastim decreases plasma clearance and increases its half-life without loss of clinical activity.[7,8] A single dose of pegfilgrastim seems as effective as many daily doses of filgrastim in cancer patients treated by conventional dose chemotherapy.[9–12]

The efficacy and tolerance of pegfilgrastim after HDC-SCT have been evaluated in non-comparative studies.[13–17] All of them reported the feasibility of using pegfilgrastim in this setting. Haematological reconstitution is similar when retrospectively compared with filgrastim. A decrease of the duration of febrile neutropenia (FN) was observed in one small randomised study in myeloma.[18] When the present study was designed, there was no convincing prospective studies comparing pegfilgrastim and filgrastim in HDC followed by Peripheral Blood Stem Cell (PBSC) and the economic issues were not properly addressed. We therefore undertook a phase II, randomised controlled trial in order to evaluate the efficacy and the cost effectiveness of pegfilgrastim in preventing FN.

2. Methods

2.1. Patients

Eligible patients had to be at least 18 years old, with a diagnosis of myeloma or lymphoma requiring HDC-SCT. Conditioning was achieved without total body irradiation. Patients undergoing a second HDC-SCT were eligible if their first such treatment was more than 100 days preceding enrolment. All patients had to have an absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/L, a platelet count $\geqslant 100 \times 10^9$/L and at least 2×10^6 cryopreserved CD34 cells/kg before conditioning. Patients were hospitalised in the participating centre during treatment and until their ANC reached $>0.5 \times 10^9$/L. Patients were not eligible if they had an acquired immunodeficiency syndrome. All patients gave written informed consent.

2.2. Study design

This study was a multicentre, open-label, not blinded, randomised phase II to assess the safety, efficacy and cost-effectiveness of a single pegfilgrastim injection versus daily filgrastim injections (Clinical Trials Registration number: ET2007 – 113).

2.3. Study drugs and G-CSF treatment procedures

Pegfilgrastim (Neulasta® – AMGEN Europe B.V.) and filgrastim (Neupogen® – AMGEN Europe B.V.) are produced by recombinant DNA technology.

Pegfilgrastim and filgrastim were administered subcutaneously; pegfilgrastim was given as a single 6 mg injection 5 days after the PBSC reinfusion. Filgrastim was given at 5 μg/kg/day from day 5 post-transplantation until resolution of neutropenia (ANC $> 0.5 \times 10^9$/L). Supportive care was provided according to the standard procedures of each participating institution.

2.4. Study data collection

Patients were screened during the week preceding transplantation. They were randomised immediately after having undergone autologous haematopoietic stem cell transplantation (D0). Patients were followed up from D0 to D100 ± 10.

2.4.1. Clinical data

Complete blood counts (CBCs) were performed daily during hospitalisation, twice weekly after hospitalisation until platelet and neutrophil recovery ($>100 \times 10^9$/L and $>1.5 \times 10^9$/L, respectively), then every 2 weeks and at D100 ± 10. Patients' temperature was taken four

times daily (at intervals of at least four hours) from D0 to the end of the first period of hospitalisation. Use of anti-infectives was recorded from medical reports during the first period of hospitalisation and from patients' note books at each subsequent visit. Transfusions were recorded from medical reports from D0 to the end of the study. Grade $\geqslant 3$ adverse events (AE), related or not to the study drugs, were assessed using NCI-CTCAE v.3.0.

2.4.2. Economic data

Alongside the clinical trial, data on consumption of resources (length of hospital stay, number of transfusions, quantity of anti-infectives and G-CSFs administered) were collected prospectively from D0 until discharge from the bone marrow unit.

The cost of hospital resources was taken as the mean unit cost across the 10 participating centres. For each patient, lengths of stay were multiplied by the daily unit cost, which covered personnel, medications (except growth factors and anti-infectious therapies), medical devices, laboratory tests, depreciation of equipment and overheads. The prices of anti-infectives and the G-CSFs were taken as the mean purchase price for the centres involved. Transfusions were costed according to the official 2009 French tariffs.[19] Centre effect was tested by the calculation, for both arms, of the mean of the average total costs of each centre. All costs are presented in 2009 euros (2009 annual exchange rate: 1.39 US dollar/euro).

2.5. Sample size

The primary end-point was the mean duration of FN defined as an ANC < 0.5 G/L and temperature >38 °C at least once a day. Assuming a mean duration of FN of 4 days (standard deviation (SD) 3.7), 75 patients were needed in the pegfilgrastim arm in order to estimate the mean duration of FN with a precision of 0.85 day and a two-sided 95% confidence interval. Given a 1:1 randomisation ratio, a total of 150 patients had to be included in the study. Randomisation, stratified by pathology (myeloma verus lymphoma) and participating centre, used a block method (with block size of 2 and 4) and was centralised by way of a specific website. No formal comparison between arms was planned for the primary end-point. The randomisation was intended to afford a substantial degree of reassurance that the control value chosen to plan the sample size was appropriate.

2.6. Statistical analyses

All analyses were performed in the intent-to-treat population. Baseline characteristics of the two arms were described and compared using the non-parametric Wilcoxon rank sum test or Fisher's exact test.

2.6.1. Clinical outcomes

The mean duration of FN was calculated for each arm with its 95% confidence interval and was adjusted for potential imbalance in baseline characteristics in multivariate analysis.

Secondary end-points included the duration of treatment in the filgrastim arm, the duration of hospitalisation from stem cell transplantation, the duration of neutropenia, thrombopenia and fever (defined as temperature >38 °C once or more per day) and the number of red blood cell and platelet transfusions.

Toxicity profiles (grade $\geqslant 3$ adverse events, related or not to the study drugs) and the occurrence of documented infections are also reported as frequencies and percentages. All clinical statistical analyses were performed using SAS software (version 9.2 SAS institute, Cary, NC).

2.6.2. Economic outcomes

2.6.2.1. Cost-effectiveness analysis. The ICER, defined as, $\frac{\overline{C}_{\text{pegfilgrastim}}-\overline{C}_{\text{filgrastim}}}{\overline{E}_{\text{pegfilgrastim}}-\overline{E}_{\text{filgrastim}}}$ was determined on the basis of the mean total costs in pegfilgrastim versus filgrastim arms. The efficacy outcome used was the mean duration of FN from D0 until discharge from the bone marrow unit. The ICER was expressed as the cost per day of FN prevented.

2.6.2.2. Sensitivity analysis. One-way sensitivity analyses were conducted by varying across the range of the purchase prices of pegfilgrastim and filgrastim paid by the participating centres. The uncertainty surrounding the ICER was captured by a probabilistic sensitivity analysis. One thousand replications were obtained by non-parametric bootstrap methods. A graphical representation of the sampling uncertainty associated with the ICER on the cost-effectiveness (CE) plane is shown in Fig. 1. The four quadrants of the CE plane are as follows: northeast, i.e. pegfilgrastim more costly and more effective than filgrastim; southeast (pegfilgrastim less costly, more effective); northwest (more costly, less effective) and southwest (less costly, less effective). The probability that the true ICER falls in each quadrant was expressed as a percentage. Confidence regions were assessed and are represented by ellipses. The outer ellipse defines the confidence region at the 95% level, and the inner ellipse at the 50% level.[20] All economic analyses were performed using STATA software (version 10.0) and Gauss software (version 9.0).

3. Results

3.1. Patient characteristics

From October 2008 to September 2009, 151 patients were enrolled by ten French centres (80 patients with lymphoma and 71 patients with myeloma). All patients except one were evaluable for the primary outcome. Patient characteristics at baseline are summarised in

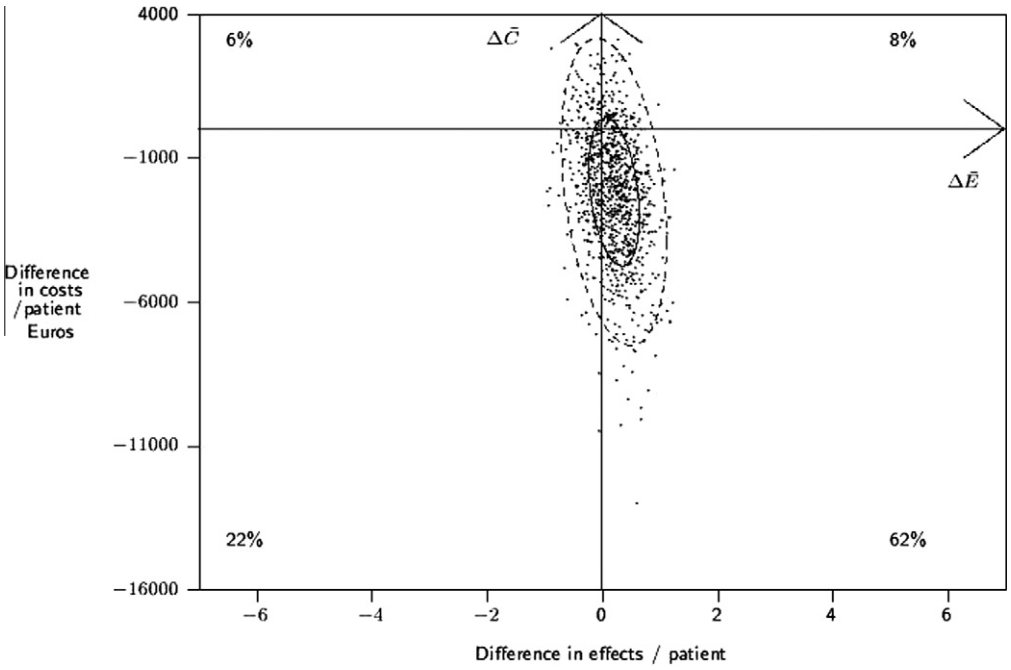


Fig. 1. $\Delta\overline{C}$ is the difference in average total costs. $\Delta\overline{E}$ is the difference in average effectiveness. The scatter of points corresponds to 1000 non-parametric bootstrap replications of the pairs $(\Delta\overline{C}, \Delta\overline{E})$. In each quadrant, the percentages quantify the probability that the true incremental cost-effectiveness ratio is in the quadrant. The external ellipse defines the confidence region at level 95%, and the internal ellipse that of level 50%.

Table 1. Disease characteristics, treatment history, conditioning protocols and number of stem calls reinfused were similar in the two groups. Median age was greater in the pegfilgrastim arm (59 years versus 55, Wilcoxon test, $p = 0.021$).

3.2. Efficacy

In the filgrastim arm, the median number of treatment days was 7 (range 4–15 days.) In the pegfilgrastin arm, there was a mean of 3.07 days of FN (SD 1.96) compared with a mean of 3.29 (SD 2.54) in the filgrastim arm. After adjustment for age, the mean values were 3.00 days (SD 2.27) and 3.35 days (SD 2.26), respectively. In the pegfilgrastin arm, among 39 patients with lymphoma, FN occurred in 38 (97.4%) with a mean duration of 3.49 days (SD 1.92]). FN occurred in 36 of the 40 lymphoma patients (90.0%) in the filgrastim arm, with a mean duration of 4.15 days (SD 2.85). Of patients with myeloma, 31 of 35 (88.6%) experienced FN in the pegfilgrastim arm, with a mean duration 2.60 days (SD 1.93). The corresponding figures in the filgrastim arm were 30 of 36 patients (83.3%), with a mean duration of 2.33 days (SD 1.72).

Table 2 shows related outcomes according to therapy arm.

Blood lymphocyte counts at D100 were similar in the two arms: 1.23 G/L (SD 0.64) for pegfilgrastim versus 1.28 G/L (SD 0.76)) for filgrastim even when analysed in subgroups (1.23 G/L (SD 0.69) versus 1.29 G/L (SD 0.90) and 1.24 G/L (SD 0.59) versus 1.26 G/L (SD 0.59) for lymphoma and myeloma, respectively).

3.3. Toxicity

No grade 3 or 4 adverse event related to pegfilgrastim or filgrastim were reported. A comparable rate of grade 3

Table 1
Characteristics of the 151 patients.

	Pegfilgrastim arm	Filgrastim arm
Number of patients	75	76
Median age (range)	59 (19–73)	55 (20–75)
Sex (M/F)	45/30	41/35
Disease, *n* (%)		
Multiple myeloma	35 (47)	36 (47)
Non-Hodgkin lymphoma	33 (44)	32 (42)
Hodgkin lymphoma	7 (9)	8 (11)
ABMT indication, *n* (%)		
First line	37 (49)	39 (51)
Second line	32 (43)	29 (38)
>2nd line	6 (8)	8 (11)
Disease status, *n* (%)		
Complete remission (CR) or near CR	29 (39)	30 (39)
Partial Remission	35 (47)	46 (61)
Stable or Progressive Disease	4 (5)	0 (0)
Not evaluable	7 (9)	0 (0)
Conditioning regimen, *n* (%)		
Melphalan	30 (40)	34 (45)
BCNU, Etoposide, Aracytine, Melphalan (BEAM)	33 (44)	32 (42)
Zevaline/BEAM	6 (8)	4 (5)
Others	6 (8)	6 (8)
Median CD34 reinfused 10^6/kg (range)	3.63 (1.3–15)	3.72 (1.2–29)
Prior transplantation, *n* (%)	9 (12)	7 (9)

Table 2
Primary end-point and related variables.

	Pegfilgrastim arm				Filgrastim arm			
	Mean	Standard deviation (SD)	Min	Max	Mean	SD	Min	Max
Mean days of febrile neutropenia	3.07	1.96	0.00	8.00	3.29	2.54	0.00	10.00
Day of ANC < 0.5 g/l	7.43	3.96	3.00	31.00	7.17	2.94	2.00	17.00
Days of ANC < 1 g/l	10.05	6.50	5.00	38.00	11.99	8.81	4.00	51.00
Days with platelets < 20 g/l	3.19	4.14	0.00	25.00	3.61	7.79	0.00	62.00
Days with fever	5.65	4.21	0.00	18.00	7.12	7.51	0.00	40.00
Number of Red Blood Cell transfusions	2.01	2.51	0.00	14.00	2.57	5.55	0.00	45.00
Number of platelet transfusions	3.43	3.49	1.00	24.00	3.99	7.64	0.00	62.00
Duration of hospital stay since reinjection of stem	15.48	4.82	11.00	40.00	16.64	9.54	11.00	67.00
Days of antibiotic therapy	5.42	6.11	0.00	40.00	9.86	34.90	0.00	286.00
	n		%		*n*		%	
Number of patients with Red Blood Cell transfusions	46		61.3		45		60.8	
Number of patients with platelets transfusions	75		100		72		97.3	
Number of documented infections								
At least 1 infection	73		97.3		73		96.1	
Fever of unknown origin	47		64.38		47		64.38	
Infection with no identified germ without fever	13		17.8		19		26.03	
Infection with identified germ with or without fever	37		50.68		37		50.68	

Table 3
Costs of treatment alternatives.

Costs (in € 2009)	Pegfilgrastim ($n = 74$)				Filgrastim ($n = 76$)			
	Mean	Standard deviation (SD)	Min	Max	Mean	(SD)	Min	Max
Hospitalisation	20,725	(6427)	14,695	53,436	22,236	(12,748)	14,695	89,505
Transfusion	1029	(1017)	216	7752	1312	(2596)	0	21,642
Anti infectious	863	(1368)	6	6663	1138	(2828)	0	20,141
Antifungal	471	(1156)	0	6217	774	(2433)	0	16,576
Antibiotics	340	(397)	0	2004	311	(479)	0	3531
Antiviral	52	(51)	0	278	53	(46)	0	296
Growth factors	639	(89)	629	1396	762	(230)	262	1396
Total	23,256	(7897)	15,871	64,726	25,448	(17,077)	16,180	131,986

or 4 chemotherapy related toxicity events was reported (52% in the pegfilgrastim arm and 52.6% in the filgrastim arm). Severe mucositis was observed in 25% of patients receiving pegfilgrastim versus 20% for those receiving filgrastim. Four patients died: one from pneumonia at D39 in the pegfilgrastim arm and three in the filgrastim arm (deaths at D120 from cardiorespiratory failure, at D65 from neuropathy with tetraplegia and respiratory failure and at D45 from pneumonia and pulmonary embolism). No death was related to the study drugs.

3.4. Costs

Table 3 reports the costs according to study treatment from D0 to discharge from the transplant unit. Mean total costs reached €23,256 ($32,326) and €25,448 ($35,373) for pegfilgrastim and filgrastim arms, respectively. Mean costs were also somewhat higher in the filgrastim arm when broken down into costs for hospitalisation, for transfusions, for use of anti-infectives and for growth factors. Mean total costs weighted according to patient inclusion rate by centrer, i.e. centres effect, were €22,978 ($31,939) and €26,075 ($36,244) for pegfilgrastim and filgrastim arms, respectively (Wilcoxon test, $p = 0.414$).

3.5. Incremental cost-effectiveness ratio

Based on the primary end-point of FN, economic analysis suggested that pegfilgrastim was less costly and more effective than filgrastim, i.e. pegfilgrastim strictly dominates filgrastim (Table 4). Since the origin of the cost-effectiveness plane was included in the inner 95% confidence ellipse, the probabilistic sensitivity analysis did not allow to conclude this with certainty (Fig. 1). However, as Fig. 1 also shows, the probability that the true ICER fell in the southeast quadrant (i.e. pegfilgrastim is less costly and more effective compared to filgrastim) is 62%. The probability that pegfilgrastim is more effective and more costly than filgrastim is 8%; and the probability that it is less effective and less costly 22%. The probability that pegfilgrastim is less effective and more costly than filgrastim is only 6%. Taking into

Table 4
Incremental cost-effectiveness analysis comparing treatment alternatives.

Intervention	Costs (€, 2009)	Effectiveness (days with FN)	Incremental cost (AC)	Incremental effectiveness (AE)	ICER (AC/AE)
Pegfilgrastim	23,256	3.07	–	–	
Filgrastim	25,448	3.29	2192	–0.22	Dominated

account the minimum and maximum prices of pegfilgrastim paid by participating centres did not change the study's conclusions.

4. Discussion

The use of GCSF after PBSC transplantation is recommended by most of the guidelines because it hastens neutrophil recovery, shortens hospital stay by 1 or 2 days and decreases the rate of documented infections.[5,6] With a longer half life, a single dose of pegfilgrastim is as effective as repeated doses of filgrastim in reducing the duration of neutropenia in cancer patients including those experiencing intensive chemotherapy prior to PBSC transplantation. In recent studies of autologous stem cell transplantation for myeloma[21,22] and lymphoma,[23] pegfilgrastim is associated with more rapid engraftment and shorter hospitalisation when compared with a historical cohort of patients treated with filgrastim.

To date, four randomised controlled trials[24–27] had compared pegfilgrastim versus filgrastim in the post-transplant setting. They included between 37 and 101 patients with lymphoma or myeloma. In all of them growth factors started at D1. Pegfilgrastim and filgrastim produced similar results on the main outcomes. A recent metaanalysis including all studies comparing pegfilgrastim and filgrastim in this setting suggests a gain in ANC recover and FN duration for patients receiving pegfilgrastim.[28] No prospective cost-effectiveness analysis was performed. In two studies, only the costs of growth factors were considered.[24,28]

The present study is a large, multicentre, randomised trial including 150 patients undergoing autologous transplantation for myeloma or lymphoma. Based on previous data and usual policy in participating institutions, pegfilgrastim or filgrastim were started at D5 after the PBSC reinfusion.[29,30] Our results confirm the feasibility, safety and efficacy of this strategy and show that use of the two agents leads to comparable results on the main outcome measures. No severe side-effect related to the drugs was observed.

We did not observe any difference in the late lymphocyte reconstitution in the pegfilgrastim arm as had been suggested in a small non-randomised study in myeloma.[31] A low D15 lymphocyte count in patients transplanted for lymphoma would be associated with a poorer survival.[32] More biological data are needed to compare the kinetics of immune reconstitution with the two drugs and to identify any potentially clinically important differences.

This prospective cost-effectiveness analysis of pegfilgrastim versus filgrastim is the first based on a randomised interventional study. Our data suggest with a quite high probability that pegfilgrastim dominates filgrastim for the primary end-point of the trial. These results complement those of studies that have examined both G-CSF strategies in patients undergoing standard chemotherapy where pegfilgrastim has a favourable ICER and position in the cost-effectiveness plane. In the study of Lyman et al. in patients with aggressive non-Hodgkin lymphoma, the ICER of pegfilgrastim versus 6-day filgrastim as primary prophylaxis was $2167 per FN event avoided. The cost per Quality Adjusted Life Year (QALY) varied from $1677 to $6190 depending on the assumptions of the model.[33] Moreover, Eldar-Lissai et al. also showed in adult cancer patients receiving chemotherapy that pegfilgrastim dominates filgrastim: the mean cost saving associated with pegfilgrastim was $2195 and the mean difference in effectiveness 0.269 Quality Adjusted Life Day (QALD).[34]

Pegfilgrastim has been also evaluated on an outpatient basis for autologous transplantation in 38 patients with myeloma.[35] This approach is feasible, safe and associated with a rehospitalisation rate of only 12%. Further clinical trials are needed to identify a well-defined subset of patients who might be safely considered for transplant on an outpatient basis with pegfilgrastim support. A single injection is associated with optimum compliance, a saving in nurses' time and less inconvenience for patients.

As this study was based on French costs data, results are relevant within the French health care system. Then, before the routine use of pegfilgrastim in the setting of autologous transplantation, further health economics, quality of life and biologic studies are needed.

Funding

This work was supported by Amgen (Europe) GmbH, Zug, Switzerland.

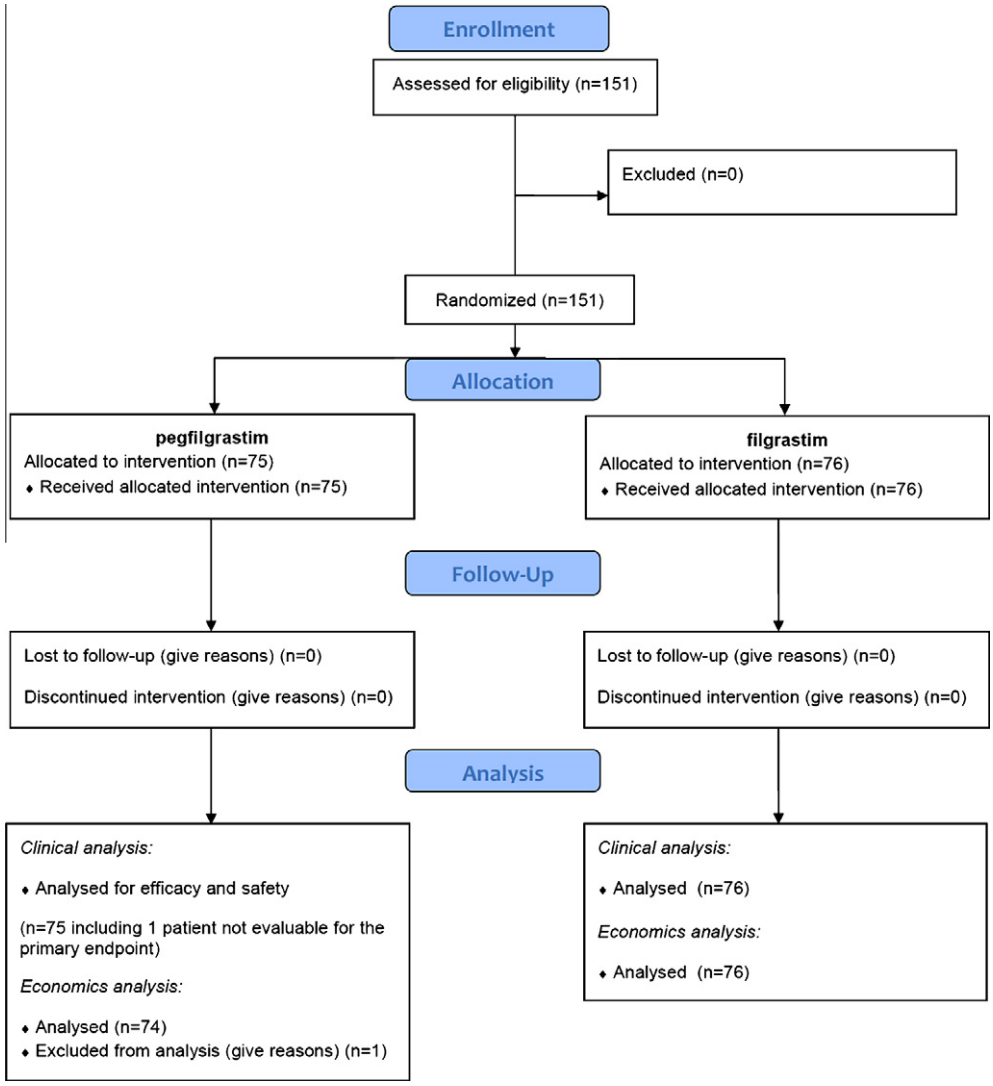
Conflict of interest statement

None declared.

Acknowledgements

Drs. Biron, Lachenal, Bouafia, Nicolini, Ducastelle (Lyon), Drs. Blin, Le Gouill (Nantes), Drs. Ifrah, Hunault (Angers), Dr. Cacheux (Clermont-Ferrand), Dr. Cartron (Montpellier), Drs. Jardin, Leprètre (Rouen), Drs. Renaud, Colombat (Tours) and their teams for patient inclusion; A. Belleville, O. Perol and M. Hureau for data-management; Amgen for financial support.

Appendix 1. Study population



References

1. Philip T, Armitage JO, Spitzer G, et al. High-dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate-grade or high-grade non-Hodgkin's lymphoma. *N Engl J Med* 1987;**316**:1493–8.
2. Crump M, Smith AM, Brandwein J, et al. High-dose etoposide and melphalan, and autologous bone marrow transplantation for patients with advanced Hodgkin's disease: importance of disease status at transplant. *J Clin Oncol* 1993;**11**:704–11.
3. Vose JM, Anderson JR, Kessinger A, et al. High-dose chemotherapy and autologous hematopoietic stem-cell transplantation for aggressive non-Hodgkin's lymphoma. *J Clin Oncol* 1993;**11**:1846–51.
4. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996;**335**:91–7.
5. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;**24**:3187–205.
6. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer* 2011;**47**:8–32.
7. Molineux G, Kinstler O, Briddell B, et al. A new form of filgrastim with sustained duration in vivo and enhanced ability to mobilize PBPC in both mice and humans. *Exp Hematol* 1999;**27**:1724–34.
8. Molineux G. Pegfilgrastim: using pegylation technology to improve neutropenia support in cancer patients. *Anticancer Drugs* 2003;**14**:259–64.
9. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol* 2002;**20**:727–31.
10. George S, Yunus F, Case D, et al. Fixed-dose pegfilgrastim is safe and allows neutrophil recovery in patients with non-Hodgkin's lymphoma. *Leuk Lymphoma* 2003;**44**:1691–6.

11. Vose JM, Crump M, Lazarus H, et al. Randomized, multicenter, open-label study of pegfilgrastim compared with daily filgrastim after chemotherapy for lymphoma. *J Clin Oncol* 2003;**21**: 514–9.
12. Lane SW, Crawford J, Kenealy M, et al. Safety and efficacy of pegfilgrastim compared to granulocyte colony stimulating factor (G-CSF) supporting a dose-intensive, rapidly cycling anti-metabolite containing chemotherapy regimen (Hyper-CVAD) for lymphoid malignancy. *Leuk Lymphoma* 2006;**47**:1813–7.
13. Jagasia MH, Greer JP, Morgan DS, et al. Pegfilgrastim after high-dose chemotherapy and autologous peripheral blood stem cell transplant: phase II study. *Bone Marrow Transplant* 2005;**35**:1165–9.
14. Staber PB, Holub R, Linkesch W, Schmidt H, Neumeister P. Fixed-dose single administration of pegfilgrastim vs daily filgrastim in patients with haematological malignancies undergoing autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 2005;**35**:889–93.
15. Vanstraelen G, Frere P, Ngirabacu MC, et al. Pegfilgrastim compared with filgrastim after autologous hematopoietic peripheral blood stem cell transplantation. *Exp Hematol* 2006;**34**:382–8.
16. Fenk R, Hieronimus N, Steidl U, et al. Sustained G-CSF plasma levels following administration of pegfilgrastim fasten neutrophil reconstitution after high-dose chemotherapy and autologous blood stem cell transplantation in patients with multiple myeloma. *Exp Hematol* 2006;**34**:1296–302.
17. Ballestrero A, Boy D, Gonella R, et al. Pegfilgrastim compared with filgrastim after autologous peripheral blood stem cell transplantation in patients with solid tumours and lymphomas. *Ann Hematol* 2008;**87**:49–55.
18. Martino M, Pratico G, Messina G, et al. Pegfilgrastim compared with filgrastim after high-dose melphalan and autologous hematopoietic peripheral blood stem cell transplantation in multiple myeloma patients. *Eur J Haematol* 2006;**77**:410–5.
19. Arrêté du 02 janvier 2008 relatif au tarif de cession des produits sanguins labiles. Journal Officiel de la République Française 2008. Available from: http://ile-de-france.sante.gouv.fr/img/pdf/joe_20080210_0014.pdf.
20. The economic evaluation at the French National Authority: principles and methods. French National Authority for Health 2011. Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2011-11/guide_methodo_vf.pdf.
21. Mathew S, Adel N, Rice RD, et al. Retrospective comparison of the effects of filgrastim and pegfilgrastim on the pace of engraftment in auto-SCT patients. *Bone Marrow Transplant* 2010;**45**:1522–7.
22. Samaras P, Blickenstorfer M, Siciliano RD, et al. Pegfilgrastim reduces the length of hospitalization and the time to engraftment in multiple myeloma patients treated with melphalan 200 and auto-SCT compared with filgrastim. *Ann Hematol* 2011;**90**:89–94.
23. Samaras P, Buset EM, Siciliano RD, et al. Equivalence of pegfilgrastim and filgrastim in lymphoma patients treated with BEAM followed by autologous stem cell transplantation. *Oncology* 2010;**79**:93–7.
24. Martino M, Pratico G, Messina G, et al. Pegfilgrastim compared with filgrastim after high-dose melphalan and autologous hematopoietic peripheral blood stem cell transplantation in multiple myeloma patients. *Eur J Haematol* 2006;**77**:410–5.
25. Rifkin R, Spitzer G, Orloff G, et al. Pegfilgrastim appears equivalent to daily dosing of filgrastim to treat neutropenia after autologous peripheral blood stem cell transplantation in patients with non-Hodgkin lymphoma. *Clin Lymphoma Myeloma Leuk* 2010;**10**:186–91.
26. Gerds A, Fox-Geiman M, Dawravoo K, et al. Randomized phase III trial of pegfilgrastim versus filgrastim after autologus peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant* 2010;**16**:678–85.
27. Castagna L, Bramanti S, Levis A, et al. Pegfilgrastim versus filgrastim after high-dose chemotherapy and autologous peripheral blood stem cell support. *Ann Oncol* 2010;**21**:1482–5.
28. Ziakas PD, Kourbeti IS. Pegfilgrastim vs. filgrastim for supportive care after autologous stem cell transplantation: can we decide? *Clin Transplant*. doi:10.1111/j.1399-0012.2011.01532.x.
29. Faucher C, Le Corroller AG, Chabannon C, et al. Administration of G-CSF can be delayed after transplantation of autologous G-CSF-primed blood stem cells: a randomized study. *Bone Marrow Transplant* 1996;**17**:533–6.
30. de Azevedo AM, Nucci M, Maiolino A, et al. A randomized, multicenter study of G-CSF starting on day +1 vs day +5 after autologous peripheral blood progenitor cell transplantation. *Bone Marrow Transplant* 2002;**29**:745–51.
31. Vanstraelen G, Frere P, Ngirabacu MC, et al. Pegfilgrastim compared with filgrastim after autologous hematopoietic peripheral blood stem cell transplantation. *Exp Hematol* 2006;**34**: 382–8.
32. Porrata LF, Inwards DJ, Ansell SM, et al. Early lymphocyte recovery predicts superior survival after autologous stem cell transplantation in non-Hodgkin lymphoma: a prospective study. *Biol Blood Marrow Transplant* 2008;**14**:807–16.
33. Lyman G, Lalla A, Barron R, Dubois RW. Cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. *Curr Med Res Opin* 2009;**25**:401–11.
34. Eldar-Lissai A, Cosler LE, Culakova E, Lyman GH. Economic analysis of prophylactic pegfilgrastim in adult cancer patients receiving chemotherapy. *Value Health* 2008;**11**:172–9.
35. Ferrara F, Izzo T, Criscuolo C, et al. Comparison of fixed dose pegfilgrastim and daily filgrastim after autologous stem cell transplantation in patients with multiple myeloma autografted on a outpatient basis. *Hematol Oncol* 2011;**29**:139–43.