COMPARISON OF EFFICACY AND SAFETY OF LENOGRASTIM AND FILGRASTIM IN STEM CELL MOBILIZATION

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*A study conducted by **HTA Consulting** **www.hta.pl***

Objective

The aim of this analysis was to compare efficacy and safety of lenograstim and filgrastim in stem cell mobilization both in healthy donors (allogenic transplantation) and in oncological patients (autologous transplantation).

Introduction

Peripheral blood stem cell transplantation (PBSCT) is an alternative to bone marrow transplantation for patients with various malignancies and blood or bone marrow disorders. Collecting haematopoietic stem cells from peripheral blood, rather than from bone marrow, provides a larger quantity of cells and does not require general anaesthesia to collect the graft from the donor. Additionally, time to engraftment seems to be shorter in case of PBSCT.

In normal, physiologic conditions only a small amount of HSC circulates in peripheral blood. HSC release from bone marrow occurs in response to injury, inflammation or myelotoxic substances in order to protect homeostasis. Administration of recombinant human granulocyte colony stimulating factor, termed mobilization, results in HSC release from bone marrow into peripheral blood. This allows collecting them for transplantation. Mobilization might be performed either in healthy donors – for allogenic transplantation – or in oncological patients – for autologous transplantation. In the second group stem cells are obtained prior to high-dose chemotherapy, frozen, stored and returned to the patient after remission has been achieved.

Two forms of recombinant human granulocyte colony stimulating factor are available for clinical use in Europe and indicated for mobilization of PBSC. Lenograstim is a glycosylated cytokine, derived from Chinese hamster ovary cells and filgrastim is a nonglycosylated molecule derived from E. coli.

Methods

Comparison of efficacy and safety of the evaluated drugs was based on randomized controlled trials (RCTs) identified by means of a systematic review, carried out according to the Cochrane Handbook for Systematic Reviews of Interventions and Polish HTA Guidelines. The most important medical databases were searched (EMBASE, MEDLINE, CENTRAL). Date of the last search was March 2008.

Two reviewers independently selected trials, assessed their quality and extracted data. Critical appraisal of the included studies was performed using the Jadad scale. Meta-analysis of head-to-head trials was performed to compare lenograstim and filgrastim in stem cell mobilization in healthy donors and oncological patients.

Table 1. Inclusion and exclusion criteria

Population	• Healthy stem cells donors (allogenic stem cell transplantation) • Patients with oncological diseases (autologous transplantation)
Intervention	• Lenograstim
Comparator	• Filgrastim
Endpoints	• Number of CD 34+ cells harvested • Number of CD 34+ cells transplanted • Number of aphaeresis procedures performed • Percentage of donors requiring second aphaeresis • Time to ANC recovery • Number of platelet transfusions • Median days to the last platelet transfusion • Median days to the last red blood cell transfusion • Number of transfused units of platelet • Number of transfused red blood cells units • Adverse events
Design of clinical trials	• Randomized clinical trials, with or without blinding
Other inclusion criteria	• Studies published in Polish, English, French or German • Studies published as full texts or conference abstracts
Exclusion criteria	• Non-randomized studies, • No G-CSF name provided, • G-CSF administered before BM harvest, • Studies comparing PBSC + BM vs BM.

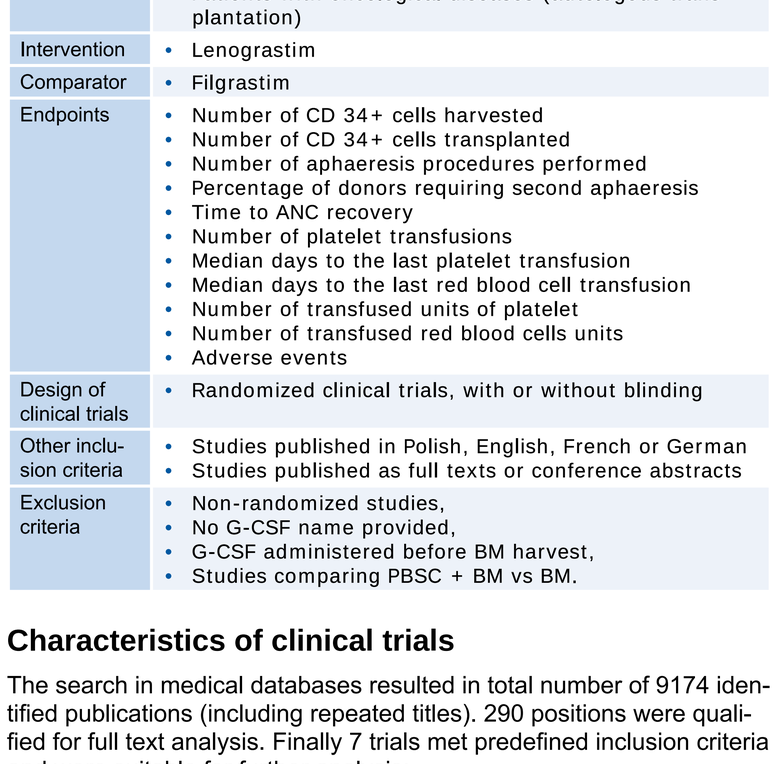
Characteristics of clinical trials

The search in medical databases resulted in total number of 9174 identified publications (including repeated titles). 290 positions were qualified for full text analysis. Finally 7 trials met predefined inclusion criteria and were suitable for further analysis:

- 4 RCTs comparing PBSC mobilization in healthy donors,
- 3 RCTs comparing PBSC mobilization in oncological patients.

Methodological credibility of the trials included in the analysis was medium.

Selection process according to QUOROM



Conclusion

In healthy donors lenograstim is more potent than filgrastim in stem cell mobilization into peripheral blood. No differences in safety profiles between two drugs were noted. In oncological patients both drugs have similar impact on stem cell mobilization, while lenograstim decreases the risk of platelet transfusion.

Results

1. Stem cell mobilization in healthy donors

Four randomized controlled trials regarding comparison of PBSC mobilization with lenograstim or filgrastim in healthy donors were identified and included in the analysis. Two of the studies had parallel design (Fisher 2005, Kishi 2003), another two (Hoglund 1997; Watts 1997) had cross-over design – both interventions were applied in all patients with a 4-week wash-out period.

Table 2. Studies included in the analysis (healthy donors)

Study	Study location	Design	No. of subjects		GCSF dose	Treatment duration	Jadad score
			LEN	FIL			
Fischer 2005	Germany	RCT (paralell)	261	240	10 µg/kg/day (qd)	5-6 days	2
Kishi 2003	Japan	RCT (paralell)	14	20	10 µg/kg/day (bid)	5 days	1
Hoglund 1997	Sweden	RCT (cross-over)	30	30	10 µg/kg/day (qd)	5 days	2
Watts 1997	UK	RCT (cross-over)	20	20	5 µg/kg/day (qd)	6 days	3

Number of CD34+ cells harvested

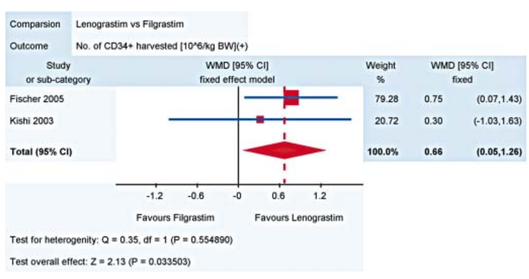
The number of CD34+ cells harvested was assessed in all studies, although methods used differed significantly. Meta-analysis was possible only for two studies (535 donors).

Pooled results of these two studies indicate that mobilization with lenograstim resulted in a higher number of CD34+ cells harvested than mobilization with filgrastim (WMD=0.66 x 10^6 per kg of BW [0.05; 1.26]). The remaining two studies were small – in one of them there was no difference, in the other the number of CD34+ cells harvested was higher in the LEN group (Table 3).

Table 3. Number of CD34+ cells harvested in the included studies

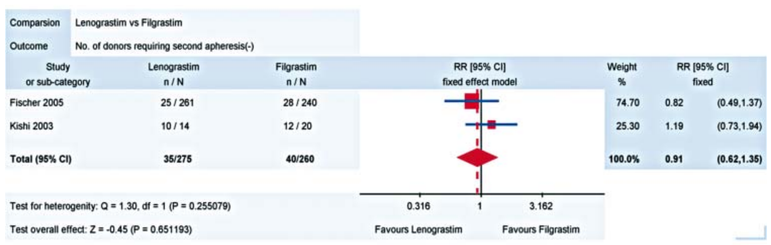
Study	Endpoint description	LEN		FIL		Difference
		N	Result	N	Result	
Fischer 2005	Mean CD34+ count [x10^6 per kg BW] in leukaphaeresis product	261	7.19	240	6.44	P<0.03
Kishi 2003	Mean (SD) CD34+ count [x10^6 per kg BW] in leukaphaeresis product	14	5.6 (2.3)	20	5.3 (1.3)	WMD=0.30 [-1.03; 1.63]
Hoglund 1997	Mean (SD) peak value of CD34+ cells in 1 µl of blood	30	104 (38)[a]	30	82 (35)[a]	WMD=22 [3.51; 40.49]; P<0.0001
	Median (range) number of CD34+ count in leukaphaeresis product[a]	6	5.5 (3.8-7.3)	6	4.2 (3.2-5.2)	nd
Watts 1997	Mean peak value of CD34+ cells in 1 ml of blood	20	53,637	20	45,964	ns

a – among 6 patients who underwent the procedure twice



Number of donors requiring second aphaeresis

The number of donors requiring second aphaeresis was reported only in two studies (535 donors). 13% of lenograstim treated donors and 15% in the filgrastim group needed a second procedure to harvest the requested number of PBSC. No significant difference was proved between lenograstim and filgrastim (RR= 0.91 [0.62; 1.35]).



Safety analysis

Safety outcomes were reported in two studies. Watts et al. (1997) observed similar rates of adverse events in both arms. The most commonly reported AEs were bone pain and arthralgia (both controlled with paracetamol).

Similarly, Hoglund et al. (1997) found no differences between lenograstim and filgrastim with respect to any adverse events (AEs) or treatment-related AEs. Bone pain, reported in all patients from both groups, was the most frequent AE. No serious AEs were reported, although two donors in the lenograstim group were withdrawn from the study due to AEs (one donor experienced dyspnoea and another grade III S-ALAT increase; both adverse effects were transient).

2. Stem cell mobilization in oncological patients

We identified 3 RCTs comparing lenograstim with filgrastim in PBSC mobilization in oncological patients. All the studies had parallel design. In one study only patients with breast cancer were recruited (Arriba 1997), in the other two studies patients with various haematological malignancies were recruited.

Table 4. Studies included in the analysis (oncological patients)

Study	Study location	Design	Group	No. of patients	G-CSF dose	Diagnosis	Jadad score
Arriba 1997	Spain	RCT (paralell)	LEN	15	6,4 (0,1)[a] µg/kg//day	breast cancer	2
			FIL	15	8,4 (0,1)[a] µg/kg/day		
Kopf 2006	Italy	RCT (paralell)	LEN	36	5 µg/kg/day	breast cancer, germ cell tumor, non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma, osteosarcoma	3
			FIL	38			
Kulkarni 1998 (abstract)	UK	RCT (paralell)	LEN	41	2x263 µg/day (≤80 kg) or 3x 263 µg/day (>80 kg)	myeloma, lymphoma, leukemia	1
			FIL	37			

a – mean (standard error)

Mobilizing efficacy

For oncological patients no differences in the number of subjects who gained target CD34+ cells count were found between treatments for either the target value of CD43+: 1 x 10^6 per kg of body weight or 2 x 10^6 per kg of body weight (Table 5).

Table 5. Number of patients who gained target CD34+ cell count

Endpoint	Study	LEN	FIL	RR
		n/N (%)	n/N (%)	[CI95%]
Percentage of patients who gained > 1x10^6 CD34 cells /kg	Kulkarni 2000	29/41 (71%)	27/37 (73%)	0.97 [0.73; 1.28]
Percentage of patients who gained 2x10^6 CD34 cells/kg	Kopf 2006 / Kulkarni 2000	35/70 (50%)	45/66 (68%)	0.72 [0.33; 1.55]

The mean number of harvested CD34+ cells was assessed in all studies. None of them showed significant differences between groups with respect to the harvested CD34+ cell count or the number of collected mononuclear cells. Kulkarni et al. (2000) observed that significantly more CD34+ cells were transplanted in the filgrastim group than in the lenograstim group (p<0.01). Kopf et al. (2006) reported that the median number of aphaeresis procedures in each group was 1, but the median day of the first aphaeresis was significantly shorter in the lenograstim group (12 vs 13 days, p<0.0001).

Table 6. Mobilizing efficacy – continuous outcomes

Outcome	Study	No. of patients		Difference
		LEN	FIL	
No. of CD34+ cells x10^6/kg	Kopf 2006	29	29	MedD=2.60; p=0.1
	Kulkarni 2000	41	37	MD=0.58; p=0.08
	Arriba 1997	15	15	MD=-0.62 [-1.91; 0.67]
Median no. of mononuclear cells	Kulkarni 2000	41	37	MedD=0.25; NS
No. of transplanted cells	Kulkarni 2000	41	37	MD=-0.53; p<0.01
Median no. of aphaeresis procedures	Kopf 2006	29	29	Median=0; NS
Median day of 1st aphaeresis	Kopf 2006	29	29	MedD=-1; p<0.0001

Haematological recovery

Results for haematological recovery are inconsistent. Kulkarni et al. (2000) observed that the median number of days to ANC recovery >0.5x10^9/liter was statistically significantly higher in the lenograstim group than in the filgrastim group (19 vs 16 days, p=0.02), whereas no differences were noted in the need for supportive care or the number of units of blood or platelets transfused. Median duration of hospitalization was 22 days in each group.

Kopf et al. (2006) reported a median number of 3 days to ANC recovery in the lenograstim group and 4 days in the filgrastim group. Platelettransfusions were necessary in significantly more patients in the filgrastim than in the lenograstim arm (34% vs 6%, respectively). The difference was statistically significant (RR=0.16 [0.04; 0.67]). The number of transfused units of platelets and RBC per patient was comparable between both groups. No significant differences in the incidence of grade IV neutropenia were noted (RR=0.72 [0.50; 1.03]; 1 study, 74 patients) whereas platelet transfusions were more frequent in filgrastim treated patients than in the lenograstim group (RR=0.16 [0.04; 0.67]). The length of hospital stay after transplantation was similar in both groups.

Table 7. Results for haematological recovery after PBSCT

Endpoint	Study	LEN	FIL	RR [CI95%]	RD [CI95%]
		n/N (%)	n/N (%)		
Percentage of patients requiring platelet transfusion	Kopf 2006	2/36 (6%)	13/38 (34%)	0.16 [0.04; 0.67]	-0.29 [-0.45; -0.12]
Percentage of patients with grade IV neutropenia	Kopf 2006	19/36 (53%)	28/38 (74%)	0.72 [0.50; 1.03]	-0.21 [-0.42; 0.01]

Non-haematological toxicity

Safety outcomes were reported in one trial (Kopf 2006). The incidence and duration of fever >38°C did not differ significantly between the groups. Among lenograstim treated patients one case of diarrhoea and mucositis and one of nausea and vomiting were reported. In the filgrastim group one patient had diarrhoea. In both groups chemotherapy-related haemorrhagic cystitis was reported in one patient. The differences between the groups were not evaluated due to low incidence and different chemotherapy regimens used.

Limitations

- Heterogeneity between trials (differences in population characteristics of the included studies).
- Two studies were published as conference abstracts only.
- In many cases meta-analysis could not be performed due to lack of indispensable data.

Table 8. Abbreviations

AEs	Adverse events	HSC	Haematopoietic stem cells	PBSCT	Peripheral blood stem cells transplantation
ANC	Absolute neutrophil count	LEN	Lenograstim	qd	Once daily (lat. quaque die)
bid	Twice daily (lat. bis in die)	MD	Mean difference	p	p-value
BM	Bone marrow	MedD	Difference between medians	RCT	Randomized controlled trial
BW	Body weight	N	Total number of subjects in the group	RD	Risk difference
FIL	Filgrastim	n	Number of subjects with outcome	RR	Relative risk
G-CSF	Granulocyte Colony-Stimulating Factor	NS	Not significant	S-ALAT	S-alanine aminotransferase
		PBSC	Peripheral blood stem cells	WMD	Weighted mean difference