COMPARISON OF CLINICAL EFFICACY AND SAFETY OF PERIPHERAL BLOOD STEM CELL TRANSPLANTATION AFTER MOBILIZATION WITH LENOGRASTIM OR FILGRASTIM

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

Objective

The purpose of the study was to compare efficacy and safety of allogenic peripheral blood stem cell transplantation after mobilization with either lenograstim or filgrastim.

Introduction

Peripheral blood stem cell transplantation is an alternative to bone marrow transplantation for patients with various malignancies and blood or bone marrow disorders. Collecting haematopoietic stem cells (HSC) 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. Moreover, 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. Release of HSC 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 and allows harvesting them for transplantation.

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 Escherichia coli.

Methods

Comparison of efficacy and safety of the analyzed 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). Two reviewers independently selected trials, assessed their quality and extracted data. No head-to-head trials were identified, therefore indirect comparison using Bucher's method was performed.

Table 1. Inclusion criteria

Population	• Patients with haematological disorders indicated for allogenic transplantation • Sibling HLA-matched donors
Intervention	• PBSCT after mobilization with lenograstim
Comparator	• PBSCT after mobilization with filgrastim
Endpoints	• Mortality • overall mortality • treatment-related mortality • non treatment-related mortality • GVHD-related mortality • relapses • donor hospitalizations • acute GvHD • chronic GvHD
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.

Conclusions

Indirect comparisons indicate similar efficacy and safety of PBSCT after mobilization with lenograstim and PBSCT after mobilization with filgrastim. No differences were found in the risk of overall or treatment-related mortality, acute or chronic graft versus host disease, or relapse. The only exception was the risk of non-treatment-related mortality, where the results might indicate superiority of lenograstim but the results for absolute and relative parameters were inconsistent.

Regarding PBSC donors, both interventions seem to be associated with comparable incidence of hospitalization.

Characteristics of clinical trials

The search in medical databases resulted in a total number of 9174 identified publications (including repeated titles). 290 positions were qualified for full text analysis. Finally 9 trials met predefined inclusion criteria and were suitable for further analysis:

- 2 RCTs comparing PBSCT after mobilization with lenograstim with bone marrow transplantation,
- 7 RCTs comparing PBSCT after mobilization with filgrastim with bone marrow transplantation.

All studies had paralell design. Methodological credibility of the trials included in the analysis was medium in most cases.

All patients in the included studies were diagnosed with haematological disorders and received disease-specific conditioning regimen – high dose chemotherapy with or without irradiation, followed by transplantation of haematopoietic stem cells. HSC (either peripheral blood stem cells or bone marrow stem cells) were obtained from a sibling donor. In all but two studies no posttransplant G-CSF was allowed. GvHD prevention regimens usually included methotrexate and Cytarabine-A. In one study T-cell depletion of PBSC was used.

Selection process according to QUOROM

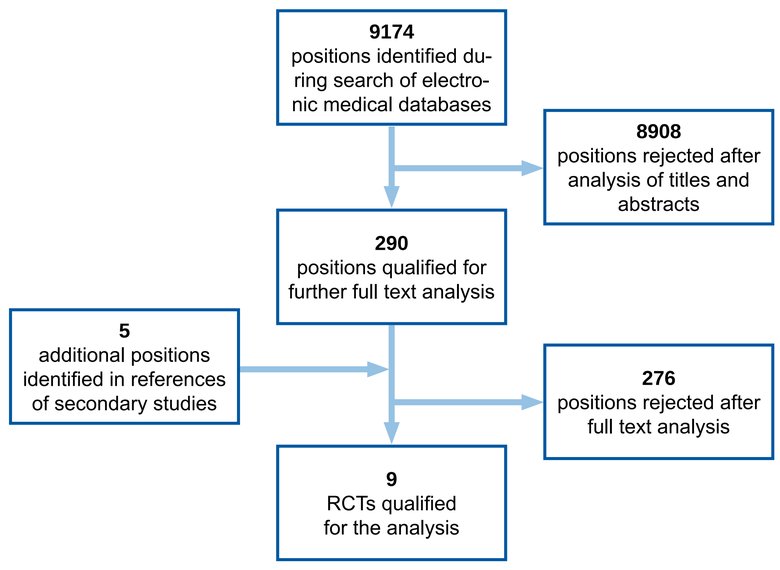

Table 2. Studies included in the analysis

Study	Study location	Design	Group	No. of patients	G-CSF daily dose	Posttransplant follow-up [months]	Jadad score
LENOGRASTIM							
Blaise 2000	France	RCT (paralell)	PBSC (LEN)	48	10 µg/kg /5 days/	22	3
			BM	53	NA	20	
Powles 2000	UK	RCT (paralell)	PBSC (LEN)	20	10 µg/kg /5 days/	NR	3
			BM	19	NA		
FILGRASTIM							
Bensinger 2001	USA	RCT (paralell)	PBSC (FIL)	81	16 µg/kg /5 days/	36	3
			BM	91	NA	36	
Cornelissen 2003	Europa	RCT (paralell)	PBSC (FIL)	56	10 µg/kg /5 days/	37(12 – 75)[b]	3
			BM	54	NA		
Couban 2002	Canada and New Zeland	RCT (paralell)	PBSC (FIL)	109	300 -600 µg[a] /4 days/	32,8	3
			BM	118	NA	NR	
Heldal 2000	Norway	RCT (paralell)	PBSC (FIL)	31	10 µg/kg /5 days/	60	3
			BM	30	NA	60	
Mahmoud 1999	Egypt	RCT (paralell)	PBSC (FIL)	15	10 µg/kg /≥4 days[c]/	7 weeks.	2
			BM	15	NA	7 weeks	
Schmitz 2002	Europe and Australia	RCT (paralell)	PBSC (FIL)	163	10 µg/kg /4 days/	36	3
			BM	166	NA	36	
Vigorito 1998	Brasil	RCT (paralell)	PBSC (FIL)	27	10 µg/kg /5 days/	34	2
			BM	29	NA	46	

a) depending on body weight; b) median (range); c) till target CD43+ cell count was gained

Table 3. Characteristics of population in the included studies

Study	Diagnosis	Conditioning regimen	Posttransplant G-CSF	GvHD prophylaxis
LENOGRASTIM				
Blaise 2000	ALL, AML, CML	CTX/TBI, Bu/CTX, Et/CTX/TBI, C/M/TBI	No[a]	MTX + Cy-A
Powles 2000	AML, ALL, ABL, CML, NHL, MDS, CLL, MM	Bu/CTX, TBI/Et, TBI/M	No	MTX + Cy-A
FILGRASTIM				
Bensinger 2001	AML, ALL, NHL, HD, CML, MM, MDS, CLL, Waldenström's disease, mycosis fungoides	TBI/Bu, TBI/CTX TBI/Et, TBI/Bu/CTX, Bu/CTX, Bu/TSPA	No[a]	MTX + Cy-A
Cornelissen 2003	AML, ALL, MDS, NHL, HD, MM	CTX/TBI, Bu/CTX	NR	Cy-A, T cell–depleted PBSCT
Couban 2002	CML, AML, MDS	Bu/CTX	NR	MTX + Cy-A
Heldal 2000	CML, AML, ALL, MDS, PMF	Bu/CTX	No	MTX + Cy-A
Mahmoud 1999	AML, CML, ALL, SAA, MDS	CTX/TBI, Bu/CTX	Yes (GM-CSF)	MTX + Cy-A
Schmitz 2002	CML, AML, ALL, MDS	TBI/CTX, TBI/Et, TBI/CTX/Et, TBI/M, TBI/Et/M, Bu/CTX, Bu/CTX/Et, Bu/M	Yes (FIL)	MTX + Cy-A
Vigorito 1998	CML ,AML, ALL, NHL, MM, MDS-RA, MDS-RAEB	Bu/CTX, Bu/CTX/Et, CTX/TBI	No	MTX + Cy-A + Pred

a) G-CSF was administered only when myeloid engraftment was delayed or impaired

Table 5. Abbreviations

aGVHD	Acute Graft-Versus-Host Disease	HSC	Haematopoietic stem cells	CML	Chronic myeloid leukaemia	PBSCT	Peripheral blood stem cells transplantation
ABL	Acute biphenotypic leukaemia	LEN	Lenograstim	CTX	Cyclophosphamide	PMF	Primary myelofibrosis
ALL	Acute lymphoblastic leukaemia	M	Melphalan	Cy-A	Cyclosporine	Rc	Risk in control group
AML	Acute myeloid leukaemia	MDS	Myelodysplastic syndrome	Et	Etoposide	RCT	Randomized controlled trial
Pred	Prednisone	MDS-RA	Refractory Anaemia	FIL	Filgrastim	RR	Relative risk
BM	Bone marrow	MDS-RAEB	Refractory Anaemia with Excess Blasts	G-CSF	Granulocyte Colony-Stimulating Factor	SAA	Severe aplastic anaemia
BMT	Bone marrow transplantation	MM	Multiple myeloma	GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor	SE	Standard error
Bu	Busulphan	NHL	Non-Hodgkin lymphoma	GVHD	Graft-Versus-Host Disease	TBI	Total Body Irradiation
C	Cytarabine	NR	Not reported	HD	Hodgkin disease	TRM	Treatment related mortality
cGVHD	Graft-Versus-Host Disease	nTRM	Non-treatment related mortality	HLA	Human Leukocyte Antigens	TSPA	Thiotepa, triethylene thiophosphoramide
CLL	Chronic lymphoblastic leukaemia	PBSC	Peripheral blood stem cells				

Results

No significant differences between lenograstim and filgrastim were found with respect to mortality rate, either overall or treatment-related mortality (RR = 0.84 [0.49; 1.42], RR= 1.11 [0.60; 2.04], respectively). For non-treatment-related mortality the results were inconsistent – relative risk indicated no significant differences between the groups (RR=0.32 [0.10; 1.06]), whereas risk difference suggested statistically significant superiority of lenograstim. Relapse rate was similar between the groups (RR=0.69 [0.19; 2.49]).

PBSCT after mobilization with lenograstim as compared to BMT was not associated with increased risk of acute graft versus host disease (GvHD) (RR=1.06 [0.73; 1.53]), whereas PBSCT after filgrastim use was associated with higher risk of acute GvHD than BMT (RR=1.19 [1.03; 1.37]). However, indirect comparison suggests similar incidence of acute GvHD (RR= 0.89 [0.60; 1.32]. There was also no difference between lenograstim and filgrastim in respect to chronic GvHD (RR=1.33 [0.84; 2.11]. Use of lenograstim or filgrastim in PBSCT resulted in similar mortality rate due to GvHD (RR=0.55 [0.19; 1.59]).

No differences in the risk of hospital admission between donors mobilized with lenograstim or filgrastim were identified (RR=1.04 [0.60; 1.79]).

Limitations

Limitations of the analysis are due to lack of clinical trials with head-to-head comparison of peripheral blood stem cell transplantation after mobilization with lenograstim vs filgrastim. Conclusions are based on indirect comparison and this is a major weakness of this study. However, because of lack of evidence from direct comparison, indirect comparison is the best available source of information about relative efficacy and safety of both recombinant G-CSFs in peripheral blood stem cells transplantation.

Table 4. Results of indirect comparison between PBSCT after mobilization with lenograstim or filgrastim

Outcome	Rc		RR [95%CI]		RD [95%CI]		PBSC (LEN) vs PBSC (FIL)	
	PBSC (LEN) vs BM	PBSC (FIL) vs BM	PBSC (LEN) vs BM	PBSC (FIL) vs BM	PBSC (LEN) vs BM	PBSC (FIL) vs BM	RR [95%CI]	RD [95%CI]
HSC recipients								
Mortality	0.38	0.40	0.81 [0.51; 1.29]	0.97 [0.75; 1.24]	0.07 [-0.09; 0.23]	0.01 [-0.08; 0.11]	0.84 [0.49; 1.42]	0.06 [-0.13; 0.25]
TRM	0.24	0.28	1.05 [0.59; 1.87]	0.95 [0.77; 1.17]	-0.01 [-0.15; 0.13]	0.01 [-0.04; 0.07]	1.11 [0.60; 2.04]	-0.02 [-0.17; 0.13]
nTRM	0.14	0.11	0.35 [0.11; 1.11]	1.10 [0.78; 1.57]	0.10 [-0.002; 0.19]	-0.01 [-0.05; 0.03]	0.32 [0.10; 1.06]	0.11 [0.01; 0.21]
aGVHD	0.44	0.41	1.06 [0.73; 1.53]	1.19 [1.03; 1.37]	-0.02 [-0.19; 0.14]	-0.08 [-0.14; -0.02]	0.89 [0.60; 1.32]	0.06 [-0.12; 0.24]
cGVHD all patients	0.28	0.47	1.70 [1.09; 2.66]	1.28 [1.14; 1.44]	-0.20 [-0.36; -0.04]	-0.13 [-0.19; -0.07]	1.33 [0.84; 2.11]	-0.07 [-0.24; 0.10]
cGVHD evaluable patients	0.29	0.50	1.74 [1.12; 2.70]	1.28 [1.11; 1.47]	0.22 [0.05; 0.38]	0.14 [0.06; 0.22]	1.36 [0.86; 2.16]	0.08 [-0.10; 0.26]
Mortality due to GVHD	0.14	0.06	0.76 [0.31; 1.87]	1.37 [0.79; 2.35]	0.03 [-0.07; 0.14]	-0.02 [-0.06; 0.02]	0.55 [0.19; 1.59]	0.05 [-0.06; 0.16]
Relapse	0.15	0.24	0.31 [0.10; 0.99]	0.45 [0.25; 0.80]	0.11 [0.01; 0.21]	0.13 [0.05; 0.22]	0.69 [0.19; 2.49]	-0.02 [-0.15; 0.11]
HSC donors								
Hospitalization	1	0.97	0.27 0.17; 0.43]	0.26 [0.20; 0.35]	0.73 [0.60; 0.85]	0.71 [0.64; 0.79]	1.04 [0.60; 1.79]	0.02 [-0.13; 0.17]