A Randomized Phase II Study Evaluating the Efficacy, Safety and Cost-Effectiveness of Pegfilgrastim and Filgrastim After High Dose Chemotherapy and Autologous Stem Cell Transplantation In Patients with Lymphoma and Myeloma (PALM Study)

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Background

G-CSF accelerates neutrophil engraftment and decreases the number of days of febrile neutropenia (FN) after chemotherapy and stem cell transplantation.

Filgrastim (F) (r-met Hu-G-CSF) has been approved in this indication. Pegylation of F, Pegfilgrastim (P) decreases its plasma clearance and increases its half-life.

One single dose of P has been shown to be as effective as many doses of F in cancer patients treated by conventional dose chemotherapy. Many studies demonstrate the feasibility of a unique injection of P after reinjection of stem cells but there were no convincing comparative studies assessing efficacy, safety and medicoecomic impact of this strategy.

Objectives

Main: To assess the efficacy of a single injection of P 6 mg subcutaneously (SC), given at D5 after reinjection of stem cells or F 5 µg/kg/day SC from D5 to the end of neutropenia.

Secondary: Key secondary objectives were to estimate, for each treatment regimen, the respective tolerance profile and to compare the cost-effectiveness of the two strategies.

Patients and methods

Design: Open, multicentre randomized phase II trial.

Inclusion criteria: Patients had to be at least 18 years old, with a diagnosis of lymphoma or myeloma, a cryopreserved graft of at least 2.10^6 CD34/kg, must have had a conditioning regimen without irradiation and an intensive chemotherapy.

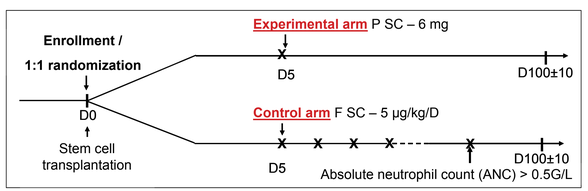

Figure 1: Study design

Statistical considerations:

Randomization was stratified on pathology and on center. The primary efficacy endpoint was the mean duration of FN defined as ANC < 0.5 G/L and temperature > 38°C. Assuming a mean duration of FN of 4 days (SD 3.7), sample size (75 pts per arm) was calculated in order to estimate, with a precision of 0.85 day, a two-sided 95% confidence interval on the mean duration of FN in P arm. No formal comparison between arms was planned for the primary endpoint. The randomization was intended to afford a substantial degree of re-assurance that the historical control value chosen to plan the sample size was appropriate.

For economics evaluation, time horizon was the primary hospitalisation, point of view was in patient and home care. Costs were provided by the departments and pharmacists of the investigator centres. All costs are presented in euros 2009. Cost-effectiveness ratios (ICER) were based on the primary endpoint. Costs were compared using the Mann-Whitney test. Uncertainty was captured by a probabilistic sensitivity analysis using 1000 non-parametric bootstrap replications. 95% rectangular confidence interval was based on the percentiles approach.

All analysis were performed in the intent-to-treat population.

Results

From October 2008 to September 2009, 151 patients were enrolled by 10 centers.

Table I: Characteristics of patients at baseline

	P arm (n=75)		F arm (n=76)	
Median age (range)	58.6 (18.6-72.8)		55.1 (20.0-74.7)	
	n	%	n	%
Male gender	45	60.0	41	53.9
Lymphoma	40	53.3	40	52.6
Myeloma	35	46.7	36	47.4
2nd transplant	9	12.0	7	9.2
Conditioning regimen				
BEAM	*33*	*44.0*	*32*	*42.1*
ZBEAM	*6*	*8.0*	*4*	*5.3*
Melphalan	*30*	*40.0*	*34*	*44.7*
Others	*6*	*8.0*	*6*	*7.9*
Mean CD34+ reinfused ×10^6/kg (SD)	4.73 (2.95)		5.11 (4.19)	

Table II: Study clinical outcomes

	P arm (n=75)		F arm (n=76)	
	Mean	SD	Mean	SD
Duration of FN	3.07	1.96	3.29	2.54
Lymphoma	*3.49*	*1.92*	*4.15*	*2.85*
Myeloma	*2.60*	*1.93*	*2.33*	*1.72*
Days with fever	5.65	4.21	7.12	7.51
Days to reach ANC>=0.5G/L	7.43	3.96	7.17	2.94
Days to reach ANC>=1G/L	10.05	6.50	11.99	8.81
Days with platelets <20G/L	3.19	4.14	3.61	7.79
Days of hospitalization from reinjection	15.48	4.82	16.64	9.54
Red blood cell transfusion units	2.01	2.51	2.57	5.55
Platelet transfusion units	3.43	3.49	3.99	7.64
Days of antibiotics	5.42	6.11	9.86	34.90
F injections			7.03	1.74
	n	%	n	%
Pts without any fever	6	8.0	6	7.9
Pts with grade 3 or 4 adverse event	39	52.0	40	52.6

Table III: Costs of the primary hospitalisation (in 2009 €)

	P arm (n=75)				F arm (n=76)				
	Mean	SD	Min	Max	Mean	SD	Min	Max	P-value
Hospitalization	20680	6438	14695	53436	22236	12748	14695	89505	0,35
Transfusion	1033	1018	216	7752	1312	2596	0	21642	0,39
Anti infectious	851	1371	0	6663	1138	2828	0	20141	0,43
Antifungal	*465*	*1157*	*0*	*6217*	*774*	*2433*	*0*	*16576*	*0,32*
Antibiotics	*336*	*399*	*0*	*2004*	*311*	*479*	*0*	*3531*	*0,32*
Antiviral	*51*	*51*	*0*	*278*	*53*	*46*	*0*	*296*	*0,80*
Growth factors	639	89	629	1396	762	230	262	1396	*<0,01*
Total	23204	7910	15871	64725	25448	17077	16180	131986	0,30

Table IV: ICER

	Costs (€)	FN (days)
P (n=75)	23,204	3.07
F (n=76)	25,448	3.29
Difference between P and F	-2,244	0.22
ICER		P dominates

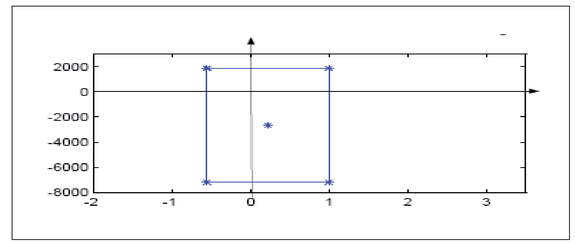

Figure 2: Confident interval of ICER

Conclusion

1. P after autologous stem cell transplantation is at least as efficient and safe than F on clinical outcomes, especially on duration of FN, either for lymphoma or myeloma.
2. These results corroborate those of other randomized studies with smaller sample size recently published.
3. P strictly dominates F in terms of economic outcomes, i.e. had better effectiveness and lower costs on the primary endpoint (FN). These economics results seem to confirm those of the literature based on Markov modeling approach.
4. P should be considered as a standard of care in patients with lymphoma and myeloma after high-dose chemotherapy and autologous stem cell transplantation.

References

- Haile SR, Buset EM, Petrausch U,et al. Renner C. 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. 2010 Aug 13. [Epub ahead of print]
- 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 Jun;10(3):186-91
- Mathew S, Adel N, Rice RD ar al. Retrospective comparison of the effects of filgrastim and pegfilgrastim on the pace of engraftment in auto-SCT patients. Bone Marrow Transplant. 2010 Oct;45(10):1522-7
- 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 May;16(5):678-85.
- 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 Jul;21(7):1482-5.
- Kobbe G, Bruns I, Fenk R et al. Pegfilgrastim for PBSC mobilization and autologous haematopoietic SCT. Bone Marrow Transplant. 2009 May;43(9):669-77.
- 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 Jan;87(1):49-55.

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