COST EFFECTIVENESS ANALYSIS OF FILGRASTIM *versus* PLACEBO IN POST ALLOGENIC BONE MARROW TRANSPLANTATION

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Abstract

Filgrastim is used to accelerate hematopoietic recovery after allogeneic bone marrow transplantation (ABMT). Its impact on the total cost of patient care remains to be explored.
We therefore undertook a cost effectiveness analysis in the context of a randomized clinical trial of Filgrastim versus placebo in post ABMT.
A primary endpoint, duration of myelosuppression, and three secondary end points (number of days of fever, length of hospital stay, survival at one hundred days) were used to assess efficacy. Direct costs were evaluated and allowed the calculation of the incremental cost-effectiveness ratios (ICER) for the major endpoints of the trial.
Sixteen patients were included in the study. The duration of myelosuppression was significantly decreased in the Filgrastim arm with medians of 15 days vs. 19 days in the placebo arm ($p<0.05$). Cost analysis showed no statistically significant difference between the two arms. According to the calculation of ICER, Filgrastim was more costly and more effective than placebo for the number of days of aplasia avoided and the number of days with fever avoided. Placebo strictly dominated filgrastim for days of hospitalization avoided.
Filgrastim has proven effective in reducing the duration of aplasia without increasing costs.

Keywords: *Filgrastim; placebo; cost; effectiveness; Allogeneic Bone Marrow Transplantation;*

1. Introduction

Allogeneic bone marrow transplantation (ABMT) remains, until the development of gene therapy, the only curative treatment of a number of constitutional deficit disorders of the hematopoietic tissue. It remains the eradicator treatment of a number of malignant hematological diseases and keeps this place in the therapeutic arsenal. However, the success of this therapy is not always guaranteed and depends on several factors such as patient age, post-transplant immunological complications, adverse reactions of the conditioning treatment, the

occurrence of infections associated with neutropenia caused by myeloablation and / or myelosuppression and the duration of the neutropenia (1).

The Filgrastim, a granulocyte colony-stimulating factor analog, is used to reduce the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation (2). Hence it represents an additional cost of drug spending in the care of patients undergoing ABMT. Widespread use should be based on a rational assessment of cost effectiveness in a context where health expenditures are increasing (3).

We intend to conduct a cost-effectiveness analysis of Filgrastim (Neupogen ©) *vs.* placebo in reducing the duration of neutropenia in patients undergoing myeloablative therapy followed by ABMT.

2. Patients and methods

This pilot study is part of the evaluation of the effectiveness and cost of Filgrastim after geno-identical ABMT. It concerns adult patients hospitalized in the sterile unit of the Hematology / Bone Marrow Transplantation service in the *Centre National de Greffe de Moelle Osseuse*-Tunisia. Patients were randomized to belong to one of two groups (Filgrastim or placebo) in a single blind conducted trial. We had the agreement of the ethics committee for the conduct of this trial.

Filgrastim is used in primary prevention on the regimen of 5µg / Kg once daily by intravenous infusion. The administration begins on day 7 of the allograft and is maintained 72 hours after the absolute neutrophil count (ANC) stabilizes above 1000 elements / microL.

Data collection has been done by means of a table including patient characteristics and different clinical parameters used to assess efficacy. The study covered a period of one hundred days from the day of the transplantation.

2.1 Effectiveness

The primary endpoint was the myelosuppression period defined by an ANC <500 /microL. The secondary endpoints were the number of days of fever, the number of days of hospital stay and survival at 100 days.

2.2 Cost data

Direct costs were calculated for both arms of the study and are expressed in euros. It includes cost of laboratory tests, cost of medical imaging, drug Costs (divided into anti-

infectives, parenteral nutrition, oral decontamination, hematopoietic growth factors and other medicines), cost of therapeutic drug monitoring (TDM) and cost of labile blood products.

2.3 Cost-effectiveness analysis

Incremental cost-effectiveness ratios (ICER) expressing the additional cost of one unit of outcome gained/avoided by one strategy compared with another, were calculated for the mainly endpoints of the trial. This is the ratio of the difference in costs between the two arms of treatment (Filgrastim and placebo) to the difference in effectiveness (4).

2.4 Statistical analysis

A statistical analysis was performed through SPSS (Statistical Package for the Social Sciences) Version 21.

Quantitative variables were described as median, mean and standard deviation. Qualitative variables were described as percentages.

The efficacy endpoints and the different costs were compared between the two independent samples (Filgrastilm arm and placebo arm). Quantitative variables were analyzed using the Mann-Witheney U test. The Fisher exact test was used to compare categorical variables. The difference was considered statistically significant when the p value was less than 0.05 in a bi-tailed test.

3. Results

3.1 Patient characteristics

A total of sixteen patients (nine in the Filgrastim arm and seven in the placebo arm) aged 17 to 37 years (Table 1) participated in the study. All underwent génoidentical ABMT and received a GvHD prophylaxis based on ciclosporin and methotrexate.

Table 1 Patient caracteristics

	Filgrastim (N=9)	**Placebo (N=7)**	***p***
Age [a] (years)	24.78 ± 7.31	25 ± 6.53	0.98
Sex ratio (males : females)	4 : 5	6 : 1	0.15
Body Mass Index (Kg/m^2) [a]	20.16 ± 1.88	24.86 ± 5.21	**0.02**
Diagnosis [b]			
Acute leukemia	5 (55.6%)	2 (28.6%)	
Aplastic anemia	4 (44.4%)	5 (71.4%)	0,36
Standard risk [b]	7 (77.8%)	6 (85.7%)	
High risk [b]	2 (22.2%)	1 (14.3%)	1
Sex Mismatch			
Present [b]	6 (66.6%)	3 (42.9%)	
Absent [b]	3 (33.3%)	4 (57.1%)	0,62
ABO compatibility			
Compatible [b]	7 (77.8%)	2 (28.6%)	
Incompatible [b]	2 (22.2%)	5 (71.4%)	
Major	1	2	0,13
Minor	1	1	
Mixed	0	1	
Mononuclear cells infused ($\times 10^8$/kg) [a]	1.89 ± 0.59	2 ± 0.75	0.78

[a] *moyenne ± standard deviation*

[b] *n (%)*

3.2 Effectiveness

The duration of myelosuppression was shorter in the Filgrastim arm relative to the placebo arm (median of 15 days vs. 19 days) ($p < 0.05$) (Table 2).

Table 2 Efficiency measured according to the treatment group

Endpoints	Filgrastim (N=9)			Placebo (N=7)			p
	Median	Mean	Standard deviation	Median	Mean	Standard deviation	
Duration of myelosuppression*	15	15,44	1,24	19	19,57	4,39	**0,03**
Number of days of fever	4	6,33	5,7	4	7,57	6,85	0,90
Duration of hospitalization*	24	26,22	6,78	25	24,43	4,86	0,98
Survival at 100 days*	100	100	0	100	87,85	32,13	0,44

**days*

3.3 Cost data

The total cost was measured higher in the Filgrastim arm but the difference between the two groups was not significant (Table 3).

Table 3 Mean total costs per patient (in 2015 euros)

Costs	Filgrastim (N=9)		Placebo (N=7)		p
	Mean	Standard deviation	Mean	Standard deviation	
Anti infectives	2347,8	1098,5	3880,5	1783,0	0,83
Growth Factors	1753,2	254,1	0,0	0,0	$< \mathbf{10^{-4}}$
Parenteral Nutrition	321,1	147,9	262,4	120,5	0,75
Oral Decontamination	91,8	85,3	79,9	36,7	0,75
Other medicines	608,8	160,0	1149,9	528,3	1
Total (medicines)	5122,8	1051,3	5372,5	2468,5	0,53
Therapeutic Drug Monitoring	517,0	70,7	397,0	182,4	0,12
Blood Derivatives	873,0	361,9	1016,6	467,1	1,00
Biological analyzes	3387,9	1802,1	2138,3	982,5	0,09
Medical imaging and anatomopathological analyzes	170,8	260,3	73,1	33,6	0,45
Total	10071,6	2145,4	8997,5	4134,1	0,35

3.4 Cost effectiveness analysis

The calculation of ICER (Table 4) showed that the amount to be paid to avoid a day of myelosuppression was 260 €. The amount to be paid to avoid a day of fever was 866.2 €.

The Filgrastim was less effective and more expensive than placebo in reducing the number of hospitalisation days (ICER = -600) as shown in Table 4.

Table 4 Incremental cost-effectiveness ratios (ICERs) of Filgrastim versus placebo

	Filgrastim	Placebo	difference	ICER
Mean cost (€, 2015)	10071,6	8997.5	1074.1	
Effects : mean days				
Myelosuppression	15,44	19,57	4,13	260.1[a]
Fever	6,33	7,57	1,24	866.2 [a]
Hospitalisation	26,22	24,43	-1,79	-600.1[b]

[a] *Filgrastim more effective and more expensive*
[b] *Placebo dominates*

4. Discussion

Our study shows that filgrastim reduces the duration of myelosuppression from 19 days (placebo group) to 15 days ($p<0.05$) as shown in Table 2. This was found in several studies, including that of Bishop et al and that of Ernst et al. (11 days and 15 days repectively for Filgrastim and 15 days and 19 days respectively for placebo (5, 6)

The acceleration of medullar engraftment by Filgrastim does not seem significantly affect 100 days survival even if it is increased in the filgrastim group *vs.* placebo group in our study. This was also found in the two studies cited above (5, 6). Due to some controversies, the real impact on survival of G-CSF still seems unclear (7, 8).

The Filgrastim is not an additional expense compared to placebo, at least among the costs measured in our study (Table 3). The ICER in reducing myelosuppression is about 260 euro. This figure should be compared to the threshold values of ICER depending on social, economical and political factors. The placebo strictly dominated filgrastim for the duration of hospitalization. Several alternatives seeking to improve the cost-effectiveness ratio of myeloid growth factors, have turned to pegfilgrastim (a covalent conjugate of Filgrastim characterized by a greater half-life (7)) and found it more efficient and cheaper (9). The pegfilgrastim has also been proposed as an alternative in some of the recommendations to Filgrastim (2, 7). The cost-effectiveness of G-CSF mimetic (second generation products) remains to be explored.

This study presents multiple bias. It is based on a reduced cohort of sixteen patients. This pilot study should be continued with a larger number of patients. The body mass index was significantly different between the two arms of treatment. This could be a source of bias such in the assessment of the cost of medicines or if it causes some comorbidities.

5. Conclusion

The Filgrastim shows an interesting effectiveness in reducing the duration of myelosuppression in allograft patients, without any significant change in the number of days of fever, length of hospital stay or survival. It does not present a significant additional cost in return compared to placebo. These data are to be discussed at the risk of an increase in graft versus host disease. Larger studies are needed to confirm our results. We mention that the cost effectiveness of filgrastim may be significantly improved by the adoption of biosimilars.

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