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Economic evaluation of new drugs

The economic evaluation of hematopoietic growth factors in high-dose chemotherapy

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Hematopoietic growth factors (HGFs) such as granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor have been shown to accelerate engraftment after transplantation and facilitate peripheral blood stem cells mobilization. Besides efficacy and safety, the economic impact of these expensive new drugs produced via biotechnological methods is of major concern. The use of HGFs in high-dose chemotherapy (HDC) therefore requires that economic evaluation starts as early as possible throughout the R&D. This can participate in the innovation development process and help predict subsequent diffusion of the technology over time, and potential evolution in expected clinical utilization and costs. Although some issues about the economic consequences of their use have been determined by 'piggyback' studies (economic evaluation alongside randomized controlled trials), several questions remain unanswered regarding the costs involved in therapeutic innovations permitted by the use of HGFs in HDC. [© **1998 Lippincott Williams & Wilkins.**]

Key words: Economic evaluation, high-dose chemotherapy, granulocyte colony stimulating factor, peripheral blood stem cells.

Introduction

High-dose chemotherapy (HDC) followed by stem cell rescue is increasingly used in therapy of advanced cancers, with promising or established results in hematological malignancies including leukemia and lymphomas as well as selected forms of chemosensitive solid tumors. Hematopoietic growth factors (HGFs) such as granulocyte colony stimulating factor (G-CSF) or granulocyte macrophage colony stimulating factor (GM-CSF) have been shown to accelerate engraftment after transplantation and facilitate peripheral blood stem (pluripotent) cells (PBPC) mobilization. Besides efficacy and safety, the economic impact of such expensive new drugs produced via biotechnological methods is of major concern. In this article, we will draw a state of the art of the economic evaluation of the use of HGFs in HDC in the autologous setting and in the allogeneic case. Future therapeutic possibilities using HGFs are also discussed.

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Methodological difficulties

In economic evaluations of medical interventions, costs are related to outcome. Ideally, the outcome measure should be related to the clinical end-point of the therapy. HGFs in HDC have several clinical applications with different clinical end-points. Hence the choice of outcome measure is far from obvious.[1,2] Different measures imply different types of economic evaluation. For example, 'cost-minimization' studies are based upon the assumption that the two therapeutic strategies compared lead to the same clinical outcome. Of course, the follow-up of the patients does not always allow demonstrating a clear-cut clinical advantage for an innovation such as HGFs during the early stages of its development process. Therefore, proximal end-points such as granulocyte and platelet recovery in the case of HDC have been used for measuring effectiveness. However, using proximal end-points leads to methodological difficulties. However, timely evaluation of a medical innovation such as PBPC could hardly wait until better effectiveness criteria such as survival and/or quality of life are documented in depth. Although unsatisfactory, the use of intermediary end-points at least allows economic issues to be discussed at an early stage of the expansion of the innovation in more valid terms than pure cost-minimization analysis.

The autologous setting

In the autologous setting, the use of HGFs permits a quicker neutrophil recovery after transplantation and mobilizing the stem cells in the peripheral circulation permits us to develop the use of PBPC as a transplant. Although the question concerning the clinical and economic advantage of autologous PBPC transplantation over autologous bone marrow (BM) transplantation now appears answered, the economic impact of the use of HGF's after transplant (blood stem cells or BM) nevertheless remains unclear. Moreover, the more cost-effective way of mobilizing and collecting PBPC also remains unknown.

PBPC collection

Among the various arguments in favor of the substitution of PBPC to BM autologous transplantation, the general idea was that PBPC collection by leukapheresis was an easier procedure than BM harvest for hematopoietic stem cell collection and was less costly for hospital departments. Indeed, early cost analyses revealed that PBPC collection under most protocols was more expensive than BM harvest. This led to the necessity of extending economic comparison to the whole therapeutic strategies using either PBPC or BM transplantation. This also led some teams to try to further reduce the cost of PBPC collection through economic optimization of this procedure.

PBPC collection versus BM harvest. Few studies in terms of costs have been carried out specifically on the stem cell collection procedure. However, the cost of the collection can sometimes be extracted from studies comparing the whole procedure of transplantation between PBPC and BM transplantation.[3,4]

The main difficulty when comparing PBPC collection and BM harvest cost is the high impact of the leukaphereses number on the PBPC total cost. This leukaphereses sessions number itself is closely related with the procedure used for mobilizing stem cells (chemotherapy + G-CSF or G-CSF alone, the G-CSF dose, G-CSF and GM-CSF combination) and its efficacy is measured by the number of $CD34^+$ collected, which is itself related to the platelet recovery after transplantation.[5-7] Moreover, the study of the stem cell collection procedure is difficult to separate from the whole transplantation procedure. Nevertheless, in order to clarify the question of the cost comparison between the two collection procedures, the results of several studies are listed in Table 1. European studies[3,8] reported a comparable magnitude in the collection cost when comparing PBPC and BM transplantation, both with a cost advantage for the BM collection (10% decrease for Le Corroller *et al.*[8] and 25% decrease for Uyl-de Groot *et al.*[3]). By contrast, Smith *et al.*[4] found that costs of PBPC collection were lower than BM harvest. However, it is worth noting that the latter study presents North American unit costs and that it is difficult to compare those costs with the European ones. At least, all studies showed that additional costs due to G-CSF stimulation are partially[3,8] or totally[4] offset by the cost reduction of the PBPC collection procedure, as compared to BM.

Here we present a review of the comparison between PBPC collection and BM harvest cost. This

Table 1. Cost comparison of PBPC collection and BM harvest

	Le Corroller *et al.*[8]			Uyl-de Groot *et al.*[3]		Smith *et al.*[4]	
	PBPC[a]		BM	PBPC[a]	BM	PBPC[b]	BM
No. of leukaphereses	2	3		3		3	
Mobilization	G-CSF 600 μg for 5 days	G-CSF 600 μg for 6 days		CT+G+CSF 300 μg for 10 days		G-CSF 10 μg/kg for 6 days	
Collections costs							
collection	1269	1937	3118	1360	2043	3067	8531
G-CSF stimulation	1273	1527	0	1380	0	1326	0
Total cost	2542	3464	3118	2740	2043	4393	8531

All costs are US$.
CT, Chemotherapy.
[a]No hospitalization between leukaphereses.
[b]We made the assumption of no hospitalization between leukaphereses while there was some in the Smith *et al.* study.

implies that only one way of collection was used for each study, with a fixed number of leukaphereses sessions. This is a restrictive point of view that offsets the main difficulty of PBPC collection, i.e. the uncertainty concerning the most cost-effective way of collecting PBPC. This uncertainty regarding the collection of PBPC necessitates an economic optimization methodology.

Optimization of PBPC collection. We have attempted to optimize PBPC collection from an economic point of view.[8] In order to take into account the remaining clinical uncertainties about the minimum level of $CD34^+$ cells which guarantees the possibility of PBPC transplantation, this study performed a cost-minimization analysis, i.e. we compared the costs of the PBPC protocol of three systematic leukaphereses with an alternative PBPC protocol in which the number of leukapheresis sessions is not decided *a priori*, but in which leukaphereses are performed until a predetermined number of $CD34^+$ cells has been collected. This analysis was carried out not only on the basis of the current 3×10^6/kg $CD34^+$ cells threshold, but for all values which have been discussed in the literature for defining a clinically reinfusable PBPC graft (from 0.5×10^6 to 10×10^6/kg $CD34^+$).[6] Results show that the cost comparison of an iterative PBPC procedure versus BM harvest depends on the $CD34^+$ threshold.[8] PBPC is less costly if collection of 2×10^6/kg $CD34^+$ becomes considered to be sufficient for clinical reinfusion, but becomes more costly if the minimum threshold for $CD34^+$ is higher. Simulation of the iterative procedure shows the major influence of the $CD34^+$ threshold on the PBPC collection average cost per patient, which varies from \$2780 (with a threshold of 0.5×10^6/kg $CD34^+$) to \$6700 (with a threshold of 10×10^6/kg $CD34^+$).[8]

If some decisions about standard practice for PBPC collection in France have been reached following our study, there are, however, remaining debates with respect to the optimal procedure. For example, there is uncertainty about the priming of the collection, i.e. the conditioning regimen to be used in order to stimulate the presence of stem cells in the peripheral blood of the patients.[6,9] Regarding the timing of the collection between stimulation and leukapheresis sessions, some teams measure the rate of $CD34^+$ circulating in the blood before the first leukapheresis and decide to perform it only if a sufficient number of cells are already present in the peripheral circulation. Additional studies on the impact of alternative priming protocols on PBPC collection cost are therefore required.

Substitution of PBPC autologous transplantation to BM transplantation

Several preliminary economic studies have shown the cost advantage of PBPC autologous transplantation over BM transplantation in patients with lymphoma and breast cancer,[3,10] multiple myeloma[11] or non-Hodgkin's lymphomas.[12] All these studies found a faster hematopoietic recovery with the use of PBPC (granulocytes and platelet recovery) and a faster discharge after transplant (with one exception: Woronoff-Lemsi *et al.*[12]). The cost advantage for the PBPC group ranged from 1% of the total treatment cost[12] up to 33%.[3] Those preliminary studies were confirmed by two 'piggyback' economic evaluations.[4,13] In both evaluations, cost estimates are real costs and therefore reflect the true social cost of the medical resources used.

In the study of Smith *et al.*,[4,14] 58 patients with advanced Hodgkin's disease or high-grade non-Hodgkin's lymphoma received either G-CSF-mobilized PBPC (n=27) or bone marrow (n=31) after HDC. All patients received G-CSF at a dose of 5 μg/kg daily starting 24 h after transplantation of PBPC, or bone marrow until an absolute neutrophil count (ANC) of 1.0×10^9/l or more for three consecutive days or 10.0×10^9/l or more for 1 day was reached. The median time to platelet recovery was 16 (8-52) days in the PBPC transplantation group and 23 (13-56) days in the ABMT group (p=0.02). The median time to recover an ANC of 0.5×10^9/l or more was significantly shorter in patients randomized to PBPC transplantation [11 (9-38) days] than in those randomized to ABMT [14 [9-25) days].[14] Estimated costs were \$8531 for BM harvest and \$760 for PBPC collection, including G-CSF mobilization. The total estimated average cost was \$59 314 for BM transplantation patients versus \$45 792 for PBPC patients.[4] Cost savings of \$13 521 (23%) were due to shorter hospitalization with less supportive care (Table 2).

In the study of Le Corroller *et al.*[13,15] 129 patients (adults and children) with solid tumors or lymphomas received either G-CSF-mobilized PBPC (n=64) or bone marrow (n=65) after HDC. All patients received G-CSF at a dose of 5 μg/kg daily starting 24 h after transplantation of PBPC or bone marrow until granulocyte recovery (to a ANC count $>1.0 \times 10^9$/l; controlled twice at 48 h intervals).[15] The economic evaluation of the trial was divided between adults and children because they require a different organization of care and necessitate different monetary valuations for each day of hospitalization. Cytopenia induced by HDC was shorter in the PBPC group; there was a significant difference (p<0.0001) between this group

Table 2. Cost results of two economic evaluations alongside two randomized control trials comparing PBPC and BM autologous transplantation

	Smith *et al.*[4]		Le Corroller *et al.*[13]			
	PBPC	BM	Adults		Children	
			PBPC	BM	PBPC	BM
Collection costs						
collection	4449	8531	2164	3384	2210	3384
G-CSF stimulation	1312	0	2025	0	1053	0
subtotal	*5760*	*8531*	*4189*	*3384*	*3263*	*3384*
Transplantation costs						
hospitalization	25828	32702	10682	12170	11663	17325
medication/nutrition	7742	8810	2635	2804	2791	2997
G-CSF post-graft	1528	1992	1763	2610	1613	2410
transfusions	2387	3993	2942	5766	2793	4784
laboratory	2548	3288	1380	1695	1415	2185
subtotal	*40033*	*50785*	*19402*	*25045*	*20275*	*29701*
Total cost	**45793**	**59316**	**23591**	**28429**	**23538**	**33085**

All costs are mean costs in 1995 US$.

and the autologous BM transplantation group for median number of days to reach 0.5×10^9/l neutrophils, i.e. 10 versus 13 days, respectively, for the adults and 10 versus 18 days for the children. Therefore, post-transplant G-CSF stimulation was significantly shorter ($p<0.0001$) in the PBPC group, meaning that the need for hematopoietic growth factor was lower in this group. The median number of days to reach an unsupported platelet count of 30×10^9/l was significantly shorter ($p<0.0001$) in the PBPC group (median=13.5 days for the adults and 15 days for the children) as compared with the autologous BM transplantation group (median=25.5 days for the adults and 42.5 days for the children). Patients in the PBPC group were discharged significantly ($p=0.0001$) earlier from the Transplantation Unit (median=24 days for the adults and 24.5 days for the children) than patients in the BM transplantation group (median=30 days for the adults and 37 days for the children).[13]

Total cost of treatment in the PBPC group ($23 591 for the adults and $23 538 for the children) is lower compared to the BM group ($28 429 for the adults and $33 086 for the children), i.e. a 17% decrease for the adult population and 29% for the pediatric population, respectively. This decrease is associated with the decrease in room costs due to shorter length of stay (12% decrease for the adult population and 33% for the pediatric population, respectively). Another interesting result is the large cost decrease for G-CSF post-transplant in the PBPC group compared to the BM transplantation group (32% decrease for the adult population and 33% for the pediatric population, respectively). See Table 2.

The overall cost of the procedure was more important in the Smith *et al.*[4] study, mainly because the daily hospitalization unit cost was more important in this study than the French ones. It should be noted that the Smith *et al.*[4] study applied North American monetary valuations to a European clinical study. Besides the methodological difficulties entailed in such a study, the North American and European health care unit costs cannot really be compared without taking the respective purchasing power into account. Nevertheless, if we focus on health economic evaluation, the main result of such studies is the comparison between groups in each study, both showing a comparable percentage cost decrease with the PBPC use (23% for Smith *et al.*,[4] and 17 and 28% for the adult and children population, respectively, for Le Corroller *et al.*[13]). This result now appears to be accepted internationally and seems to have contributed greatly to replacing autologous BM transplantation by PBPC transplantation as it is showed in Figure 1 in the case of Europe.[16]

HGF post-transplant

Several economic evaluations have explored the impact of post-ABMT G-CSF administration. If all agree about a faster neutrophil recovery and a shorter hospitalization length of stay,[3,17–19] cost comparison appears to be more controversial. Souêtre *et al.*[18] and Kucharski *et al.*[19] found a cost advantage with the

administration of G-CSF. However, these results were not confirmed by Faucher *et al.*[17] and Uyl-de Groot *et al.*[3] Nevertheless, the clinical advantage demonstrated by all randomized studies[20–22] led G-CSF users to optimize its administration by studying the best timing to administrate G-CSF after BM transplantation. Khwaja *et al.*[23] were the first to propose to delay administration of G-CSF and showed that treatment with G-CSF starting 8 days after BM reinfusion was as effective in accelerating neutrophil recovery as historical control groups in which patients did not receive G-CSF after transplant. Following this analysis, several studies have shown that starting G-CSF on day 6[24] or 7[25] offers the same hematological recovery as G-CSF administration on day 1. One economic analysis studied the delayed administration of G-CSF after autologous BM transplantation [on day 10 (n=13) or 7 (n=6)] in comparison with patients who did not receive G-CSF post-transplant. Results showed that the cost of the G-CSF therapy was offset by the decreased bed utilization, so that the median combined antibiotic, G-CSF and hospitalization cost was £754 less for G-CSF-treated patients.[26]

With regard to the PBPC transplantation, several randomized trials have shown that G-CSF administration after stem cells reinfusion (from day 1 on) accelerates the rate of neutrophil recovery and shortens the duration of hospitalization in patients who receive autologous PBPC with or without autologous BM following HDC[27–29] (Table 3). One of these randomized study from McQuaker *et al.*[27] included a cost-minimization analysis that showed that a low-dose of G-CSF (50 $\mu g/m^2$) permits £1042 mean savings per patient compared with no G-CSF administration.

In order to reduce the costs associated with the growth factor purchase, some teams studied the delayed administration of G-CSF post-transplant, from day 3, 5 or 6 after transplant. Faucher *et al.*[17] demonstrated that administration of G-CSF on day 6 after transplant does not modify the hematological recovery when compared with the administration from day 1 after reinfusion. Similarly, in a recent randomized trial, Bolwell *et al.*[30] showed that delayed G-CSF on day 3 or 5 after transplant gives the same hematological recovery as G-CSF on the day of transplant.

If the delayed administration of G-CSF after PBPC transplantation seems interesting from an economic point of view, this administration scheme is not yet sustained by any economic analyses. The optimal timing of HGFs after PBPC transplantation remains to be determined by economic analyses.

Sequential chemotherapy

New therapeutic opportunities were offered by the HGFs, e.g. sequential chemotherapy with PBPC support. This new strategy is currently in feasibility and efficacy analysis, and first results appeared promising.[31–34] One study evaluated the clinical and economic benefit of G-CSF given with intensive sequential chemotherapy.[34] Women with poor-prog-

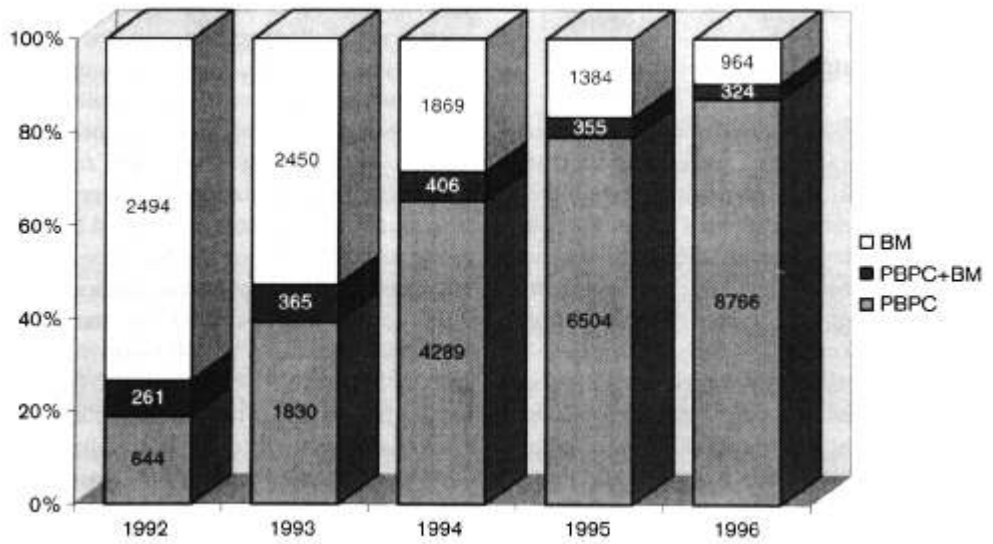

Figure 1. Evolution of autologous stem cells transplantation in Europe (1992–1996). Data from European Group for Blood and Marrow Transplantation.[16]

Table 3. Results of randomized trials of growth factors following PBPC autologous transplantation

	McQuaker *et al.*[27]		Spitzer *et al.*[28,a]		Klumpp *et al.*[29,b]	
	HGF	Placebo	HGF	Placebo	HGF	Placebo
No. of patients	19	19	10	10	22	19
Growth factor dose	G-CSF 50 $\mu g/m^2$		G-CSF 7.5 $\mu g/kg$ +GM-CSF 2.5 $\mu g/kg$		G-CSF 5 $\mu g/kg$	
ANC $> 0.5 \times 60^9$/l (day to reach)	10*	14	10*	16	10.5*	16
	12	14	13	12	13	15
Platelet $> 20 \times 10^9$/l	13*	16	19*	21	18*	24
Post-graft stay (days)	2	4	2	3	5	3
Fever (days)						

[a]All patients received BM in addition to PBPC.
[b]Twenty patients received BM in addition to PBPC.
*Significant ($p < 0.05$).

nosis breast cancer received four cycles of HDC, followed by G-CSF, stem cell collection after cycle 1, and stem cell reinfusion after cycles 3 and 4. The first cohort received G-CSF after the fourth cycle (33 patients) but the second cohort did not (13 patients). Results show that the duration of grade IV neutropenia was shorter in the group receiving G-CSF as was the median time to recover an ANC $> 1.0 \times 10^9$/l. The rate and duration of the hospitalizations for complications were higher in the group not receiving G-CSF. Costs were found significantly higher in the non-G-CSF-treated group. Using granulocyte recovery (ANC $> 1.0 \times 10^9$/l) as an intermediary efficiency criteria, G-CSF administration appeared to be more cost-effective.[34]

The allogeneic setting

The first reports with clear evidence of engraftment of G-CSF-mobilized allogeneic PBPC were published in 1993.[35,36] The allogeneic transplantation of hematopoietic progenitor cells using PBPC is currently being studied in many centers. However, there are several problems concerning the donor and the recipient. These include (i) the long-term effect of mobilization with G-CSF in normal donors, (ii) the optimal G-CSF dose and schedule for G-CSF mobilization, (iii) the incidence of acute and chronic graft-versus-host disease (GVHD) following the transplantation of large numbers of T cells, (iv) PBPC transplantation and long-time engraftment, and (v) the effect on PBPC transplantation on the graft-versus-leukemia effect. Most of these questions may be answered by long-term clinical studies. Nevertheless, some preliminary analyses offer a comparison of PBPC allogeneic transplantation with ABMT with regard to short-term outcomes such as hematological recovery and acute GVHD.[37-39] All these retrospective case control studies show a faster granulocyte and platelet recovery with PBPC use, a faster discharge from the hospital, fewer platelet transfusion requirements, and a comparable incidence of acute GVHD grade 2-4. The follow-up of the PBPC group in these studies is too limited to permit definitive conclusions about chronic GVHD, survival and relapse, and randomized trials are necessary to definitely answer these questions.

Only one economic analysis from Faucher *et al.*[37] studied the comparison between PBPC and BM allogeneic transplantation. This analysis considers costs during the initial hospitalization and additional costs due to follow-up between discharge and day 100 to capture the additional costs during the period of time corresponding to the possibility of acute GVHD and associated infectious complication to occur. Results of this study show that total cost of PBPC allogeneic transplantation is lower than that of BM allogeneic transplantation ($40 123 for the PBPC group and $56 257 for the BM group) when considering costs during initial hospitalization ($30 104 for the PBPC group and $40 080 for the BM group) and additional costs due to follow-up between discharge and day 100 ($10 019 for the PBPC group and $16 177 for the BM group). This difference is partly due to the shorter duration of initial hospitalization (28 median days to discharge for the PBPC group and 32 for the BM group), but also due to the lower cost of follow-up between discharge and day 100 after transplantation in the PBPC group because these patients are re-admitted less after discharge.

These results concerning the clinical and economic impact of PBPC allogeneic transplantation still remain preliminary and must be taken with caution before results from randomized trials aimed to determine the long-term effect of this type of transplantation.

Perspectives and conclusion

Although some decisions about standard practice for PBSC collection and autograft have been reached, the optimal procedure is still debated. For example, HDC with autologous stem cell rescue was successfully carried out in the out-patient setting. Patients are hospitalized for HDC, discharged on completion and maintained as out-patients unless toxicity requires hospitalization. All these technical improvements of the PBPC autograft will certainly have economic consequences that should be measured by further economic analyses. Concerning the allogeneic setting, the clinical and economic impact of PBPC transplantation is not yet established and is still under analysis. Of course, earlier evaluation certainly includes some R&D costs for the innovative procedure and not for the reference strategy, but if this argument must be taken into account, it does not have to slow down early economic assessment in the innovation cycle. Indeed, earlier initiation of economic analysis facilitates ongoing reassessment as soon as new data are available or innovative modifications of the technology itself appear. The case of the use of HGFs in HDC suggests that ongoing economic evaluation starting as early as possible throughout the R&D process can participate in the innovation development process and help predict subsequent diffusion of the technology over time. It can also predict any potential evolution in expected clinical utilisation and costs.

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