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OPTIMIZATION OF PERIPHERAL BLOOD STEM CELL COLLECTION BY LEUKOPHERESIS

Interaction between Economic and Clinical Assessment of an Innovation

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Abstract

Using the example of substitution of peripheral blood stem cell (PBSC) collection to bone marrow harvest for autologous transplantation in cancer patients, our study attempts to illustrate how economic assessment, starting at an early stage of medical innovation, can influence the development and diffusion process of a new technological procedure whose optimal design has not yet been established. Two cost minimization studies comparing costs for obtaining a clinically reinfusable graft using bone marrow harvest or alternatively various protocols of PBSC collection contributed to a change in the French clinical standard for this procedure.

Keywords: Hematopoietic Stem Cell Collection, Economics, Optimization, Cost

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Researchers in technology assessment in health care share a widespread concern for the way in which new medical technologies are clinically and economically evaluated during the development process (13;14). It is largely established that evidence supporting the development and dissemination of most new technologies and clinical procedures in health care remain inadequate from a scientific point of view; many common treatments have been launched without ever having been subjected to thorough scientific evaluation (8;29). Among the multiple explanatory factors for inadequate patterns of diffusion of medical innovations, research often emphasizes the influence of market and industry forces, the lack of effective regulatory mechanisms, and physicians' behavior, including various hypotheses about supplier-induced demand (10;30).

However, it must be recognized by researchers in the field that findings from evaluative efforts using the best techniques also may not lead to the best clinical and/or economic decisions to the extent that they are not available at the appropriate timing in the life cycle of an innovation. The quality of evidence that the evaluation of medical care is able to produce, even through randomized controlled trials, is itself limited (6), and is available in forms and at times that often make it difficult for practitioners and regulators to use (20). With the current extent of regulations and evaluative institutions and procedures aimed at better controlling the dissemination of medical innovations, the question of timing and timeliness in medical care evaluation is of growing importance (3).

In this paper, we attempt to illustrate the potential role for decision making and the limits of economic assessment, starting at an early stage of a medical innovation when the design of the technology, as well as its diffusion, remains unclear, using the example of peripheral blood stem cell (PBSC) collection for therapeutic use in treating cancer. We will also try to draw some lessons from that experience that may be useful for other medical technologies and other health care systems.

BLOOD STEM CELL COLLECTION BY LEUKOPHERESIS

High-dose chemotherapy with the support of autologous bone marrow transplantation has been increasingly used in a variety of hematological and epithelial cancers over the last decade. Clinical benefits of dose intensification have been difficult to prove, especially in care for solid tumors, and there are still scientific controversies about the development of such therapeutic strategies (16). In the late 1980s, the availability and diffusion of hematopoietic growth factors made it possible and feasible to collect hematopoietic stem cells directly from the peripheral blood of patients (15). With this technical possibility of collecting PBSC, a very rapid substitution of PBSC collection rather than bone marrow harvest for autologous transplantation, as supportive care for cancer therapies, has occurred. As in the case of Europe (Figure 1), substitution of PBSC for autologous bone marrow transplantation has been rapid, even before any confirmation of the clinical interest of such substitution by randomized controlled studies (17).

Various arguments were nonetheless used in favor of this substitution since the early stage of development of the new technology. First, PBSC collection by leukopheresis is an easier procedure than bone marrow harvest. Before any formalized evaluation, it was suggested that PBSC collection is less costly for hospital departments, as well as for the patients themselves in terms of inconvenience, iatrogenic risk, and quality of life during the procedure. It could also be argued that PBSC collection and reinfusion would not necessitate highly specialized transplantation units, as is the case with bone marrow transplantation, therefore facilitating a wider diffusion of chemotherapy dose intensity in cancer therapies.

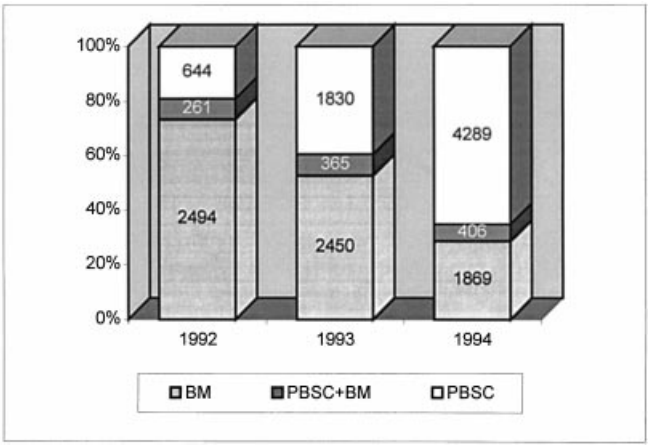

Figure 1. Evolution of autologous stem cells transplantations in Europe (1992–94). From the European Group for Blood and Marrow Transplantation (EBMT) (17).

However, at the initial stage of its development, technological uncertainties remained about the optimal conditions of the PBSC collection procedure, with important variations in the protocols used by various clinical centers all over the world (4;25). The first uncertainty about PBSC collection concerned the way the collection must be performed: some clinical conditions absolutely require central venous access through a catheter (CVA), while collection for the majority of patients can be less invasive by using peripheral venous catheter access (PVA). The second and main uncertainty about PBSC collection came from the fact that there was no clinical consensus about the quality standards that should be used to control the collected stem cells before autologous transplantation. Medical teams now agree that the number of CD34+ cells collected should be used for assessing the quality of PBSC collection, but there is still controversy about the minimum threshold of CD34+ that should be reinfused to guarantee a good hematologic reconstitution (5). Of course, choice of such a threshold directly influences collection protocols, for example, the number of leukopheresis sessions that the patient will undergo.

In order to contribute to clinical decision making about the optimal PBSC collection protocol, we carried out an economic study at the Institut Paoli-Calmettes (Regional Cancer Hospital of Marseille, south-eastern France) in parallel with the experimental introduction of the procedure for clinical use. The aim of the study was first to compare costs of stem cell collection using PBSC versus classic bone marrow harvest, and to assess the consequences of ongoing technical and clinical debates about the optimal design of the new procedure (PBSC collection) on this comparison. The second goal of the study was to contribute to optimization of PBSC collection by comparing alternative PBSC protocols for obtaining a clinically reinfusable graft.

MATERIALS AND METHODS

Patients

All cancer patients with nonleukemic malignant diseases scheduled for autologous transplantation in the clinical practice of the Institut Paoli-Calmettes between January 1992 and April 1994 (n = 149) were included in the analysis.

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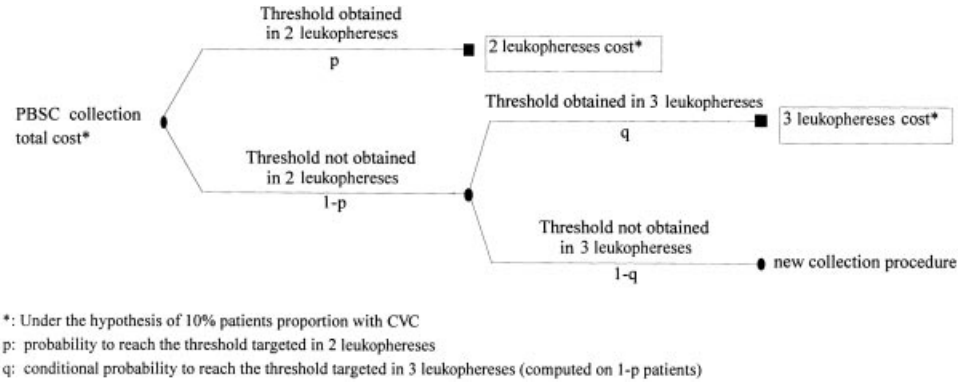

Figure 2. Iterative procedure simulation for the PBSC collection.

Bone marrow harvest was a routine practice at the Institut Paoli-Calmettes. It consisted of general anesthesia for about 4 hours and 2 days of conventional hospitalization.

The protocol in place for PBSC collection at the Institut Paoli-Calmettes consisted of three leukophereses (about 4 hours each) and three consecutive days with a CVA or a PVA, depending on the clinical status of the patient. Patients with a PVA underwent stem cell collection as outpatients but were hospitalized for collection through a CVA. In our sample, 10% of the patients had leukopheresis through a CVA. Granulocyte colony-stimulating factor (G-CSF) stimulation was administered subcutaneously at 600 μg per day, starting 5 days before the first leukopheresis until the day before the last leukopheresis.

Statistical Analysis

Patients' characteristics were compared using the chi-square test for categorical data, Student's *t* test for normally distributed quantitative variables, and the Mann-Whitney nonparametric test for the other quantitative variables. Nonnormality of the sample was tested using the Kolmogorov-Smirnov test. Polynomial fit of the iterative PBSC collection cost was estimated using the least-square method. Statistical analysis was made using SPSS software (26).

Costing Methodology

Our analysis was restricted to direct medical costs for the hospital. Therefore, the perspective of the analysis is that of French hospital management. We attempted to measure true opportunity costs in spite of the insurance-based French health care financing system, where hospital charges do not tend to reflect true costs. Direct medical costs of the procedures were estimated by measuring physical quantities (capital and labor) arising from detailed observation carried out at the Institut Paoli-Calmettes.

In complement to the ergonomic observation of the procedures, average quantities were computed for variable cost factors (such as the number of transfusion events or the length of general anesthesia) on the 79 patients for the bone marrow harvest and the 70 patients for the PBSC collection of our sample. Monetary values were attributed to these quantities on the basis of average 1995 French prices.

The following cost factors were measured in physical units for each of the patients included in the study:

- Inpatient length of stay (days) in the hematologic unit for patients submitted to bone marrow harvest and patients submitted to a CVA leukopheresis;
- Units of blood products used by category (red blood cells, apheresis platelet unit);
- Number of days and prescribed dose per day of G-CSF;
- Number of laboratory tests; and
- Time spent in the operating and recovery rooms for bone marrow patients and in the leukopheresis room for the PBSC patients

Unit costs were separated into two cost classes.

Hospitalization Costs. Because of the known problem of differences between hospital charges and real costs, especially in the context of a publicly funded health care system such as in France, per diem charges were not used for assessing room costs associated with the patients' stay in the hematological unit. Total yearly costs of consumable supplies, hotel cost, personnel cost of the unit, and amortization of equipment (10 years) were measured to calculate a per diem cost for each stay in the unit. A step-down method was used to add overheads to those per diem unit room costs (9).

Collection Costs. We undertook a detailed analysis of each item associated with collection. Supply and drug costs were estimated using purchase prices of our institution for those supplies. An 8% depreciation rate and 5-year depreciation period were used to estimate equipment cost. As an assumption for labor planning for the collection unit, we considered a maximum equipment utilization, at 5 days of work per week for 44 weeks a year. For PBSC collection, we assumed that the unit possesses two cell separators, thus allowing economies of scale, since one nurse can monitor two cell separators at the same time. A detailed observation was performed to assess the per-hour recovery room and the per-hour operating room costs. Costs of laboratory tests in France are established by the Social Security System at a national level based on a point system. For each point a price unit rate is attributed, which may differ across types of laboratories. The price list established for our institution was used. Staff cost included time devoted by technical hospital to perform collection; the National Federation of Specialized Hospitals for Cancer Treatment wages were used as monetary values. A detailed ergonomic observation was conducted to establish the cell treatment and cryopreservation cost; this cost included equipment amortization, supplies, and staff.

Cost-minimization Studies

Comparison between bone marrow harvest and PBSC collection was difficult because the technical criterion for assessing the quality of the cell product collected was not the same for the two procedures: mononuclear cells for bone marrow harvest and CD34+ cells for PBSC collection. For bone marrow harvest the graft was considered clinically reinfusable if the target of 2×10^8/kg mononuclear cells was reached, with this threshold corresponding to the already established clinical international standard.

For patients undergoing to PBSC collection, the criterion of mononuclear cell count was very quickly abandoned at the international level in favor of CD34+, cell count which is considered the appropriate indicator for measuring hematopoietic stem cells (24). This measurement technique has been available and standardized in our institution since 1992. In the routine practice of Institut Paoli-Calmettes, a minimum number of 3×10^6/kg CD34+ cells was considered as the criterion for a

Table 1. Patient Characteristics

	Bone marrow harvest ($n = 79$)	PBSC collection ($n = 70$)
Age (yr)[a,d]	44 (16–64)	44 (16–64)
Sex (M/F)[b]	41/38	34/36
Diagnosis		
Non-Hodgkin's lymphoma	29 (37%)	18 (26%)
Hodgkin's disease	6 (8%)	6 (9%)
Myeloma	19 (24%)	20 (28%)
Breast cancer	13 (16%)	19 (27%)
Other solid tumor	12 (15%)	7 (10%)
Time between diagnosis & collection (months)[c,d]	13 (0.5–182)	8 (1–108)
Number of previous chemotherapy courses[c,d]	6 (0–35)	6 (2–30)

[a] Student's *t* test.
[b] Chi-square test.
[c] Mann-Whitney test.
[d] Median (range).
No statistical difference was found between groups.

clinically reinfusable graft. However, the adequate CD34+ threshold for optimizing PBSC autologous transplantation remains a matter of debate (5).

We first performed a cost minimization study that compared the costs of obtaining a clinically reinfusable graft through classic bone marrow harvest (at least 2×10^8/kg mononuclear cells) or through a PBSC collection protocol of three systematic leukophereses (at least 3×10^6/kg CD34+ cells).

In order to take into account the remaining clinical uncertainties about the minimum level of CD34+ cells that guarantees the possibility of a PBSC transplantation, we performed a second cost minimization analysis comparing the costs of the PBSC protocol of three systematic leukophereses versus an alternative PBSC protocol in which the number of leukapheresis sessions is not decided a priori, but rather in which leukophereses 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+ cell threshold, but for all values that have been discussed in the literature for defining a clinically reinfusable PBSC graft (from 0.5×10^6/kg to 10×10^6/kg CD34+).

RESULTS

Table 1 presents the patients' characteristics. No statistically significant difference was found between patients in the PBSC arm (n = 70) and bone marrow group (n = 79) for diagnosis, age, sex, and time between diagnosis and collection.

Collection Unit Cost Comparison

Unit costs of each stem cell collection procedure are presented in Table 2. These results illustrate the cost heterogeneity of the PBSC collection. It varies from US$2,542 for two leukophereses with a PVA to US$4,803 for 3 leukophereses with a CVA (+47%), and as much as US$9,606 (a 74% increase) when the patient must undergo to a second round of three leukophereses with CVA. PBPC appears to be less costly than bone marrow harvest only under the technical constraint of two leukophereses per patient and collection using the less invasive PVA.

Table 2. Unit Costs of Stem Cell Collection Procedures[a]

Cost categories	Two leukophereses		Three leukophereses		Bone marrow harvest
	PVA	CVA	PVA	CVA	
Hospitalization		800		1,200	800
Equipment	108	108	215	215	257
Consumable supplies	393	494	590	690	472
Laboratory tests	93	93	120	120	98
Staff	157	197	236	275	839
Cell treatment	518	518	776	776	652
G-CSF stimulation	1,273	1,273	1,527	1,527	
Total cost	2,542	3,483	3,464	4,803	3,118

[a] In 1995 US$.
Abbreviations: PVA = peripheral venous access; CVA = central venous access.

Cost-minimization Study

The study of 79 patients who underwent bone marrow harvest shows that 33% of patients did not reach the target of 2×10^8/kg mononuclear cells and underwent a second harvest. The average cost per patient of the bone marrow harvest, including those harvest failures, is then US$4,146 (Table 3).

The study of the 70 patients undergoing three leukophereses shows that 42% of patients did not reach the target of 3×10^6/kg CD34+ and underwent a second

Table 3. Stimulation Procedure Cost for Stem Cell Collection[a]

CD34+ threshold	p	q	Cost of the iterative procedure[b]
0.5	.96	1.00	2,780
1	.73	.90	3,223
1.5	.63	.76	3,705
2	.51	.68	4,100
2.5	.41	.63	4,365
3	.36	.54	4,661
3.5	.28	.43	5,100
4	.27	.37	5,354
4.5	.23	.29	5,650
5	.18	.24	5,831
5.5	.17	.24	5,912
6	.14	.24	5,954
6.5	.12	.21	6,097
7	.10	.21	6,140
7.5	.09	.19	6,223
8	.08	.16	6,368
8.5	.08	.14	6,452
9	.06	.13	6,514
9.5	.06	.10	6,638
10	.06	.08	6,700
Cost of bone marrow (including recollection)			4,146
Cost of the three systematic leukophereses procedure[a]			5,113

[a] Costs are presented in 1995 US $.
[b] With 10% of central venous catheter.
p = probability to reach the threshold targeted in two leukophereses.
q = probability to reach the threshold targeted in three leukophereses.

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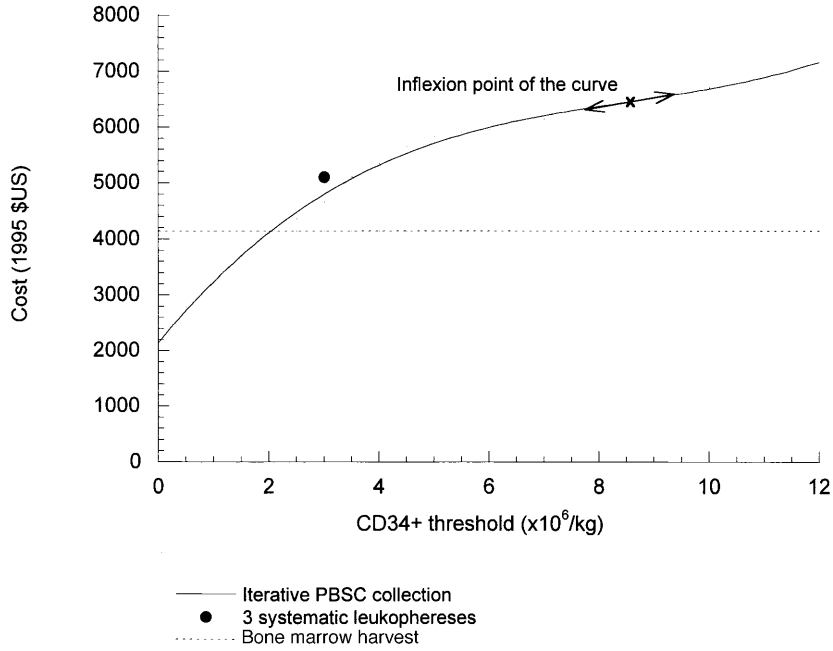

Figure 3. PBSC collection cost depending on CD34+ threshold (10% CVC). Iterative PBSC collection cost curve fit: $y=2141.2+1213.7\ x-124.22\ x^2+4.83\ x^3$; $R^2=0.99$; Fisher test: $F < 0.0001$. x=CD34+ threshold targeted; y=cost of iterative PBSC collection cost.

collection cycle. The average cost per patient of the three systematic leukophereses collection is then US$5,113, 19% more costly than bone marrow harvest (Table 3).

Simulation of an iterative procedure shows that 36% of patients who underwent three systematic leukophereses reached the 3×10^6/kg CD34+ threshold in two leukophereses, and that it would have been less costly to collect with the iterative procedure. Table 3 shows that the cost comparison of an iterative PBSC procedure versus bone marrow harvest depended on the CD34+ threshold. PBPC is less costly if collection of 2×10^6/kg CD34+ is 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 PBSC collection average cost per patient, which varies from US$2,780 (with a threshold of 0.5×10^6/kg CD34+) to $6,700 (with a threshold of 10×10^6/kg CD34+). Polynomial fit gives the iterative PBSC collection cost curve depending on CD34+ threshold presented in Figure 3. The iterative procedure cost curve changes of direction when the CD34+ threshold reaches 8.57×10^6/kg CD34+. Before this threshold the cost curve is convex (the marginal cost decreases), and after this threshold the curve is concave (the marginal cost increases).

Sensitivity Analysis

A sensitivity analysis was performed on the unit cost of stem cell collection. This sensitivity analysis concerned the mean values used for the quantity of blood products consumed, the operating room length of stay, and the recovery room length of stay. It shows that, using the 95% confidence interval limits of each mean, results vary from −1.4% to +1.1%, and do not significantly change the cost comparison between the alternatives.

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In our sample, 10% of the patients were submitted to PBSC collection through a CVA. We also performed a sensitivity analysis on this factor, which widely influences the cost of the procedure. We have considered several hypotheses on the percentage of patients requiring a CVA, which we set at between 0% and 30% (since considering a percentage over 30% does not seem realistic). With 0% CVA, the iterative procedure offers a cost advantage over bone marrow harvest up to the threshold of 2×10^6/kg CD34+. For 30% CVA, the iterative procedure offers a cost advantage over bone marrow harvest up to the threshold of 1.5×10^6/kg CD34+.

DISCUSSION

Technological innovation in medicine covers the wide range of events by which a new medical technology is discovered or invented, developed, and disseminated into health care. One of the most vulnerable links in this innovation chain today is the development phase, in which research findings are brought into clinical practice. More specifically, medical technology development can be defined as a multi-stage process through which a new biological or chemical agent, prototype medical device, or clinical procedure is technically modified and clinically evaluated until it is considered ready for general use. Although this definition suggests an organized and systematic process, most developmental activity occurs in a nonorderly fashion in everyday clinical practice (13). Not all uncertainty associated with a new technology can be resolved before its use in practice, and development does not end with the adoption of an innovation, but continues for an extended period afterward as additional indications emerge during its use in clinical practice (18).

Because hematopoietic recovery after autologous transplantation occurs earlier with this new technique than with bone marrow transplantation, PBSC has been widely substituted for bone marrow, even before any confirmation by randomized controlled trials (11;22;23). However, aside from improving supportive care, no demonstration yet exists that the use of PBSC improves the overall outcome and survival of cancer patients. Although the substitution was already effective, neither the optimal cell dose to collect for PBSC transplantation nor the PBSC collection technology itself has been standardized, and as a result, a lot of variation in procedure has existed from center to center.

The aim of our study was to perform an ongoing evaluation of this innovation through its development in order to participate in the establishment of the technical and clinical standards to be used in routine practice, at least in France.

In the current atmosphere of economic pessimism and cost constraint, every practitioner will face cost issues at one time or another. In the case of PBSC collection, costs of each collection procedure alternative were poorly documented. Although some studies have documented the cost of PBSC transplantation (1;11;21;27), none of them had taken into account the impact of technical uncertainties on this collection cost.

Our cost-minimization studies clearly showed that, contrary to initial expectations of most clinical units, PBSC collection is more costly than bone marrow harvest if it respects the minimal clinical threshold for a better postgraft hematologic recovery recommended by most studies (3×10^6/kg CD34+) (5;12). This result emphasized the importance of minimizing cost of PBSC collection. One consequence of our study was to demonstrate that an iterative collection protocol (stopping leukophereses sessions as soon as the threshold is reached) was an efficient way of minimizing cost. Following the study, the initial protocol at our institution (a priori planning of three leukophereses sessions for all patients) was modified, and an iterative procedure was adopted (CD34+ are measured after each leukopheresis and a new session is only initiated if the 3×10^6/kg CD34+ threshold has not

been reached). This protocol has ultimately been adopted in most French cell therapy units.

If there is a growing consensus about the minimal threshold associated with clinical feasibility of reinfusion, there is still controversy about the optimal CD34+ level that maximizes hematologic recovery (25). The recent literature estimates that levels between 6×10^6/kg and 8×10^6/kg CD34+, are the optimal ones (6). Our study shows that above a level of 8.57×10^6/kg CD34+, the marginal cost of PBSC collection tends to increase very quickly. Our study helped convince clinicians that economic production constraints in PBSC collection should be taken into account when discussing this issue of an optimal CD34+ threshold.

Although some decisions about standard practice for PBSC collection in France have been reached following our study, debates still exist about the optimal procedure. There is uncertainty about the priming of the collection, that is, the conditioning regimen to be used in order to stimulate the presence of stem cells in the peripheral blood of the patients. For this purpose, some teams used chemotherapy associated with G-CSF, a protocol that necessitates hospitalization of the patients and a more precise timing between stimulation and leukopheresis sessions. Other stimulation protocols only use G-CSF alone, which creates fewer technical and practical constraints. Concerning the timing of the collection between stimulation and leukopheresis sessions, some teams measure the rate of CD34+ circulating into the blood before the first leukopheresis and decide to perform it only if a sufficient number of cells are already present in the peripheral circulation. Finally, clinical teams are currently experimenting ex vivo CD34+ cell selection before reinfusion, which may improve effectiveness by using very expansive new molecular biotechnologies. Additional studies about the impact of alternative priming protocols on PBSC collection cost are therefore required.

As our study has established that PBSC collection is more costly than bone marrow harvest, the substitution of this procedure for bone marrow harvest must be justified by other arguments. One of them can be to refer to patients' intangible costs: a recent study showed that PBSC collection generates less anxiety, pain, and discomfort than bone marrow harvest (2). Of course, the main arguments come from the fact that bone marrow and PBSC collections are only the first step of a therapeutic strategy using autologous transplantation, and have to be compared considering the whole treatment. As an illustration, it appears that despite the increased cost of collection of PBSC versus bone marrow, patients treated with PBSC spend less time in hospitals and need fewer antibiotics and blood products, leading to an overall reduction in the cost of a transplant (11;21). Moreover, for many malignancies, particularly solid tumors, the primary question still to be answered is the value of high-dose therapy itself, with the source of hematopoietic rescue (bone marrow or peripheral blood stem cells) remaining a secondary issue.

Our study illustrates the problem of timing and timeliness of economic evaluation. Not all decisions require the same information at the same time. Determining the optimal time to perform economic evaluation remains a challenge in technology assessment. Evaluation at the wrong time of the cycle of an innovation can mislead decisions.

It is often argued that economic evaluation alongside clinical trials is the most appropriate solution for adequate timing in the assessment of an innovation (7). Our experience suggests that initiation of economic evaluation at an earlier step in the cycle of an innovation may indeed be even more appropriate to influence the establishment of the clinical and technical standards associated with a new technological procedure. If we had started economic evaluation at a later stage of

development of PBSC, it is quite likely that some irreversible, although nonoptimal, choices would have been made in the design of the collection procedure and the associated clinical standards, introducing further biases in evaluation of the impact of this innovation. Of course, early evaluation necessarily implies, as was the case with PBSC collection, the use of intermediary endpoints as criterion for effectiveness and to focus them on some specific aspects rather than the global therapeutic strategies. The fact that, contrary to expectations, our preliminary study has demonstrated that PBSC collection cost was not a way of reducing cost for autologous transplantation was a powerful argument for introducing economic evaluation in further studies, in particular the clinical trials comparing alternative therapeutic strategies based on the two techniques (19;21). This integration of economic analysis in a clinical trial is currently extending to comparison of autologous transplantation versus standard treatment for breast cancer (28). Of course, earlier evaluation certainly included some research and development costs for the innovative procedure and not for the reference strategy. This argument should be taken into account, but 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, innovative modification of the technology itself appears, or changing epidemiology leads to changes in patient care, resource consumption, or treatment options.

Finally, the case of PBSC suggests that ongoing economic evaluation should start as early as possible. Throughout the research and development process, economic evaluations can contribute to innovation development, help predict subsequent diffusion of the technology over time, and participate in the evolution of clinical utilization and costs.

REFERENCES

1. Ager, S., Scott, M. A., & Mahendra, P. Peripheral blood stem cells transplantation after high dose therapy in patients with malignant lymphoma: A retrospective comparison with autologous bone marrow transplantation. *Bone Marrow Transplantation* 1995, 16, 79–83.
2. Auquier, P., Macquart-Moulin, G., & Moatti, J. P. Comparison of anxiety, pain and discomfort in two procedures of hematopoietic stem cell collection: Leukopheresis and bone marrow harvest. *Bone Marrow Transplantation*. 1995, 16, 541–47.
3. Bloom, B. S., & Fendrick, A. M. Timing and timeliness in medical care evaluation. *PharmacoEconomics.* 1996, 9, 183–87.
4. Champlin, E. Peripheral blood progenitor cells: A replacement for marrow transplantation? *Seminars in Oncology.* 1996, 23(suppl. 4), 15–21.
5. Dercksen, M. W., Rodenhuis, S., & Dirkson, M. K. A. Subsets of CD34+ cells and rapid haematopoietic recovery after peripheral-blood stem-cell transplantation. *Journal of Clinical Oncology.* 1995, 13, 1922–32.
6. Dickersin, K., & Herxheimer, A. The quality of medical evidence: Is it good enough? *International Journal Techno Assessment in Health Care.* 1996, 12, 187–89.
7. Drummond, M., & Stoddart, G. Economic analysis and clinical trials. *Controlled Clinical Trials* 1984, 5, 115–28.
8. Eddy, D. M., & Billings, J. The quality of medical evidence: Implications for quality of care. *Health Affairs* 1988, Spring, 20–32.
9. Eisenberg, J. M. New drug and clinical economics: Analysis of cost-effectiveness in the assessment of pharmaceutical innovations. *Review of Infectious Disease* 1984, 6, S905–09.
10. Evans, R. G. Supplier-induced demand, some empirical evidence and implications. In M. Perlmen (ed.). *The economics of health and medical care*. London: Macmillan, 1974.
11. Faucher, C., Le Corroller, A., & Blaise, D. Comparison of G-CSF primed peripheral blood progenitor and bone marrow autotransplantations: Clinical assesment and cost-effectiveness study. *Bone Marrow Transplantation* 1994, 14, 895–901.
12. Faucher, C., Le Corroller, A. G., Chabannon, & C. Autologous transplantation of blood stem cells mobilized with G-CSF alone in 93 patients with malignancies: The number

of CD34+ cells is the only factor predicting both granulocyte and platelet recovery with G-CSF primed peripheral blood progenitor cells (PBPC). *Journal of Haematotherapy* 1997, 5, 663–70.
13. Gelijns, A. C. Medical innovation at the crossroad. In A. C. Gelijns (ed.), *Modern methods of clinical investigation,* vol. 1. Washington DC: National Academy Press, 1990.
14. Gelijns, A. C. Medical innovation at the crossroad. In A. C. Gelijns & E.A. Halm (eds.), *The changing economics of medical technolgy,* vol. 2. Washington DC: National Academy Press, 1991.
15. Gianni, A. M., Sienna, S., & Bregni, M. Granulocyte-macrophage colony-stimulating factor to harvest circulating hmatopoietic stem cells for autotransplantation. *Lancet* 1989, 2, 580–84.
16. Gradishar, W. J., Tallman, M. S., & Abrams, J. S. High-dose chemotherapy for breast cancer. *Annals of Internal Medicine,* 1996, 125, 599–604.
17. Gratwohl, A., Hermans, J., & Baldomero, H. Hematopoietic precursor cell transplants in Europe: Activity in 1994. Report from the European Group for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplantation,* 1996, 17, 137–48.
18. Halm, E. A., & Gelijns, A. C. An introduction to the changing economics of technological innovation in medicine. In A. C. Gelijns & E. A. Halm (eds.), *The changing economics of medical technology,* vol. 2. Washington DC: National Academy Press, 1991, 1–20.
19. Hartmann, O., Le Corroller, A. G., & Blaise, D. Peripheral blood stem cells and bone marrow transplantation for solid tumors and lymphomas: Hematologic recovery and costs. A randomized controlled trial. *Annals of Internal Medicine,* 1997, 126, 600–07.
20. Hyde, C. J. Using the evidence: A need for quantity, not quality? *International Journal of Technology Assessment in Health Care,* 1996, 12, 280–87.
21. Le Corroller, A. G., Faucher, C., & Aupérin, A. Autologous blood stem cells transplantation versus autologous bone marrow transplantation for adult and children with nonleukemic malignant disease: A randomized economic study. *PharmacoEconomics,* 1997, 11, 454–63.
22. Schmitz, N., Linch, D. C., & Dreger, P. Randomised trial of filgrastim mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. *Lancet* 1995, 347, 353–57.
23. Sheridan, W. P., Begley, C. G., & Juttner, C. A. Effect of peripheral-blood progenitor cells mobilised by filgrastim (G-CSF) on platelet recovery after high-dose chemotherapy. *Lancet,* 1992, 339, 640–44.
24. Siena, S., Bregni, M., & Brando, B. Flow cytometry for clinical estimation of circulating hematopoietic progenitors for autologous transplantation in cancer patients. *Blood,* 1991, 77, 400–09.
25. Smith, A. M., & Keating, A. Peripheral blood progenitor cell transplantation: Clinical, practical and economic considerations. *Journal of Hematotherapy,* 1994, 3, 331–48.
26. *Statistical Processor for Social Sciences, user's guide.* S.P.S.S release 6.0, 1993.
27. Uyl-de Groot, C. A., Richel, D. J., & Rutten, F. F. H. Peripheral blood progenitor cell transplantation mobilised by r-metHuG-CSF (filgrastim); A less costly alternative to autologous bone marrow transplantation. *European Journal of Cancer,* 1994, 30A, 1631–35.
28. Viens, P., Janvier, M., & Fabbro, M. *Outpatient high dose intensity doxorubicine cyclophosphamide 5FU with Rh-GCSF and stem cell support (BSC) for inflammatory breast cancer: Pathologic response rate toxicity, quality of life and cost analysis. A French national study (PEGASE 2)*. Denver, CO: American Society of Clinical Oncology, 1997.
29. Wennberg, J. E. Improving the medical decision making process. *Health Affairs,* 1988, Spring, 99–106.
30. Wennberg, J. E. Innovation and the policies of limits in a changing health care economy. In A. E. Gelinjs (ed.), *Technology and health care in an area of limits*. Washington DC: Institute of Medicine, National Academy Press, 1992.