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Costs of high-dose salvage therapy and blood stem cell transplantation for resistant-relapsed malignant lymphomas in a Southern Italian hospital

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ABSTRACT

Background and Objective. Analysis of costs of high technological procedures such as peripheral blood stem cell (PBSC) autotransplantation in lymphomas are generally finalized at disclosing whether the improvement of survival in a subset of patients is cost effective and whether the cost of the procedure could be reduced. With the aim of revealing a possibility of reducing costs with respect to conditions of safety, we present our experience with PBSC autotransplantation in a particularly poor prognosis subset of patients with lymphoma.

Design and Methods. The expenses are analyzed for groups of cost and main resources necessary at unitary cost are considered separately. Groups of cost include various phases of the PBSC autotransplantation such as preparative procedures, execution of myeloablative therapy, reinfusion of CD34 cells, supportive therapy after reinfusion until discharge of the patient, general support for the management of patient. All costs are calculated according to 1997 prices and salaries and reported in dollars. The analysis was conducted on 21 patients with lymphoma resistant to other therapies treated by myeloablative therapy and PBSC autotransplantation in an hematologic unit in an open ward; the assistance was provided by staff not exclusively dedicated to bone marrow transplant procedures, with some help from a family member.

Results. The PBSC procedure, including all phases, costs from $17,761.9 to $18,259.9 depending on the type of myeloablative therapy employed; the mean cost was $18,092.6. The preparative phase with mobilization of CD34 cells, cryopreservation and reinfusion costed $3,538.7 (19.6% of the total cost); a major cost of this phase was cryopreservation and CD34 manipulation ($857.1). The second phase with myeloablative therapy and reinfusion of CD34 cells had a mean cost of $2,785.9 (15.4% of the total cost); a major cost of this phase was the hospitalization ($ 1,119.8). The third phase of patient's support after treatment had a total cost of $7,649 (42.3% of the cost of the total procedure) with the major cost being due to hospitalization ($2,571) calculated on a mean of 15 days after the reinfusion of CD-34. The last group of costs, including management support, accounted for $4,119 (22.7%) with a major cost being amortization of the structure ($1,600). The general cost for nurse's assistance to the patient was $1,355.1 (7.5%).

Interpretation and Conclusions. A procedure of PBSC autotransplantation in resistant lymphoma is affordable without the strict precautions generally given in intensive care units. This provides a substantial reduction of expenses because of the low number of specifically trained staff members and the generally low cost of the necessary supplies. Before, however, proposing PBSC autotransplantation in most patients with resistant lymphoma, an evaluation of whether costs could be further reduced and whether the procedure has a cost benefit impact is needed.

Key words: PBSC, lymphoma, costs

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Autologous peripheral blood stem cell (PBSC) transplantation following myeloablative therapy is now a world-wide strategy for the cure of malignant lymphomas in relapse or in partial remission after conventional therapy;[1-8] more recently new strategies using PBSC at the beginning of the disease have also been reported for patients with high grade lymphoma and worse prognostic factors,[9,10] and as part of sequential therapy for patients with low grade lymphomas.[3,11] All of these approaches, however, have been validated when the disease is in responding phases[12,13] and potentially cost effective with respect to standard procedures. Most of the analyses recently reported concerning costs in the setting of autologous bone marrow transplantation are focused on a comparison between the use of conventional bone marrow transplants (ABMT) and peripheral blood progenitor cells (PBSC) especially in lymphomas[14-17] and multiple myelomas.[18] Almost all these reports present data on patients with responsive disease and long life expectancy, the transplantation procedure being finalized to prolonging survival or curing most of the patients. Such strategies are generally the most accredited in the scientific community and, obviously, the cost of the procedure per se is considered relatively, most of the efforts

being finalized at disclosing the impact of different schedules or whether the use of growth factors is convenient in specific procedures.[19] Few reports are available on an analysis of costs performed with the specific objectives of discovering whether a myeloablative therapy may be repaid by an increase of survival, free of disease, of patients responding to the therapy.[13,20]

This work is finalized at showing our experience in patients with lymphomas who were resistant to one or more therapeutic strategies and who had been submitted as salvage therapy to myeloablative schemes followed by PBSC. The specific aim of this presentation is the analysis of costs in this particularly poor prognosis subset of patients as part of a policy of cost minimization in a hospital in southern Italy. The efficacy of a strategy such as salvage therapy and comparison with some costs of similar procedures done in other Countries or Institutions are discussed.

Design and Methods

Patients

Since December 1995, 21 patients with malignant resistant lymphomas have undergone myeloablative therapy, as salvage treatment, followed by autologous PBSC reinfusion as hematologic rescue in our hospital. Patients were candidates for a myeloablative protocol when there had been early recognition of resistance to previous conventional therapy or the detection of relapse to other therapies and if they had no signs of major organ failure; there were no age limitations. Patients were primary referrals to our Institution for diagnosis and first line therapy or were secondary referrals from other Institutions after relapse or documented resistance. After informed consent both groups of patients underwent mobilization of PBSC by conventional schemes including high dose cyclophosphamide (CTX) (5-7 g/m^2) followed by granulocytic growth factor (Filgrastim or Lenograstim) at 5 µg/kg/day.[21] Collection of PBSC was performed 10 to 15 days after CTX by a Cobe-Spectra separator with one to 6 leukaphereses (median 2.5) with the specific aim of reaching a minimum number of CD34 of 2.5×10^{-6}/kg.

Table 1 shows all principal characteristics of patients entered in this cost evaluation. There were 21 patients aged between 17 and 71 years; 11 males and 10 females. Their occupations were: house keeper (7), farmer (4), employee (3), laborer (2), university student (1), policeman (1), trader (1), university teacher (1) and truck driver (1). Their diseases included anaplastic large cell lymphoma (ALC) (4 pts), mantle cell lymphoma (MCL) (5 pts), centroblastic lymphoma (CB) (3 pts), lymphoplasmacytic lymphoma (LP) (2 pts), immunoblastic lymphoma (IB) (4 pts), Hodgkin's lymphoma (HD) (2 pts) and T mediastinal lymphoma (T MED) (1 pt). The previous therapy before PBSC autotransplant included one regimen in 5 pts, 2 in 14 pts and 3 in 2 pts, using second or third generation regimens. The myeloablative therapy included BAVC[22] employed in 3 pts, CBV[23] in 5 pts, BEAM[24] in 11 pts and Bu-MPH[25] in 2 pts.

Organization of the hematologic unit

The hematologic unit is located in a 30-year-old hospital originally designed for patients with chronic diseases, with six beds per room. At present no more than four beds per room are used and the unit has 16 beds unprotected by air filtration and three beds in an isolated section with filtered air and positive pressure. Patients receiving autologous PBSC transplantations, whatever their disease, are ususally cared for in unprotected beds with broad spectrum antimicrobial prophylaxis. The staff following PBSC transplantations are not specifically trained in this field. Generally two nurses plus an ancillary for each shift are involved in the assistance to all patients; there are 6 doctors providing all the assistance to patients in the different sections.

Apart from official staff, doctors and nurses in training are also present during the morning and involved in the general assistance; also one instructed family member per patient is involved in less specific primary assistance such as helping the patient to wash and eat.

Determination of costs

The costs are reported divided into four main groups; each of these includes several resources, materials and supplies. Table 2 (a,b,c,d) lists these main groups of costs which include those for preparative procedures to PBSC autotransplantation (Table 1a), myeloablative therapy and reinfusion of CD-34 cells (Table 2b), the supportive phase until discharge of patient (Table 2c) and general assistance and amortization (Table 2d). Each cost was assessed by the relevant departments: Pharmacy, Administration, Transfusional Medicine and Economics departments. Costs are reported in dollars calculated from an exchange rate of 1 US$=1750 Italian Lire, which was about the mean value for 1997. Prices of drugs and supplies and salaries were considered to have been almost stable during the period of study (2.5 years) and were taken to be those of 1997. The cost of resources employed are reported according to the real mean costs to the hospital and not charges generally made to public health institutions. Main resources utilized are reported in number of units per procedure or phase; when the resource was used on a daily basis, for example assistance to the patient, the number of units was expressed in days; when the resource was a drug the units could be the number of vials or the amount employed. The costs are reported as cost per unit of resource or as mean cost per unit depending on the possibility of having a fixed price or an average price for the resource under analysis; very low cost materials, drugs or other supplies are grouped under miscellaneous. The four groups of costs reported in the table account for all medical

Table 1. Clinical data of patients with resistant lymphoma who underwent PBSC transplantation. Follow-up data of health conditions.

UPN	Name (initials)	Age	Sex	Profession	Date of diagnosis	Disease	Previous therapy	Date of ABMT	Conditioning Regimen at ABMT	Response	Relapse or progression	Actual status	Months of health condition
1	FU	37	M	Laborer	4/95	IB	F-MACHOP	12/95	BAVC	RC	No	AW	27
2	CAM	61	F	House keeper	3/95	LNH-T MED	CHOP, MACOP-B	1/96	BAVC	RP	Yes	Dead (5/97)	8
3	BAM	53	F	House keeper	2/95	IB	CHOP, MACOP-B	1/96	BAVC	None	Yes	Dead 2/96	____
4	GC	48	F	House keeper	9/95	IB	CHOP, MACOP-B	4/96	CBV	None	Yes	Dead 6/96	____
5	MA	17	F	Student	10/95	ALC	MACOP-B	5/96	CBV	RC	No	AW	22
6	PAM	33	F	House keeper	12/95	ALC	MACOP-B	6/96	CBV	RC	No	AW	21
7	BA	26	M	Worker	3/95	LH-NS	ABVD-MOPP	7/96	CBV	RC	No	AW	20
8	GAM	34	F	University teacher	10/95	ALC	MACOP-B, CHOP	10/96	CBV	RC	Yes	AL	6
9	LC	59	F	House keeper	1/96	IB	MACOP-B, CHOP	11/96	BEAM	RP	Yes	Dead, 1/97	---
10	CR	29	M	Policeman	3/88	LH-NS	ABVD MOPP, CEP RxT	1/97	BEAM	RC	No	AW	14
11	GF	67	M	Farmer	8/96	MCL	CVP, MACOP-B	1/97	BEAM	RP	Yes	AL	10
12	LV	53	F	House keeper	6/96	MCL	MACOP-B, CHOP	1/97	BEAM	None	Yes	Dead, 3/97	-------
13	BM	58	M	Employed	6/96	MCL	MACOP-B, CHOP	1/97	BEAM	None	Yes	Dead, 3/97	-------
14	CR	53	M	Trader	8/88	CB	MACOP-B, CVP, CHOP	2/97	BEAM	None	Yes	Dead, 4/97	-------
15	SL	54	M	Farmer	6/96	CB	MACOP-B, CHOP	2/97	BEAM	None	Yes	Dead, 4/97	
16	CA	48	F	House keeper	1/96	ALC	MACOP-B, CHOP	2/97	BEAM	RP	Yes	Dead, 12/97	4
17	LN	67	M	Farmer	6/96	CB	MACOP-B	3/97	BEAM	RC	Yes	AL	6
18	DDR	36	M	Driver	9/96	MCL	DHAP, APO	4/97	BEAM	RP	Yes	Dead, 10/97	3
19	CC	54	M	Employed	4/96	MCL	MACOP-B	4/97	BEAM	RP	Yes	AL	6
20	DD	53	M	Employed	3/90	LP	CVP, CHOP	9/97	BU-MPH	RP	No	Dead, 2/98*	-----
21	SG	71	M	Farmer	4/96	LP	CVP, CHOP	10/97	BU-MPH	RP	No	AL	------

**Dead brain hemorrhage; AW = alive and well; AL = alive with lymphoma; LP = lymphoplasmacytoid; ALC = anaplastic large cell lymphoma; MCL = mantle cell lymphoma; CB = centroblastic lymphoma; IB = immunoblastic lymphoma; NS = nodular sclerosis Hodgkin's disease.*

and nursing assistance which was calculated separately for each group taking into consideration differences in the duration of assistance in the phases of PBSC autotransplant; in detail the nursing assistance to patients was considered to be 2.5 hours/day in the preparative and supportive phases and 4 hours per day during the myeloablative therapy; assistance from doctors was considered to be one hour a day during the preparative phase and one and a half hours/day during myeloablative therapy. The phases of PBSC autotransplantation include mobilization and collection together with manipulation of PBSC, execution of myeloablative therapy and PBSC reinfusion, and supportive therapy until hematologic rescue and the patient's discharge.

Each phase was performed following standard guidelines, as described here briefly. PBSC mobilization was obtained by high dose CTX (5-7 g/m^2 as one day administration) and granulocyte growth factor (G-CSF) until CD34 cells exceeded 20/µL. The collection of PBSC was done by 1 to 6 leukaphereses (mean 2.5) by a Cobe Spectra separator. In order to ensure adequate blood processing a central venous catheter (CVC) was positioned in the subclavian vein in most patients. CD34 cells were measured with a cytofluorimeter (Becton Dickinson) by specific monoclonal antibodies; a minimum number of 2.5 $\times 10^{-6}$/kg body weight was considered appropriate for hematologic recovery following myeloablative therapy. The cost of these procedures was almost standard except for CVC insertion because of the large variation of catheters and their costs (Groshong = $560, Hickman = $200, Vygon = $17). Cryopreservation of PBSC was done in a tank with liquid nitrogen (–196°) in specific bags (Gambro) resistant to very low temperatures; all costs of materials or supplies necessary in the phases and amortization of the instruments used are accounted for in each of the main categories or phases taken into consideration. Myeloablative therapy consisted of a combination of several drugs (2 to 4) at a high dose according to schemes reported in the literature, e.g. BAVC, CBV, BEAM, BU-CY and BU-MPH;[22-25] these combinations include BCNU (nitrosourea), cyclophosphamide, VP-16 (CBV, BAVC) aracytin (BAVC, BEAM), melphalan (BEAM, BU-MPH), and busulfan (BU-CY, BU-MPH). Costs of these therapies are widely variable and include materials and supplies separate from the costs of drugs employed. Each therapy was administered in an in-patient setting in a normal ward without particular measures except those of hyperhydration (3 liters minimum per day), and chemoprophylaxis (antifungal, antibacterial, antiviral); two days after finishing the therapy patients received back their PBSC via a CVC with specific antireactional drugs whose costs are included under the costs of reinfusion of PBSC.

Supportive therapy consisted of chemoprophylaxis, antibiotic therapy and transfusions. Chemoprophylaxis included a quinolone given orally until pyrexia, during cytopenia, disappeared or until complete hematologic recovery was recorded. In addition, antifungal prophylaxis with low dose intravenous amphotericin and antiviral prophylaxis with intravenous acyclovir were also given routinely. Finally, prophylaxis with high dose intravenous immunoglobulin was given weekly for three weeks in patients at higher risk of infections. The antibiotic therapy consisted of a combination of two or three antibiotics aimed empirically to cover, in the case of pyrexia, both Gram$^+$ and Gram$^-$ bacteria including *Staphylococcus* methicillin resistant species. Pyrexia lasting longer than 5 days during cytopenia was treated with the addition of amphotericin (Fungizone®) 1 mg/kg/day.

Transfusional support consisted of either packed red blood cell (RBC) or platelet (PLT) transfusions; PLT were given as standard concentrates (6 to 8) or apheretic units (one) each time platelet count fell below 10×10^{-3}/µL or whatever the count when a hemorragic syndrome was recognized. RBC were given in order to mantain the hemoglobin level over 9.0 g/dL. Costs of transfusions were determined according to standards recognized in the lists of prices recently approved and reimbursed by the Apulia region and reported in Table 2.

The pre-transplant consultation and post-transplant evaluations are excluded from the account of costs, these being identical to those of patients treated conventionally or by intensive therapy, taking into account that this study was finalized at an analysis of costs of a transplantation procedure in a particular subset of patients with resistant lymphoma.

Results

Seven patients (33%) obtained a complete remission (CR) after the conditioning regimen for PBSC transplantation (Table 1) and 8 pts (38%) a partial remission (PR) with an overall response rate of 71%. Twelve patients (56%) were free of treatment for a minimum of 3 months and a maximum of 27 months, 5 patients still being in CR 14 to 27 months from PBSC autotransplantation. A further 5 patients are alive with persistent lymphoma 6 to 10 months after transplantation. Eleven patients died 1 to 16 months following PBSC autotransplantation. One early procedure-related death was recorded (4.8%). The mean duration of hospitalization (Table 2) was 5.5 days for the preparative phase including mobilization and collection of CD34 cells, 7 days for the execution of myeloablative therapy and CD34 cell reinfusion, and 15 days (minimum 10 days, maximum 27 days) for medical support after myeloablative therapy and reinfusion. The hematologic recovery of neutrophils (>than 500/uL) was obtained, on average, on the 11th day, platelet recovery (> than 20×10^{-3}/µL), on average, on the 13th day.

Table 2 shows the costs of each resource utilized and the costs of different phases of PBSC autotrans-

Table 2. Costs of PBSC autotransplantation in patients with resistant lymphomas according to the experience of a southern Italian hospital; data are reported per groups of costs and phases of the procedure. a) preparative phase; b) myeloablative therapy; c) supportive phase until discharge; d) general assistance and amortization. Costs are reported in dollars.

Main resources	*N.° or units*	*Unitary or mean cost ($)*	*Total cost ($)*
A. Preparative phase			
CC implantation	1 procedure	302	302
Radiology and ultrasound	1 detection	257	257
G-CSF	12 (vials)	65.714	789
Cyclophosphamide (CTX)	10 (grams)	0.754	7.54
Leukapheresis	2.5 (sets)	187	467.5
Cryopreservation	2.5 (procedures)	342.8	857
Nursing assistance	5.5 (days)	23.8	130.9
Medical assistance	5.5 (days)	16.6	91.6
Ancillary assistance	5.5 (days)	16.3	89.7
Hospitalization	3 (days)	171.4	514.3
Miscellaneous	Minor drugs & supplies	/	32.1
Total			3538.8
B. Myeloablative therapy and reinfusion			
BAVC	1	619	619
CBV	1	664	664
Bu-MPH	1	229	229
BEAM	1	727	727
Nursing assistance	5 (days)	38.1	190.5
Medical assistance	5 (days)	24.9	124.5
Reinfusion of CD34	1 (procedure)	21.9	21.9
Antiemetics	20 (vials)	13.7	274
Laboratory investigations	5 (days)	32.8	164
Ancillary assistance	5 (days)	16.3	81.5
Hospitalization	7 (days)	171.6	1199.8
Radiology	1(chest-x rays)	85	85
Ultrasound	1 (cardiac)	85	85
TOTAL			2226.2 ± (229 to 727)

Main resources	*N.° or units*	*Unitary or mean cost ($)*	*Total cost ($)*
C. Supportive phase until discharge			
G-CSF	12 (vials)	65.714	789
Antimicrobials (prophylaxis)	12 (days)	18	216
Antimicrobials (therapy)	5 (days)	15	75
Red blood cells	3.5 (units)	127.7	439.9
Platelets (standard)	3 (units)	125.7	377.1
Platelets (apheresis)	3 (units)	368.6	1106
Parenteral nutrition*	7 (days)	17.2	120.5
High dose IgG*	1.5 (vials 6 g)	251.4	377
Laboratory	15 (days)	32.8	492
Microbiology	15 (detections)	10	150
Chest X-rays	1 (procedure)	85	85
Hospitalization	15 (days)	171.4	2371
Nursing assistance	15 (days)	23.8	357
Medical assistance	15 (days)	16.6	249
Ancillary assistance	15 (days)	16.3	244.5
TOTAL			7649
D. General assistance and amortization			
Medical (round-discussions)	27.5 (days)	16.6	456.5
Nursing supervision	27.5 (days)	9.5	261.2
Services (cleaning technical assistance)	27.5 (days)	19	522.5
Economical	27.5 (days)	16.6	456.5
Pharmacy	27.5 (days)	13.3	365.8
Administration	27.5 (days)	16.6	456.5
Structural amortization	27.5 (days)	58.1	1600
TOTAL			4119

**Resources utilized only in some patients.*

plantation which are recognizable as groups of cost. The mean cost of the entire procedure is $17,532.9 plus the cost of myeloablative therapy which varies from $229 to $727 (mean $559.7) giving a mean total of $18,092.6. The preparative phase (Table 2a) included central venous catheter (CVC) insertion, mobilization of $CD34^+$ cells as described, collection of CD34 cells and their cryopreservation. The total cost of this phase was $3,538.7 (19.6%). Major costs of this phase were growth factor ($789), leukaphereses ($467.5), cryopreservation of CD34 cells ($857.1) and hospitalization (5.5 days) ($514.3). The second phase (Table 2b) including the execution of myeloablative therapy and reinfusion of CD34 cells cost $2,226.2 (12.3% of the total cost) excluding the cost of chemotherapy which varied from $229 (Bu-MPH), to $619 (BAVC), to $664 (CBV) and to $727 (BEAM) with a mean cost of $559.7. The total mean cost of this phase was $2,785.9 (15.4%). Major costs of this phase were the BEAM chemotherapy ($727) and 7 days of hospitalization ($1,119.8). The third phase (Table 2c) included the supportive therapy until discharge of the patient and consisted of antimicrobials, transfusions, investigational procedures, nutrition and growth factor. The total cost of this phase was $7,649 (42.3%). Major costs were those of hospitalization which was of a mean duration of 15 days after reinfusion of CD34 cells ($2,571), platelet transfusions from a single donor by apheresis ($1,106), growth factor ($789), laboratory investigations ($492), and red blood cell transfusions ($439). The fourth group of costs (Table 2d) focused on general expenses involving the management of each patient including services, economic facilities, pharmacy costs, administration and amortization of the hospital structure. The total cost of this group was $4,119 (22.7%). Major costs were amortization of structures ($1600) which was calculated on daily basis and referred to expenses for renovations, repairs and mantainance, technical assistance and cleaning ($522.5), administration ($456.5), medical rounds and discussions about the patient ($456.5) and economic evaluation ($456.5).

The sum of expenses for nursing assistance in all phases was $939.4, that of ancillary's assistance $415.7 with an overall cost of nursing of $1,355.1 being 7.5% of the total cost.

Discussion

This report focuses on a group of patients with malignant lymphoma resistant to or relapsed after previous therapies and directed to salvage therapy with myeloablative protocols and PBSC. The expected median survival in such patients treated with conventional therapy is less than 10 months, with generally no survivors after 3 years;[30-32] myeloablative therapy preceeding ABMT or PBSC offers a possibility of salvaging 20% to 40% of patients with resistant relapsed malignant lymphoma;[33] furthermore, this approach is validated by the fact that the procedure of ABMT or PBSC is relatively safe with a low risk of related mortality. Despite the number of reports concerning ABMT in lymphomas, few of them are focused on cost analysis[14-20] and none on the subset of patients with resistant conditions; this particular subset of patients creates a number of considerations for future perspectives of their general management which are not created by patients with earlier phases of disease.

Major considerations were whether PBSC autotransplantation is advantageous for outcome in a particularly poor prognosis subset of patients and whether the cost of their treatment can be sustained. Our study shows how a substantial percentage of patients, almost 25%, can be salvaged and that the entire cost of the necessary procedure can be contained and indeed substantially reduced. In fact, a comparison with other reported experiences[15,26-29] suggests that our global costs were one third of those in other Italian experiences[28] and one half of those in other European and American experiences.[26,27,29] We are, of course, aware that the value of life cannot be calculated in medical decisions/cost analysis: any analysis of costs must hold this paradox central. Nevertheless, rationalization of health costs in general and a creation of guidelines for the therapy in each disease status should be scrupulously adhered to. Our data overlap with those reported by others in similar patients[5,23,33] with a perspective of long-lasting survival in almost one quarter of patients, perhaps some of them definitively cured. Despite these data and the limitation of costs, we believe that PBSC autotransplantation in patients with resistant lymphoma is applicable with difficulty in a large proportion of patients due to the still high cost. Alternatives in the future could be to reduce costs further to simplify the procedure and to facilitate the management. In fact many reports point out that patients relapsed after first conventional therapy have a better prognosis with ABMT or PBSC if they are in a sensitive phase of their disease.[12,13,34] None of these reports emphasizes the role of myeloablative therapy in truly resistant patients with lymphoma. The considerations on the whole matter given above will in the near future be the basis for discussion on dealing with the demands of patients who have a chance of cure, the growing number of indications for PBSC use, and the strong limitation of funds available in the community, either as a private patient or as a publicly assisted patient.

A second group of considerations concerns the management aspects of PBSC autotransplantation, ie the general organization of the procedure and the executive phase. Simplification of these aspects automatically means a reduction of costs. As for organization is concerned, we know that in most institutions the staff involved in transplantations are specifically trained and organized in an intensive care unit generally separated from the general wards; having a chronic reduction of staff specifically dedicated to bone marrow transplantation is a bias under this point of view. However, in our experience this has been a stimulus to improving the organization of staff not totally dedicated and interchangeable, creating greater responsability in each staff member. In fact, the growing demands of care with high technological procedures need an efficient response complying with the criteria that the procedure must be safe. Our experience with a particularly poor prognosis subset of patients demonstrates that the procedure of myeloablative therapy and PBSC, done as we have presented it is almost as safe as that reported by other authors.[5,12,22-23,33] One fundamental aspect was that of involving a family member, sufficiently instructed in first level assistance, which gained a positive reaction from both the patient and the staff, without a negative impact on the incidence of infections or outcome of patients. In the context of difficulties of having halved the number of dedicated doctors and nurses specifically assigned to the patient's care due to deficiencies in public health organization in our area (which has not employed new staff in the last 5 years), our experience deserves consideration from other centers in similar conditions. This experience, however, also warrants consideration from any center now making efforts to reduce costs.

A third point of discussion is connected to the possibility, if any, of reducing costs, yet further, of a procedure that has growing indications and is now safer than in the past and, although not curative for most patients, is certainly more effective than other conventional therapies. In this case, reducing costs yields the idea that intensive therapy, such as a myeloablative therapy and PBSC autotransplantation, could be an alternative early approach to patients with lymphoma instead of much less intensive but longer lasting conventional cyclic chemotherapy. This near-future goal requires a further substantial reduction in costs that we believe could be reached by means of a series of possible modifications of the management of the procedure. We showed in this study that the

major costs of hospitalization of patients, amortization of structures, supportive transfusions and growth factor represent one half of the total cost. These costs could be decreased by a great reduction in hospitalization (a possible total reduction of 20 to 40% in the expense of PBSC autotransplantation), as reported by others.[35] The choice of a less expensive conditioning regimen implies a 2.5% reduction of the total cost. The costs of assistance, as discussed before, are already low but a further reduction could be reached by involving humanitarian associations with members specifically trained in the assistance of patients with hematologic problems. Integration between official, qualified assistance and other supportive assistance obviously needs accreditation from public health controls. The reduction of consumption of drugs or supplies by shortening hospitalization can create a further reduction of up to 5% of total costs.

Our analysis focuses on a modern and highly technological therapy which could be proposed to all patients earlier in the course of their disease as an alternative to more conventional treatments if costs could be reduced further and more substantially. This challenge for the future to give to all patients the possibility of highly technological therapeutic procedures, requires primarily coordination between public assistance and other sources of assistance, such as family and humanitarian associations with specific and qualified training. This integration has been designated and asked for in the lastest proposals of reorganization of the national health system.[36]

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MP formulated the design of the study, analyzed data and wrote the paper, SE, PG and AB handled and collected data and followed patients, MN critically revised the manuscript, MG furnished the information for the calculation of costs of resources, MR provided all details of costs involving the Pharmacy.

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Disclosures

Conflict of interest: none.

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References

1. Kessinger A, Vose JM, Bierman PJ, Bishop M, Armitage JO. Peripheral stem cell transplantation in non-Hodgkin's lymphoma patients. J Hematother 1993; 2:361-2.
2. Has R, Brittinger G, Meusers P, et al. Myeloablative therapy with blood stem cell transplantation is effective in mantle cell lymphoma. Leukemia 1996; 10:1975-9.
3. Corradini P, Astolfi M, Gherasco C, et al. Molecular monitoring of minimal residual disease in follicular and mantle cell non Hodgkin's lymphomas treated with high dose chemotherapy and peripheral blood progenitor cell autografting. Blood 1997; 89:724-31.
4. Dregger P, Von Neuhoff N, Kuse R, et al. Sequential high dose therapy and autologous stem cell transplantation for treatment of mantle cell lymphoma. Ann Oncol 1997; 8:401-3.
5. Hurd DD, Haake RJ, Lasky LC, et al. Treatment of refractory and relapsed Hodgkin's disease: intensive chemotherapy and autologous bone marrow or peripheral blood stem cell support. Med Pediatr Oncol 1990; 18:447-53.
6. Federico M, Clo V, Carella AM. High dose therapy and autologous stem cell transplantation vs conventional therapy for patients with advanced Hodgkin's disease responding to first-line therapy: analysis of clinical characteristics of 51 patients enrolled in the HD01 trial. Leukemia 1996; 10(Suppl 2):S69-S71.
7. Sweetenham JW, Tachipour G, Milligan D, et al. High dose therapy and autologous stem cell rescue for patients with Hodgkin's disease in first relapse after chemotherapy: results from the EBMT. Lymphoma Working Party of the European Group for blood and marrow transplantation. Bone Marrow Transplant 1997; 20:745-52.
8. Majolino I, Pearce R, Tachipour G, Goldstone AH. Peripheral blood stem cell transplantation versus autologous bone marrow transplantation in Hodgkin's and non-Hodgkin's lymphomas: a new matched-pair analysis of the European Group for blood and marrow transplantation registry data. Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 1997; 15:509-17.
9. Gianni AM, Bregni M, Siena S, et al. High dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med 1997; 336:1290-7.
10. Vitolo U, Cortellazzo S, Liberati AM, et al. Intensified and high dose chemotherapy with granulocyte colony-stimulating factor and autologous stem cell transplantation support as first-line therapy in high risk large cell lymphoma. J Clin Oncol 1997; 15:491-8.
11. Fredman AS, Gribben JG, Neuberg D, et al. High dose therapy and autologous bone marrow transplantation in patients with follicular lymphoma during first remission. Blood 1996; 88:2780-6.
12. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy sensitive non-Hodgkin's lymphoma. N Engl J Med 1995; 333:1540-5.
13. Gianni AM, Bonadonna G. High dose chemo-radiotherapy for sensitive tumors: is sequential better than concurrent drug delivery? Eur J Cancer Clin Oncol 1989; 25:1027-30.
14. Messori A, Bonistalli L, Costantini M, Alterini R. Cost-effectiveness of autologous bone marrow transplantation in patients with relapsed non-Hodgkin's lymphoma. Bone Marrow Transplant 1997; 19:275-81.
15. Smith TJ, Hillner BE, Schmitz N, et al. Economic analysis of a randomized clinical trial to compare filgrastim-mobilized peripheral blood progenitor cell transplantation and autologous bone marrow transplantation in patients with Hodgkin's and non-Hodgkin's lymphoma. J Clin Oncol 1997; 15:5-10.
16. Hartmann O, Le Corroller AG, Blaise D, et al. Peripheral blood stem cell and bone marrow transplantation for solid tumors and lymphomas: hematologic recovery and costs. A randomized, controlled trial.

Ann Intern Med 1997; 126:600-7.
17. Tarella C, Castellino C, Locatelli F, et al. G-CSF administration following peripheral blood progenitor cell (PBPC) autograft in lymphoid malignancies: evidence for clinical benefits and reduction of treatment costs. Bone Marrow Transplant 1998; 21:401-7.
18. Jagannath S, Vesole DH, Zhang M, et al. Feasibility and cost-effectiveness of outpatient autotransplants in multiple myeloma. Bone Marrow Transplant 1997; 20:445-50.
19. Uyl-de Groot CA, Richel DJ, Rutten FFH. Peripheral blood progenitor cell transplantation mobilized by r-metHuG-CSF (Filgrastim); a less costly alternative to autologous bone marrow transplantation. Eur J Cancer 1994; 30A:1631-5.
20. Costantini M, Bonistalli L. Trapianto autologo di midollo in pazienti con linfoma non Hodgkin in ricaduta: analisi dei dati di sopravvivenza e valutazione costo-efficacia. Giornale di Farmacoeconomia 1997; 1:155-60.
21. Craig JI, Anthony RS, Stewart A, Thompson EB, Gillon J, Parker AC. Peripheral blood stem cell mobilization using high-dose cyclophosphamide and G-CSF in pretreated patients with lymphoma. Br J Haematol 1993; 85:210-2.
22. Tura S, Mazza P, Gherlinzoni F, et al. High dose therapy followed by autologous bone marrow transplantation (ABMT) in previously untreated non-Hodgkin's lymphoma. Scand J Haematol 1986; 37:347-52.
23. Philip T, Armitage JO, Spitzer G, et al. High dose therapy and autologous bone marrow transplantation after failure of conventional chemotherapy in adults with intermediate grade or high grade non-Hodgkin's lymphoma. N Engl J Med 1987; 316:1493-8.
24. Mills W, Chopra R, McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. J Clin Oncol 1995; 13:588-95.
25. Kanfer E. Bone marrow transplant conditioning regimen schedules. In: J.Treleaven, J. Barrett, eds. Bone Marrow Transplant in Practice. Edinburgh: Churchill Livingstone Press; 1992. p. 247-55.
26. Bennet CL, Armitage JL, Armitage GO, et al. Cost of care and outcomes for high dose therapy and autologous transplantation for lymphoid malignancies: 1997 through 1991. J Clin Oncol 1995; 13:969-73.
27. Uyl-de Groot CA, Okhuijsen SY, Hagenbeek A, et al. Costs of introducing autologous BMT in the treatment of lymphoma and acute leukemia in the Netherlands. Bone Marrow Transplant 1995; 15:605-10.
28. Barosi G, Marchetti M, Casula S, et al. A model for analyzing the cost of peripheral blood progenitor cell transplantation. 24th Annual Meeting European Group for Blood and Marrow Transplantation and 14th Meeting of the Nurses's Group. Courmayeur, Italy, March 22-26, 1998. Bone Marrow Transplant 1998; 21(suppl 1):S374.
29. Donnet-Descartes A, Cometta A, Wasserfallen JB, Kovacsovics T. Hospital costs of intensive chemotherapy followed by peripheral stem cell reinfusion. 24th Annual Meeting European Group for Blood and Marrow Transplantation and 14th Meeting of the Nurses's Group. Courmayeur, Italy, March 22-26, 1998. Bone Marrow Transplant 1998; 21(suppl 1): S375.
30. Armitage JO. Treatment of non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1023-30.
31. Koziner B, Little C. Treatment of advanced diffuse histiocytic lymphoma: an analysis of prognostic variables. Cancer 1982; 49:1571-9.
32. Bordonaro L, Zagonel V. Fattori prognostici nei linfomi. In: Salvagno-Fiorentino, eds. Piccin. 1996. p. 247-58.
33. Philips LG, Herzig RH, Lazarus HM, et al. Treatment of resistant malignant lymphoma with cyclophosphamide, total body irradiation, and transplantation of cryopreserved autologous marrow. N Engl J Med 1984; 310:1557-61.
34. Martelli M, Vignetti M, Zinzani PL, et al. High dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin, and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line therapy: a prospective randomized Italian multicenter study. J Clin Oncol 1996; 14:534-42.
35. Waters TM, Bennett CL, Vose JM. Economic analyses of new technologies: the case of stem-cell transplantation. J Clin Oncol 1997; 15:2-4.
36. Decreto Legge 30/12/92 n. 502. Riordino della disciplina in materia sanitaria, a norma dell'articolo 1 della legge 23 ottobre 1992, n. 421. Art. 14. Diritti dei cittadini. Gazzetta Ufficiale n. 305 30/12/92. p. 5-22.