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Risk Factors for Early Mortality in Allogeneic Bone Marrow Transplantation. A Multivariate Analysis on 174 Leukaemia Patients

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Allogeneic bone marrow transplantation in patients with leukaemia is an aggressive therapeutic procedure which implies high early mortality. Current opinion trends attribute the greater part of the procedure toxicity to the preparative regimen. The results of a multivariate analysis on data of 174 leukaemia patients conditioned with total body irradiation (TBI), 10–12 Gy, single dose or fractionated, and lung shielding at 8 Gy, plus chemotherapy: cyclophosphamide 120 mg/kg, before or after TBI, are presented. The variables statistically related with early mortality are age, Karnofsky index (KI) and acute graft-versus-host disease (GvHD). No variable depending on radiotherapy reached the significance level. The relative risk of early mortality for patients older than 26 years, in bad general condition (KI < 90%), or developing acute severe (grades II–IV)GvHD, is 3.99, 5.68, and 6.71, respectively. We conclude that in the range of TBI schedules analysed, radiation therapy is not an important factor in early death, but acute severe GvHD, or recipient's bad general condition are factors to be improved by bone marrow transplantation teams if they want to improve the therapeutic index of the procedure.
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INTRODUCTION

IN LEUKAEMIA patients, bone marrow transplantation (BMT) after total body irradiation (TBI) plus chemotherapy, yields a long-term disease-free survival of approximately 50% [1]. Risk of life-threatening or fatal complications in this procedure is high [2, 3]. Main causes of death may be classified as disease relapse and non-relapse mortality [4] or transplant-related mortality [5].

For patients conditioned with TBI and cyclophosphamide, leukaemia relapse accounts for 10–20%, depending on diagnosis and phase of disease [6]. Otherwise, most deaths are due to other causes, mainly regimen-related toxicity and graft-versus-host disease (GvHD) [7, 8], appearing shortly after BMT: approximately 80% of deaths due to transplant procedure occur within the first 4 months [9, 10].

Relapses could be diminished by increasing the eradicative effects of preparative treatment [11]; regimen-related toxicity by the selection of a less toxic but equally effective regimen; and severity of GvHD by improving its prophylaxis and treatment.

The role of TBI in the preparative regimen is: disease eradication, immunosuppression and creation of space to allow graft implant [12]. Despite theoretical radiobiological considerations [13–15], bone marrow transplant teams have to select their TBI schedules according to availability of radiation equipment and patient load. Different schemes of fractioning and hyperfractioning, dose rates, and critical organ shielding have been employed [16–18]. At present, analysis of these different approaches fails to disclose any regimen that is clearly superior [19].

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We began to use TBI for BMT [20] by giving 10 Gy single dose with lung shielding at 8 Gy. During later years, total dose, fractioning and lung shielding have been modified following current literature data and availability of radiation facility [21–24]. Up till now, more than 300 patients with malignant haematological disorders (leukaemia, myeloma, lymphoma, and myelodisplastic syndromes) have been conditioned for BMT with TBI.

As a team involved in BMT, we try to improve the therapeutic ratio of the preparative regimen by the identification of variables related to transplant toxicity, especially those depending on radiotherapy. Death due to causes other than relapse is an expression of procedure toxicity [4, 5]. In a previous report [9, 10] we analysed the causes of non-relapse mortality in 221 leukaemia patients. In this series, 80% of deaths occurred during the first 120 days after BMT. We now present the results of a multivariate analysis of data of 174 leukaemia patients treated with allogeneic BMT, to discover which variables are related to death due to the procedure during this critical period (120 days).

PATIENTS AND METHODS

174 patients with a mean follow-up of 29.6 months (6–122 months) have been included. This series is made up of 100 males and 74 females, mean age 25.1 years (S.D. = 10.5), 56 with acute lymphoblastic leukaemia (ALL), 72 with acute non-lymphoblastic leukaemia (ANLL), and 46 with chronic myeloid leukaemia (CML). Characteristics of patients before BMT are presented in Table 1. Acute leukaemia patients classified as complete remission (CR) include: 56% first CR, and 44% other CR.

Preparative regimen

Patients were conditioned with cyclophosphamide, 60 mg/kg for 2 consecutive days and TBI. Chemotherapy was given before or after irradiation in 100 and 74 patients, respectively. TBI was

administered with a Co-60 unit, with three different schedules: 10 Gy single dose (90 patients); 6 × 200 Cgy in 3 days (68 patients); or 4 × 300 Cgy in 2 or 4 days (16 patients). The choice of one or another TBI schedule was made according to availability of radiation equipment and patient load.

Doses were calculated at midplane, axis and at different points of interest: head, neck, mediastinum, lung, abdomen, pelvis and knees. Minimum dose was chosen as the point of reference. Areas overdosed were shielded with appropriate thickness of copper sheets. Heterogeneity of dose distribution was accepted when less than 10%. In patients treated with single dose, lungs were shielded during the last part of the treatment, when absorbed lung dose reached 8 Gy. In fractionated schedules lungs were shielded during the whole treatment. Characteristics of the three TBI schedules are listed in Table 2.

Transplantation procedure

All patients received an allogeneic BMT from HLA (negative mixed-lymphocyte culture) matched related donors. The transplant procedure was performed following the technique reported by Thomas and colleagues [25] and has already been described [21].

Supportive care

Supportive care used in our patients has been previously published [26]. Briefly, patients were isolated in a positive pressure filtered air ward, and decontaminated from day 5 until recovery of granulocyte count ($> 0.5 \times 10^9$/l). During this period they received non-absorbable oral antibiotics, total parenteral nutrition, prophylaxis against haemorrhagic cystitis (Mesna), irradiated non-selected cytomegalovirus (−) hematic derivatives and antibiotics upon clinical evolution. From day 32 after BMT patients received prophylaxis against *P.carinii* infection with cotrimoxazole.

Table 1. Characteristics of patients before transplantation

Variable	(*n*)	%
Sex		
Male	100	57.5
Female	74	42.5
Karnofsky index		
< 90	160	92.0
≥ 90	14	8.0
Diagnosis		
ALL	56	32.2
ANLL	72	41.4
CML	46	26.4
Phase		
CR	108	84.4
NCR	20	15.6
CP	42	91.3
AP	4	8.7

	Mean	S.D.	Range
Age			
DG-BMT-	25.1	10.5	4–44
Delay	586.8	703.2	90–4484

CR = complete remission; NCR = non-complete remission; CP = chronic phase; AP = accelerated or blastic phase; DG = diagnosis.

Table 2. Characteristics of treatment schedules in three different facilities

	First	Second	Third
No. of cases	90	54	30
Patient position	Lat. Decubitus	Sitting	Lat. Decubitus
Total dose	10	12	12
Fractions	1	4–6	4–6
Dose/fraction	10	2–3	2–3
Axis dose rate (midplane)	4.9 ± 1.3	5.3 ± 0.4	4.0 ± 0.3
Lung dose	8	8.2 ± 0.2	8.2 ± 0.2
Lung dose rate	6.5 ± 1.6	3.6 ± 0.3	2.6 ± 0.2
Lung shielding	Lead*	Copper†	Copper†

Doses are expressed in Gy; dose rates are expressed in cGy/min. *Lungs shielded at the end of treatment when lung-absorbed dose reached 8 Gy. †Lungs partially shielded during the whole treatment with copper sheets.

Prophylaxis, diagnosis and treatment of graft-versus-host disease

All patients received prophylaxis against GvHD with methotrexate (MTX), 10–15 mg/m^2 for 11 doses (65 patients), cyclosporin-A (Cs-A) (9 patients), both: MTX, 4 doses and Cs-A (96 patients), or T-depleted bone marrow plus Cs-A (4 patients). Cs-A was always administered following Storb's schedule (27): intravenous 8 mg/kg/day from day 1 to 3;4 mg/kg/day from day 4 until oral food intake, and oral 6.25 mg/kg at 12 h intervals until day 50, followed by a decreasing dose until day 270, always trying to maintain Cs-A plasma levels between 200 and 500 μg/l [27].

Diagnosis and grading of GvHD were established according to the criteria accepted by the International Bone Marrow Transplant Registry (IBMTR) [28]. Patients with acute GvHD received methylprednisolone (5–10 mg/kg/day). Antithymocyteglobulin was added only if response to glucocorticoid was poor.

Endpoints and events of interest during follow-up

Causes of death were ascertained following clinical and biological criteria and, in most cases, according to autopsy findings. Infection (bacterial, viral, fungal or parasitical) and interstitial pneumonitis or hepatic veno-occlusive disease, were always documented by laboratory or cyto-histological studies. Interstitial pneumonitis (IP) was referred as idiopathic (IIP) when no pathogenic organism was identified. Patients with IP in whom a pathogenic micoorganism was isolated were classified as having an infectious process and were included in this group. GvHD has never been considered an ultimate cause of death. When more than one possible cause of death was present only the most important was recorded. For example, a patient with acute severe GvHD and IP by cytomegalovirus was classified as a viral infection death.

Fourteen potential prognostic variables (Table 3) classified as non-controllable, sometimes controllable and controllable by the BMT team [29] were included in the analysis.

Statistical method

Descriptive results are presented for continuous variables with their mean and standard deviation (S.D.), and with their

Table 3. Variables analysed

Non-controllable
- Age (cutpoint: 26 years)
- Sex (male/female)
- Diagnosis (ALL, ANLL, CML)

Sometimes controllable
- Karnofsky index (cutpoint 90)
- Disease phase (CR versus non CR; CP versus AP)
- Radiotherapy technique (first, second or third)
- Donor–recipient sex (male–male, female–male, male–female, female–female)
- GvHD grade (0–1 versus II–IV)

Controllable
- Diagnosis-BMT Delay (cutpoint 365 days)
- TBI total dose (10 versus 12 Gy)
- Fractioning (yes/no)
- Number of fractions (1, 4 or 6)
- Axis midplane dose-rate (cutpoint 5 cGy/min)
- Radio-chemotherapy sequence (before or after TBI)
- Number of infused cells (cutpoint 2.5 × 108/kg)
- GvHD prophylaxis (MTX, MTX-CsA, CsA, T Dep +CsA)

proportions in categorical variables. Median and range of values are also presented when the distribution of a variable deviates from normality. The association between each factor and the occurrence of early mortality was tested with the χ^2 test for categorical variables [30]; Fisher exact test was applied when necessary [31]. For continuous variables, means of two groups were then compared with the *t*-test or Mann-Whitney U test when the distribution of at least one group deviated from normality [32]. Relative risk (RR) and the probability of early mortality were estimated by means of an unconditional logistic regression model [33]. Selection of variables that entered such a model was performed on a stepwise procedure basis among all factors significantly associated with early mortality in the univariate tests, all the TBI variables, and other variables considered to be of clinical interest. The probability of early mortality was calculated with the logistic model for the presence of different profiles of factors. Significance level was set at 0.05 and only two-sided contrasts were considered. Statistical analysis was done with the BMDP statistical package [34] at the Institut Municipal d'Investigació Médica (IMIM) of Barcelona.

RESULTS

Of the 174 patients who entered the study, 76 (43.7%) died from causes related to the transplant procedure during the first 120 days after BMT. Recorded causes of death were: infection (63.2%), haemorrhage (15.8%), interstitial idiopathic pneumonitis (10.5%), and other causes (10.5%) including cardiac, hepatic, or renal failure, and hepatic veno-occlusive disease. Acute severe GvHD (grades II–IV) was present in 43/76 (56.6%) of the deceased.

Univariate analysis

The univariate analysis included 174 patients. Age was significantly associated with early mortality either when taken as a continuous variable or when categorised ($P < 0.0001$) (Tables 1 and 4). Diagnostic group ($P = 0.0498$) and acute GvHD ($P < 0.0001$) also showed a statistically significant relation with early mortality (Table 4). No TBI variables, nor preparative sequence showed statistical significance.

Multivariate analysis

The logistic model selected GvHD, age, and Karnofsky index (KI) in the stepwise procedure. The RR of dying during the first 120 days after BMT was 3.99 for patients older than 26 years (95% confidence interval (C.I.): 1.95–8.15). A Karnofsky index lower than 90% had a RR of 5.68 (95% C.I.: 1.62–19.98). Acute severe GvHD (II–IV) accounted for a RR of 6.71 (95% C.I.: 3.18–14.12). No TBI variables, nor preparative sequence were selected by the logistic model.

The probability of death within the first 120 days after allogeneic BMT was: 42% for patients older than 26 years with no other risk factor present, 51% when Karnofsky index was lower than 90% and no other risk factor was present, and 55% when the patient developed an acute severe GvHD (II–IV) and no other risk factor was present. The RR and probability of mortality for other combinations of risk factors during this period are shown in Table 5. The worst prognostic combination was for patients older than 26 years in bad general condition (KI < 90%) and with acute severe GvHD who had 96% probability of death and a RR of 152.07 (95% C.I.: 150.20–153.94).

Table 4. Results of univariate analysis

Variable		Mortality (%)	(*n*)	χ^2	*P*
Age	≤ 26	30.3	99		
	> 26	61.3	175	16.70237	<0.0001
Sex	Male	41.0	100		
	Female	47.3	74	0.68577	0.4077
Diagnosis	ALL	35.7	56		
	ANLL	40.3	72	5.99925	0.0498
	CML	58.7	46		
Karnofsky	< 90	64.3	14		
	90–100	41.9	160	2.62826	0.1050
Phase	CR	39.8	108		
	NCR	30.0	20	0.68800	0.4068
	CP	54.8	42		
	AP	100.0	4		0.1075*
TBI	First	42.2	90		
technique	Second	44.4	54	0.19936	0.9051
	Third	46.7	30		
BMT delay	< 365	41.7	96		
(days)	> 365	46.2	78	0.35223	0.5529
Total dose	10 Gy†	42.2	90		
	12 Gy‡	45.2	84	0.16064	0.6886
Fractions	1	42.2	90		
	4	37.5	16	0.64172	0.7255
	6	47.1	68		
Dose rate	≤ 5	43.1	102		
(cGy/min)	> 5	44.4	72	0.29324	0.8640
Sequence	TBI+CHT	47.3	74		
	CHT+TBI	41.0	100	0.68557	0.4077
Donor–recipient					
sex	Male–male	41.4	58		
	Female–male	40.5	42		
	Male–female	59.1	44	6.83007	0.0775
	Female–female	30.0	30		
GvHD	MTX	40.0	65		
Prophylaxis	MTX–CsA	45.8	96		
	CsA	55.6	9	1.62210	0.6544
	T Dep+CsA	25.0	4		
GvHD	0–I	29.2	113		
Grade	II–IV	70.5	61	27.45201	>0.0001

*Fisher exact test. †Single dose. ‡Fractionated.

Table 5. Relative risk and probability of mortality for a patient with various combinations of two or three risk factors

Factors	Relative risk	Interval	Probability of mortality
>26 years + KI < 90%	22.66	21.11– 24.21	80%
>26 years + severe GvHD	26.77	25.67– 27.87	83%
KI <90% + severe GvHD	38.11	36.52– 39.70	87%
>26 years + KI <90% + severe GvHD	152.07	150.2 –153.94	96%

On the other hand, the best prognostic profile was that of patients under 26 years, in good general condition (KI ≥ 90) and grade 0–1 acute GvHD with only 15% probability of death and in the relative risk reference group (RR = 1).

DISCUSSION

Generally, reports on BMT results are based on the analysis of wide series of patients included in National–International BMT Registries [35], and therefore treated at different institutions with a wide range of variables. From these studies, it is now clear that overall survival for leukaemia patients undergoing BMT depends on many factors. Most of them are interrelated and should be analysed in large series of subjects. Many investigators have analysed the causes of death and the prognostic factors associated with the more relevant complications after BMT, i.e.: relapse [36, 37], interstitial pneumonitis [29, 38, 39], hepatic veno-occlusive disease [40, 41], graft rejection [42], or GvHD [43]. All these reports and many others include the conditioning regimen in their analysis, and most of them find a relation between TBI and acute, often fatal complications. When modifications in the preparative regimen are introduced to improve one of these endpoints, their relationships are noteworthy. An increase in TBI total dose to decrease relapse [44] is correlated with higher regimen-related mortality and GvHD [45–47]; fractioning of TBI attempting to decrease IP incidence or the administration of T-depleted grafts to decrease GvHD are followed by an increase in relapse rate [37, 48–50].

Thus, after the introduction of fractionated TBI, many reports referred favourably to this therapeutic approach. A lower incidence of severe complications, especially interstitial pneumonitis [19, 29, 37, 38], supported this hypothesis. Recent results fail to disclose any advantage of multifractioning [51]. Now the question is the difficulty in comparing non-randomised series of patients to different TBI schedules [52, 53] and the role of radiotherapy in the preparative regimen [54].

We have attempted to improve our conditioning regimen and its therapeutic index. Among the valuable endpoints: acute and late side-effects, immunosuppression, and tumoricidal yield [52], we analysed early mortality due to treatment procedure as a valuable parameter of acute severe toxicity, and its relationship with the preparative regimen. Our work has been done with a less numerous but more homogeneous group of patients than those in International Registry series, treated by the same BMT team and, therefore, with a limited range in the variables analysed.

In this group, as in other series of BMT patients [2, 7, 8, 12, 21, 23, 55], mortality not related to disease evolution is high and predominates in the first 3–4 months following marrow infusion.

In the univariate analysis, age, diagnosis, and GvHD are the variables significantly related with early mortality. In the multivariate analysis, diagnosis loses significance, probably due to the higher incidence and severity of GvHD in our CML patients than in acute leukaemia patients. On the other hand, the KI, non-significant in the univariate analysis, acquires significance in the multivariate analysis because of its higher statistical power. No TBI factor appears to be related with early mortality, either in univariate or multivariate analysis.

In the present study the most significant prognostic factor is acute GvHD. Patients developing this complication in grades II–IV have the highest RR: almost seven times higher than patients with grades 0–1, with a 55% probability of dying during the first 4 months. Such a severe complication has been recognised as one of the most deleterious on BMT outcome [41, 56] and many efforts are being undertaken to prevent and treat its occurence [27, 48, 49].

The second significant factor is age. In our series, patients older than 26 years had four times more risk of dying due to causes not related with the underlying disease than younger ones. This increased risk has been depicted for allogeneic BMT by Gratwohl *et al.* [57] in leukaemia patients, and by Thomas *et al.* [58] in ANLL patients in first CR. These authors relate it to a better tolerance to the preparative regimen. In fact, comparing chemotherapy alone *versus* chemo-radiotherapy followed by BMT for ANLL in first CR, Tallman and colleagues [59] found the same relationship and provided a similar explanation.

The third significant factor is KI. Patients with a KI lower than 90 have close to seven times the risk of dying than patients in good general condition. Obviously, this factor was expected to be a good predictor. Freedman *et al.* [60] attributed the low incidence of regimen-related mortality to the excellent performance status of their patients, and Bearman *et al.* [3] demonstrate a significant relationship between this factor and the tolerance to regimen-related toxicity in lymphoma patients treated with BMT.

Unfortunately, among the variables related with early mortality, age is non-controllable [29]. GvHD and KI may be partially modified by increasing prophylaxis and treatment of GvHD [61], and by entering patients in BMT programs when in good general condition.

Nevertheless, our analysis demonstrates that in our patients, TBI variables, within the limits of total dose, dose rate, fractioning and lung shielding analysed here, are not significantly related to early mortality.

Briefly, in our series and in the range of factors studied here, analysis fails to disclose a relationship between TBI variables and early mortality. Other variables such as GvHD, age and Karnofsky index are significantly related with early mortality. In patients undergoing BMT, and especially in those with high risk profiles, new preparative regimens and prophylaxis and treatment of GvHD have to be tested.

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Laser Surgery for Small Perianal Neoplasms

Gaetano Bandieramonte, Aldo Bono, Stefano Zurrida, Cesare Bartoli and Giuseppe de Palo

Excisional laser surgery was used to treat 62 patients suffering from perianal, perineal, and anal canal neoplasms. 48 patients had benign epithelial or pigmented tumours, 12 had carcinoma *in situ* and 2 had invasive squamous cell carcinoma. Laser surgery was performed under local anaesthesia, in association with the operating microscope on an outpatient basis. 59 out of 62 patients (95%) had clear margins of resection after primary laser surgery, and 3 patients required a second excision for uncleared margins. 3 patients of the group of carcinoma *in situ* recurred, and 2 had new disease in an untreated area. These patients underwent re-section with the same technique. No significant local complications were observed for single or multiple operations at the perianal and anal canal level. All patients are disease-free in a follow-up ranging from 4 to 113 months, with a median of 25 months. Laser excisional surgery appears to be a suitable method for treating superficial tumours.
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INTRODUCTION

IDEAL MANAGEMENT for surface lesions of the perineal, perianal and anal canal area should satisfy the following requirements: accurate intraoperative diagnostic information, easy execution, low morbidity, preservation of anatomy and function, successful long-term results. A variety of alternative treatment modalities have been reported recently for perianal neoplasms [1–7]. Sharp knife resection for the removal of surface lesions of the perineal and perianal areas is hampered by the high vascularisation, such that intraoperative bleeding prevents the precise assessment of the lesion margins. Destructive treatment modalities, such as cautery, cryosurgery or topical chemotherapeutic agents, do not allow complete examination of the lesion.

In order to verify the technical and clinical effectiveness of the laser surgical tool, we developed a unified approach to the treatment of perianal lesions, by performing laser excisional procedures.

MATERIALS AND METHODS

Instrumentation

Three CO_2 surgical lasers were used: Valfivre L SS 25, Coherent 450 and Cooper 250 Z Models. Output power reached 25–35 W, continuous wave; the various irradiances used were related to the spot diameters of the beam (0.5–2 mm). The operating microscopes, Zeiss OPMI-1 and OPMI-6H (magnification power ranging from 2 to 24X) were coupled with the articulated arm of the laser instrument. The focal length of the focusing lens was 300 mm.

The excisional method was used to obtain the entire surgical specimen for pathological examination [8]. By using the laser beam as a surgical scalpel, adequate incisions were obtained by deepening the sulcus of incision at higher irradiances (region of 1.500–10.000 W/cm^2). CO_2 laser was used at a mean output of 20 W, continuous wave, with 1 mm mean spot diameter. Important adjunctive instruments were the suction apparatus for the fumes and microcalipers.

Study population

From August 1981 to November 1991, in the day hospital of the Division of Diagnostic Oncology and the outpatient clinic a total of 62 patients underwent excisional laser surgery for perineal, perianal and anal canal lesions. The distribution of the 62 patients according to histology, sex and age is shown in Table 1. Fifty-four of the 62 neoplasms were located in the perineal and perianal skin, seven were confined to the anal canal and one involved both the anatomic sites. The size of the neoplasms ranged from 0.4 to 2.3 cm of maximum linear extent, with a median value of 0.9 cm (Table 2). Mechanical bowel preparation was carried out before surgery only for anal canal involvement. Mean depth of laser resection was 2 mm. After the laser resection the wound bed was left to heal by second intention with sutures (Fig. 1).

Neither preoperative nor postoperative antimicrobial pro-

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