EARLY MORTALITY IN BONE MARROW TRANSPLANTATION FOR ACUTE LYMPHOCYTIC LEUKAEMIA A MULTIVARIATE ANALYSIS OF RISK FACTORS

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SUMMARY

***Objectives*: Bone marrow transplantation is still associated with a high case-fatality rate. This study was conducted to identify the risk factors for early mortality in acute lymphocytic leukaemia patients treated with bone marrow transplantation.**

***Methods*: Prospectively collected data on 76 acute lymphocytic leukaemia patients, treated with 60 mg/kg cyclophosphamide for two consecutive days, before (32 patients) or after (44 patients) total body irradiation who received an allogeneic (56 patients) or autologous (20 patients) bone marrow transplantation were considered in the multivariate analysis including fifteen potentially prognostic variables for early mortality.**

***Results*: In the entire group, patients older than 20 years had a relative risk for early mortality of 3.96 (95% confidence interval (CI): 1.33-11.76) and those with a Karnofsky Index lower than 90% had a relative risk of 5.56 (95% CI: 1.29-25). In the subgroup of allogeneic patients, those over 20 years had a relative risk of 5.17 (95% CI: 1.30-20.6); the relative risk for patients with a Karnofsky index < 90% was 10.55 (95% CI: 1.55-71.43) and 8.04 (95% CI: 43-45.07) for acute severe graft-*versus*-host disease. Among radiation therapy variables only dose-rate showed a trend towards better prognosis in patients treated with less than 5 cGy/min.**

***Conclusions*: In our patients and within the range of treatment variables studied, age, Karnofsky index, and graft-*versus*-host disease are the most important factors related with early mortality. *Eur J Med* 1993; 2:386-392**

***Key words*:**

bone marrow transplantation, acute lymphocytic leukaemia, total body irradiation, risk factors, mortality

Long-term survival after bone marrow transplantation (BMT) in leukaemia patients is the result of a delicate balance between relapse rate and transplant toxicity (1-5). An increase in preparative regimen agressivity yields a low relapse index (6) but is counterbalanced by an increase in morbidity and mortality (7). The more extended conditioning regimens include total body irradiation, because most investigators recognize the role of total body irradiation in disease erradication, immunosuppression and creation of space to allow graft implant (8), although its action mechanism is not well understood and has been questioned (9). So far, in absence of controlled prospective trials (10), no regimen is clearly superior. Thus, transplant teams select their total body irradiation schedules not only according to radiobiological considerations but also taking into account their patient overload and technical availabilities (11-16).

We began to use total body irradiation for BMT giving a 10 Gy single dose and lung shielding at 8 Gy (17). During the last few years, total dose, fractioning, and lung shielding, have been modified following current literature data and availability of radiation facilites (18-23). In our experience, most deaths after BMT are due to causes not related with disease progression, and occur shortly after the procedure. In previous reports (22, 23) we analyzed the causes of mortality in 221 leukaemia patients: 80% occurred during the first 120 days after BMT and were due to infection (60.7%), haemorrhage (15.5%), idiopathic interstitial pneumonitis (9.5%), and parenchymatous failure (14.3%). Like other BMT teams we attribute these deaths to the procedure – « regimen related toxicity » (24) or « transplant toxicity » (25-27). In this context, identification of factors related to the occurrence of « early mortality » may help to introduce changes in preparative regimens in an attempt to increase the therapeutic ratio of the procedure.

In a first multivariate analysis, including 215 leukaemia patients, we reported on two predictive factors for early mortality (28): age and patient general condition (Karnofsky Index). Later, we analyzed a more homogeneous group of leukaemia patients treated with allogeneic BMT. The results on 174 subject is showed that, besides age and Karnofsky index which were already known, acute graft-*versus*-host disease (GVHD) was a predictive factor of prime importance.

In this report we present the results of a multivariate analysis on an even more specific group, including 76 acute lymphocytic leukaemia patients whose clinical data have been collected prospectively in order to

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identify factors related with early mortality among these patients.

PATIENTS AND METHODS

Seventy-six patients with a minimum follow-up of 6 months have been included. Their characteristics before BMT and type of marrow infused are shown in Table I.

TABLE I. Characteristics of patients before bone marrow transplantation (BMT).

Variable		n	%
sex	male	44	57.9
	female	32	42.1
Karnofsky index	< 90	10	13.2
	> 90	66	86.8
disease phase	complete remission	66	86.8
	incomplete remission	10	13.2
BMT type	allogeneic	56	73.7
	autologous	20	26.3
		Mean ± SEM	Range
age (yr)		19.4 ± 8.8	4-42
BMT delay (days)		615.8 ± 583.6	97-2733

Preparative Regimen

Patients were conditioned with 60 mg/kg cyclophosphamide for two consecutive days and with total body irradiation. Chemotherapy was given before or after irradiation in 32 and 44 patients respectively. Total body irradiation was administered with a Co-60 unit, following one of these schedules: 10 Gy single dose (29 patients); 6 × 200 cGy in 3 days (36 patients); or 4 × 300 cGy in 2 or 4 days (11 patients). Subjects were entered in one or other total body irradiation schedule, regardless of their haematological or clinical status.

Radiation dose was calculated for every patient at midplane, in the axis and at different points of interest: head, neck, mediastinum, lungs, abdomen, pelvis and knees. The point of minimum absorbed dose was taken as reference. Overdosed areas were shielded with appropriate thickness of copper sheets. Heterogeneity of dose distribution was accepted when less than 10%. In patients treated with a single fraction, lungs were completely shielded during the last part of the treatment, when absorbed lung dose reached 8 Gy. In fractionated schedules, lungs were partially shielded during the whole treatment. Characteristics of total body irradiation schedules are listed in Table II.

Transplant Procedure

Patients received allogeneic or autologous BMT. Allogeneic marrow was obtained from HLA-matched related donors and negative mixed-lymphocyte culture. Autologous bone marrow was collected during a complete remission phase, treated *ex vivo* with monoclonal antibodies in T and B leukaemias, and cryopreserved until infusion day (29). Details of our technique have been described elsewhere (18).

TABLE II. Characteristics of treatment schedules in three different facilites.

Characteristic	Treatment Schedule		
	1	2	3
cases (n)	29	27	20
patient position	lat. decubitus	sitting	lat. decubitus
total dose	10	12	12
fractions	1	6	4-6
dose/fraction	10	2	2-3
axis dose rate (midplane)	5.0 ± 1.3	5.5 ± 0.4	4.0 ± 0.2
lung dose	8	8.3 ± 0.4	8.2 ± 0.1
lung dose rate	6.6 ± 1.7	3.8 ± 0.2	2.6 ± 0.1
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 time with Cu sheets.

Supportive Care

The supportive care applied to our patients has been published elsewhere (30), and has been modified successively following current literature data. 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, irradiated haematic derivatives and antibiotics upon clinical evolution. From day 32 after BMT all patients received prophylaxis against *P. carinii* infection with cotrimoxazole (Septrin® 2 pills/12 hours).

Prophylaxis, Diagnosis and Treatment of Graft-*versus*-Host Disease

Patients treated with allogeneic BMT received prophylaxis against GVHD with methotrexate (MTX), 10-15 mg/m^2 for 11 doses (21 patients), cyclosporine-A alone (Cs-A) (2 patients), or both: MTX, 4 doses and Cs-A (33 patients). Cs-A was administered following Storb's schedule (31), always trying to maintain plasmatic levels between 200 and 500 µg/L (31), monitored with a specific monoclonal antibody.

Diagnosis and grading of GVHD was done according to the International Bone Marrow Transplant Registry (IBMTR) criteria (32). Patients who developed

acute GVHD received methylprednisolone (5-10 mg/kg/day).

End-points and Follow-up

During the first 120 days, causes of mortality were classified into four groups: infection, haemorrhage, idiopathic interstitial pneumonitis and other causes (cardiac, hepatic or renal failure, and hepatic veno-occlusive disease), following clinical or biological criteria, and post mortem studies. Patients with interstitial pneumonitis, in whom a pathogenic microorganism was isolated were classified as having an infectious processus, and are included in this group. Only when no pathogenic organism could be identified, interstitial pneumonitis was referred to as idiopathic. When more than one possible cause of mortality was present, only the most important was recorded. GVHD was never considered an ultimate cause of mortality.

Statistical Methods

Fifteen potential prognostic variables (Table III), classified as non-controllable, sometimes controllable, and controllable by the BMT team (33) were considered in the analysis.

Descriptive results are presented as means with standard deviation (SD) for continuous variables and as 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 (34); Fisher exact test was applied when necessary (35). The relative risks and probability of early mortality were estimated by means of an unconditional logistic regression model (36). Selection of variables that entered in the multivariate analysis was done on a stepwise procedure basis, including all factors significantly associated with early mortality in the univariate analysis, all the total body irradiation variables, and others considered of clinical interest. The probability of early mortality was calculated with the logistic model for the presence of different profiles of factors. Significative level was set to 0.05 and only two-sided contrasts were considered. The statistic analysis was done with the BMDP statistical package (37) at the Institut Municipal d'Investigació Médica of Barcelona.

TABLE III. Potential prognostic variables analyzed (see ref. 33).

Classification	Variable
uncontrollable	age (cut-point 20 years)
	sex (male/female)
sometimes controllable	Karnofsky Index (cut-point 90)
	disease's phase (CR *vs* non-CR)
	radiotherapy technique
	BMT Type*
	donor-recipient sex: (male-male, female-female, male-female, female-male)†
	GVHD grade (0 – I *vs* II-IV)†
controllable	diagnosis-BMT delay (cut-point at 550 days)
	TBI total dose (10 *vs* 12 Gy)
	fractionation (yes/non)
	number of fractions (one, four, or six)
	axis midplane dose-rate (cut-point at 5 cGy/min)
	radio-chemotherapy sequence (before or after TBI)
	GVHD prophylaxis (MTX, MTX-CsA, and CsA)†

* only entire group.
†only allogeneic BMT.
CR = complete remission; BMT = bone marrow transplantation; GVHD = graft-*versus*-host disease; TBI = total body irradiation; MTX = methotrexate; CsA = cyclosporine-A.

RESULTS

Twenty-three patients (30.3%) died from causes related with transplant procedure during the first 120 days after BMT. Recorded causes of mortality were: infection (56.5%), haemorrhage (13.0%), idiopathic interstitial pneumonitis (4.3%) and other causes (26.2%). In the allogeneic BMT group acute severe GVHD (grades II-IV) was present in 10/56 patients (17.9%).

Univariate Analysis

The first univariate analysis included all patients (76 subjects). The incidence of early mortality was significantly associated with age ($p = 0.0191$) and Karnofsky index ($p = 0.0445$). Allogeneic BMT type showed a trend towards worse prognosis when compared with autologous BMT type but without reaching statistical significance (Table IV).

The second univariate analysis included 56 patients treated with allogeneic BMT. As shown in Table V none of the analyzed variables reached statistical significance. Nevertheless, patients who developed acute severe GVHD tended to have a worse prognosis than those with grades 0 – I (recorded early mortality: 60 *vs* 30% respectively), as well as patients over 20 years *versus* younger ones (recorded early mortality: 50 *vs* 35% respectively).

Multivariate Analysis

In the multivariate analysis of the entire group, the logistic model selected two variables in the stepwise procedure. Age and Karnofsky index were significantly related with early mortality. The relative risk of mortality during the critical period, for patients over 20 years was 3.96 (95% confidence interval (CI): 1.33-11.76) while a Karnolsky index lower than 90% had a relative risk of 5.65 (95% CI: 1.29-25.0) (Table VI).

TABLE IV. Univariate analysis. Entire group of 76 bone marrow transplant recipients.

Variable		% Mortality	n	χ^2	p
age	< 20 years	20.8	48	5.48494	0.0191
	> 20	46.4	28		
sex	Males	27.0	44	0.44280	0.5058
	Females	34.4	32		
Karnofsky index	< 90	60.3	10		0.0445*
	90-100	25.8	66		
phase	CR	33.3	66		0.1476*
	non-CR	10.0	10		
BMT type	allo	35.1	56	2.99632	0.0835
	auto	15.0	20		
TBI technique	first	37.9	29	1.31110	0.5192
	second	25.9	27		
	third	25.0	20		
BMT delay (days)	< 550	32.0	50	0.20891	0.6476
	> 550	26.9	26		
total dose and fractionation	10 Gy†	37.9	29	1.30643	0.2530
	12 Gy§	25.5	47		
fractions	one	37.9	29	2.10481	0.3491
	four	36.4	11		
	six	22.2	36		
dose-rate (c Gy/min)	< 5	30.0	40	0.20891	0.6476
	> 5	30.6	36		
radio-chemotherapy sequence	TBI + CHT	22.7	44	2.81195	0.0936
	CHT + TBI	40.6	32		

* Fisher exact test; † Single dose; § Fractionated.
BMT = bone marrow transplantation; CR = complete remission; TBI = total body irradiation; CHT = chemotherapy.

TABLE V. Univariate analysis. Allogeneic group.

Variable		% Mortality	n	χ^2	p
age	< 20 years	25.4	32	3.73333	0.0533
	> 20	50.0	24		
sex	males	32.3	31	0.36129	0.5478
	females	40.0	25		
Karnofsky index	< 90	62.5	8		0.1164*
	90-100	31.3	48		
phase	CR	41.3	46		0.0671*
	non-CR	10.0	10		
TBI technique	first	37.9	29	0.50207	0.7780
	second	30.0	20		
	third	42.9	7		
BMT delay (days)	< 550	39.5	38	0.72775	0.3936
	> 550	27.8	18		
total dose and fractionation	10 Gy†	37.9	29	0.12874	0.7197
	12 Gy§	33.3	27		
fractions	one	37.9	29	1.76207	0.4144
	four	66.7	3		
	six	29.2	24		
dose-rate (cGy/min)	< 5	34.6	26	0.02553	0.8733
	> 5	36.7	30		
radio-chemotherapy sequence	TBI + CHT	29.2	24	0.78426	0.3758
	CHT + TBI	40.6	32		
donor-recipient sex	male-male	35.7	14	3.87247	0.2756
	female-male	29.4	17		
	male-female	58.3	12		
	female-female	23.1	13		
GVHD prophylaxis	MTX	38.1	21	4.07273	0.1305
	MTX-CsA	30.3	33		
	CsA	100	2		
GVHD grade	0-I	30.4	46		0.1000*
	II-IV	60.0	10		

* Fisher exact text; † Single doese, § Fractionated.
BMT = bone marrow transplantation; CR = complete remission; TBI = total body irradiation; CHT = chemotherapy.

TABLE VI. Multivariate analysis. Entire group.

Factor	Relative risk	Confidence interval	Probability of death
> 20 years	3.96	1.33 - 11.76	42 %
Karnofsky index < 90 %	5.65	1.29 - 25.0	51 %
> 20 years and Karnofsky index < 90 %	22.37	20.34 - 24.40	81 %

The probability of early mortality was 42% for patients over 20 years when no other risk factor was present and 51% when the Karnofsky index was lower than 90% and no other risk factor was present. The relative risk and probability of early mortality for patients with association of the both factors is shown in Table VII. The worst prognosis corresponded to a patient over 20 years in poor general condition (Karnofsky index < 90%), who had an 81% probability of early mortality and a relative risk of 22.37 (95% CI: 20.34-24.40).

TABLE VII. Multivariate analysis. Allogeneic group.

Factor	Relative risk	Confidence interval	Probability of death
> 20 years	5.17	1.30 - 20.60	24%
Karnofsky index < 90%	10.53	1.55 - 71.43	39%
severe GVHD	8.04	1.43 - 45.07	33%
dose-rate > 5 cGy/m	3.42	0.79 - 14.83	17%*
> 20 years and Karnofsky index < 90%	54.44	51.76 - 57.12	77%
> 20 years and severe GVHD	41.56	39.13 - 43.99	72%
Karnofsky index < 90% and severe GVHD	84.66	81.68 - 87.64	84%
> 20 years and Karnofsky index < 90% and severe GVHD	437.70	434.03 - 441.37	99%

* Not significant, but contributes in mathematical model.

The best prognostic profile corresponded to a patient under 20 years in good general condition (Karnofsky index 90), with only a 16% probability of early mortality, being the relative risk reference group (RR = 1).

In the allogeneic BMT subgroup (56 patients), the stepwise procedure of the logistic model only selected the haematological status variable. Paradoxically, advanced disease protected patients from early mortality, with a relative risk of 0.158. When excluding this variable, age Karnofsky index and acute GVHD appeared as variables significantly related with early mortality. Furthermore, total body irradiation dose-rate improved the model at a significance level of 0.08 which is acceptable for our tentative purposes. However, the confidence interval of its relative risk was not significant (Table VII). The relative risk for patients over 20 years was 5.17 (95% CI: 1.30-20.60). Subjects in poor general condition (Karnofsky index < 90) had a relative risk of 10.53 (95% CI: 1.55-71.43). Acute severe GVHD (grades II-IV) accounted for a relative risk of 8.04 (95% CI: 1.43-45.07). Dose-rate is the only radiotherapy variable that contributed to the model: patients treated with dose-rate over 5 cGy-min had 3.42 times more risk (95% CI: 0.79-14.83) than patients treated with dose-rates lower than 5 cGy/min.

The probability of early mortality for each variable when no other risk factor was present, was 24% for patients over 20 years, 39% for patients with a Karnofsky index lower than 90, 33% for patients who developed acute severe GVHD and 17% for patients treated with dose rates higher than 5 cGy/min. In the allogeneic group (Table VII), the worst profile corresponded to patients over 20 years, with a Karnosfsky index lower than 90 and who developed acute GVHD (grade II – IV): these had a 99% probability of early mortality. In contrast patients under 20 years, in good general condition and without acute GVHD only had a 6% probability of dying during this critical period (120 days).

DISCUSSION

Bone marrow transplant teams are aware that this therapeutic approach for leukaemia patients yields decreasing but still high mortality (25). It is clear now, that overall survival depends on many factors, most of which are interrelated. Many investigators have analyzed the causes of mortality and the prognostic factors associated with the more relevant complications of the procedure, *i.e.* relapse (38, 39), interstitial pneumonitis (33, 40, 41), hepatic veno-occlusive disease (42, 43) graft rejection (44), or GVHD (45). All this reports and many others include the conditioning regimen in their analysis and most of them find a relationship between total body irradiation and acute, often fatal, complications. When modifications in the preparative regimen are introduced to improve one of these endpoints, their interrelations emerge. An increase in total body irradiation dose to decrease relapse (46) is correlated with higher regimen-related mortality and incidence and severity of GVHD (47, 48); dose fractioning in an attempt to decrease incidence of interstitial pneumonitis, or the administration of T-depleted grafts to decrease GVHD, are associated with an increase in relapse rates (39, 49, 50). Thus, after the introduction of fractionated total body irradiation many reports favour this therapeutic approach. Later, results did not demonstrate any clear advantage (51). Nevertheless, the difficulty lies in comparing non-randomized series of patients with different total body irradiation schedules (52, 53). The mechanism of action and the real role of radiation therapy in the preparative regimen is being discussed (54).

We considered early mortality due to treatment procedure as a valuable parameter of acute severe toxicity. Its relationship with the preparative regimen has been evaluated in other series of BMT patients (3, 8, 18, 20, 24, 55). Mortality related to procedure is high and predominates in the first 3-4 months following marrow infusion.

In the multivariate analysis of the entire group, age and Karnofsky index remain in the significance level. In the allogeneic group, the first multivariate analysis selects disease phase as statistically significant. Paradoxically, advanced disease seems to be a protective factor. This is an erroneous interpretation. Patients in advanced phases do not die because of regimen-related toxicity. They die of disease progression. In a second analysis excluding disease phase, all variables that showed a trend in the univariate analysis reached the significance level. Furthermore, dose-rate contributed to the mathematical logistic model but without attaining statistical significance.

In both series (entire and allogeneic group), patients over 20 years had a higher risk of early mortality (Tables VI and VII). This increased risk has already been depicted for allogeneic BMT by Gratwhol *et al.* (56) in leukaemia patients, and by Thomas (57), and Tallman (5) in non-lymphocytic leukaemia patients in first complete remission. In their studies these authors demonstrate that younger patients tolerate the preparative regimen better than older ones. The importance of this factor was also significant in previous analysis (28).

Karnofsky index is another important variable, attaining statistical significance in both analyzed groups. Patients with a Karnofsky index lower than 90 have an increased risk of early mortality (Tables VI and VII). The importance of this factor in BMT outcome has been reported by Bearman *et al.* (3) in lymphoma patients. Freedman *et al.* (58) share the same opinion when attributing their low regimen-related mortality rate (4%) to the excellent performance status of patients. The importance of KI was also significant in previous analysis (28).

In the allogeneic group, another significant prognostic factor was acute GVHD. Patients developing this complication in grades II-IV had a 33% probability of early mortality with a relative risk eight times higher than patients with grades 0 – 1. Incidence and severity of GVHD has been widely recognized as closely influencing BMT outcome in adults (43, 59, 60), and children (61). In a similar series of patients, analyzed in the Johns Hopkins Hospital (62), which included 78 acute lymphocytic leukaemia patients treated with allogeneic BMT, this complication was associated with most cases of death. Many efforts are currently being invested in the prevention and treatment of this complication (31, 49, 50). This opinion is supported by Thomas (63): « one area of progress includes the prevention and control of graft-*versus*-host disease ».

The last variable with statistical importance in our study was dose-rate. In the allogeneic group, patients treated with dose-rate lower than 5 cGy/min had a better prognosis than those irradiated with higher rates. This variable has been frequently related with some severe complications, specially interstitial pneumonitis. In their analysis, Weiner (33) and The Japan BMT Group (64), demonstrate a close relationship between dose-rate and mortality due to this complication.

CONCLUSION

Briefly, our analysis demonstrates once again that the most important variables related with early mortality are: age, general condition, and GVHD. Unfortunately, patient age is a non-controllable factor (33), and GVHD and Karnofsky index can only be partially modified by increasing prophylaxis and treatment of GVHD, and by entering patients in BMT programs when in good general condition. In contrast, the easily controllable variables of total body irradiation schedules, that is total dose and fractioning, were not significantly related with early mortality. Within the limits of total dose, fractioning and dose rate included in our analysis, only the last showed a trend towards increased early mortality in the allogeneic subgroup of bone marrow transplant patients.

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