Autologous Transplantation in 1st Cr Aml Patients with Purged or Unpurged Bone Marrow: Good Clinical Results in Favorable Cytogenetic Group and in those Infused with a Low Number of Marrow Cells

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Abstract

In a single institution, 31 patients affected with Acute Myeloid Leukaemia (AML) in 1st Complete Remission (CR) received autologous bone marrow transplantation (ABMT). Mafosfamide was employed in a non-randomized fashion to purge marrows, in 15 cases bone marrow cells were purged, while in 16 they were left unpurged. Dose of infused Total Nucleated Cells (TNC) was an important factor for myeloid engraftment (P=0.02). LFS was 58% in purged and 40% in unpurged groups (P=0.26). Patients having a good prognosis cariotype had a LFS of 100% while the group of all other patients had a LFS of 37.5%. Patients receiving a dose of TNC below to median had a LFS of 65% and those receiving a dose of TNC>median had a LFS of 28% (P=0.017). Purging significantly improved LFS in patients "not harbouring good cytogenetic abnormalities" (53% LFS in purged group versus 18% in unpurged group, P=0.05). In conclusion, ABMT is associated with excellent results in "good prognosis cytogenetic". Purging may improve results in patients belonging to "intermediate cytogenetic group". A high number of infused TNC produces a fast myeloid engraftment but a poor LFS.

Keywords: Mafosfamide; Acute myeloid leukemia; Autologous bone marrow transplantation

Introduction

In adult patients affected by Acute Myeloid Leukaemia (AML), Autologous Bone Marrow Transplantation (ABMT) offers a clinical advantage over conventional chemotherapy in terms of Disease Free Survival (DFS), although relapse still remains a frequent cause of failure [1-3]. Pharmacological *in vitro* purging of bone marrow inoculum using mafosfamide or 4-hydroperoxycyclophosphamide (4HC) could reduce relapse risk [4,5], hence this technique has been used extensively by some groups over the last decade [6-8]. Comparative data on the efficacy of *in vitro* purging in AML obtained in multi-centre retrospective studies [9,10] result in beneficial effect of purging. No randomized study comparing purged and unpurged ABMT is available. A randomized study comparing ABMT using maphosphamide purged marrow versus chemotherapy failed to demonstrate advantages in purged ABMT arm in term of OS or DFS [11]. On the other hand, in retrospective multicenter studies, purging resulted in a reduced rate of treatment failures [9,10] with respect to unpurged ABMT. Furthermore, direct comparisons between purged and unpurged marrow in AML patients, obtained in a single institution, are scarce [12,13]. We report clinical results obtained in our institution using ABMT unpurged or mafosfamide-purged ABMT in the treatment of AML.

Patients and Methods

Thirty-one patients affected by AML in 1st Complete Remission (CR) were treated with ABMT in our Institution from October 1994 to July 2002. Patient selection criteria for ABMT eligibility were: a diagnosis of AML other than type M3, 1st CR; age ≤ 65 years; normal liver, heart and pulmonary functions. Chemotherapy treatment received by patients before bone marrow harvest and ABMT was administered according to GIMEMA AML 8, GIMEMA AML 10 and GIMEMA AML 12 trials. Once in complete remission, all patients received a chemotherapy consolidation course and bone marrow was harvested 6-7 weeks later. Patient characteristics are summarised in Table 1. Although inclusion criteria excluded FAB M3, one patient initially classified as FAB M2 was observed to be affected by AML M3 after transplant, due to the detection of PML/rar alpha transcript in BM cells.

Bone marrow harvest evaluation, processing and purging

Bone marrow was harvested by multiple bilateral aspirations from iliac bone using standard techniques with 10% ACD as anticoagulant [5]. In all cases, bone marrow cells underwent volume reduction and depletion of red cells by means of a Cell Separator (CS3000 Plus – Baxter) before cryopreservation, as reported elsewhere [14]. In 15/31 cases, Bone Marrow cells were treated *in vitro* with mafosfamide. Purging was offered to patients with a bone marrow harvest containing at least 2×10^8/kg TNC. Use of purging was not randomised and it was limited to some cases due to an irregular availability of mafosfamide. In the case of marrow purging, 15-25% of harvested bone marrow was cryopreserved and unpurged to provide an unpurged back-up inoculum.

Mafosfamide was obtained from ASTA-Medica (Frankfurt, Germany). It was freshly prepared and employed at a final concentration of 50 mcg/ml at 37°C for 30 min in TC199 media (GIBCO); CD34+ cells were determined by cytofluorometry, and CFU-GM by methylcellulose culture stimulated by GM-CSF as already reported [15].

	ALL CASES (31 pts)	UNPURGED GROUP (15 pts)	PURGED GROUP (16 pts)	DIFFERENCE BETWEEN PURGED AND UNPURGED
AGE median (range)	42.5 (13-63)	42.0 (13-63)	42.8 (28-56)	P>0.9§
SEX Male: / Female: n (% male / % female)	M: 13 / F: 18 (42/58)	M: 9 / F: 7 (56/43)	M: 4 / F: 11 (26/73)	P=0.09*
WBC x 10^9/l at diagnosis median (range)	36.7 (1.7-237.0)	22.8 (1.7-213.0)	71.5 (2.9-237.0)	P=0.1§
FAB % (n)	M1: 22.5 (7) M2: 22.5 (7) M3: 3.0 (1) M4: 35.5 (11) M5: 16.5 (5)	M1: 31.2 (5) M2: 31.2 (5) M3: 6.2 (1) M4: 18.7 (3) M5: 12.5 (2)	M1: 13.3 (2) M2: 13.3 (2) M3: 0.0 (0) M4: 53.3 (8) M5: 20.0 (3)	P=0.19*
INTERVAL DIAGNOSIS/ TRANSPLANT (Days) median (range)	214. (101.-392.)	212. (101. -348.)	216. (133.-392.)	P=0.6§
GOOD PROGNOSIS CYTOGENETIC	7/20 (35,0 %)	5/11 (45,4%)	2/9 (22,2%)	P=0.27*

= Chi Square; § = Mann-Whitney

Table 1: Characteristics of Patients and Comparison between Unpurged and Purged Groups.

	All cases	Unpurged Group	Purged Group	Difference in purged and unpurged (Mann-Whitney test)
Harvested TNC x 10^8/kg median (range)	3,9 (1.6-9.4)	3,3 (1.6-7.5)	4,3 (2.0-9.4)	P=0,3
Harvested CD34+ x 10^6/kg median (range)	3,8 (0.3-19.0)	2,3 (0.6-8.0)	4,1 (0.3-19.1)	P=0,3
Harvested CFU-GM x 10^5/kg median (range)	0.94 0.4-11.2	0,99 0.4-11.2	0,92 0.5-5.5	P=0,5
Infused TNC x 10^8/kg median (range)	1,0 (0.5-2.5)	1,1 (0.58-1.9)	0,9 (0.56-2.5)	P=0,08
Infused CD34+ x 10^6/kg median (range)	1,79 (0.4-8.5)	1,2 0.4-3.7	2,4 0.4-8.5	P=0,4
Infused CFU-GM x 10^5/kg median (range)	0,48 (0.0 – 4.75)	0,79 (0.2-4.7)	0,04 (0.0-0.8)	P=0,001

Table 2: Characteristics of Harvested and Infused Bone Marrow Cells and Comparison Between Unpurged and Purged Groups.

Eradication regimen and supportive therapy

High dose chemotherapy administered before autologous BMT was based on high dose Busulphan and Cyclophosphamide (BU-CY), [6]. G-CSF was administered to 7/31 patients, in 4/15 patients of the purged group and in 3/16 of the unpurged group.

Cytogenetic analysis

Patients were divided in 3 risk groups: favourable, intermediate and adverse. The favourable risk group included patients with t(8;21) (q22;q22) without a del(9q) and inv(16) (p13q22)/t(16;16)(p13;q22). The intermediate risk group included patients with +8,-Y,+6,del/12p, normal cariotype and in addition to all cytogenetic aberration of unknown prognostic significance because of their low frequency in AML. The adverse risk group was defined by the presence of one or more of: –5/del(5q), -7/del(7q), inv(3q), abn 11q, 20q,21q, del(9q), t(6;9), t(9;22) abn 17p and complex cariotype.

Data studied and statistical analysis

Neutrophil (N) engraftment was defined as the first day in which N count reached at least the value of $0.5×10^9$/l, PLT engraftment was defined as the first day of three consecutive days in which unsupported PLT count reached the value of $20.0×10^9$/l. Differences between groups were assessed, for non-normally distributed continuous variables, using Mann-Whitney test, and for categorical variables using Chi test. Correlation was calculated using Spearman rank test. Since all patients were transplanted in 1st CR, Leukaemia Free Survival (LFS) was computed in months from transplantation to relapse or death from any cause. Kaplan-Meier method was also used to study time of engraftment and LFS. Log rank test (Mantel-Cox) was used to compare engraftment and LFS in different groups. A statistic software (Statview CA, USA) was used to record data and perform all statistical analyses.

Results

Characteristics of harvested and infused bone marrow cells

Features of marrow Total Nucleated Cells (TNC) "harvested" and "infused" are reported in Table 2. Median recovery of TNC, after processing to deplete RBC, was 34% (range 12-69%). No correlation between harvested TNC and infused TNC was found (Rho=0.127; P=0.5), whereas there was a significant correlation between infused TNC and post-processing recovery (Rho=0.418; P=0.03). Due to the

cytotoxic effect of maphosphamide, median number of infused CFU-GM in "purged" group was significantly lower than in unpurged group (Table 2), (P=0.001). In "Purged" and "unpurged" groups, all other features of "infused" bone marrow cells were comparable (Table 2).

Engraftment

All patients reached a Neutrophil count above $0.5 \times 10^9/l$ in a median of 25 days (range 8-49). Time for Neutrophil engraftment
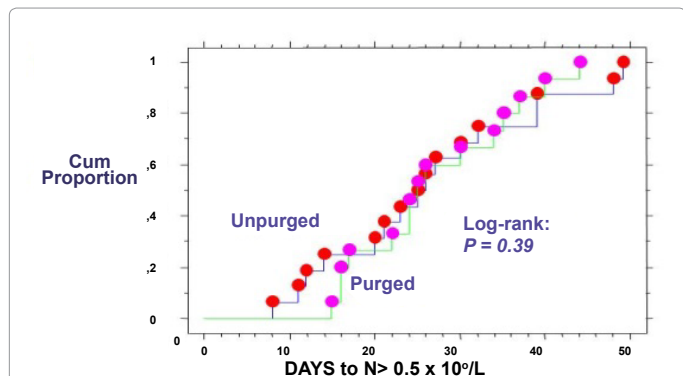

Figure 1: Neutrophil engraftment after purged and unpurged marrow. Time to achieve 0.5 x 109 Neutrophil/l after ABMT is not different in group receiving purged marrow in respect to patients receiving unpurged marrow (p=0.39).
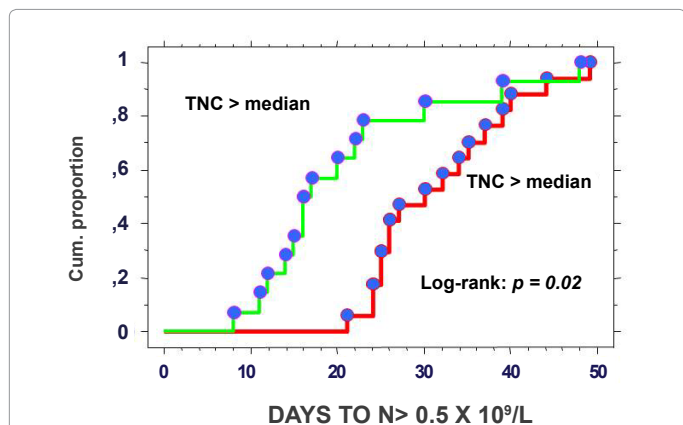

Figure 2: Effect of Infused TNC on time for Neutrophil engraftment. Time to achieve 0.5 x 10⁹ Neutrophil/l is significantly shorter in group receiving "Infused TNC > median" in respect to group receiving "Infused TNC < median" (p=0.02).

was not different in purged group compared to unpurged patients; 24 days versus 25.5 days (log rank P=0.39) (Figure 1). A statistically significant correlation was found between infused TNC/Kg and day to $N>0.5 \times 10^9/l$ (P=0.002), (Table 3). Furthermore, patients receiving a TNC/Kg dose<median had an engraftment time for N longer than the group receiving a TNC/Kg dose>median; 30 days vs. 16 days, (P=0.02) (Figure 2). There was no significant correlation between time for N. engraftment and either infused CD34+ (P=0.76), infused CFU-GM (P=0.5) or harvested TNC (P=0.51).

All patients reached a PLT count of $20.0 \times 10^9/l$ and median time for PLT engraftment was 60 days (range 17-270), which was significantly longer in purged transplants than unpurged ones; 85 days vs. 59 days (log rank P=0.041). No statistical correlation was found between times for $PLT>20.0 \times 10^9/l$ and number of infused CD34+ (P=0.75), infused TNC (P=0.7) and infused CFU-GM (P=0.74).

Toxicity

No cases of TRM were observed. Purged and unpurged groups did not show significant differences in the incidence of fever (80% vs. 75%, P=0.7). No difference was observed between purged and unpurged groups with regard to the requirement of RBC transfusions (P=0.8) and PLT-aphaeresis transfusions (P=0.4).

Relapse and lfs

In the patients taken as a whole, 16/31 patients relapsed. All relapses were haematological and were diagnosed between 4 and 14 months from transplantation. 15 patients were still in complete remission when mean follow-up for patients was still within response time of 40 months (range 9-96). The Kaplan-Meier estimate of LFS for the entire group of patients is 50.5 % (Figure 3). LFS was 58% in purged group and 40% in unpurged group (log rank: P=0.26) (Figure 4).
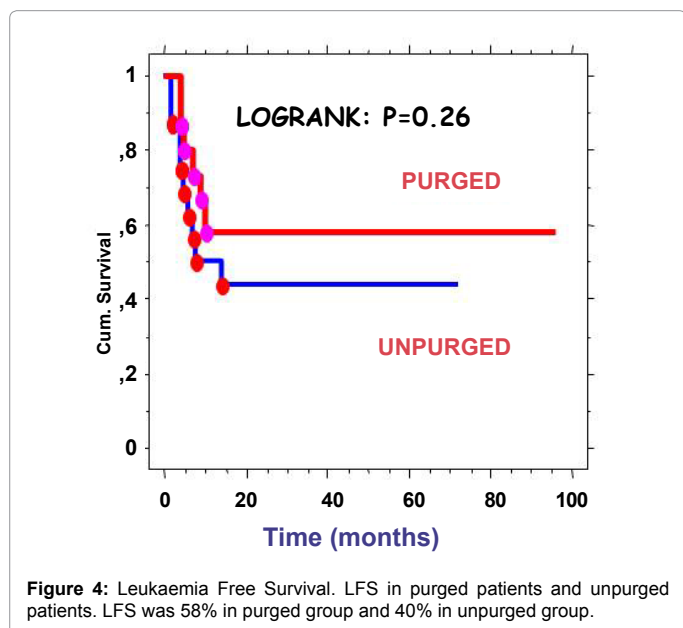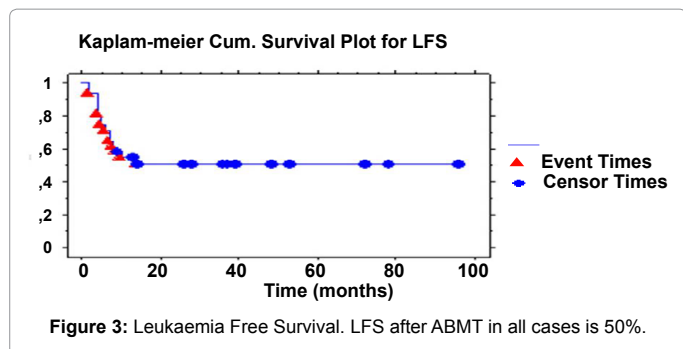
Importance of Infused Tnc for Lfs

Patients receiving an "Infused TNC<median" (median=1.0×10^8/kg) had a LFS of 65% while those with an "Infused TNC>median" showed a LFS of 28% (P=0.017) (Figure 5). These two groups did not differ in age (P=0.8), diagnosis-transplant interval (P=0.11), number of harvested TNC (P=0.54), FAB M5 frequency (P=0.08), use of purging (P=0.14) and percentage of patients requiring more than 1 cycle to reach CR (P=0.3). Recovery post processing of TNC in the group who received an infused TNC< median was significantly lower than those who received infused TNC>median; 28% vs. 46% (P=0.004).

	INFUSED TNC	HARVESTED TNC	INFUSED CD34+	INFUSED CFU-GM
ALL CASES	Spearman: P=0.002 Log rank: P=0.02 Regression analysis: Exp (coef): 2.964 95% lower CI: 1.180 95% upper CI: 7.448 P=0.02	Spearman: P=0.51 Log rank: P=0.17	Spearman: P=0.76 Log rank: P=0.35	Spearman: P=0.5 Log rank: P=0.7
UNPURGED GROUP	Spearman: P=0.18 Logrank: P=0.2	Not evaluated	Not evaluated	Not evaluated
PURGED GROUP	Spearman: P=0.001 Logrank: P=0.0001	Not evaluated	Not evaluated	Not evaluated

Relationship between Time for N > 0.5 x 10⁹/l and the considered variable was studied using: Spearman Rank correlation test; Log rank test after categorisation of the considered variable in two groups (< median and > median); Univariate regression analysis was also used to allow for evaluating the Infused TNC as a continuous variable in a time dependent analysis.

Table 3: Importance For Time For N > 0.5 X 10⁹/L of The Following Variables: Infused Tnc, Harvested Tnc, Infused Cd34+ and Infused Cfu-Gm

Figure 3: Leukaemia Free Survival. LFS after ABMT in all cases is 50%.

Figure 4: Leukaemia Free Survival. LFS in purged patients and unpurged patients. LFS was 58% in purged group and 40% in unpurged group.

As opposed to what was found for an "infused TNC", patients with a number of "harvested TNC>median" (median=3.75×10^8/Kg) had a LFS not different in respect to patients with a TNC<median at harvest, 63% vs. 40% (P=0.20).

Cytogenetic defined groups and lfs

A favourable cytogenetic abnormality was found at diagnosis in 35% of patients in which cytogenetic was available (7/20 cases), this group had a LFS of 100% (Figure 6).

Group of patients with intermediate prognosis cytogenetic abnormalities or normal cytogenetic represented 60% of patients in which cytogenetic was available, in this group LFS was 50% (Figure 6).
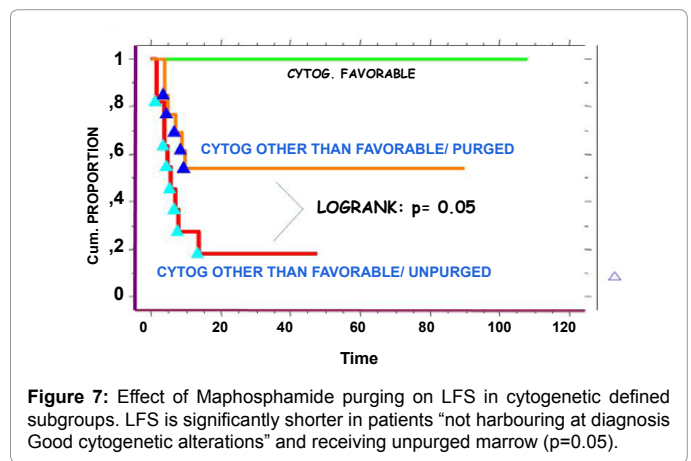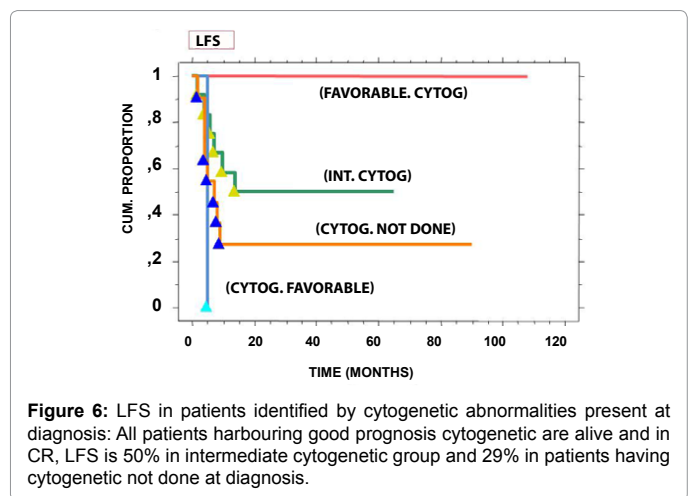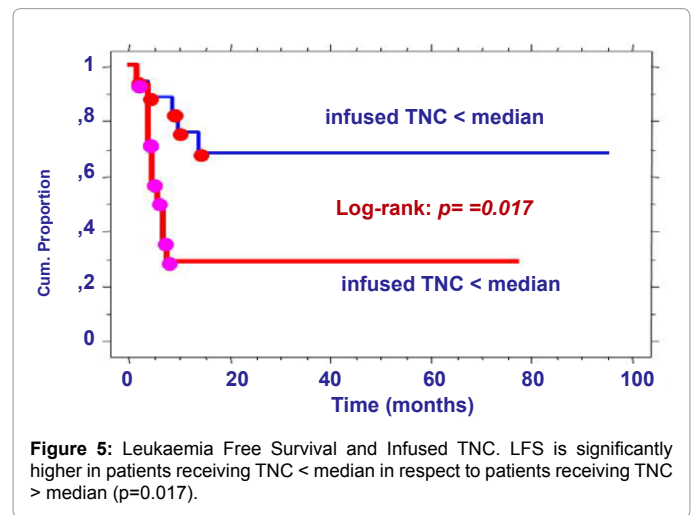
Bad prognosis cytogenetic was present in only one patient while cariotype at diagnosis was not available in 35.4% of patients and this subgroup had a LFS of 27% (Figure 6).

Distribution of cytogenetic subgroups was different, although not significantly, in the two strata of patients that received a TNC>median and TNC<median. In the group that received Infused TNC<median, good cytogenetic abnormalities were present at diagnosis in 46.1% (6/13) while in the group that received infused TNC>median, good prognosis cytogenetic patients were 14.2 % (1/7) (Chi square p=0.15).

Effect of purging (Figure 7) was studied in the strata of patients

"not having at diagnosis good prognosis cytogenetic abnormalities" or in which "cytogenetic was not done".

In this strata, composed of large part of patients having intermediate cytogenetic, LFS was 53% in purged group (n=13) versus a LFS of 18% in unpurged marrow group (n=11), (P=0.05). All patients with good prognosis cytogenetic (n=7) were in continuous complete remission either after purged or unpurged marrow.

Figure 5: Leukaemia Free Survival and Infused TNC. LFS is significantly higher in patients receiving TNC < median in respect to patients receiving TNC > median (p=0.017).

Figure 6: LFS in patients identified by cytogenetic abnormalities present at diagnosis: All patients harbouring good prognosis cytogenetic are alive and in CR, LFS is 50% in intermediate cytogenetic group and 29% in patients having cytogenetic not done at diagnosis.

Figure 7: Effect of Maphosphamide purging on LFS in cytogenetic defined subgroups. LFS is significantly shorter in patients "not harbouring at diagnosis Good cytogenetic alterations" and receiving unpurged marrow (p=0.05).

Discussion

After unpurged bone marrow transplantation in AML patients, myeloid and platelet engraftment were delayed [9,10,16-18]. Such lengthy marrow aplasia is a clinically significant relevant problem, resulting in high transfusion requirements and prolonged hospitalisation. It is also believed to contribute to a discrete rate of TRM. Using purged marrow, myeloid engraftment time may be further delayed, and a period of 28-45 days for $N>0.5\times10^9/l$ was reported in this context [7-10,16,19]. However comparison between purged and unpurged marrow obtained in a controlled study of AML patients was not available, while data using purged and unpurged ABMT generated in a single institution were scarce [12,13]. In our study, we observed that purging can prolong the period of PLT engraftment but not that of myeloid engraftment. Although the low number of patients limits the statistical power of our study, nevertheless no difference in myeloid engraftment time was also reported when comparing purged and unpurged marrow in acute leukaemia patients in two recently published large multi-centre studies [9,20]. The absence, of any evidence of a prolonged myeloid aplasia in purged bone marrow transplantation together with good clinical tolerability may further encourage the study of purging in acute leukaemia patients as a means of decreasing the relapse rate.

In leukaemia patients undergoing syngeneic Bone Marrow Transplantation, a high marrow cell dose has been shown to favourably affect Transplant Related Mortality (TRM) and relapse rate and hence increased the probability of this procedure being successful [21]. After autologous BMT in patients affected with AML, a low dose of Total Nucleated Cells (TNC) predict a high Transplant Related Mortality (TRM) [16,22], while a high CFU-GM content has been associated with improved Leukaemia Free Survival (LFS) [23]. Various authors have studied the role of infused marrow cell dose on engraftment after ABMT for AML. Demirer et al. [16] reported that dose of harvested TNC is important for engraftment as well as for TRM. Abdallah et al. found in patients undergoing purged ABMT [19] a significant correlation between infused TNC dose and time of engraftment. Other authors after unpurged transplant [18,24], did not found that marrow cell dose was an important factor for engraftment. These discrepancies regarding the role of marrow cell dose on engraftment could be explained by differences in status of the disease at transplant, the amount and type of chemotherapy previously administered [25], the techniques of bone marrow processing, and the use of TBI as eradication treatment [18] with respect to purging. We found that time of myeloid engraftment is correlated to the number of TNC obtained after processing and infused.

Besides these effects on the speed of engraftment, in our study, we observed that TNC dose is important for LFS. In fact the group of patients receiving a TNC dose below median had a better LFS. The more obvious explanation is that TNC dose and neoplastic contamination of inoculum are proportional, and thus an increase in TNC dose could be associated with a higher probability of neoplastic contamination and, in turn, will lower LFS. Conversely, a reduced TNC dose implies a reduction in neoplastic contamination of bone marrow inoculum and thus a reduction in relapse risk.

An alternative possible explanation for the high LFS of patients having a low infused TNC is that these patients have a higher sensitivity to chemotherapy both in leukaemia cells and in normal myeloid precursors. In fact, high sensitivity to chemotherapy could lead to a lower minimal residual disease and therefore to a better LFS while higher sensitivity of normal non-leukemic marrow cells lead to higher percentage of differentiated cells in marrow at CR, and hence to a lower

recovery after cell processing and also a low number of "infused TNC". An association between chemo-resistance of normal non-leukemic marrow cells in AML and of leukemic cells persisting in complete remission could, indeed, exist and this may be based on an "activated functional status of microenvironment cells" in some patients. This hypothesis has been put forward recently by our group [26] on the basis of experimental work in marrow cell of AML patients in complete remission. In these experiments, we found that a chemo-sensitivity of normal non-leukemic cells in complete remission is heterogeneous and that this heterogeneity correlated with LFS [27].

In this regard, it should be recalled that there has been a recent report on the existence of a group of AML patients having a low ability of CD34+ cells mobilization, low level of minimal residual disease in P.B., long length of aplasia after chemotherapy and good DFS [28,29]. The bone marrow features in this group of patients were not described. The group of patients with a low infused TNC and a good prognosis after ABMT may indeed belong to this recently identified group of AML patients.

In our study, clinical usefulness of purging is less evident in the stratum of "good risk cytogenetic"; these patients had excellent clinical results using unpurged marrow so that their low relapse risk was not further be lowered by purging. Excellent results, with OS ranging from 70% to 80% have been, indeed, reported in AML belonging to "good cytogenetic group" using unpurged ASCT [30-35]. However, after purging, we observed in the group of patients "not harbouring good prognosis cytogenetic abnormalities", a better LFS was present, compared to the group that received unpurged marrow.

Conclusion

It was observed that ABMT is associated with excellent results in "good prognosis cytogenetic". Purging may improve prognosis in patients belonging to "intermediate cytogenetic group". The number of "infused" TNC determines the rate of myeloid engraftment and also the rate of LFS i.e. the higher the number, the faster the engraftment but the poorer the LFS.

References

1. Zittoun RA, Mandelli F, Willemze R, de Witte T, Labar B, et al. (1995) Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Malignedell'Adulto (GIMEMA) Leukemia Cooperative Groups. N Engl J Med 332: 217-223.

2. Burnett AK, Goldstone AH, Stevens RM, Hann IM, Rees JK, et al. (1998) Randomised comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukaemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukaemia Working Parties. Lancet 351: 700-708.

3. Slovak ML, Kopecky KJ, Cassileth PA, Harrington DH, Theil KS, et al. (2000) Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. Blood 96: 4075-4083.

4. Yeager AM, Kaizer H, Santos GW, Saral R, Colvin OM, et al. (1986) Autologous bone marrow transplantation in patients with acute nonlymphocytic leukemia, using ex vivo marrow treatment with 4-hydroperoxycyclophosphamide. N Engl J Med 315: 141-147.

5. Gorin NC, Douay L, Laporte JP, Lopez M, Mary JY, et al. (1986) Autologous bone marrow transplantation using marrow incubated with Asta Z 7557 in adult acute leukemia. Blood 67: 1367-1376.

6. Laporte JP, Douay L, Lopez M, Labopin M, Jouet JP, et al. (1994) One hundred twenty-five adult patients with primary acute leukemia autografted with marrow purged by mafosfamide: a 10-year single institution experience. Blood 84: 3810-3818.

7. Linker CA, Ries CA, Damon LE, Rugo HS, Wolf JL (1998) Autologous bone marrow transplantation for acute myeloid leukemia using 4-hydroperoxycyclophosphamide-purged bone marrow and the busulfan/etoposide preparative regimen: a follow-up report. Bone Marrow Transplant 22: 865-872.

8. Smith BD, Jones RJ, Lee SM, Piantadosi S, Vala MS, et al. (2002) Autologous bone marrow transplantation with 4-hydroperoxycyclophosphamide purging for acute myeloid leukaemia beyond first remission: a 10-year experience. Br J Haematol 117: 907-913.

9. Reiffers J, Labopin M, Sanz M, Korbling M, Blaise D, et al. (2000) Autologous blood cell vs marrow transplantation for acute myeloid leukemia in complete remission: an EBMT retrospective analysis. Bone Marrow Transplant 25: 1115-1119.

10. Miller CB, Rowlings PA, Zhang MJ, Jones RJ, Piantadosi S, et al. (2001) The effect of graft purging with 4-hydroperoxycyclophosphamide in autologous bone marrow transplantation for acute myelogenous leukemia. ExpHematol 29: 1336-1346.

11. Woods WG, Neudorf S, Gold S, Sanders J, Buckley JD, et al. (2001) A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission. Blood 97: 56-62.

12. Tomás JF, Gómez-García de Soria V, Pinilla I, Lamana M, Figuera A, et al. (1997) [Bone marrow autotransplantation in acute myeloblastic leukemia in its first complete remission. The clinical results in 41 patients]. Med Clin (Barc) 108: 201-206.

13. Chao NJ, Stein AS, Long GD, Negrin RS, Amylon MD, et al. (1993) Busulfan/etoposide--initial experience with a new preparatory regimen for autologous bone marrow transplantation in patients with acute nonlymphoblastic leukemia. Blood 81: 319-323.

14. Schanz U, Gmür J (1992) Rapid and automated processing of bone marrow grafts without Ficoll density gradient for transplantation of cryopreserved autologous or ABO-incompatible allogeneic bone marrow. Bone Marrow Transplant 10: 507-513.

15. Milone G, Leotta S, Indelicato F, Mercurio S, Moschetti G, et al. (2003) G-CSF alone vs cyclophosphamide plus G-CSF in PBPC mobilization of patients with lymphoma: results depend on degree of previous pretreatment. Bone Marrow Transplant 31: 747-754.

16. Demirer T, Gooley T, Buckner CD, Petersen FB, Lilleby K, et al. (1995) Influence of total nucleated cell dose from marrow harvests on outcome in patients with acute myelogenous leukemia undergoing autologous transplantation. Bone Marrow Transplant 15: 907-913.

17. Chopra R, Goldstone AH, McMillan AK, Powles R, Smith AG, et al. (1991) Successful treatment of acute myeloid leukaemia beyond first remission with autologous bone marrow transplantation using busulfan/cyclophosphamide and unpurged marrow: the British autograft group experience. J Clin Oncol 9: 1840-1847.

18. Pendry K, Alcorn MJ, Burnett AK (1993) Factors influencing haematological recovery in 53 patients with acute myeloid leukaemia in first remission after autologous bone marrow transplantation. Br J Haematol 83: 45-52.

19. Abdallah A, Egerer G, Weber-Nordt RM, Korbling M, Haas R, et al. (2002) Long-term outcome in acute myelogenous leukemia autografted with mafosfamide-purged marrow in a single institution: adverse events and incidence of secondary myelodysplasia. Bone Marrow Transplant 30: 15-22.

20. Locatelli F, Labopin M, Ortega J, Meloni G, Dini G, et al. (2003) Factors influencing outcome and incidence of long-term complications in children who underwent autologous stem cell transplantation for acute myeloid leukemia in first complete remission. Blood 101: 1611-1619.

21. Barrett AJ, Ringdén O, Zhang MJ, Bashey A, Cahn JY, et al. (2000) Effect of nucleated marrow cell dose on relapse and survival in identical twin bone marrow transplants for leukemia. Blood 95: 3323-3327.

22. Mehta J, Powles R, Singal S, Horton C, Tait D, et al. (1995) Autologous bone marrow transplantation for acute myeloid leukaemia in first remission: identification of modifiable prognostic factors. Bone Marrow Transplant 16: 499-506.

23. Gorin NC, Labopin M, Laporte JP, Douay L, Lopez M, et al. (1999) Importance of marrow dose on posttransplant outcome in acute leukemia: models derived from patientsautografted with mafosfamide-purged marrow at a single institution. Exp Hematol 27: 1822-1830.

24. Meloni G, Vignetti M, Avvisati G, Capria S, Micozzi A, et al. (1996) BAVC regimen and autograft for acute myelogenous leukemia in second complete remission. Bone Marrow Transplant 18: 693-698.

25. Damon LE, Rugo HS, Ries CA, Linker CA (1996) Delayed engraftment of 4-hydroperoxycyclophosphamide-purged autologous bone marrow after induction treatment containing mitoxantrone for acute myelogenous leukemia. Bone Marrow Transplant 17: 93-99.

26. Avola G, Camuglia MG, Milone G (2013) In AML patients treated by allogeneic hematopoietic transplantation, CD34+ supermobilization is a negative prognostic factor. Leuk Res 37: 853-854.

27. Milone G, Avola G, Leotta S, Strano A, Camuglia MG, et al. (2012) Chemosensitivity of nonleukemicclonogenic precursors in AML patients in complete remission: association with CD34(+) mobilization and with disease-free survival. Exp Hematol 40: 35-47.

28. Keating S, Suciu S, de Witte T, Zittoun R, Mandelli F, et al. (2003) The stem cell mobilizing capacity of patients with acute myeloid leukemia in complete remission correlates with relapse risk: results of the EORTC-GIMEMA AML-10 trial. Leukemia 17: 60-67.

29. Feller N, Schuurhuis GJ, van der Pol MA, Westra G, Weijers GW, et al. (2003) High percentage of CD34-positive cells in autologous AML peripheral blood stem cell products reflects inadequate in vivo purging and low chemotherapeutic toxicity in a subgroup of patients with poor clinical outcome. Leukemia 17: 68-75.

30. Fernandez HF, Sun Z, Litzow MR, Luger SM, Paietta EM, et al. (2011) Autologous transplantation gives encouraging results for young adults with favorable-risk acute myeloid leukemia, but is not improved with gemtuzumabozogamicin. Blood 117: 5306-5313.

31. Nakasone H, Izutsu K, Wakita S, Yamaguchi H, Muramatsu-Kida M, et al. (2008) Autologous stem cell transplantation with PCR-negative graft would be associated with a favorable outcome in core-binding factor acute myeloid leukemia. Biol Blood Marrow Transplant 14: 1262-1269.

32. Schlenk RF, Taskesen E, van Norden Y, Krauter J, Ganser A, et al. (2013) The value of allogeneic and autologous hematopoietic stem cell transplantation in prognostically favorable acute myeloid leukemia with double mutant CEBPA. Blood 122: 1576-1582.

33. Jung AS, Holman PR, Castro JE, Carrier EK, Bashey A, et al. (2009) Autologous hematopoietic stem cell transplantation as an intensive consolidation therapy for adult patients in remission from acute myelogenous leukemia. Biol Blood Marrow Transplant 15: 1306-1313.

34. Novitzky N, Thomas V, du Toit C, McDonald A (2011) Is there a role for autologous stem cell transplantation for patients with acute myelogenous leukemia? A retrospective analysis. Biol Blood Marrow Transplant 17: 875-884.

35. Eto T, Takase K, Miyamoto T, Ohno Y, Kamimura T, et al. (2013) Autologous peripheral blood stem cell transplantation with granulocyte colony-stimulating factor combined conditioning regimen as a postremission therapy for acute myelogenous leukemia in first complete remission. Int J Hematol 98: 186-96.