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SINGLE-INSTITUTION RESULTS OF AUTOLOGOUS BONE MARROW TRANSPLANTATION IN ACUTE MYELOID LEUKEMIA

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ABSTRACT

Background. **Current results of autologous bone marrow transplantation (ABMT) suggest that this procedure may prolong disease-free survival (DFS) in patients with acute myeloid leukemia (AML).**

Materials and Methods. **Over the last ten years, 29 AML patients received unpurged autologous bone marrow (BM) after a conditioning regimen including Ara-C (3 g/m²/12h, days –9, –8), CTX (60 mg/kg/day, days –6, –5) and TBI (3.33 Gy/day, days –3 through –1). In 21 patients, ABMT was performed as late intensification after first CR. Eight more relapsing patients were autografted after the achievement of second CR.**

Results. **Three patients died from transplant-related complications. In the remaining patients, mean times to WBC and platelet recovery were, respectively, 23 days (range 13-55) and 55 days (range 22-790). Follow-up for censored patients ranged from 1 to 120 months. Relapse occurred in 7 patients (5 in first and 2 in second CR). Overall 5-year DFS and event-free survival (EFS) chances were, respectively, 67.3% and 60%, with no statistically significant differences between first (DFS=67.3%, EFS=60.3%) and second CR (DFS=68.6%, EFS=60%).**

Discussion. **Apart from obvious selection biases, our study suggests that outcome in first CR AML patients is improved by ABMT. Long-term DFS and EFS are clearly better than when conventional post-remission chemotherapies are used. The greater antileukemic potential of ABMT is further underlined by the results in patients autografted in second CR, when conventional chemotherapy is almost never curative.**

Key words: acute myeloid leukemia, autologous bone marrow transplantation

In spite of high CR rates, no more than 25-30% of previously untreated acute myeloid leukemia (AML) patients under 60-65 years old achieve long-term disease-free survival (DFS) after conventional chemotherapy.[1,2] The corresponding percentages are much worse for older patients and those with more advanced disease.[3] Over the last twenty years allogeneic bone marrow transplantation (BMT) has been investigated in an attempt to improve the DFS of AML patients. However, this procedure can only be performed in a minority of subjects, and the reduction in relapse rate offered by BMT is partially offset by an increase in transplant-related mortality.[4] In patients lacking an HLA-matched sibling donor, autologous BMT (ABMT) has been proposed as a possible alternative to allogeneic BMT, since it allows a supramaximal therapy to be delivered with an acceptable risk of inducing leukemic relapse through the infusion of pre-harvested bone marrow.[5]

The data in the literature concerning the effects of both allogeneic BMT and ABMT on prolonging DFS in AML patients are largely derived from observational studies which have led to contradictory results.[6] The results of only

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a limited number of randomized trials have been published so far, and not even currently ongoing studies[2,7,8] can be expected to resolve the question definitively, since different variables (regarding previous treatments, disease phase, time to BMT, purging and conditioning regimens) need to be taken into account and evaluated separately.[9]

It is generally agreed that ABMT does have an advantage over conventional chemotherapy in prolonging DFS in AML.[10] Nevertheless, the extent of this advantage cannot be precisely indicated because the differences found in some studies between ABMT and conventional chemotherapy are of questionable statistical significance.[9,11,12]

Furthermore, the outcome of ABMT may itself be affected by various factors. There is no conclusive evidence concerning the superiority of any particular type of conditioning regimen.[13] The better DFS experienced by patients receiving ABMT late in first CR may simply reflect the increased probability that these patients were already cured by chemotherapy alone.[14] The largest available survey reports a statistically significant DFS advantage for patients receiving mafosfamide-purged marrow over those receiving unpurged bone marrow,[10] but the issue of bone marrow purging is complicated by the increased risk of graft failure and the fact that it is still not known which of the alternative purging techniques is most effective.[15,16]

The aim of the present paper is to present the results of a single Institution's experience concerning the efficacy of unpurged ABMT in 29 AML patients in first or second CR.

Materials and Methods

Over the last ten years, 21 AML patients in first and eight in second CR have undergone ABMT in our Institution (16 males and 13 females; median age 32 years, range 3-50). No patient selection according to FAB subtype was performed. The main characteristics of the patients are summarized in Table 1.

Participants had been referred to our Center by a number of different hematological Divisions where they had been treated with various induction regimens, including an intercalating agent in association with either conventional or high doses of Ara-C.

Table 1. Characteristics of 29 AML patients receiving ABMT.

#	Age	Sex	FAB	CR	Previous idarubicin	Time to ABMT (months)
1	26	M	M3	1st	no	7
2	34	F	M1	1st	yes	10
3	49	F	M5	1st	yes	13
4	38	F	M1	1st	yes	12
5	36	M	M3	1st	no	7
6	28	M	M3	1st	yes	10
7	26	F	M2	1st	no	9
8	42	M	M1	1st	yes	7
9	50	M	M1	1st	no	6
10	26	M	M5	1st	yes	12
11	32	M	M3	1st	yes	8
12	40	F	M3	1st	no	8
13	46	F	M1	1st	yes	7
14	48	F	M2	1st	yes	9
15	20	M	M4	1st	yes	10
16	40	F	M1	1st	yes	9
17	38	M	M1	1st	yes	11
18	42	F	M1	1st	no	10
19	28	F	M6	1st	no	19
20	30	F	M5	1st	no	12
21	37	M	M1	1st	yes	6
22	20	M	M1	2nd	no	21
23	27	M	M2	2nd	yes	4
24	11	M	M1	2nd	no	1
25	11	M	M5	2nd	no	6
26	3	M	M5	2nd	no	6
27	28	M	M4	2nd	yes	6
28	48	F	M2	2nd	no	6
29	23	F	M3	2nd	no	4

Median time to CR was 37 days (range 24-45) in patients autografted in first CR; thereafter, they received at least 3 cycles of post-remission therapy. Fifteen of these 21 patients had been treated according to an idarubicin-based protocol published elsewhere.[17] The eight patients in second CR had received various second-line regimens after first relapse. Median time to first CR was 35 days (range 29-61); median duration of first CR was 23 months (range 7-41).

In all but one of the transplanted patients, the bone marrow (BM) had been harvested in the same disease phase as that in which the autografting was performed. Median interval

between CR and ABMT was 9 months in patients autografted in first CR and 6 months in those receiving ABMT in second CR (range 6-19 and 1-21, respectively). CR and relapse were defined according to conventional criteria, and the persistence of CR was assessed by means of BM aspiration and biopsy before both the BM harvesting and the transplantation itself.

The BM was collected, processed and cryopreserved according to routine techniques; no *ex vivo* purging procedures were performed.

The pretransplant conditioning regimen included Ara-C (3 g/m^2/12 h on days –9 and –8), CTX (60 mg/kg/day on days –6 and –5) and TBI at a total dosage of 10 Gy, fractionated into 3 equal doses over days –3, –2 and –1 (dose rate, 5 cGy/min). Six patients, who were autografted after December 1992, also received VP-16 (30 mg/kg/day on days –12 and –11). The unpurged autologous BM was infused on day 0.

The patients were treated in a laminar air flow room; antimicrobial prophylaxis and therapy, parenteral nutrition and transfusional support with irradiated blood products were given according to the usual criteria. Peripheral neutrophil and platelet levels of $>0.5\times10^9$/L and $>50\times10^9$/L, respectively, on two consecutive days without transfusions were selected as markers of successful engraftment. Extra-hematological toxicity was graded according to the WHO scoring system.

Survival was calculated from the day on which the ABMT was performed; relapses and toxic deaths were selected as events. The DFS and EFS curves were calculated according to the life-table method and compared by means of the Lee-Desu log-rank test.

Results

The median number of infused nucleated cells and CFU-GM were 1.58×10^8/kg (0.86-3.2) and 6.83×10^4/kg (0.57-15.6), respectively.

In the post-transplant period before engraftment, almost all of the patients experienced grade 2 or higher nausea, vomiting and oropharyngeal mucositis; the incidence of mild diarrhea was similar. No other significant forms of extra-hematological toxicity were recorded; there were no cases of clinically evident hepatic veno-occlusive disease. Twenty-four patients had a constant temperature of more than 38°C.

Three patients died before engraftment in the absence of leukemic disease (of *Geotrichum* sepsis, lung hemorrhage and acute hepatitis, respectively). One patient achieved peripheral neutrophil recovery but still needed periodic platelet transfusions four months after ABMT. Successful engraftment was achieved in the other 25 patients; the median times to neutrophil and platelet recovery were, respectively, 23 (13-55) and 55 days (22-790). Clinical observation was interrupted in May 1994 when the median follow-up for censored patients was 53 months (range 1-120). Seven patients had relapsed 3-26 months (median 8) after ABMT; five of them had received ABMT in first and 2 in second CR (Table 2). None of the relapsing patients achieved a further remission and all of them died 1-11 months after relapse. No CNS relapses were recorded.

The 5-year DFS and EFS probabilities for the whole series were 67.3% and 60%, respectively (Figure 1); the corresponding figures were 67.3% and 60.3% for patients autografted in first CR (Figure 2), and 68.6% and 60% for those autografted in second CR (Figure 3). The differences were not statistically significant. No difference in either DFS or EFS was observed even when the patients receiving ABMT in first CR after idarubicin-based chemotherapy were

Table 2. Follow-up data on 10 poor outcome AML patients.

#	CR	Outcome	Time to relapse (months)	DFS (months)	EFS (months)
1	1	Relapse	18	18	18
2	1	Early death	–	>1	1
3	1	Relapse	8	8	8
4	1	Relapse	17	17	17
5	1	Early death	–	>4	4
6	1	Relapse	6	6	6
7	1	Relapse	6	6	6
8	2	Early death	–	>1	1
9	2	Relapse	3	3	3
10	2	Relapse	26	26	26

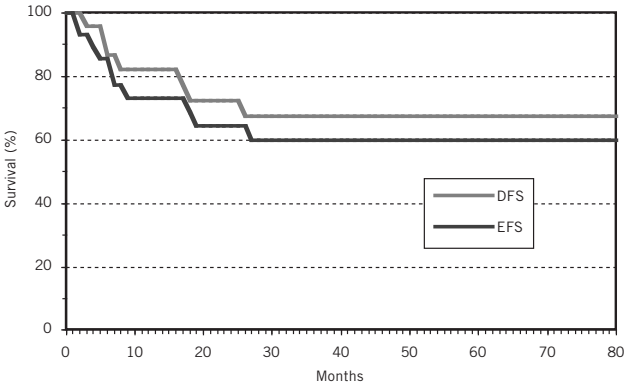

Figure 1. Survival of 29 AML patients autografted in 1st and 2nd complete remission.

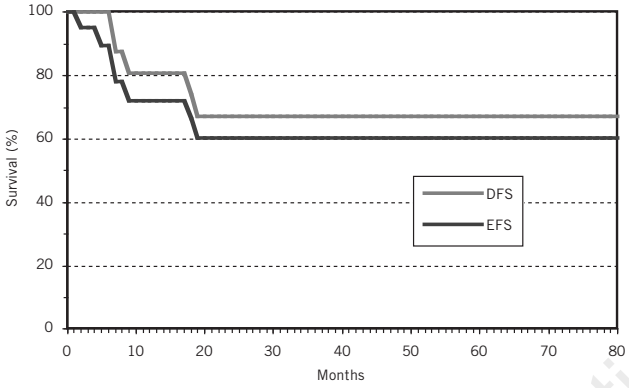

Figure 2. Survival of 21 AML patients autografted in first complete remission.

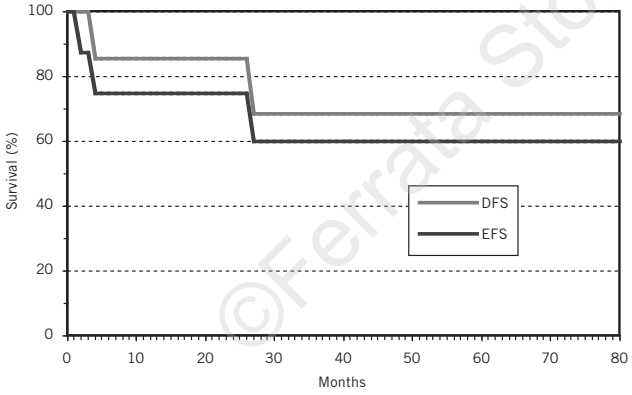

Figure 3.Survival of 8 AML patients autografted in second complete remission.

compared with those treated with other protocols.

Discussion

The overall EFS probability in our series can be regarded as favorable. However, it is necessary to be cautious about drawing any conclusion regarding the real effectiveness of ABMT in AML.

The 5-year EFS probability for patients autografted in first CR undoubtedly exceeds that of any other first CR series after conventional chemotherapy.[2] It is also better than that of most other experiences reported in the literature[15,16,18-22] and compares favorably with the results of allogeneic BMT.[11] Nevertheless, in our series a number of factors other than ABMT seem to have played a role in prolonging EFS. The most obvious is the rather long time

between CR and ABMT, which led to the exclusion of patients in early relapse and increased the number of patients already cured by chemotherapy alone. Furthermore, the uncontrolled design of this study may have favored the selection of low-risk patients. In fact, age selection is an obvious bias, since patients older than 50 were excluded; however, the weight of age should not be overestimated. It is worth noting that more than half of the first-CR patients came from a series in which an idarubicin-based protocol was employed as induction and post-remission therapy. The results of this previous study were characterized by a high CR rate after one induction course, an encouragingly long DFS even in patients not receiving ABMT, and the minimization of the role of some common prognostic factors; in this setting, age failed to predict DFS at both univariate and multivariate analysis. On the other hand, long-term relapses in that study were not infrequent among the patients who did not undergo autografting.[17] It can be argued that a chemotherapeutic strategy that includes an aggressive post-remission phase may lead to a greater reduction in leukemic burden but not necessarily to the cure of this disease.

The therapeutic positioning of autografting as late intensification is supported by the fact that this allows previous chemotherapy to achieve optimal results in terms of reducing residual disease. The additional 2 log reduction achievable with a pretransplant conditioning regimen might allow more reliable disease eradication. In the present series, this is also supported by the absence of CNS or late relapses (after more than 2 years). It is possible that patients undergoing ABMT as late intensification are *purged in vivo* because their previous chemotherapy minimizes the probability of *infusing* residual leukemic cells.[1] Furthermore, the benefits of *ex vivo* purging need to be carefully weighed against the possible risk of a significant loss of normal stem cells, which is undesirable in heavily pretreated patients.[23]

As far as the usefulness of BM purging is concerned, the present data could be interpreted as conflicting with those from the EBMT survey.[10] However, any contradiction is more apparent than real, because the term ABMT covers a wide range of heterogeneous and barely comparable therapeutic strategies. This is particularly true if ABMT is performed as early or late intensification. The aim of early ABMT is to manage a group of patients at high risk of relapse because of a presumably high leukemic burden, in whom it is unlikely that the short duration of previous chemotherapy can conspicuously reduce the normal stem cell compartment.[19-21] Under such conditions, the benefits deriving from *ex vivo* purging can largely be expected to outweigh the risks. As discussed above, ABMT as late intensification involves different problems, and so it is not surprising that it may lead to different conclusions.

In Europe, ABMT is performed as both early and late intensification therapy; however, its efficacy as early intensification is now arousing more interest.[10] The results reported in the EBMT survey could simply reflect the fact that the benefits offered by *ex vivo* purging in early ABMT are greater than those of infusing unpurged autologous BM in late transplant.

There is no clearcut answer to the question as to which is the best conditioning regimen for ABMT.[2,10,13] Although our limited experience cannot provide any reliable conclusions, the use of HD Ara-C might be recommended because of its well-known high level of activity on both medullary and extramedullary (particularly CNS) disease in post-remission and advanced-phase AML; nevertheless, other drugs (such as VP-16) are frequently used in pre-transplant conditioning regimens.[19,21] The conditioning regimen selected for the last six patients in our series included short courses of three drugs as well as TBI. This proved to be devoid of any significant short-term toxicity, although a longer follow-up is necessary before it can be said whether or not this combination offers any advantage in terms of antileukemic activity.

In the present study the survival of the patients in second-CR can be considered good. It is well known that relapse usually follows second CR,[3] and so ABMT in this disease phase can be considered as prolonging DFS. However, given the very small number of our patients, the extent of this benefit cannot be measured.

The presence of the 3 children did not affect DFS since they had an unfavorable outcome.

Another significant element emerging from our study is the possibility of achieving good quality CR in relapsing AML through second-line regimens, as corroborated by the infusion of unpurged BM harvested in second CR. In this setting, AML proves to be different from adult acute lymphoblastic leukemia, where ABMT in second CR is regarded as an unsatisfactory procedure.[24] Furthermore, our data, unlike those from other experiences,[25,26] indicate that neither *ex vivo* purging (even in second CR) nor the pre-harvesting of first CR BM are indispensable. Second CR AML patients are an even more heterogeneous population than first CR patients, and the risks and benefits of the different ABMT techniques need to be carefully weighed in order to offer the best treatment to each patient subgroup.

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