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Evaluating the contribution of allogeneic and autologous transplantation to the management of acute myeloid leukemia in adults

Abstract It has been widely accepted that patients in first remission of acute myeloid leukemia (AML) with a donor should receive an allograft, and many also believe that autologous transplantation is the next best option. Several factors cast doubt on these assumptions. For example, it is understood that patients who receive transplants are already selected to be at lower risk of relapse, and in addition the risk of relapse varies considerably among patients. This can be predicted by several risk factors, the most powerful of which is cytogenetics. Major collaborative group trials have attempted to evaluate the contribution of autograft and allograft to AML treatment in CR1. The EORTC-GIEMEMA, GOELAM, UK MRC, and US Intergroup trials randomized approximately 1200 patients to autograft versus, or in addition to, chemotherapy. Although relapse risk was reduced in all studies, overall survival was not better in three of the trials. Only the MRC trial showed a survival benefit, but only in patients beyond 2 years of follow-up. Patients in these trials for whom donors were available were allocated to allogeneic transplant. This enabled the evaluation of allograft in a donor versus no donor (intent-to-treat) analysis. No study showed a survival benefit for the donor arm, although there was a substantial reduction in relapse risk. Analysis within risk groups suggests that transplantation for good-risk patients is not appropriate and the role of transplantation is uncertain in other groups.

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Introduction

Since the early 1980s allogeneic transplantation from a sibling donor has been the accepted treatment for consolidation therapy in acute myeloid leukemia (AML) in first remission. The procedure cures a high proportion of cases by a combination of enabling myeloablative treatment to the bone marrow and a graft-versus-leukemia (GVL) effect of the graft. The relative contribution of each of these components has not been fully quantitated. However, approximately 55–60% of patients who have undergone allografting survive. Despite many improvements in supportive care, about 20–30% fail transplantation due to nonleukemic causes.

During the 1980s enthusiasm developed for autologous transplantation to support myeloablative treatment. While this approach has the potential disadvantages of lacking the putative GVL effect and possible contamination of the graft with residual disease, many considered these to be outweighed by the benefits of effective anti-leukemic treatment and relative lack of toxicity. Autografting was predicted to be less toxic and therefore applicable to older patients, e.g. up to 60 years of age, as well as those who lacked a donor. Several single-center and registry studies confirmed these predictions with a long-term survival rate of 50–55% being consistently reported [3, 6, 7, 12, 15]. Not unexpectedly, the main reason for failure was relapse, which usually occurred in the first 18 months after grafting. Both these outcomes appeared superior to contemporary chemotherapy results.

Sources of bias

Patients who undergo transplantation are selected. The risk of relapse declines with time, and therefore a

number of patients who could have received transplants are already excluded. The clinical condition of patients may preclude transplantation. In some situations, e.g. infection, this may be unrelated to a tendency to relapse, but in others, e.g. dysplastic remission or failure to obtain a harvest, may reflect a higher risk potential or adverse disease biology. The "time censoring" effect has been clearly demonstrated [8]. As discussed below, the results of prospective trials show that a substantial proportion of patients who are eligible for allograft or autograft fail to receive it.

Evaluation of the role of transplantation

The gold standard is a prospective, randomized trial with an intention-to-treat analysis. This has never been attempted with respect to allografting, but a useful substitute has been "biological randomization" between those for whom a donor was available and those for whom a search was made but no donor found. In addition, a degree of time correction is needed in the analysis to compensate the no-donor arm for the delay in undergoing transplantation. For autologous transplantation a straightforward randomization comparison can be made.

In recent years, chemotherapy has become more intensive and as a consequence survival has improved in patients in the transplantable age group. It is therefore not appropriate to accept the superiority of transplantation based on the results that the chemotherapy of the 1980s could deliver.

As treatment outcomes have improved in the past decade or two, it has become possible to predict widely differing risks of relapse among patients. In the UK Medical Research Council (MRC) Trial AML10, three factors stood out as the most powerful on multivariate

Table 1 Results of recent trials of autologous bone marrow transplantation in patients with AML in first remission (*ABMT* autologous bone marrow transplantation, *ADE* cytosine arabinoside, daunorubicin, and etoposide, *Ara-C* cytosine arabinoside, *Bu* busulfan, *CR* complete remission, *Cyclo* cyclophosphamide, *D* daunorubicin, *DAT* daunorubicin, cytosine arabinoside, and thioguanine, *4-HC* 4-hydroperoxycyclophosphamide, *Ida* idarubicin, *MACE* amsacrine, cytosine arabinoside, and etoposide, *MidAc* mitoxantrone and cytosine arabinoside, *Rub* rubidazone, *TBI* total body irradiation)

Trial	Induction	Consolidation	Marrow purging	Randomization
EORTC-GIMEMA	D + Ara-C (3 + 7)	Ara-C 1 g twice daily, days 1–6	Optional	Cyclo/TBI or Bu/Cyclo + ABMT vs Ara-C 1 g twice daily, days 1–6, amsacrine days 5–7
	Second course if not in CR	Amsacrine days 5–7		
GOELAM	Ida or Rub + Ara-C	Ida or Rub + Ara-C 3 g/m^2×8	No	Bu/Cyclo + ABMT vs amsacrine days 1–5 + Epo days 1–5
	Second course if not in CR			
MRC	DAT or ADE (3 + 10)	DAT or ADE	No	Cyclo/TBI + ABMT vs no further treatment
		MACE MidAc		
Intergroup	Ida + Ara-C (3 + 7)	Ida + Ara-C	4 HC	Bu/Cyclo + ABMT vs Ara-C 3 g/m^2 twice daily, days 1–6

Table 2 Results of recent trials of autologous bone marrow transplantation in patients with AML in first remission (*auto* autografted, *CR* complete remission, *NA* not available, *NS* not significant)

	EORTC-GIMEMA ($n = 941$)	GOELAM ($n = 517$)	MRC ($n = 1966$)	Intergroup ($n = 772$)
CR (%)	66	71	80	70
Follow-up (years)	33	4	4.8	4
Age group (%)				
< 25 years	35	NA	38	NA
25–45 years	58	NA	32	NA
> 45 years	7	NA	29	NA
% in CR randomized	63	61	34	60
No. randomized	254	164	381	233
Compliance (%)	71	87	66	54
Relapse (auto vs other) (%)	41 vs 57	39 vs 55 (of treatment given)	37 vs 58 ($P = 0.0007$)	48 vs 62
Disease-free (auto vs other) (%)	48 vs 30 ($P = 0.05$)	44 vs 40 (NS)	58 vs 40 ($P = 0.04$)	35 vs 35 (NS)
Death rate (%)	10	6.5	12	14
Survival (auto vs other) (%)	56 vs 46 (NS)	50 vs 54 (NS)	57 vs 45 (NS[a])	43 vs 52 ($P = 0.05$)

[a]But $P = 0.0007$ for patients with > 2 years of follow-up

analysis: cytogenetics, the extent of blast clearance in the bone marrow after course 1, and age [18]. The first two in combination give a predictive risk index for survival for good-, intermediate-, and poor-risk patients who have 5-year survival rates of 68%, 44%, and 18%, respectively [18]. Other major trial groups have also found useful prognostic value in cytogenetics [9, 14]. Alternative prognostic indicators include various combinations of French-American-British (FAB) group classification, white blood cell count at diagnosis, and time to achieve complete remission [10, 11]. One of the most relevant current issues is which patients benefit from transplantation. Evaluation of the information available from clinical trials with respect to relapse risk of the patient may provide valuable guidance in this respect.

Prospective clinical trials

Major collaborative groups have conducted and reported the results of trials in the past decade with the issues discussed above in mind. Three trials were confined to children [1, 13, 19] and three to adults [5, 10, 20], with one trial (MRC) involving both [4]. The trial designs were of two broad categories: those randomizing patients to autograft or further chemotherapy; or two (UK MRC and Dutch HOVON group) in which patients were randomized to receive or not receive the transplantation in addition to consolidation treatment.

Trials in adults

Five major trials have been undertaken that randomized approximately 1200 patients. The trial of the Dutch (HOVON) group has not been reported. Details of trial designs are shown in Table 1, with the major results in Table 2. In all trials, patients with matched sibling donors were allocated to allogeneic transplantation. This provided the opportunity to compare allograft with contemporary chemotherapy on a donor versus no-donor basis.

The European Organization for Research and Treatment of Cancer-Gruppo Italiano Malattie Ematologie Maligne Dell' Adulto (EORTC-GIMEMA) trial [20] was the first to be reported. The relapse rate was reduced by autografting, even though 29% of patients in that arm did not receive the autograft. There was a significant disease-free survival advantage in favor of autografting, but the overall survival rate was not different because it was possible to salvage those who relapsed after chemotherapy. While it should be noted that the chemotherapy results in this trial were suboptimal, it demonstrated that autografting could be usefully delayed until second remission.

The Groupe Ouest Est Leucémies Aiguës Myéloblastiques (GOELAM) trial [10] had high compliance with randomization and in many ways provides the most valid data. No benefit with respect to disease-free or overall survival rate was seen. The procedural mortality was low and therefore the potential of the autograft was not compromised. The feature of interest in the GOELAM trial was how well the chemotherapy arm performed. The protocol included high-dose cytosine arabinoside (Ara-C).

The UK MRC [4] had a poor overall randomization rate of available patients (34%), perhaps reflecting the intensity of prior therapy, but survival from diagnosis in this trial of almost 2000 patients was 40% at 7 years. Despite this effective chemotherapy, the addition of an

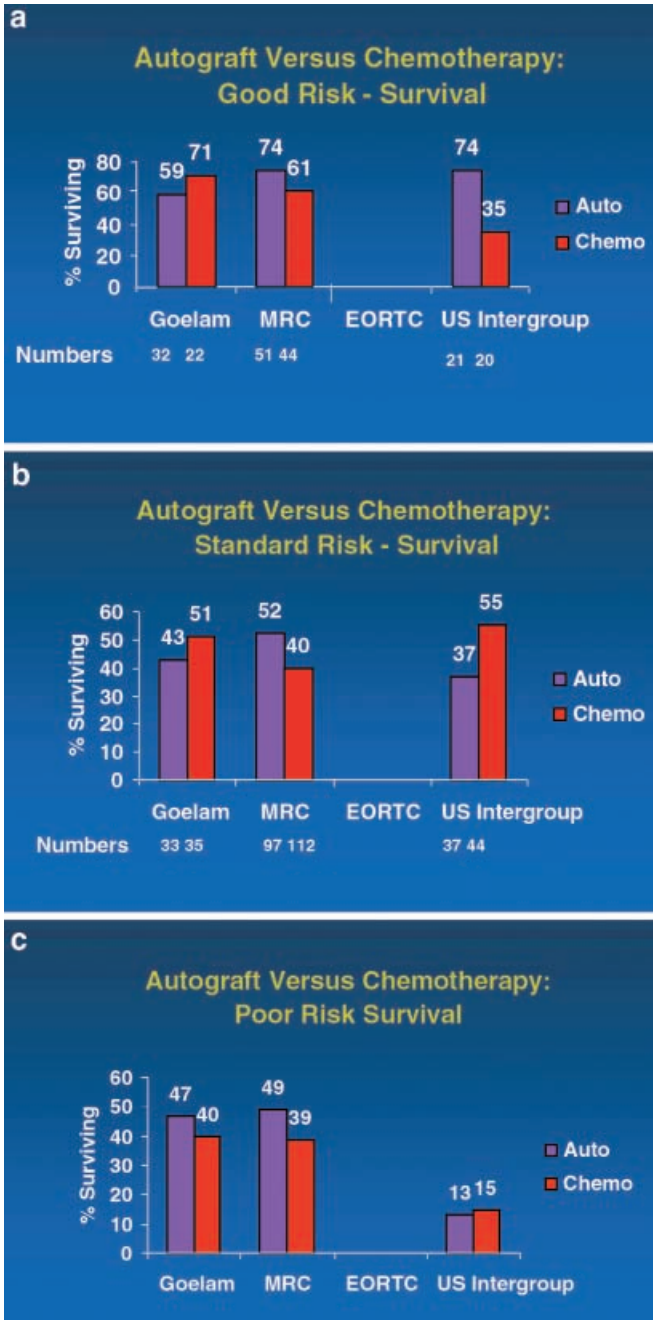

Fig. 1a–c Results of collaborative group trials of autologous transplant in adults: analysis by risk group (■ autograft group, ■ chemotherapy group; numbers above the columns represent the number of patients surviving in each trial)

autograft had a significant impact on relapse risk (37% vs 58%, $P = 0.0007$) even though 34% of randomized patients did not receive the autograft. This advantage translated into an improved disease-free survival rate although there was a mortality rate of 12% in the autograft arm. This rather high figure reflects the fact that after patients were randomized they were required to undergo a further course of chemotherapy with a risk of 4% of death in remission before receiving the autograft. The addition of autografting to a chemotherapy schedule that was already curing 40% of patients was still able to deliver a substantial additional antileukemic effect. The overall effect on survival was only apparent at follow-up beyond 2 years when it became advantageous in favor of autografting.

Although the US Intergroup Trial [5] showed a reduced relapse risk in patients undergoing autografting, it did not demonstrate any benefit with respect to disease-free or overall survival rate when compared with a high-dose Ara-C-containing chemotherapy schedule. Unfortunately this trial also had some flaws, principally poor compliance with allocated randomization (54%). There was also a delay in delivering the autograft compared with chemotherapy, during which time some patients relapsed.

Analysis by risk group

When the risk group definition used by each study group (see below) is used, the patient numbers in each subgroup become small or a risk subdivision is not available. The effect on relapse, disease-free, and overall survival rate is shown in Fig. 1. Taken as a combined experience, a number of observations can be made. First, autografting reduces the risk of relapse in addition to, or when compared, effective chemotherapy. Second, the associated mortality is higher than anticipated from the original phase II trials. Third, it has proved to be difficult to randomize most of the available patients and for patients to comply with the randomization. Therefore there is a problem with the ability to deliver treatment.

It may be possible to address some of these issues with the use of peripheral blood rather than bone marrow as the stem cell source, but this awaits the results of an ongoing comparative EORTC trial. To increase compliance, it may be necessary to perform autografting earlier in the treatment schedule. This introduces some practical difficulties in obtaining stem cells and balancing the need to deliver sufficient consolidation chemotherapy as a method of "in vivo" purging.

Evaluation of allogeneic transplantation

While the main aim of these trials was to evaluate autografting, it was also possible to evaluate its role on a donor versus no-donor analysis and within risk groups. More than 1000 patients with donors were available for comparison with over 1500 control

Table 3 Results of recent trials evaluating allogeneic transplantation on a donor vs no-donor basis

Trial	No. of patients allografted[a] vs chemotherapy	Disease-free survival rate (% at ≥4 years)		Overall survival rate (% at ≥4 years)	
		Allograft	Chemotherapy	Allograft	Chemotherapy
EORTC-GIMEMA	295 vs 377	46	33*	48	40
GOELAM	88 vs 157	44	38	53	53
MRC	428 vs 870	49	42	55	50
US Intergroup	113 vs 117	43	35	46	52

*$P = 0.01$
[a]i.e. donor available

Table 4 Risk group definitions used by transplantation trial groups (*CR* complete remission, *FAB* French-American-British classification, *WBC* white blood cell count $\times 10^9$/l)

Risk group	MRC	US Intergroup	EORTC-GIMEMA	GOELAM
Good	Md, t(15;17), t(8;21), inv(16)	t(15/17) with other: inv(16), t(8/21) without del(9q) or complex	CR first course + FAB M2/M3/ M4eM1/M4 + WBC < 25	M2, M3 + WBC < 30
Standard	Not good or poor	+8, –Y, +6, del(12p) normal	CR first course with unfavorable FAB or WBC > 25 CR > first course with favorable FAB + WBC < 25	M0, 1, 2, 4, 5, 6, 7 and WBC > 30
Poor	–5/del(5q);del(7q),3q–, complex	–5/del(5q),–7/del(7q), inv(3q),11q,20q,21q,17pdel(9q), t(6;9),t(9;22) complex	CR > first course FAB 5, 6, 7 M1, 2, 3, 4, + WBC > 25	M0, 1, 2, 4, 5, 6, 7 and WBC < 30

patients. In the US Intergroup report a donor versus no-donor analysis was not presented, and the overall figures are reported together with the donor versus no-donor analysis from the other three trials in Table 3. There was no overall benefit of allografting on survival in any trial. This becomes more poignant when the detrimental impact of allografting on quality of life [17, 21] is borne in mind, together with the expense of the procedure.

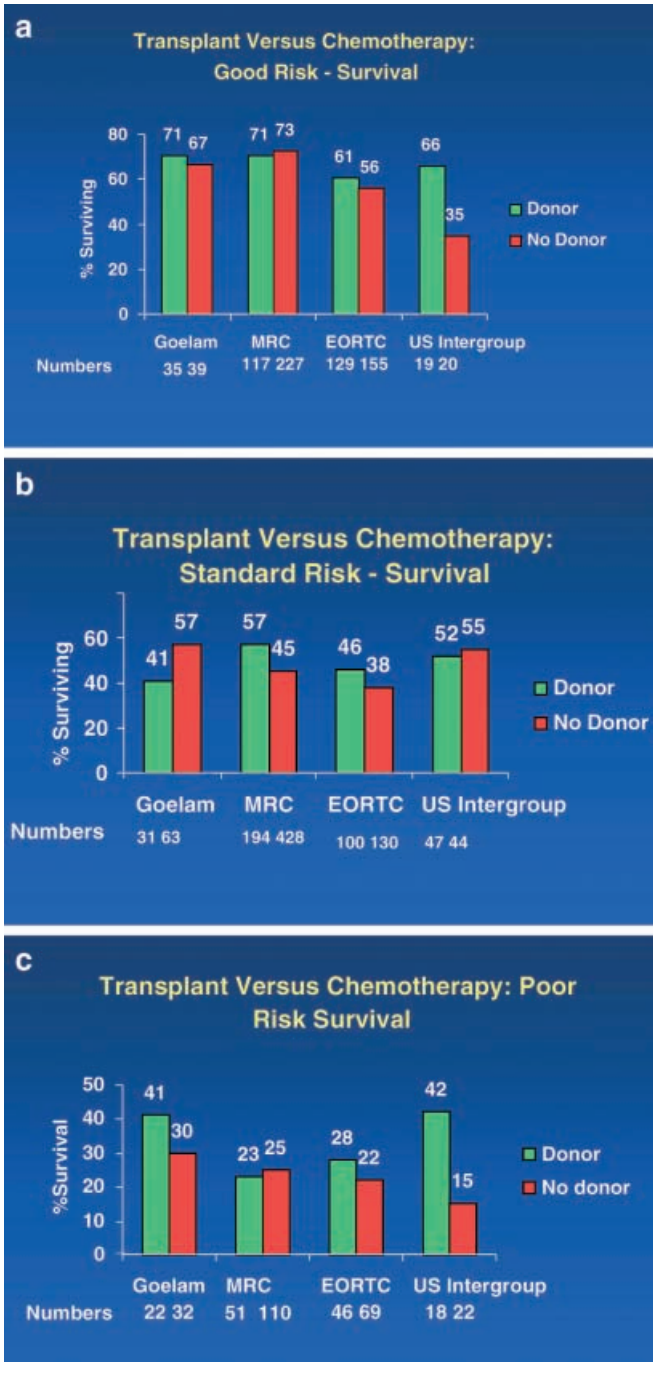

Fig. 2 Results of collaborative group trials of allogeneic transplant in adults: analysis by risk group (■ donor available, ■ no donor)

Analysis of risk

The substantial differences in relapse risk among patients, which reflects the heterogeneity of AML, has been increasingly recognized in recent years. In the transplant trials described above, cytogenetic results were only available in the MRC and US Intergroup studies, where they played the major role in determining risk [14, 18]. In the EORTC-GIEMEMA and GOELAM trials, FAB group, time to achieve complete remission, and presenting white blood cell count were found to have prognostic value and were used to formulate risk groups [10, 11]. The actual definitions used by the different trial groups are detailed in Table 4.

It is of interest to note that when the criteria derived using different treatment protocols were applied to the 1966 patients in the MRC 10 database, the results using the US Intergroup and MRC definitions were nearly identical, demonstrating the appropriateness of cytogenetics as an intertreatment standard in determining outcome [2].

The analysis of the three risk groups is shown in Fig. 2. Overall, there was no survival benefit for good-risk patients (Fig. 2a) except in the US study. This is perhaps explained by a poor outcome in the chemotherapy arm and by the small numbers available for analysis. In poor-risk patients (Fig. 2c), where the numbers are small in all groups, an advantage was demonstrated only in the US Intergroup study. The MRC trial alone showed a significant survival advantage in standard-risk patients (Fig. 2b).

Conclusions

Much time and effort, involving several hundred randomized patients, have been devoted to defining the role of autologous and allogeneic transplantation in the context of modern intensive chemotherapy. Previously it was widely accepted that patients with donors should receive an allograft and those who did not should receive an autograft. These trials have highlighted a number of points. First, chemotherapy is improving, and the comparison arm is a moving target. Second, only a proportion of patients who could receive a transplant actually received one. Third, in a stringent intent-to-treat analysis, transplantation of either type reduced the relapse risk in all trials and in all risk groups. Fourth, it is difficult to see a consistent survival benefit overall or within any risk group.

The implication of these observations is that transplantation in good-risk patients should be reserved for relapse. In the absence of a satisfactory alternative, it is justifiable to transplant poor-risk patients as soon as they are identified. However, these patients remain at high risk of relapse and some additional antileukemic modality, e.g. prophylactic donor lymphocyte infusion, should be developed and evaluated. For standard-risk

patients, transplantation might be effective delivered early [16] and be more suitable than four or five courses of intensive chemotherapy. In any event, undertaking transplantation in the context of a trial is recommended because the results of chemotherapy have continued to improve.

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