

# CLINICAL UPDATE

Updates on study findings in essential therapeutic areas of cancer and blood disorders

## Long-term Results of the MRC AML10 Trial

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### Keywords

Acute myeloid leukemia, allograft, autograft

**Additional update of:** Hann IM, Stevens RF, Goldstone AH, et al. Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia: results of the Medical Research Council's 10th AML trial (MRC AML 10). *Blood*. 1997;89:2311-2318.

The tenth acute myeloid leukemia (AML) trial conducted by the United Kingdom Medical Research Council (MRC) Working Party (AML10) recruited 1,966 patients between May 1988 and April 1995.<sup>1-4</sup> This study, the first MRC AML trial to include children and infants, was limited to patients 55 years of age or younger because a major focus of the study was to evaluate the role of stem cell transplantation in AML. For several years the standard induction schedule used by the MRC Group was the combination of daunorubicin, cytarabine, and thioguanine (DAT). The precise value of the addition of thioguanine is not currently known, but with satisfactory remission rates there was a reluctance to omit it from the standard arm. In 1990, however, the Australian Leukemia Study Group demonstrated that the addition of etoposide as a third drug improved disease-free survival (DFS).<sup>5</sup> The AML10 trial therefore tested the value of etoposide as an alternative to thioguanine. The trial compared DAT with cytarabine, daunorubicin, and etoposide (ADE) for the first two courses of induction therapy. It was common practice in contemporary protocols for patients to move to consolidation therapy only after remission had been achieved. The result was a variable number of courses of induction treatment and total treatment among patients in the same study. Since the principal question in AML10 was the role of stem cell transplantation, it was planned that all patients who came to transplant should have had the same number of prior treatment courses, and would be off study if not in complete remission (CR) after a second course of treatment. In designing the deployment of the autograft it was decided that methods of marrow purging were neither validated nor practical

in a multicenter setting. It was, however, recognized that in vivo purging was potentially important because of the known association with higher rates of relapse in patients autografted early in first remission.<sup>6</sup> This means that the CR-to-transplant interval will result in an inevitable selection of patients. Therefore patients were randomized after three courses of chemotherapy.

To be eligible for randomization, a marrow harvest had to be completed. Patients were then randomized to receive either one further course followed by high-dose chemoradiotherapy with autograft or no further treatment until relapse, at which time the autograft would be used. The preferred preparative regimen was cyclophosphamide plus total body irradiation, the same regimen as was used in patients who received a sibling allogeneic transplant, thus allowing a direct comparison of outcomes. The value of allogeneic transplantation was assessed in a prospective manner using a donor-versus-no-donor comparison method.

**Materials and Methods**

A total of 1,966 patients less than 56 years of age with de novo or secondary AML were recruited (Table 1), of whom 1,857 were randomized to treatment with DAT or ADE. One hundred sixty centers in the United Kingdom, Ireland, and New Zealand took part. This recruitment represented 40% of available adult cases in the UK and 75% of children.

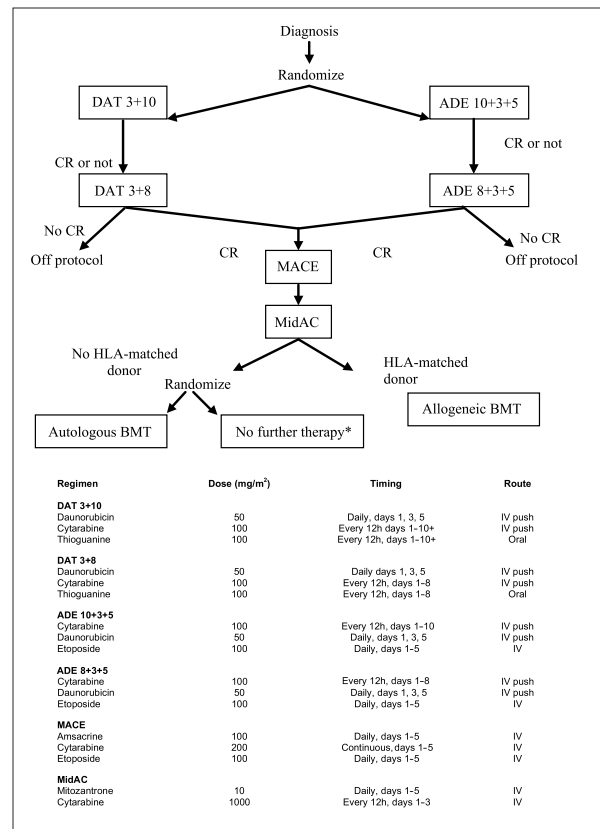
Seventeen randomized patients were excluded before receiving treatment because their diagnoses could not be confirmed and an additional 8 patients were diagnosed as having acute lymphoblastic leukemia and did not receive treatment; these patients are excluded from the analysis. Patients were treated according to the schema shown in Figure 1. For patients lacking a human leukocyte antigen–matched donor, a bone marrow harvest was undertaken after course 3 and patients were then eligible for the second randomization.

**High-dose Treatment**

The preparative regimen for both allogeneic and autologous procedures was cyclophosphamide 120 mg/m<sup>2</sup> over 2 days and total body irradiation given either as a single fraction of 750 or 1,050 cGy or, more frequently, eight fractions of 180 cGy (1,440 cGy). Children younger than 2 years of age were given busulfan 16 mg/kg over 4 days and cyclophosphamide 200 mg/kg over 4 days. Supportive care and graft-versus-host-disease prophylaxis was decided within each transplantation center.

**Risk Groups**

Cytogenetic characterization was carried out in 41 local laboratories that were monitored in a central quality



**Figure 1.** Randomization schema and treatment regimens.

ADE = cytarabine/daunorubicin/etoposide; BMT = bone marrow transplant; CR = complete remission; DAT = daunorubicin/cytarabine/thioguanine; HLA = human leukocyte antigen.

control scheme. Cytogenetic risk groups were defined as: favorable, which comprised t(15;17), t(8;21), and inv(16), including those with additional abnormalities; adverse, which included -7, -5, del 5q, abn(3q), or the presence of a complex karyotype (defined as a clone with at least five unrelated abnormalities); and intermediate, which comprised all other changes and normal karyotype.<sup>7</sup> The risk group definitions included information on acute promyelocytic morphology and the percentage of blast cells in the bone marrow 18–23 days after the end of course 1.<sup>2</sup> Good risk was defined as French-American-British (FAB) M3 morphology or favorable cytogenetics; poor risk was defined as adverse cytogenetics or more than 15% residual blasts in the bone marrow after course 1, except with favorable cytogenetics. Standard risk included patients not defined as good or poor risk.

**Endpoints**

The following definitions were used: overall survival is the time from achievement of first CR to death; DFS is the time from achievement of first CR to first event (either relapse or death in CR); and relapse risk is the

**Table 1.** Baseline Characteristics of Patients in the MRC AML10 Trial

Parameter	Value	Number of Patients		Patients, %*
		DAT, n	ADE, n	
Age, yr	0–1	27	25	3
	2–14	116	118	13
	15–24	131	128	14
	25–34	147	149	16
	35–44	224	226	24
	45–55	280	278	30
	56+	4	4	<1
Sex	Male	475	471	51
	Female	454	457	49
Type of AML	De novo	863	859	93
	Secondary	66	69	7
White blood cell count ( $\times 10^9/L$ )	0–9	417	412	45
	10–99	366	385	40
	100–199	84	72	8
	200+	31	38	4
	Unknown	31	21	3
FAB type	M0	16	12	2
	M1	136	172	17
	M2	254	253	27
	M3	143	130	15
	M4	184	184	20
	M5	79	81	9
	M6	28	24	3
	M7	24	18	2
	RAEB-t	13	17	2
	Bilineage	2	0	<1
	ALL	2	6	<1
Unknown	48	31	4	
Performance status	Asymptomatic	250	245	27
	Minimal symptoms	485	489	52
	Ill	172	173	19
	Very ill	22	21	2
Cytogenetic group	Favorable	178	187	20
	Intermediate	505	4838	53
	Adverse	68	80	8
	Unknown	178	186	20

\* Percentages may not add up to 100 due to rounding.

ADE = cytarabine, daunorubicin, and etoposide; ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; DAT = daunorubicin, cytarabine, and thioguanine; FAB = French-American-British; MRC = Medical Research Council; RAEB-t = refractory anemia with excess blasts in transformation.

cumulative probability of relapse, censoring at death in CR. A normocellular bone marrow aspirate containing less than 5% leukemic blast cells and showing evidence of normal maturation of other marrow elements was the criterion for the achievement of CR.

**Statistical Methods**

Kaplan-Meier life tables were constructed for each endpoint and were compared by means of the log-rank test. The data for surviving patients were censored on May 1, 2004, when follow-up was up to date for 97% of patients (the small number of patients lost to follow-up were censored at the date they were last known to be alive). All point estimates quoted for endpoints are at 10 years from first CR (except for survival from relapse, which is 8 years from relapse). The number in parentheses after each odds ratios (OR) is the 95% confidence interval of the OR shown in the figures. An OR less than 1.0 indicates benefit for the donor group. All *P* values are two-tailed. In addition to overall analyses, analyses were performed within important prognostic risk groups (good, standard, poor, and unknown) and age groups (0–14, 15–34, and >35 years), and tests for heterogeneity of and/or trend in treatment effect between subgroups were performed. To obtain greater numbers in each age subgroup (and, therefore, greater statistical reliability), analyses are presented in three age groups. All analyses are performed on the intention-to-treat principle with all patients (donor or no donor) analyzed in their allocated arm, irrespective of whether or not transplant was received by patients in the donor group.

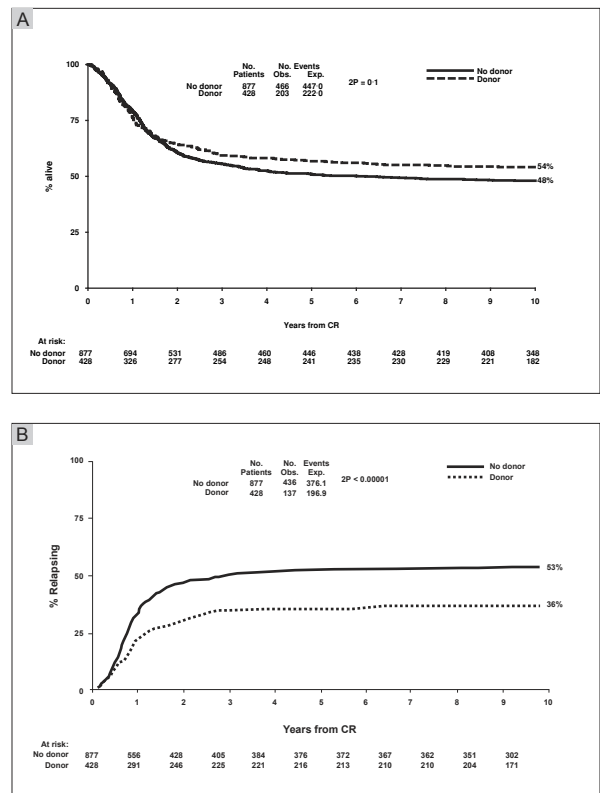
**Results**

**DAT versus ADE**

The median follow-up of remitters was 142 months (range, 26–193 mo). The overall survival at 10 years was 38%, with 312 patients at risk at that time point. The overall DFS, relapse risk, death in remission, and survival from relapse was 40%, 50%, 18%, and 10%, respectively, with no differences between the randomized arms.

**Outcome in Relation to Risk Groups**

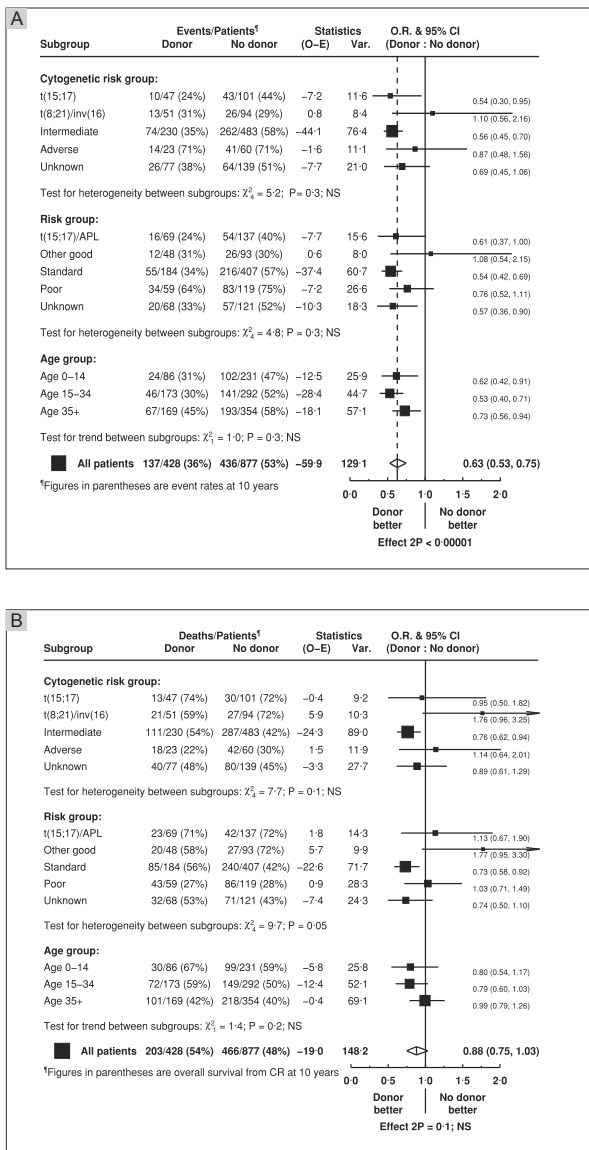
This trial was used to develop a simple risk score based on cytogenetics and bone marrow blast response following the first course of induction therapy. The three risk group designations produced clear discrimination with respect to overall survival (good 68%, standard 44%, and poor 23% at 12 years; *P*<.00001). These differences are explained by differences in relapse risk (good 34%, standard 52%, poor 77%; *P*<.00001). These cohorts allowed the impact of transplantation to be assessed.



**Figure 2.** Donor versus no donor. (A) AML10: survival from complete remission (CR); (B) AML10: relapse.

**Allogeneic Transplantation**

Patients (n=1,063) who entered CR were tissue typed and a matched sibling donor was identified for 428 patients (Figure 2). Transplantation was undertaken in 269 (63%) of these patients. During the latter part of the recruitment period it was becoming clear that the potential benefits of transplantation for patients with favorable risk cytogenetics were less obvious, resulting in few patients who had a donor receiving the transplant in first remission. Patients were not tissue typed for the following reasons: relapse (n=17), too old for allograft (n=170), no siblings (n=224), other known reason (n=53), or reason unknown (n=75). In assessing the role of allogeneic transplantation, patients who had donors were compared with patients who were tissue typed but did not have a donor. Relapse was significantly reduced in the donor arm (36% vs 53%, *P*<.00001). This resulted in an improvement in DFS (49% vs 41%; *P*=.02) but not in overall survival (54% vs 48%; *P*=.1), because there was a higher percentage of deaths in remission in the donor arm (23% vs 12%; *P*<.00001). When examined by risk group, allogeneic transplantation reduced the risk of relapse in all risk groups and age groups, although the reduction among the good-risk patients is almost completely attributable to



**Figure 3.** Donor versus no donor by risk group. (A) AML10: relapse; (B) AML10: survival from first complete remission (CR).

CI = confidence interval; NS = not significant; OR = odds ratio.

the t(15;17) subset, and these patients are unlikely to be considered for transplant in the current era. In terms of overall survival, only patients who were classified as standard risk derived any benefit, and no benefit was seen in patients over 35 years of age (Figure 3).

**Autologous Transplantation versus No Further Therapy**

Of the patients who lacked a donor, 381 (35%) were randomized to receive either autologous transplantation or no further treatment. During the course of the trial the

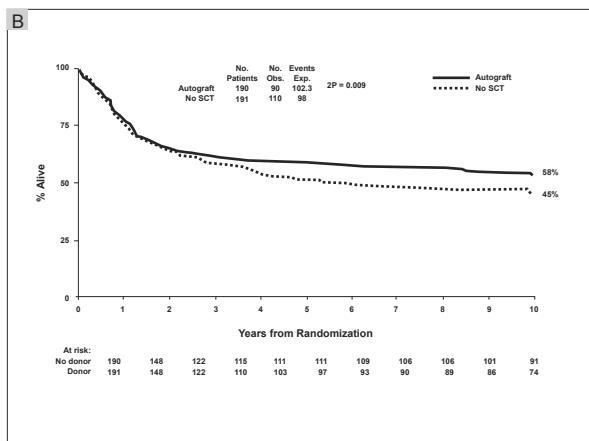
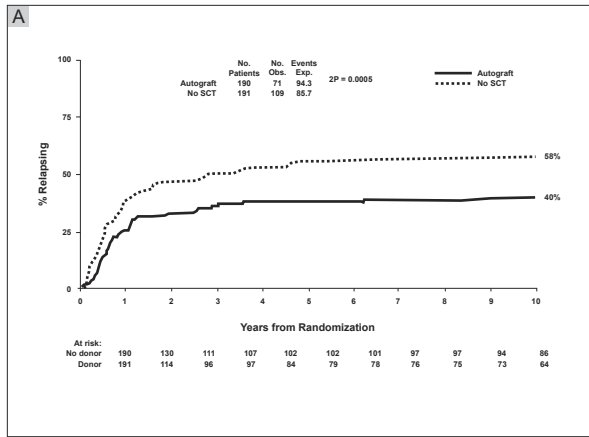
time point for the second randomization was moved from after course 3 to after course 4 in an attempt to improve the rate of randomization.

The overall survival of patients allocated to autologous transplantation was better than for those in the no-further-therapy arm (53% vs 45%) at 10 years, with 165 patients at risk at that time point (Figure 4). This difference is not statistically significant on a log-rank analysis ( $P=.09$ ). The Kaplan-Meier plots are identical for the first 3 years, at which point they diverge and the difference becomes significant (Figure 4). There was a highly significant reduction in relapse risk in the autograft arm (40% vs 58%;  $P=.0005$ ), which is offset by a higher risk of death in remission (16% vs 6%;  $P=.02$ ), but the DFS was superior in patients allocated to autograft (50% vs 39%;  $P=.03$ ). There was little long-term difference in outcome from relapse after autograft or no further therapy. The reduction in relapse risk is an underestimate of the antileukemic potential of the autograft, because only 66% of randomized patients received the autograft. Conversely the increased mortality in the autograft arm is an underestimate, although some of the deaths occurred after the fourth treatment course, before the autograft was due to be delivered.

With respect to the risk of relapse, autograft showed a reduced risk in all risk and age groups, which is attributable to the 66% of patients who underwent the procedure. There was a suggestion of survival benefit in patients in the good- and standard-risk groups but not in the poor-risk group. It was unclear if any specific age group benefited (Figure 5).

**Discussion**

This trial illustrates that achievement of a high remission rate in younger patients with AML is now a consistent and realistic aspiration. In several consecutive MRC trials, the DAT combination has proved to be as effective as any other schedule, although there is still uncertainty about the need for a third drug. With such a high rate of remission, it is statistically challenging to demonstrate a benefit with an alternative regimen. However it is well known that the quality of remission, which is reflected in duration, is influenced by the induction treatment even if the rate of CR is not improved. The main challenge is to prevent relapse. In the late 1980s it was generally believed that the best treatment to prevent relapse was allogeneic transplant when a sibling donor was available. It was because many patients lacked a donor or were excluded from the allograft option that an incentive to explore autologous transplantation as an alternative emerged. This was based on the belief that it was the myeloablative component of the allograft that had the major antileukemic effect. The pioneering work

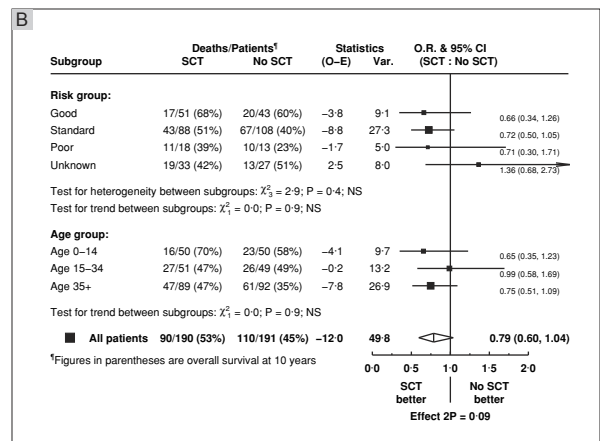
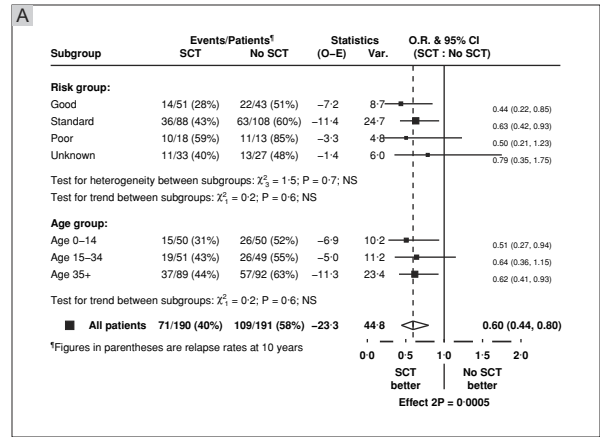


**Figure 4.** Donor versus no donor by risk group. (A) AML10: relapse; (B) AML10: survival from first complete remission (CR).

SCT = stem cell transplantation.

of Dicke and coauthors<sup>8</sup> demonstrated that bone marrow collected in remission could be used in subsequent relapse to restore marrow function after myelablative cyclophosphamide and total body irradiation, although when used as the primary treatment for relapse it failed to control the disease. Several nonrandomized phase II studies in first and second remission confirmed that this approach was feasible, with an apparent reduction in relapse rate.<sup>9-12</sup>

All transplanted patients are selected, not least because the intervention takes place several weeks into remission and excludes patients who have relapsed or are in other respects not fit for the procedure. The main aim of the AML10 trial was to evaluate prospectively the role of autologous transplantation given in addition to, not as an alternative to, effective induction and consolidation. To this end it was important that the chemotherapy chosen was not suboptimal. This turned out to be the case



**Figure 5.** Autologous transplants by risk group. (A) AML10: relapse from second randomization; (B) AML10: survival from second randomization.

CI = confidence interval; NS = not significant; OR = odds ratio; SCT = stem cell transplant.

with 38% of all entrants to the trial who only received chemotherapy and who were alive at 10 years. Even against that background both autologous and allogeneic transplants were able to reduce the relapse rate very significantly. However, the overall survival was not significantly improved, largely because of mortality associated with the procedure. This finding suggested that even patients who received four courses of intensive chemotherapy could have the relapse rate further reduced by more treatment. This led to a prospective comparison of a total of four versus five courses of treatment in the successor AML12 trial, which posed the question of whether adding a fifth course of chemotherapy can achieve the same reduction in relapse as the transplant option. This proved not to be the case.<sup>13</sup>

AML10 afforded the opportunity to define simple prognostic factors that could be used to direct treatment. The prognostic impact of cytogenetics was already known

from smaller series and was confirmed in this trial, which together with an assessment of blast response in the bone marrow after course 1 provided a simple prognostic discriminant that was subsequently validated in the AML12 trial.<sup>13</sup> For patients in remission, the risk of relapse varies considerably. This study was the first to suggest that patients who are at low risk of relapse (ie, favorable-risk cytogenetics) do not require transplantation, provided they are given effective chemotherapy. We were also not able to demonstrate that patients with poor-risk disease could benefit from a transplant, which has recently been endorsed by a retrospective analysis of the lack of clear benefit for patients with a *FLT3* mutation.<sup>14</sup>

As well as defining which risk groups may or may not benefit from transplant, these data also suggested that any trend of benefit ceased at an upper age limit of 35 years, at which point the procedure-related mortality increased, although the potential antileukemic benefit was retained. If the antileukemic effect of reduced-intensity transplant is confirmed, this may assist in defining the lower age limit at which it could be offered.

The design of AML10 resulted in only a minority of patients in remission receiving the intended treatment. Therefore the conclusions apply only to that selected group; different conclusions might have been reached if a higher proportion of those in remission had received the intended treatment, particularly if transplantations were done earlier. However, other prospective trials addressing the same issue in which less chemotherapy was given reached broadly similar conclusions as AML10.<sup>15-18</sup> The original questions posed in this trial remain relevant and controversial and there are still no convincing data to show if, for example, poor-risk patients benefit from allogeneic transplantation. In spite of substantial evidence indicating little benefit, good-risk patients still receive transplants in first CR. Chemotherapy has improved, particularly in children, since the AML10 trial, which suggests that evaluation should continue, particularly as the feasibility of unrelated transplants and reduced-intensity transplants develops.

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