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Duration of second complete remission in patients with acute myeloid leukemia treated with chemotherapy: a retrospective single-center study

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Abstract A total of 168 patients with de novo AML were retreated with chemotherapy at relapse following first CR; 66 patients (39%) achieved a second complete remission (CR). The probability of achieving a second CR was highly dependent on the duration of the first remission. Patients who received no or conventional postremission chemotherapy after second CR had a median remission duration of 7.5 months, and the probability of remaining in remission at 3 years was 24%. Patients with a first CR of more than 12 months had a median second remission duration of 18 months. The probability of a second CCR was 35% at 3 years and 24% at 5 years, whereas none of the patients with a first CR of less than 12 months was in remission at 3 years. Only a poor correlation ($p=0.31$) was found when the durations of the first and second CR were compared in patients with a second relapse. Patients with long-lasting remissions and long-term survivors after second CR are characterized by a first CR duration of >12 months and favorable or normal cytogenetics. The type of salvage treatment seems to be less important for achievment of long-term remission, but it is probably important to administer consolidation chemotherapy after second CR. Other so-far ill-defined factors may be responsible for the supression of the leukemic clone in patients with long-lasting remissions following chemotherapy for relapse after second CR.

Key words Acute myeloid leukemia · Salvage chemotherapy · Long-term remission

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Introduction

Relapse of acute myeloid leukemia is a serious event which drastically reduces the probability of cure. Due to the lack of randomized trials, uncertainty exists about the optimal reinduction therapy and the most effective postremission treatment for responding patients. High-dose chemoradiotherapy followed by allogeneic bone marrow transplantation from an HLA-compatible sibling or unrelated donor is likely the most effective therapy in early relapse or second CR [7], but this option is available for only a few patients. Favorable results have also been reported for autologous bone marrow transplantation (ABMT) in second CR [4, 8, 16, 17, 20, 21]. These series, however, included highly selected groups of patients and were not analyzed on an intent-to-treat basis. Only a few studies have evaluated the long-term efficacy of conventional salvage chemotherapy [2, 5, 14, 15, 19, 23].

The aims of this study were (a) to evaluate the long-term efficacy of salvage chemotherapy in patients who have achieved a second CR (excluding patients who underwent bone marrow transplantation), and (b) to analyze the factors which determine the duration of second CR and survival in a closely followed and well-characterized cohort of patients with AML at a single center.

Material and methods

Patients and treatment regimens

A total of 370 patients (median age 53 years, range 15–88) with de novo AML were treated between 1978 and 1995 at our institution. Induction chemotherapy consisted of one or two courses of the 3+7 regimen [daunorubicin 45 mg/m^2 or adriamycin 30 mg/m^2 days 1–3 and continuous infusion of cytosine arabinoside (ARA-C) 100–200 mg/m^2 daily days 1–7, $n=306$], the DAV protocol [9] ($n=39$), ATRA ($n=12$), or various other protocols ($n=14$). Of these patients, 245 (66%) achieved a complete remission. Postremission treatment consisted of regimens similar to the

induction protocol (but usually in a reduced dose) in 94 cases and of high-dose ARA-C alone or combined with daunorubicin or AMSA in 76 patients. Twenty patients (8.2%) underwent allogeneic or autologous bone marrow transplantation in first CR. The remaining patients received various chemotherapy regimens or no consolidation treatment.

Of the 225 patients who received chemotherapy only following first CR, 168 relapsed after a median time of 11 months; 114 patients received reinduction therapy, and 66 (39%) of the patients who were given one of the various salvage regimens achieved a second CR (CR 2). Eleven CR 2 patients underwent bone marrow transplantation (BMT) (two allogeneic and nine autologous) and 35 received one or two courses of conventional consolidation treatment.

Statistical analyses

The Kaplan-Meier technique was used to analyze the probability of survival (SV), disease-free survival (DFS), and continuous complete remission (CCR). Survival was calculated from the time of CR 2 until death from any cause, DFS from the time of CR 2 until second relapse or death from any cause, and CCR from the time of CR 2 until relapse. For the Kaplan-Meier analysis, all patients who received only conventional chemotherapy (with or without consolidation treatment) after CR 2 ($n=55$) were considered (BMT patients were excluded at the time of transplantation). For the comparison of the duration of first and second CR, only patients who had received conventional chemotherapy and had a second relapse ($n=42$) were considered. For the comparison of the survival curves of patients with early and late relapse, the log-rank test was used.

Results

Efficacy of salvage treatment in patients with first relapse

Among the 168 patients who had relapsed following first CR and had received reinduction treatment, 66 (39%) achieved a complete remission. The probability of a second CR was clearly dependent on the duration of the first CR (Table 1). Patients with a long-lasting first CR (>18 months) had a CR rate (70%) almost equivalent to that of patients at diagnosis.

Characteristics of patients who have achieved a second CR

The demographic, hematological, and cytogenetic characteristics of patients who have achieved second CR and did not undergo bone marrow transplantation in CR 2 are shown in Table 2.

Table 1 Rate of second CR depending on duration of first CR

Duration of first CR (months)	*n*	CR 2 (%)
1– 6	16/59	27.1
7–12	24/62	38.7
13–18	12/27	44.4
>18	14/20	70.0
	66/168	

Table 2 Characteristics of patients who achieved a second complete remission and received no or conventional postremission chemotherapy (*DAV*, *HAM* high-dose ARA-C+mitoxantrone, *HidaC* high-dose ARA-C, *AMSA (amsacrine), FLAG (Fludarabin Hidac G-CSF), ATRA (all trans retinoic acid), DNR* daunorubicin)

Age (median, range)		50 (16–75)
Male/female		29/26
FAB type	M 0	1
	M 1	11
	M 2	12
	M 3	6
	M 4	18
	M 5	6
	M 6	1
Karyotype (at diagnosis)	Normal	15
	t(8;21)	7
	inv 16	8
	t(15;17)	6
	t(9;22)	1
	Various	10
	No data	8
Reinduction chemotherapy	3+7	13
	DAV	3
	HAM	23
	HidaC+AMSA	5
	FLAG	1
	ATRA	1
	Various	9
Consolidation	HidaC±DNR	
	Mito or AMSA	19
	DNR+ARAC	7
	Various	9
	None	20

Relationship between duration of first and second CR

Following conventional chemotherapy as salvage treatment, the median duration of second CR was shorter (171 days, range 30–1738) than that of their first CR (275 days, range 30–1386) ($p=0.08$). Surprisingly, there was a very poor correlation ($p=0.31$) between the duration of the first and second CR. As shown in Fig. 1, a number of patients had a short second CR after a long first CR; on the other hand, some patients had an unexpectedly long CR 2 after a relatively short CR 1. In 22% of patients the second CR was longer than the first.

Survival, disease-free survival, and continuous complete remission after second CR

The median duration of the second remission was 7.5 months. The probability of SV, DFS, and CCR of all patients after second CR at 3 years was 19%, 16%, and 24%, respectively. The probability of SV, DFS, and

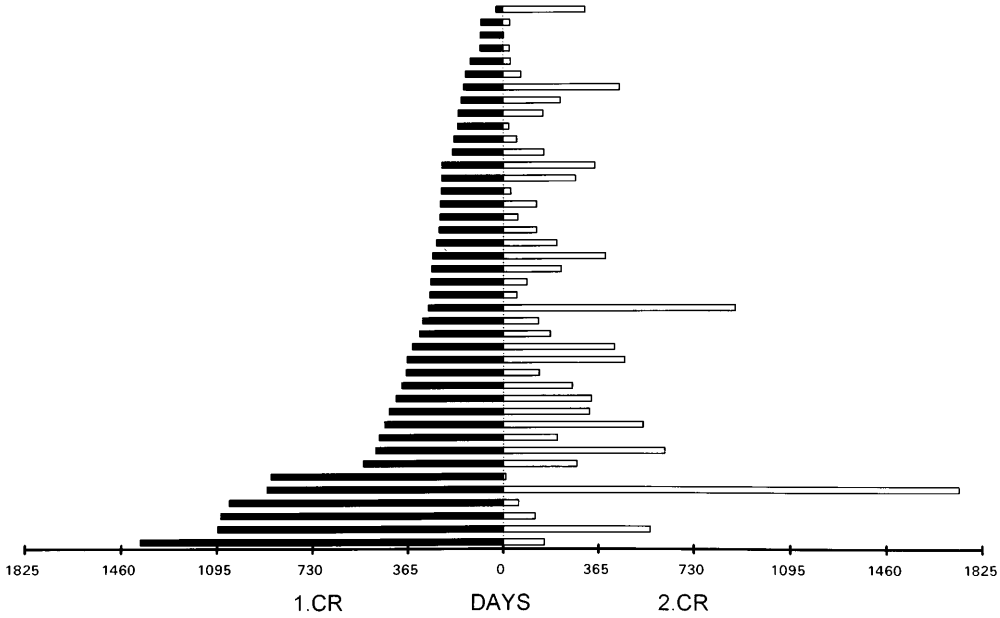

Fig. 1 Duration of the first and the second complete remission (only patients who had a second relapse were considered)

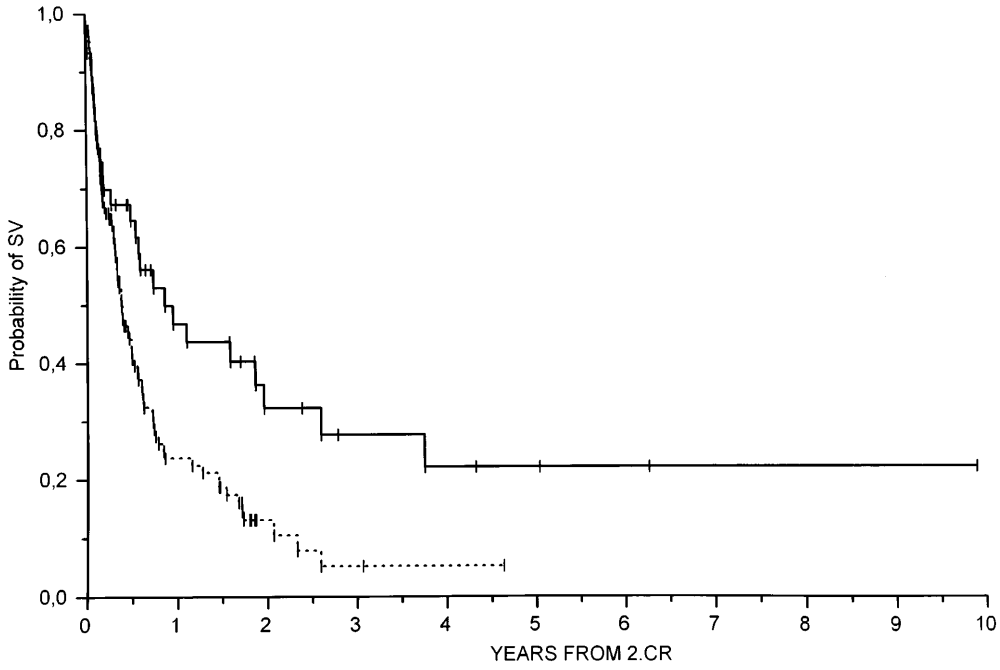

Fig. 2 Survival (*SV*) of patients from second CR. Patients with first CR > 12 months ($n = 27$, ●—●); patients with first CR < 12 months ($n = 39$, ●– – –●). The difference is statistically significant ($p = 0.03$)

CCR was highly dependent on the duration of the first CR. Patients with a first CR of more than 12 months had a significantly higher probability of SV, DFS, and CCR at 3 years than patients with a first CR duration of < 12 months (28% vs 5%, $p = 0.003$; 31% vs 0, $p = 0.006$; and 36% vs 0, $p = 0.003$) (Figs. 2–4). The median duration of CR 2 was 18 months in patients with a long first CR duration (> 12 months).

Characteristics of patients with a long second CR (> 2 years)

Table 3 shows the hematological, cytogenetic, and molecular characteristics and the first-line and salvage treatment of the seven patients with a second CR of more than 2 years. Five of the patients (nos. 3–7) had a duration of the second CR which considerably exceeded that of their first CR. One patient (no. 1) had a molecular remission (PML/RAR negative). Common features of these patients are the absence of FAB types M 0, 1, 6 and 7, the absence of unfavorable karyotype abnormalities, and the presence of favorable karyotype changes in three patients. The median age was not different from that of patients at diagnosis (50 years). It should also be noted that in most of the patients the salvage treatment was not more intensive than the first-line treatment; five patients had received at least one consolidation course.

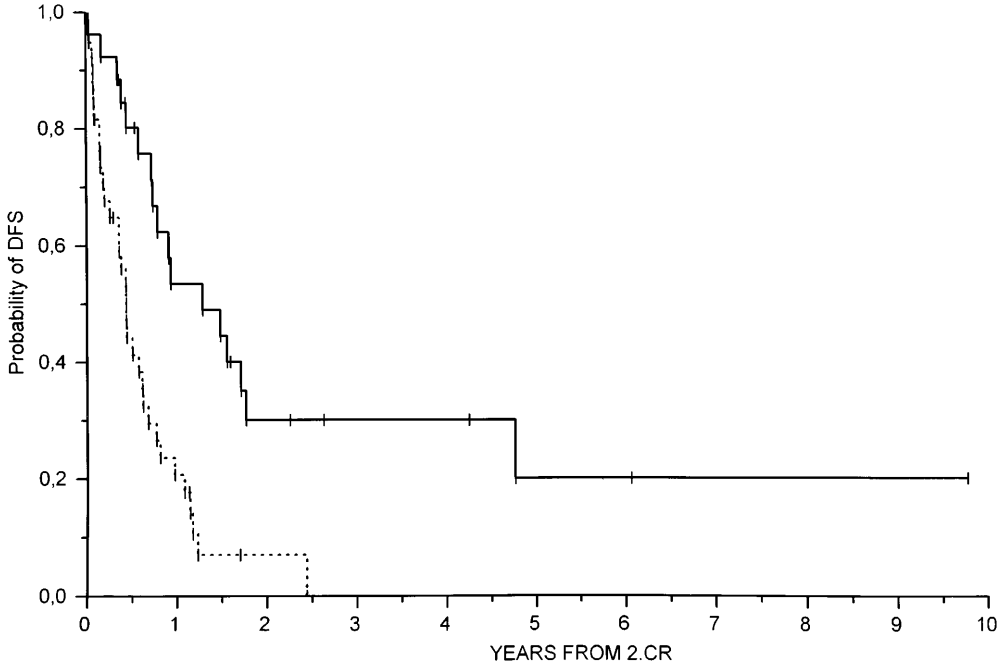

Fig. 3 Disease-free survival (*DFS*) of patients from second CR. Patients with first CR > 12 months ($n = 27$, ●—●); patients with first CR < 12 months ($n = 39$, ●– – –●). The difference is statistically significant ($p = 0.006$)

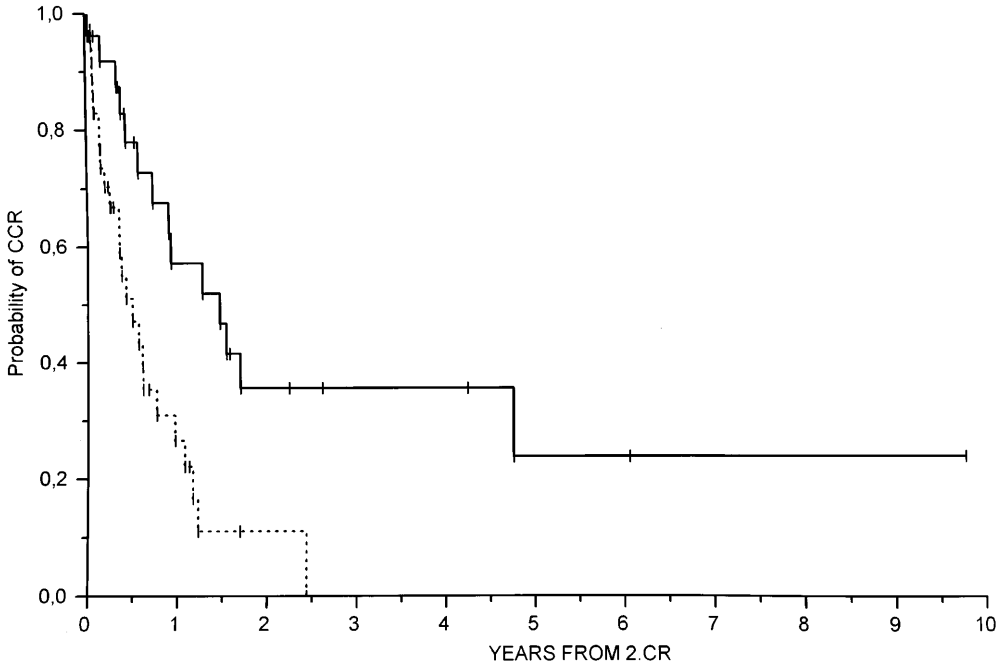

Fig. 4 Continuous complete remission (*CCR*) of patients from second CR. Patients with first CR > 12 months ($n = 27$, ●—●); patients with first CR < 12 months ($n = 39$, ●– – –●). The difference is statistically significant ($p = 0.003$)

Discussion

Among patients with de novo AML, 50–80% achieve CR with current induction protocols. Durable remissions or high cure rates may be achieved in younger patients undergoing allogeneic bone marrow transplantation [7], in patients with favorable karyotype abnormalities such as t(8;21) or inv 16 when treated with high-dose ARA-C [3], or in patients with M3 after treatment with ATRA and chemotherapy [6].

For the majority of patients with de novo AML, however, the duration of the first CR is short, and 60–80% eventually relapse. Various studies [1, 11–13, 15, 22, 24–26] have shown that a second complete remission can be obtained in a considerable proportion of relapsed patients with either the same or an altemative chemotherapy regimen. The probability of a second CR greatly depends on the duration of the first CR [10, 15]. Our findings confirm this observation.

In most studies on relapsed AML, the efficacy of the salvage treatment to induce a second CR was investigated, but there are only a few data on the duration of second remission and on the factors which have an impact on remission duration. It is generally believed that

Table 3 Characteristics of patients with a second CR > 2 years. *HidaC* high-dose ARA-C, *DNR* daunorubicin, *DAV* [9], *HAM* high-dose ARA-C + mitoxantrone, *EMA*[2] etoposide, mitoxantrone, ARA-C

Patient	1	2	3	4	5	6	7
Sex	male	female	female	female	male	male	female
Age (years)	65	74	25	64	49	55	52
FAB type	M3	M4	M4	M4	M4	M2	M4
Karyotype	t(15;17)	Normal	iso 17q	Normal	Normal	t(8;21)	inv 16
Induction CT	3+7	3+7	3+7	3+7	3+7	3+7	3+7
Consolidation	1+7	1+7; 1+7	1+7	3+7 HidaC/ AMSA	3+7; HidaC/ AMSA	HidaC/ DNR	HidaC/ DNR
First CR (days)	1754	1146	518	906	930	582	286
Salvage CT	3+7	3+7	HidaC/ AMSA	3+7	HAM	3+7	HAM
Consolidation	–	DAV	HidaC/ DNR	HidaC/ DNR	–	EMA	HAM
Second CR (days)	819+	956+	3568+	1738	2211+	1549+	891
Current status	Alive in CR PML/RARA neg	alive in CR	alive in CR	Alive in relapse (MDS) day 1824+	alive in CR	alive in CR AML1/ ETO pos	alive in third CR day 1573+
Remarks	–	–	Crohn's disease	– –		Probable *M. avium* infection	Tuberculous spondylitis after second CR

the chance of cure or long-term remission in patients after second CR is low if only conventional chemotherapy is given. Allogeneic BMT is regarded as the most effective treatment in younger patients and is most likely the treatment of choice, provided an HLA-compatible sibling is available. In the absence of a compatible sibling, unrelated-donor BMT is another option [18]. Since the search for an unrelated marrow donor usually takes considerable time, it would be important to have an estimate of the duration of the second remission. One could assume that a patient in CR 2 who had a long-lasting first remission may have a relatively long-lasting second CR, providing there is enough time to search for a suitable unrelated donor. However, our data argue against the concept of the predictability of the duration of a second CR from the duration of the first CR. This means in practical terms that a search for an unrelated donor should be started at the time of first CR, even when marrow transplantation is not considered until early relapse or second CR.

Another important result of our study is the finding that patients with a first CR of more than 12 months may have a definite chance of long-term remission or even cure. There are only scarce data on the long-term results after salvage treatment with chemotherapy alone. Archimbaud et al. [2] applied a very intensive salvage regimen (EMA – mitoxantrone, etoposide, and cytarabine) and found 25% survival and 20% DFS at 5 years in patients in second CR after a duration of the first CR >6 months, while survival and DFS were only 12 and 3%, respectively, in primary refractory or early-relapse patients. In the study of Davis et al. [5], CCR was 15% at 14 years in patients with second CR with conventional salvage therapy. The authors did not differentiate between early and late relapses. Kantarjian et al. [14] showed that patients with CR after late relapses (defined as duration of the first CR of >18 months) had a significantly higher probability of sustained second CR than patients with earlier relapses (median duration 11 vs 3.5 months). The CCR at 3 years was 25%. A longer remission duration in second CR in late relapses (>9 months) was also reported by Uhlmann et al. [23].

Thus, there is convincing evidence from the literature, as well as from our data, that the chance of a patient achieving second CR following a late relapse of long-term remission (or even cure) after consolidation with conventional chemotherapy is approximately 20%. On the other hand, a patient in second CR after early relapse (CR 1 6–12 months) has only a slight chance of cure, irrespective of the chemotherapy regimen administered.

Autologous BMT (ABMT) is often performed in patients with second CR. Disease-free survivals of 28–52% at 2–5 years have been reported in various studies [4, 8, 16, 17, 20, 21]. There is a great heterogeneity in these studies regarding the conditioning regimens, purging or not, use of CR 1 or CR 2 bone marrow, and the time from second CR to transplantation. In only two studies was the efficacy of ABMT analyzed according to the duration of first remission. Petersen et al. [17] reported a 2-year DFS of 47% in patients with long first CR (>13 months) compared with 23% in patients with shorter first CR. On the other hand, Chopra et al. [4] found no correlation between DFS after ABMT with duration of first CR. The main weakness of all ABMT

studies in second CR is the selection bias, since in none of these studies was an intent-to-treat analysis performed. Although not stated, it is likely that poor-prognosis patients (those with severe infection after salvage therapy or older patients) did not proceed to ABMT. Therefore, these favorable results should be considered with caution and cannot be compared easily with the chemotherapy results. There is an urgent need for randomized trials comparing conventional chemotherapy vs ABMT in particular in patients with second CR after late relapses (12–18 months). In patients with early relapses (<12 months), the chance of cure by conventional postremission chemotherapy is small and, therefore, experimental treatment protocols, among them ABMT, are justified.

It would be important to identify patients with second CR after late relapses who benefit from conventional postremission chemotherapy. Among our seven long-term remitters (>2 years), two had a relatively long-lasting first CR, but five patients had a second CR which was considerably longer than the first CR. The probably most important predictive factor is the karyotype; 3/7 patients had a favorable karyotype (t(8;21), inv 16, t(15;17)). Archimbaud et al. [2] noted that patients with M4E0 had a significantly longer second CR following chemotherapy, and Kantarjian et al. [14] reported that the proportion with favorable cytogenetics was high among patients with late relapses, but they did not report the karyotype of patients in long-term remission after CR 2.

The reasons for the longer duration of the second than the first CR in a subgroup of patients remains unclear. One possibility may very well be a higher dose intensity of chemotherapy given in relapse compared with that of first-line treatment. In particular, high-dose ARA-C during salvage therapy, but not during first-line chemotherapy would be a likely explanation. This explanation does not apply for the majority of our patients, however, since two long-term remitters did not receive high-dose ARA-C after first and second CR, and four long-term remitters received high-dose ARA-C after the first and second CR. In only one patient was high-dose ARA-C given not after first CR but after second CR. Chemotherapy at relapse is usually initiated at an earlier time point than at the first manifestation. Administration of chemotherapy at the time when the tumor burden is less could be considered as a possible reason for a more sustained effect of antineoplastic treatment. Considering the small difference in tumor burden at early relapse and at overt leukemia, however, early initiation of treatment could at best explain minimal differences. Finally, other factors, in particular immunological factors, have to be considered. There is substantial evidence in the literature that the immune system may play a pivotal role in the suppression of a leukemic clone and in the prevention of relapse. It is of interest that three of our patients had long-lasting infectious and/or inflammatory complications which may have caused an unspecific immune stimulation. Whatever the mechanism of a long second CR may be, a uniform explanation cannot be given for this group of patients.

In conclusion although this and other studies show that a small number of patients after the first relapse may enjoy a second long-term remission, the overall chance of long-term remission of a relapsed patient with AML is <5%. Therefore, the main efforts have to be concentrated on the prevention of relapse.

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