Improved outcome after relapse in children with acute myeloid leukaemia

European studies have shown that the 5-year survival in acute myeloid leukaemia (AML) in children has improved, from 40% for patients diagnosed from 1984 to 1989 to 60% for those diagnosed after 1992 (Creutzig et al., 2005; Gibson et al., 2005; Lie et al., 2005; Perel et al., 2005). This is generally attributed to intensification of chemotherapy facilitated by improvements in supportive care. The current therapy for AML is now so intensive that several groups have reported that further intensification may lead to inferior results because of excessive toxicity (Lie et al., 2003); (Creutzig et al., 2000). Therefore, while awaiting novel methods for targeted strategies, many AML trials now attempt to improve prognosis by stratifying therapy to different patient subgroups, mainly defined by cytogenetic characteristics and initial response to therapy.

Despite the progress made, relapse remains the leading cause of failure in therapy for childhood AML. Previous reports on outcome following relapse have shown a survival of 20–25%, with only 10% in patients with a first remission duration of <1 year (Stahnke et al., 1998; Webb et al., 1999). However, recent data, in particular, the Nordic Society for Paediatric Haematology and Oncology (NOPHO) AML93 study and the Leucémie Aiguë Myéloblastique Enfant (LAME) 89/91 trial, have shown a difference between event-free survival (EFS) and
overall survival (OS) of more than 10%, implying that a significant proportion of patients were cured following relapse (Lie et al, 2005; Perel et al, 2005). In the latter trial, one-third of all relapsed patients survived, including a survival of 24% in patients with early relapse (Aladjidi et al, 2003).

To optimise relapse treatment, it is important to identify factors related to outcome in these patients. Issues needing to be resolved are, for example, how to define those patients for whom curative therapy using current methods may not offer a realistic chance of cure, and which patients should be selected for experimental therapy. Furthermore, data evaluating the efficacy of different re-induction regimens are lacking and the relative merit of autologous bone marrow transplantation (ABMT) and allogeneic stem-cell transplantation (SCT) with a matched unrelated donor (MUD) needs further investigation. A higher cure rate of relapse may influence the choice of frontline therapy by narrowing the indications for SCT in first complete remission (CR1).

In the Nordic countries, all children with AML, diagnosed between 1988 and 2003, were treated and prospectively registered on two consecutive protocols (NOPHO-88 and -93). In this population-based material, we analysed therapy and factors associated with outcome in the 146 patients who relapsed after treatment on these protocols. The report confirmed that an increasing proportion of children with relapsed AML can be cured, including a subgroup of patients with early relapse.

Patients and methods

From January 1988 to December 2003 all children in the Nordic countries below 15 years of age with AML were registered and treated according to two consecutive study protocols, NOPHO-88 and -93. Patients with myeloid leukaemia of Down syndrome were also included. Some adolescents between 15 and 18 years were treated on the protocols and 11 of these relapsed and are included in this study. Patients with secondary AML and myelodysplastic syndrome were excluded. Data on patient and disease characteristics, including French–American–British (FAB) type, immunophenotype, cytogenetics, response to therapy, toxicity and treatment specifics, were entered into the NOPHO database. Additional data on relapse therapy were requested from the treating clinics.

Nordic Society for Paediatric Haematology and Oncology-88 was a very dose-intensive protocol with three induction blocks given at short intervals (Lie et al, 2003). The antileukaemic effect was significant, with an EFS of 41% and OS of 47%. However, toxicity was severe with a high frequency of death during induction or on remission. NOPHO-93 contained the same treatment blocks but patients were stratified according to response to the first course. Patients with good response were allowed to recover before continuation of therapy and received only two induction courses. This approach led to a significant reduction of toxicity and to an EFS of 50% and OS of 66% (Lie et al, 2005). Figure 1 shows the outline of treatment in the trials. In both protocols, patients with a human leucocyte antigen identical sibling were recommended for SCT in CR1. At the discretion of the responsible physician, patients without a donor could, after completing standard consolidation, be treated with ABMT. This practice was more common in NOPHO-88 (12/38) than in NOPHO-93 (6/108).

The study includes all patients who entered remission on the treatment protocols and subsequently experienced a first relapse before 1st January 2004. Bone marrow relapse was
defined as the presence of more than 5% leukaemic cells on morphological bone marrow examination and central nervous system relapse if the cerebrospinal fluid contained more than five leukaemic cells /μl. Remission was defined as <5% blast cells on morphological examination of a non-hypoplastic bone marrow.

**Statistical methods**

Analysis was performed using the statistical package for the social sciences (SPSS) software, version 11.0. Differences in proportions were assessed with Fischer’s exact test for 2 × 2 contingency tables and Pearson’s chi-squared for higher order tables. Differences in median values were tested with the Mann–Whitney *U*-test. The Kaplan–Meier method was used to construct survival curves and differences between factors were tested with the log-rank test. Survival time was calculated from day of relapse until death. All living patients were censored at time of last follow-up but no later than 1st February 2005. Cox regression was employed to evaluate the impact on survival of both categorical and continuous variables. All *P* values were twosided, and were considered significant when <0.05. Estimates of survival were at 5 years and are given as % probability of survival ± SE.

**Results**

In all, 38 of the 108 patients treated on NOPHO-88 and 108 of the 281 treated on NOPHO-93 had a relapse. The median observation time of the survivors was 4.9 years (ranges: 1.0–15.7). Table I shows patient characteristics in relation to outcome. The vast majority of patients had isolated bone marrow relapse. The median time from date of CR1 to relapse was 0.9 years with four occurring later than 3 years. Early relapse, defined as relapse within 1 year of entering CR1, and late relapse occurred in 80 and 66 patients, respectively. Five children had Down syndrome of whom two survived.

**Remission induction**

Treatment data were available for 143/146, including data on second complete remission (CR2) in 139 patients. Figure 2 gives an overview of the number of patients that received re-induction therapy, entered CR2 and proceeded to consolidation therapy.

Overall, 66% (92/139) of patients achieved a documented remission. Only 42% (8/19) and 41% (7/17) of those treated in CR1 with SCT and ABMT, respectively, entered CR2 as compared with 74% (77/104; *P* = 0.002) that received chemotherapy only in CR1. Patients with early relapse had a remission rate of 53% (40/76) as compared with 81% (52/64; *P* < 0.001) in late relapse. Patients treated on NOPHO-88 were less likely to achieve CR2 than those on NOPHO-93 (47% 17/36 vs. 72% 75/104; *P* = 0.007). However, several patients did not receive treatment with curative intent and, as this correlated with both protocol and type of consolidation therapy in CR1, these patient groups were analysed separately.
Patients not receiving re-induction treatment. No attempt at curative therapy was made in 21 patients whereas re-induction therapy was given in 122. The children receiving only palliative treatment more often had early relapse (18/21 vs. 59/122; \( P = 0.002 \)) or had SCT (9/21 vs. 10/122; \( P < 0.001 \)) or ABMT in CR1 (6/21 vs. 12/122; \( P < 0.001 \)).

Seventy-eight percentage (29/37) of children treated on NOPHO-88 received re-induction treatment versus 88% (93/106; NS) on NOPHO-93. Three of the patients given palliative treatment entered remission but all 21 children died with a median survival of 7 weeks.

Patients receiving re-induction treatment. No specific relapse therapy was indicated in the protocols. In patients receiving re-induction therapy, 77% (92/122) entered CR2 and treatment details were available in 115. Forty-four received re-induction therapy, 77% (92/122) entered CR2 and 10 patients who had SCT in CR1 and 12 patients who had ABMT had a similar remission rate to those treated with only chemotherapy in CR1. Gender, FAB type, specific cytogenetic abnormalities and protocol at initial diagnosis did not correlate with remission rates. Multivariate analysis confirmed that time to relapse was the only independent predictor of remission rate.

Early death, defined as death within 3 months from diagnosis of relapse, occurred in 10 patients. Three of these children had progressive disease (one after second relapse), five were in CR2, and two had aplasia after the first course of therapy. Five had received NOPHO upfront blocks, one FLAG, one FLAG+ and one MACE.

Remission rates were lower in patients with early relapse, in whom 65% (37/57) entered remission versus 85% (52/61; \( P = 0.01 \)) in late. Of those with early relapse, 34% had resistant disease as compared with 11% (\( P = 0.001 \)) in late. In patients receiving re-induction therapy, 10 patients who had SCT in CR1 and 12 patients who had ABMT had a similar remission rate to those treated with only chemotherapy in CR1. Gender, FAB type, specific cytogenetic abnormalities and protocol at initial diagnosis did not correlate with remission rates. Multivariate analysis confirmed that time to relapse was the only independent predictor of remission rate.

Survival

Consolidation therapy in CR2 and survival. Of all patients, 33% (48/146) survived. Projected probability of survival at five years was 34 ± 4%. All survivors were from the group receiving re-induction therapy, of whom 39% (48/122) survived. In the patients with documented CR2, 51% (47/92) survived; the only additional survivor was a patient who received SCT in partial remission.

Of the 92 patients entering CR2, five had early toxic death in CR2 and three suffered a further relapse within 3 months. Of the remaining patients, 62 received consolidation therapy with allogeneic SCT at a median of 117 d from relapse, 18 with chemotherapy and four had palliative therapy. Two additional patients received SCT, one in partial remission and one with no data on CR2 status.

The individual reasons for choosing chemotherapy as only consolidation therapy in CR2 is not evident from the data, but 6/18 had had SCT in CR1 as opposed to none of those transplanted in CR2. As these groups differ so much, no unbiased comparison can be made of the effect of different consolidation regimens in CR2.

Table II. Remission rate for patients receiving different induction regimens for relapsed acute myeloid leukaemia*.

<table>
<thead>
<tr>
<th>Remission achieved</th>
<th>NOPHO upfront</th>
<th>FLAG</th>
<th>FLAG+</th>
<th>MACE</th>
<th>Other</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>34 (77%)</td>
<td>36 (78%)</td>
<td>3 (43%)</td>
<td>11 (69%)</td>
<td>84 (74%)</td>
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<td>No data</td>
<td>10</td>
<td>10</td>
<td>4</td>
<td>5</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>44</td>
<td>46</td>
<td>7</td>
<td>18</td>
<td>115</td>
<td></td>
</tr>
</tbody>
</table>

*Two patients lacked data on remission achieved. NOPHO, Nordic Society for Paediatric Haematology and Oncology upfront was either ATEDox (cytarabine, etoposide, thioguanine, doxorubicin) or AM (cytarabine and mitoxantrone) induction courses, FLAG, fludarabine, cytarabine; G-CSF, FLAG+: FLAG with idarubicin or liposomal daunorubicin; MACE, amsacrine, cytarabine and etoposide.
Nonetheless, 61% (39/64) of children transplanted for relapse survived, with a 5-year survival probability of 62 ± 6%. There was no significant difference in survival between those having matched unrelated donor (MUD; 72% (13/18) or MUD; 57% (26/46)]. Treatment-related deaths in CR2 occurred in 20% (9/46) of MUD and 11% (2/18) of MFD transplanted patients.

Of those receiving chemotherapy, 44% (8/18) survived. However, the majority surviving in this group had unusual features, such as Down syndrome (n = 2), isolated extramedullary disease (n = 2), or received experimental therapy, such as donor lymphocyte infusion and/or all trans-retinoic acid after SCT in CR1 (n = 3).

Factors associated with survival. Both in univariate and multivariate analysis, the most important determinant of survival was length of remission before relapse. Only 21% (17/80) of patients with early relapse survived as compared with 47% (31/66) of those with late relapse. The Kaplan–Meier plot showed a significant difference in survival with a survival after relapse of 21 ± 5% in early and 48 ± 6% in late relapse (P < 0.001, log-rank test; Fig 4). Analysis of survival in only those who received re-induction therapy (Fig 4B) demonstrated a survival of 29 ± 6% in early and 51 ± 6% (P = 0.006) in late relapse. In patients treated with SCT for relapse, 56% (13/27) with early and 65% (24/37) with late relapse survived.

As shown in Fig 5, univariate analysis demonstrated that type of consolidation therapy in CR1 had a significant impact on survival. Only 1/18 treated with ABMT and 4/20 treated with SCT in CR1 survived.

The survival rate increased from 16% (6/38) treated on NOPHO-88 to 39% (42/108, P = 0.009) on NOPHO-93. When analysing the whole cohort or only those receiving re-induction therapy, no significant effect on survival of gender, FAB type, karyotype or response to frontline treatment was found.

As factors related to outcome were interrelated, a Cox regression model was assessed using length of CR1, consolidation treatment in CR1, initial treatment protocol, relapse treatment regimen, FAB type, karyotype, age and gender as predictors entered with a forward stepwise conditional algorithm. The analysis was performed both in all patients and.
after excluding those not receiving re-induction therapy and demonstrated that only length of remission and consolidation therapy in CR1 were strong and independent predictors of survival after relapse.

Of the 98 patients who died, 90 were evaluable for cause of death; 45 died of progressive disease without entering remission, 26 after further relapse, 18 of toxicity in remission (11 after SCT) and one of a second malignant neoplasm.

Discussion

Current therapy for childhood AML can achieve an EFS of 50% and OS of 60–65% (Kaspers & Creutzig, 2005). The leading cause of treatment failure is relapse, which, even in studies with the highest cure rates, occurs in 35–43% of patients (Gibson et al., 2005); (Lie et al., 2005); (Perel et al., 2005). The prognosis for patients with relapse has been shown to be poor, with survival rates of 20–25%, but the French LAME 89/91 study has recently reported a survival after relapse of 33% (Aladjidi et al., 2003). As in adults, the main prognostic factor found was length of CR1 (Kern et al., 2000; Graddock et al., 2005).

From 1984, the Nordic countries have treated AML according to common protocols with recruitment of all patients <15 years of age. As for other collaborative groups, the results have improved and, particularly in the NOPHO-93 study, a large difference between EFS of 50% and OS of 66% was observed, indicating that a significant proportion of relapsed patients were salvaged (Lie et al., 2005). The present report analysed the outcome for all patients with relapse in the NOPHO-88 and -93 trials and showed a 5-year survival of 34%.

As the protocols did not include guidelines for relapse therapy, the analysis of variables related to outcome was confounded by several factors. Most important was that 15% of all patients, at the discretion of the physician and families, did not receive re-induction therapy. These patients were more likely to have early relapse and/or previous transplant, so it is reasonable to assume that the main reasons for withholding therapy were expectations of a low chance of cure and high toxicity.

In accordance with previous studies, length of CR1 was the strongest predictor of survival. When including all patients, those with early relapse (<1 year in CR1) had a survival after relapse of 21% when compared with 47% with late relapse. However, for those who received re-induction therapy, survival was 40% (29% in early relapse and 51% in late relapse). The UK Medical Research Council (MRC) AML10 trial, which is one of three relatively recently published large studies on relapsed childhood AML, reported a 3-year survival of 24% with only 11% for early relapse (Webb et al., 1999). The median time to relapse was the same in NOPHO and MRC AML10 but, in the latter study, almost 30% of patients did not receive re-induction therapy. The Berlin–Frankfurt–Münster (BFM) study, which only included the 76% of patients who actually received re-induction therapy, reported a survival of 21% with very poor results in early relapse (Stahnke et al., 1998). Our results can best be compared with the LAME 89/91 study, in which 91% of all patients were given re-induction and resulted in a survival of 33% with 24% in early relapse (Aladjidi et al., 2003). However, the French trial was not population-based, included adolescents up to the age of 20 years, and excluded those with FAB M7.

Although the prognosis for patients with early relapse still must be recognised as poor, it is evident that a significant proportion of these patients can be cured. Importantly, although one-third of early relapse had resistant disease, of those who entered remission and were consolidated with SCT, 55% survived as compared with 64% in late relapse. Taken together, these data strongly encourage that a majority of patients with relapse should be offered re-induction therapy.

Prior SCT in CR1 also correlated with poor prognosis. Only one of 18 patients with ABMT in CR1 survived. As no toxic deaths occurred it may be that relapse after ABMT is associated with more chemo-resistant disease. Only half of the patients relapsing after allogeneic SCT received re-induction but three of the four survivors were treated with immunomodulating or differentiation therapy. No patient had a second transplant but several reports indicate that, although long-term sequelae are common, children with good performance status in general tolerate the procedure (Aladjidi et al., 2003; Eapen et al., 2004). Providing adequate disease control is achieved, a second SCT may be seriously considered. Alternatively, particularly in very early relapse...
after SCT, treatment with donor lymphocyte infusion is an option (Collins et al, 1997; Choi et al, 2004).

Remission rates were high with 65% in early and 88% in late relapse. As rates for the re-induction regimens were comparable and numbers low, no firm conclusion can be drawn on which is preferable. It is, however, noteworthy that induction blocks used in front-line therapy are equally effective as FLAG therapy and that the remission rate in late relapse approaches that of primary treatment. In vitro studies also showed that AML blasts at relapse are no more drug resistant than at primary diagnosis (Styczynski & Wysocki, 2004). This may not hold true following low-intensive maintenance therapy, as a randomised study within LAME 89/91 showed that remission rates and survival was much lower in those receiving maintenance therapy (Perel et al, 2002). Moreover, the BFM study, which incorporated maintenance in primary therapy, had a remission rate of only 50%.

It could be argued that FLAG has several advantages as re-induction therapy. The anti-leukaemic effect in this and other studies is significant and we and others observed a very low-toxic mortality (McCarthy et al, 1999). Furthermore, most upfront AML protocols contain high doses of anthracyclines and, with the prospect of including cardiotoxic treatment in conditioning regimens prior to SCT, it is preferable to avoid further anthracycline load.

The large differences between patients receiving allogeneic SCT and chemotherapy as consolidation in CR2 precluded any comparison between these modalities. It is, however, encouraging that patients who received SCT after relapse had a 5-year survival of 62%. In all, 44% of all patients with relapse and 70% of those achieving remission had an allogeneic transplant. This is higher than in other paediatric relapse studies. Most patients received MUD transplant and the treatment-related mortality was only slightly higher with MUD than MFD and survival was similar. In relapsed acute lymphoblastic leukaemia, SCT with MUD has been shown to be at least as effective as MFD, and our data imply that this may also be the case in AML (Saarinen-Pihkala et al, 2001).

In conclusion, cure rates following intensive re-induction and SCT are encouragingly high for late AML relapse. In early relapse, the subset of patients who achieve remission also have a good chance of cure. Treatment with curative intent is therefore justified in the majority of patients with first relapse. Remission rates were high with many re-induction regimens but FLAG may be preferable because of the low risk of toxic mortality and minimal cardiotoxicity.

**Authorship contributions**

All authors were, as members of the NOPHO–AML study group, involved in the design of the study. JA, NC, HH, BZ, GJ and LH, were responsible for data collection within each Nordic country. EF reviewed cytogenetic data and JH flow cytometry data. GG collected and constructed the database and made quality controls of the data. Data was analysed and the paper written by JA but all co-authors contributed to the analysis and writing of the paper, in particular HH as chairman of the AML group.

**References**


