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## Optimal treatment intensity in children with Down syndrome and myeloid leukaemia: data from 56 children treated on NOPHO-AML protocols and a review of the literature

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**Abstract** Children with Down syndrome (DS) and myeloid leukaemia have a significantly higher survival rate than other children, but they also experience considerable treatment-related toxicity. We analysed data on 56 children with DS who were treated on the Nordic Society for Paediatric Haematology and Oncology-acute myeloid leukaemia (NOPHO-AML)88 and NOPHO-AML93 protocols and reviewed the literature. In the dose-intensive NOPHO-AML88 protocol, 8 out of 15 patients (53%) experienced an event. In the less dose-intensive NOPHO-AML93 protocol, 7 out of 41 patients (17%) had an event. Therapy was reduced in 29 patients (52%) with in average 75% and 67% of the scheduled dose of anthracycline and cytarabine, respectively. Treatment-related death occurred in seven who all received full treatment. Relapse and resistant disease occurred at a similar rate in those receiving full and reduced treatment. Review of major series of myeloid

leukaemia of DS showed no clear relationship between dose and survival; however, it appears that both a reduction in treatment dose and a less intensively timed treatment regimen improved the outcome. Further studies are needed to define the optimal regimen for treating myeloid leukaemia of DS.

**Keywords** Down syndrome · AML · Therapy · Children

### Introduction

Children with Down syndrome (DS) have a significantly increased risk of developing myeloid leukaemia described as myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML). Due to the unique features of MDS and AML in DS children, including the presence of GATA1 mutation in vast majority [1], the unifying term myeloid leukaemia of DS (ML-DS) has been used for this disorder [2]. Recent years have seen a number of studies with AML therapy producing event-free survival (EFS) of more than 75% [3–5] in ML-DS compared with EFS of around 50% in AML children without DS [6–8]. The favourable outcome in ML-DS has been explained by the increased sensitivity to cytarabine and daunorubicin [9–11] as well as a higher susceptibility of DS cells to apoptosis [4, 12].

ML-DS typically occurs at 1–2 years of age, and in contrast to the transient leukaemia seen in some newborns with DS, it is the universal experience that without anti-leukaemic treatment, all patients with ML-DS die from progressive disease [13, 14]. Very intensive therapy is associated with a significantly higher mortality in ML-DS [15], and chemotherapy doses are often reduced in DS patients. The optimal balance between dose intensity and the risk of treatment-related toxicity has not yet been defined. We studied the association between treatment intensity and outcome in children with ML-DS by reviewing the literature and analysing data on patients treated on the Nordic Society for Paediatric Haematology and Oncology (NOPHO)-AML protocols.

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## Patients and methods

### Design

All children with leukaemia in the Nordic countries are treated according to common Nordic protocols [16]. Data are registered in the NOPHO database at Barncancerforskningsenheten, Astrid Lindgrens Barnsjukhus in Stockholm.

We reviewed data on patients with DS who had been diagnosed as having myeloid leukaemia in the period from 1988 to 2002 and treated according to the NOPHO-AML88 or NOPHO-AML93. We included two Danish patients diagnosed as having MDS, treated as AML, but not reported to the AML database. Two children reported to the NOPHO-AML88 received no treatment and were excluded from this study.

We identified 56 DS children (13%) treated according to the NOPHO-AML88 ( $n=15$ ) and the NOPHO-AML93 ( $n=41$ ) protocols.

The treatment has been described previously [6]. The flow charts of the NOPHO-AML88 and NOPHO-AML93 are shown in Fig. 1. In short, the treatment courses consisted of ATEDox: cytarabine 200 mg/m<sup>2</sup> continuous infusion days 1–4, 6-thioguanine 100 mg/m<sup>2</sup> b.i.d. orally days 1–4, etoposide 100 mg/m<sup>2</sup> continuous infusion days 1–4, doxorubicin 75 mg/m<sup>2</sup> day 5; AM: cytarabine 100 mg/m<sup>2</sup> continuous infusion days 1–5, mitoxantrone 10 mg/m<sup>2</sup> days 1–3; HA<sub>1</sub>M: cytarabine 1 g/m<sup>2</sup> 2-h infusion b.i.d. days 1–3, mitoxantrone 10 mg/m<sup>2</sup> days 3–5; HA<sub>2</sub>E: cytarabine 2 g/m<sup>2</sup> 2-h infusion b.i.d. days 1–3, etoposide 100 mg/m<sup>2</sup> days 2–5; HA<sub>3</sub>: cytarabine 3 g/m<sup>2</sup> 2-h infusion b.i.d. days 1–3. For children less than 2 years of age, chemotherapy was calculated per bodyweight.

No special treatment recommendations for DS patients were given in the protocol; however, no haematopoietic stem cell transplantations were performed in the DS children.

Data were retrieved from the NOPHO-database, and when necessary, treatment details were requested from the treating clinics.

### Statistics

The Kaplan–Meier plot was applied to estimate the EFS from the day of diagnosis. Events were defined as resistant disease, relapse or death of any reason. Patients with resistant disease were considered failures at time zero. EFS was compared using log-rank test and Cox regression analysis. Univariate analysis was conducted by Wilcoxon rank-sum test for quantitative variables and Fisher's Exact Test for qualitative variables. Computations were performed using Intercooled Stata 8.2. Outcome data were analysed as of January 1, 2004.

## Results

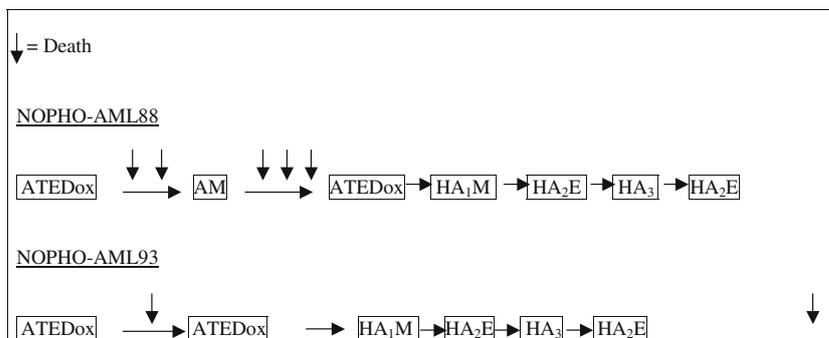
### Patients' characteristics

The epidemiological and clinical characteristics of the Nordic DS patients were published recently [16]. The median age in the present cohort was 2.0 years, with only one patient more than 4 years of age at the time of diagnosis. There were no statistically significant differences in the distribution of gender, age and white blood cell between patients on protocols NOPHO-AML88 and NOPHO-AML93 or between patients receiving reduced or full-treatment dose (data not shown). The majority of patients were diagnosed as having AML M7, the proportion of M7 increased with time due to improved diagnostics.

### Treatment modifications

Twenty-nine patients (52%) were given reduced therapy, receiving in average 75% of the anthracycline and 67% of the cytarabine dose compared with the doses scheduled in the protocol. Eighteen children received all scheduled courses but with dose reduction (one relapse and one resistant disease); six patients received a reduced number

**Fig. 1** Flow chart of NOPHO-AML88 and NOPHO-AML93 with temporal occurrence of the TRDs. For abbreviations, please see text



**Table 1** Outcome with reduced and full therapy among 56 DS children treated on the NOPHO-AML88 and NOPHO-AML93

	Full therapy	Reduced therapy
Patient number	27	29
Treatment-related death	7 (26%)	0 (0%)
Relapse/Resistant	4 (15%)	4 (14%)
Surviving in CR1	16 (59%)	25 (86%)

of courses (one resistant disease); five were reduced both in doses and number of courses (one resistant disease).

Four of the 18 patients who received all courses but with dose reduction were reduced during induction only, 2 during consolidation only, and 12 were reduced during both induction and consolidation.

### Outcome

Eight of the 15 patients (53%) treated on the NOPHO-AML88 experienced an event; 5 died from treatment-related deaths (TRDs), 2 had resistant disease and 1 relapsed.

Seven of the 41 patients (17%) treated on the NOPHO-AML93 had an event; 2 died from TRD, 2 had resistant disease and 3 suffered from relapse.

All seven patients who died from TRD received full-treatment dose. Of the eight patients who had a relapse or resistant disease, four received full dose and four reduced dose therapy (Table 1).

Figure 1 illustrates the temporal occurrence of TRDs. All seven cases of TRD were caused by infections. No deaths were due to cardiac toxicity, and no patients developed late cardiac failure (median follow-up 8 years). Six patients died during therapy; five were treated on the NOPHO-AML88 and one on the NOPHO-AML93. All patients except one died in relation to the induction courses. One patient died from pneumonia 2 months from the last consolidation course after recovering from cytopenia.

Many patients experienced respiratory distress following induction chemotherapy. Five children required treatment

at an intensive care unit because of the respiratory problems. These adverse effects all occurred in relation to the first course of induction.

The EFS increased from 47% in the NOPHO-AML88 to 85% for children treated on the NOPHO-AML93 (hazard ratio=4.7,  $p=0.005$ ). The Kaplan–Meier plot illustrates that almost all events occurred within the first 12 months since diagnosis (Fig. 2).

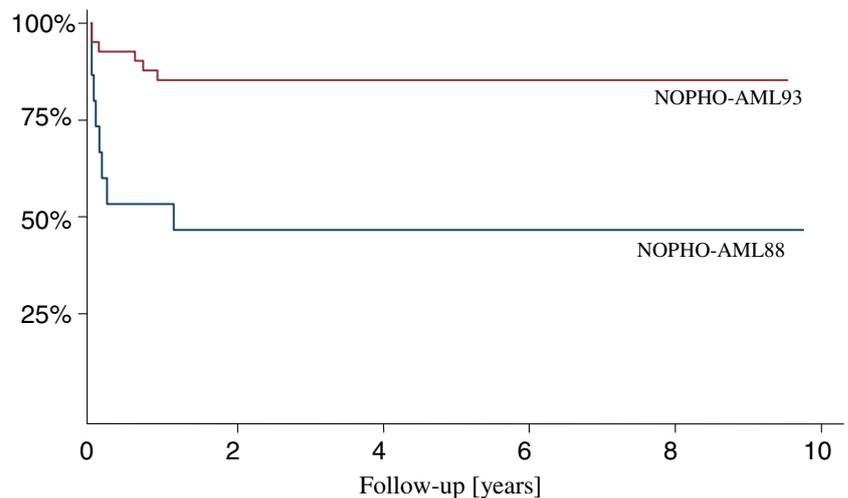
On the NOPHO-AML93, 17 patients received full-treatment dose, and 24 patients received reduced treatment. Figure 3 shows the EFS of the two groups. Those receiving reduced treatment had an EFS of 92% compared with an EFS of 76% in the group receiving full treatment (hazard ratio=3.2,  $p=0.17$ ). The data indicated no difference in outcome for patients who received reduced treatment dose compared with those who received reduced number of courses. Nine of ten patients who received less than the recommended four consolidation courses were alive in continuous complete remission.

The NOPHO-AML88 was intended to have an interval of only 16 days from the start of the first induction course to the beginning of the second. But the condition of the patients made it impossible to enforce this in most cases. The interval between the first two courses in DS patients was in average 28 days. The interval was 14, 19 and 29 days in the three patients who died after the second induction course. In the NOPHO-AML93, the second course should not be given until bone marrow (BM) recovery was achieved, which lasted in average 43 days for the DS patients. No patients died from TRD following the second induction course in the NOPHO-AML93.

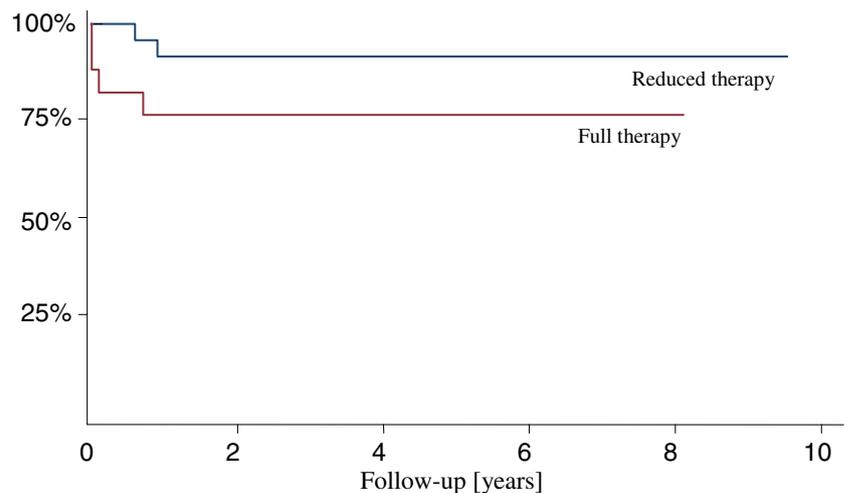
### Review of the literature

Major series of ML-DS from North America, Japan, Germany and United Kingdom were reviewed.

Comparing the studies, anthracycline dose was converted into daunorubicin equivalents using a conversion factor of 1 for doxorubicin and 5 for idarubicin and mitoxantrone. The cumulative doses of anthracyclines and

**Fig. 2** EFS in NOPHO-AML88 and NOPHO-93

**Fig. 3** EFS in NOPHO-AML93 according to reduced or full-dose therapy



cytarabine in relation to survival are illustrated in Table 2. The survival rates are not directly comparable because of different types of survival analyses and follow-up. When available, we used EFS, but two studies only reported overall survival [13, 14]. The time of follow-up varied in the different studies from 4 to 8 years, but no events occurred after 4 years of follow-up, and therefore, the variation in follow-up is of minor importance.

The Pediatric Oncology Group (POG) published in 1992 [17] the results of AML Study 8498 including 12 DS children treated with standard AML induction therapy followed by post-remission therapy with high-dose cytarabine (HdA) with or without L-asparaginase. The therapy was relatively well tolerated without any toxic deaths resulting in a remarkable 4-year EFS of 100%.

The Children's Cancer Group studies 2861 and 2891 [3, 15] included 118 children with ML-DS. The children were randomised to either an intensively timed or standard-timed induction therapy. Outcome data were available for 110 patients.

The treatment consisted of two induction cycles with a five-drug, dexamethasone, cytarabine, 6-thioguanine, etoposide and daunorubicin (DCTER), regimen and consolidation courses based on HdA.

The children with DS on Children Cancer Group (CCG)-2861 and CCG-2891 had an EFS of 68%. The intensively timed therapy was associated with unacceptably high mortality and no significant reduction in relapse rate in children with DS. In contrast to non-DS children, standard-timed therapy significantly improved the EFS in DS to 74% compared with 52% on intensively timed therapy [15].

A Japanese study [18] used a treatment regimen specifically designed for children with DS. Each chemotherapy course consisted of low-dose daunorubicin, cytarabine and etoposide and was used for both induction and consolidation. The number of courses varied between two and eight. The protocol included no HdA.

The 8-year EFS for the 33 children was 80%. Three children relapsed, three children died of TRD, two children with congenital heart anomalies developed congestive heart

**Table 2** Studies of AML in DS

Study	N	Dauno (mg/m <sup>2</sup> )	AraC (g/m <sup>2</sup> )	TRD (%)	RD (%)	Relapse (%)	EFS (%)
AML-BFM-98 [5]	66	220–240	23–29	5	0	6	89
AML-BFM-87/93 [13]	21	220–400	23–43	33	0	14	48 <sup>a</sup>
POG 8498 [17]	12	230	40.7	0	0	0	100
Japan [18]	33	300	4.2	9	0	9	80
NOPHO-AML93 [present study]	41	300	49.6	5	5	7	85
CCG-2861/2891 [15]							
Standard timing	85	320	15.2	2	2	ND	74
Intensive timing	25	320	15.2	32	4	ND	52
NOPHO-AML88 [present study]	15	450	50.1	33	13	7	47
MRC AML 10 [14]							
Less intensive	13	ND	ND	8	8	38	46 <sup>a</sup>
AML 10 like	32	650	10.6	34	0	8	59 <sup>a</sup>

The studies are ranked by increasing daunorubicin dose. N number of patients, Dauno cumulated dose of daunorubicin equivalents [19], AraC cumulated dose of cytarabine, TRD treatment-related death, RD resistant disease, EFS event-free survival, ND no data

<sup>a</sup>Overall survival

failure and died, and one child died due to septic shock in complete remission (CR). Although the treatment regimen of the induction and the consolidation therapy were exactly the same, the frequency of fever and infections was higher during the induction compared with the last consolidation. The protocol used no prophylactic central nervous system (CNS) therapy and observed no CNS relapses.

The German AML-BFM-87 and AML-BFM-93 studies [13] included induction with cytarabine, daunorubicin and etoposide, consolidation with cytarabine, doxorubicin, vincristine, 6-thioguanine, cyclophosphamide and prednisone, intensification with HdA and etoposide, and 1 year of maintenance treatment (6-thioguanine and cytarabine). Only 21 of the 40 patients were treated according to the protocol, and only 14 received full therapy. Among the 21 patients, the 5-year survival was 48%.

The AML-BFM-98 study used the same therapy as the BFM93 protocol but with recommendations for dose reduction and supportive care. The compliance with the protocol increased and resulted in a significant improvement in EFS to 89% [5].

The British Medical Research Council (MRC) AML 10 trial [14] compared the outcome of patients treated on the MRC 10 protocol ( $n=24$ ) with other intensive protocols ( $n=8$ ) or on individualised less intensive protocols ( $n=13$ ). The MRC 10 included cumulative doses of anthracyclines and cytarabine of  $650 \text{ mg/m}^2$  and  $10.6 \text{ g/m}^2$ , respectively. There were some modifications made to the protocol (two patients did not receive all courses) mostly because of excessive toxicity. The 5-year survival rate for the 32 children treated on the intensive protocol was 59%.

There was no difference in the remission and survival rates between the group that received full-treatment dose and the group with individualised treatment. However, deaths among the patients receiving full-treatment dose were mostly due to toxicity, whereas deaths in patients treated on individualised protocols mostly were the result of relapse or resistant disease.

## Discussion

The NOPHO database is considered to be population based [16]. When reviewing the DS data, we noticed two patients diagnosed as having MDS not reported to the database. There has been no consensus on whether children with DS and MDS should be included in the NOPHO-AML database. Therefore, there may be a few more patients with DS diagnosed as having MDS and not reported to the AML database. Today, there is an international agreement considering MDS and AML in DS as one disease [2].

Out of 15 patients treated on the NOPHO-AML88, 8 experienced an event (53%). This is much higher than for patients on the NOPHO-AML93, where only 7 out of 41 patients had an event (17%). The main difference between the two protocols was that the second course of induction on the NOPHO-AML93 was not given until BM recovery

was achieved. This resulted in a longer period between the first and the second induction courses (43 days in average on the NOPHO-AML93 compared with 28 days on the NOPHO-AML88) and thereby a less intensively timed induction regimen. The decreased time intensity arm of the CCG study also showed a reduction in TRD without worsening remission rates or number of relapse [15].

Twenty-nine patients received a reduced treatment in our study. Among them three patients had resistant disease and one relapsed. The low number of patients does not allow further analyses of the extent of reduction and the risk of relapse and resistant disease.

Six out of seven TRD and the most severe side-effects occurred in relation to the induction courses where the highest dose of anthracyclines is given. Furthermore, the long-term irreversible side-effects in the form of cardiomyopathy favour a reduction in anthracyclines. Several studies recommend a reduction in the use of anthracyclines with cumulative doses not exceeding  $250 \text{ mg/m}^2$  [13, 18].

Consolidation in the NOPHO protocol is based on four courses of HdA. No TRD occurred in relation to the consolidation, and we did not observe any major CNS toxicity. In addition, the CCG used HdA-based post-remission therapy without excessive toxicity in DS patients [15].

Intrathecal chemotherapy varied between the protocols from zero to eight injections. The Japanese protocol included no prophylactic CNS therapy and no HdA and experienced no CNS relapses [18]. None of the other studies reported any CNS relapses. CNS involvement at diagnosis is relatively rare in DS [3], suggesting that CNS-directed therapy may be reduced or even omitted without increased risk of relapse.

Etoposide was included in the BFM, NOPHO, MRC and Japanese studies but not in the CCG and POG protocols. It is difficult to evaluate the role of etoposide in the complex treatment regimens, but it may not be essential considering the favourable outcome reported by POG and the standard timing arm of CCG [15].

No apparent association is seen between survival and the cumulative doses of anthracycline and cytarabine (Table 2). The differences in the type of survival analyses and follow-up cannot explain the lack of correlation between dose and outcome. The poorest outcome was found among patients not treated according to protocol [13, 14] or patients receiving very time-intensive therapy as in CCG [15] and the present study (NOPHO 88). TRD was also high among those receiving the highest anthracycline doses [14]. The frequency of relapse showed no clear correlation with cumulated doses except a high relapse rate in those treated with non-intensive schedules [14]. There are good evidence for new treatment protocols to be less intensive regarding both timing and dose intensity [3, 13, 15, 18].

Only older age has been associated with an increased relapse rate [3]. DS children above 3 or 4 years of age may need more intensive therapy. Further studies are needed to identify those DS patients with a poor outcome on the reduced therapy schedules.

## Conclusion

A reduction in treatment dose as well as a less intensively timed treatment compared with standard AML regimens seems to improve the outcome for patients with DS and myeloid leukaemia. However, without intensive therapy, the relapse rate increases, and the optimal regimen for treating ML-DS is still not known. An international cooperative study including guidelines for supportive care may help define the best therapy for ML-DS.

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