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Chapter 7

Myeloid Leukemia Associated with Down Syndrome

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1. Introduction

Children with Down syndrome (DS) have a 10- to 20-fold increased risk of developing acute leukemia. [1-4] The relative risk of developing acute megakaryoblastic leukemia (AMKL) is estimated to be 500 times higher in children with DS than in those without DS. Interestingly, five to 10 % of neonates with DS develop transient abnormal myelopoiesis (TAM). In most cases, it resolves spontaneously within 3 months. However, approximately 15% of the severe cases are fatal and 20% of patients develop AMKL until 3 year-old (Fig.1). AMKL in DS has a number of distinct features and it is now considered a specific subtype of acute myeloid leukemia (AML) in the 4th edition of the World Health Organization (WHO) classification called Myeloid Leukemia of Down syndrome (ML-DS).

2. Acute Myeloid Leukemia (AML)

The majority of cases of AML with DS (70-100%) are megakaryoblastic [5] and occur within the first 4 years of life. [6] The characteristic antecedent preleukaemic TAM is observed in 20–30% of cases. Overt leukemia in DS children is preceded in 20- 60% of cases by an indolent myelodysplasia, characterised by thrombocytopenia and bone marrow fibrosis, which may last several months before overt AML. [1, 7] The median age at presentation of AML is 1.8 years. [7] The bone marrow aspirate shows dysplasia, increased blasts, abnormal megakaryocytes and variable myelofibrosis.[5, 7-8] Immunophenotypically, ML-DS blasts typically express megakaryocytic (CD42b and CD41) and erythroid markers (CD36 and Glycophorin A) as well as the T cell marker, CD7. [9]Neither the favorable cytogenetic changes, such as t(8;21), t(15;17), t(9;11) and inv(16), nor the AMKL-associated translocations, t(1;22) and t(1;3), occur in ML-DS.[1] Additional copies of chromosome 8 and/or 21 (in addition to the +21c, 10-15%), monosomy 7 and –5/5q- (together in 10–20%) are observed. [10]

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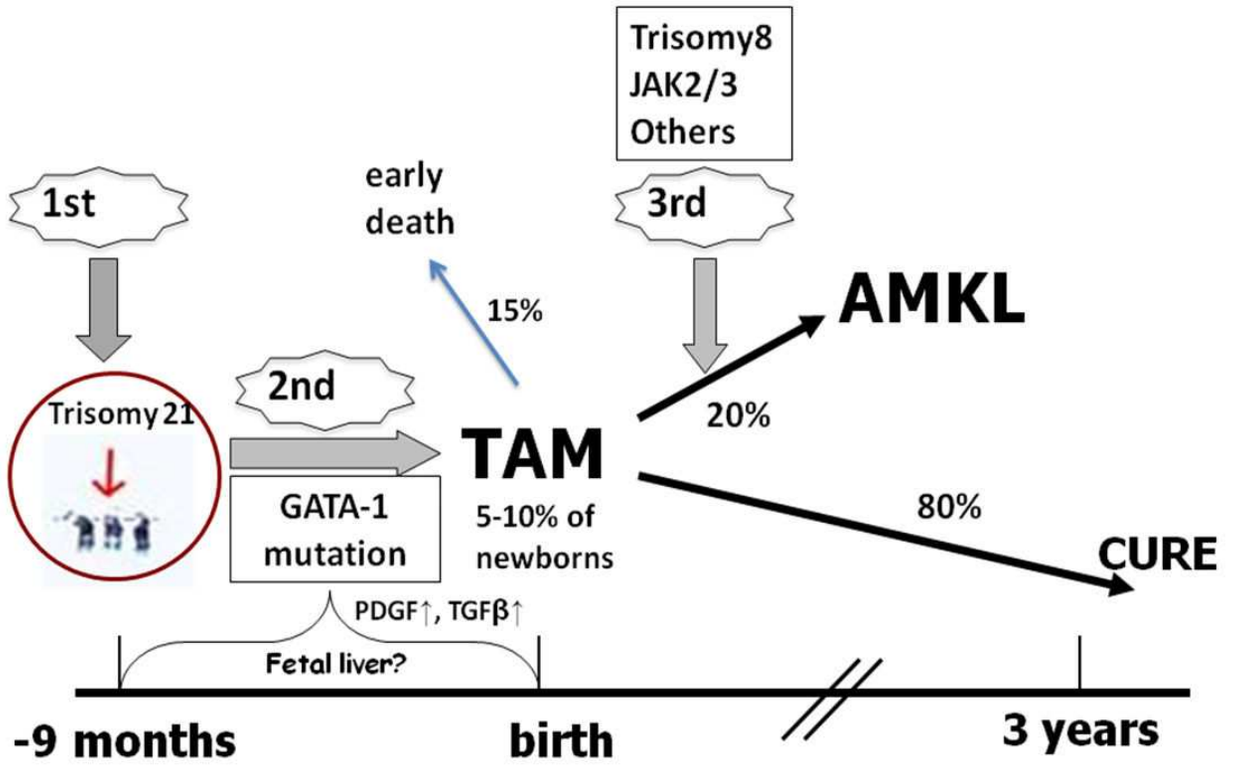

Figure 1. Multi-step model of myeloid leukemogenesis in DS. Trisomy 21 enhances the proliferation of fetal liver megakaryo-erythroid progenitors via PDGF and/or TGF beta. The acquisition of GATA1 mutation further enhances the clonal proliferation of immature magakaryoblasts diagnosed at birth as TAM. GATA1 mutations are necessary but insufficient for the development of AMKL. Additional genetic events such as trisomy 8, or JAK2/3 mutations have been proposed in progression from TAM to AMKL.

2.1. Treatment for AML-DS

Conventional treatment of AML-DS has been associated with excessive treatment-related mortality (TRM), cardiac toxicity due to anthracyclines and serious infections. Zwaan et al demonstrated a 12-fold increase in sensitivity to cytarabine in DS-AML cells compared with non-DS AML cells, as well as increased sensitivity to anthracyclines (two- to seven-fold) and etoposide (20-fold).[11] Several collaborative study groups have adapted their standard AML protocol for AML-DS by reducing the dose of drugs (Table 1).[5, 8, 12-17] In the Children's Oncology Group (COG) trial A2971 (n=132), [13] etoposide, dexamethasone, and the maintenance course were eliminated from the previous CCG2891 protocol. COG A2971 achieved a 5-year EFS rate of 79% plus or minus 7% (versus 77% plus or minus 7% in the CCG2891 trial) while maintaining a low induction failure rate of 6.4%, attaining a 0% CNS relapse rate, and sustaining an acceptably low 5-year postremission. In the AML-BFM98 study (n=66), [7] AML-DS patients were treated with reduced doses of anthracyclines and cytarabine compared with the previous AMLBFM93 protocol (n = 44). The cumulative doses of anthracyclines and cytarabine were 220 to 240mg/m2 and 23 to 29g/m2 in the BFM98 study, and 440mg/m2 and

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23.3 g/m2 in the AMLBFM93 study, respectively. Outcome improved significantly for patients treated in the AMLBFM98 study, with a 3-year EFS of 91% plus or minus 4% versus 70% plus or minus 7% in the AMLBFM93 study.

					Drugs administered			
Protocol	No of patients	EFS (%)	Relapse (%)	death in CCR (%)	Cytarabine (g/m2)	Daunorubicin (mg/m2)	Mitoxantrone (mg/m2)	Etoposide (mg/m2)
POG9421[12]	57	77 (5y)	7	14	20.7	135	80	1,000
CCG2891[5]	161	77 (6y)	14	4	15.8	320	0	1,600
COG-A2971[13]	132	79 (5y)	11	3	24.8	80	0	0
NOPHO-AML93[14]	41	85 (8y)	7	5	49.6	150	30	1,600
AML-BFM98[7]	67	89 (3y)	6	5	23-29	Ida; 26-36	0-14	950
MRC-AML10/12[8]	46	74 (5y)	3	15	7.8	300	50	1,500
AT-DS(Japan)[15]	33	80 (8y)	6	9	4.2	100-400	0	2,700
AML99 DS[16]	72	83 (4y)	12.5	1.4	3.5	THP; 250	0	2,250
JCCLSG 9805DS[17]	24	83 (5y)	0	13	12.6	THP; 135	10	200

POG, Pediatric Oncology Group; CCG, Children's Cancer Group; COG, Children's Oncology Group; NOPHO, Nordic Society for Paediatric Haematology and Oncology; BFM, Berlin-Frankfurt-Munster; MRC, Medical Research Council; JCCLSG; Japan Children's Cancer and Leukemia Study Group DS, Down syndrome; Ida, Idarubicin; THP, pirarubicin

Table 1. Comparison of the results in DS-AML patients

A treatment regimen specifically designed for AML-DS has been used in Japan since the mid- 1980s.[15, 16] AML 99 DS protocol consisted of pirarubicin (25 mg/m2/d, on days 1 and 2), which was estimated to be equivalent as 25mg/m2/d of daunomycin (DNR), cytarabine (100 mg/m2/d on day 1 through 7), and etoposide (150 mg/m2/d on day 3 through 5). Pirarubicin is much less cardiotoxic and more myelosuppressive than daunorubicin.A total of 70 of the 72 patients (97.2%) achieved a CR. The 4-year EFS was 83.3% plus or minus 9.1% and the 4-year OS was 83.7% plus or minus 9.5%. The regimen-related toxicities were relatively tolerable. Only one patient died as a result of pneumonia in the second course of intensification. The 3-year EFS in the five patients with monosomy 7 was significantly worse than in the 65 patients without monosomy 7 (40,0% plus or minus 26.3% v 86.2% plus or minus 8.8%). Future treatment protocols could include adherence to a very low-intensity chemotherapy for the majority of ML-DS patients, identification of the subgroup with a poor prognosis using minimal residual disease (MRD), and stratification of these patients to receive a more intensive chemotherapy containing high-dose and/or continuous infusion of intermediate-dose cytarabine.

3. Transient Abnormal Myelopoiesis (TAM)

Transient abnormal myelopoiesis (TAM), also known as transient leukemia (TL) or transient myeloproliferative disorder (TMD) occurs in approximately 10% of infants with DS.[1, 4] TAM was considered to be ''self-limiting''; the prognosis of TAM was favorable, except for the risk of the subsequent development of acute leukemia. Most of newborns are asymptomatic and only present with circulating blast cells, with or without leucocytosis. Other clinical features include hepatomegaly, splenomegaly, serous effusions and, in up to 10% of patients, liver fibrosis due to blast cell infiltration that can rarely cause fulminant liver failure. Leucocytosis and thrombocytopenia are common. About a quarter of patients have abnormal liver transaminases and abnormal laboratory coagulation tests. The blast cells in TAM usually have the 'blebby' appearance characteristic of megakaryoblasts and typically express CD41, CD42b. Most neonates with TAM do not need chemotherapy as the clinical and laboratory abnormalities spontaneously resolve within 3–6 months after birth. However, symptomatic babies with TAM, especially those with high blast counts or liver dysfunction, may benefit from low-dose cytarabine.

In 2006, Children's Oncology Group (COG) reported a prospective study of the natural history of 48 children with DS and TAM. [18] Early death occurred in 17% of infants and was significantly correlated with higher WBC count at diagnosis, increased bilirubin and liver enzymes, and failure to normalize the blood count. Recurrence of leukemia occurred in 19% of infants at a mean of 20 months. In the AML-BFM study, 22 children among total 146 children (15%) died within the first 6 months. The 5-year OS and EFS were 85% plus or minus 3% and 63% plus or minus 4%, respectively. [19]A total of 28 children received a short course of cytarabine treatment. Interestingly, EFS and OS did not differ significantly in the treated versus the untreated group. Among the 124 children who survived the first 6 months of life, 29 (23.4%) subsequently developed ML-DS. The 5-year EFS after diagnosis of ML-DS for all 29 patients was 91% plus or minus 5%, which is significantly higher than the 5-year EFS of those of ML-DS patients without documented TAM (70% plus or minus 4%). According to the retrospective study from Japan, estimated gestational age (EGA), higher WBC counts and higher direct bilirubin levels were significant predictive factors for poor prognosis. [20, 21] Muramatsu et al devised a simple risk stratification system based on the EGA and the peak WBC count. The high-risk group (HR) was defined as preterm infants with WBC >100 x 10^9/l, the intermediate-risk group (IR) was defined as preterm infants with WBC <100 x 10^9/l and term infants with WBC >100 x 10^9/l, and the low-risk group (LR) was defined as term infants with WBC< 100 x 10^9/l. In the LR group, only three of 39 patients (7.7 %) died early. Based on their data, patients in the LR group should receive no interventions. However, since the probability of early death in patients in the HR group exceeded 50%, active intervention including low dose cytarabine should be tried in the context of a clinical trial for these patients.

3.1. Treatment for TAM

In patients with a severe form of TAM, the main causes of death in early life are progressive hepatic fibrosis, cardiopulmonary failure, and disseminated intravascular coagulation. These

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complications may be caused by blast cell infiltration into visceral organs. In the Pediatric Oncology Group (POG) study 9481, 10 mg/m2 per dose or 1.2–1.5 mg/kg per dose was given subcutaneously or intravenously by slow injection twice a day for 7 days (Table 2). [18] In the AML-BFM study, 0.5–1.5 mg/kg was administered for 3–12 days. [19] As TAM blasts are highly sensitive to cytarabine, there is generally a rapid response, characterized by the disappearance of peripheral blasts by day 7 of treatment.

Study group	No of patients	Early death (%)	Leukemia (%)	OS (%)	No of treated patients	Cytarabine
POG9481[18]	48	17	19	78 (3y)	2	10mg/m2 x 2 x 1-2 days
AML-BFM[19]	146	15	23.4*	85 (5y)	28	0.5-1.5 mg/kg x 3-12 days
COGA2971[20]	135	21	16	77 (3y)	29	3.33mg/kg/24 hrs x 5 days
Tokai (Japan)[21]	70	23	22*	74.3(1y)	3	0.7 mg/kg x 5days, 10mg/m^2 x 2/day
Kikuchi (Japan)[22]	73	22	23	71.2(3y)	9	

POG, Pediatric Oncology Group; BFM, Berlin-Frankfurt-Munster;

COG, Children's Oncology Group; *. Alive > 6 mo

Table 2. The outcomes of transient abnormal myelopoiesis with Down syndrome.

Although TAM resolves in the majority of DS infants, 20– 30% subsequently develop ML-DS, usually within in the first 4 years of life. [18-22] In the COG study 2971, twenty-one patients among total 135 TAM patients (16%) developed ML-DS, including 3 received cytarabine.[20] The development of AMKL after remission of TAM has been interested as a model of myeloid leukaemogenesis, presumably from a subclone of persisting TMD cells that acquire a selective advantage. This hypothesis can be verified by monitoring minimal residual disease, either by immunophenotype or quantitative GATA1[23] polymerase chain reaction.

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