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Pediatric Acute Myeloid Leukemia

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1. Introduction

Acute leukemias are clonal diseases characterized by a maturation arrest and by enhanced proliferation of hematopoietic precursor cells, which normally would differentiate into mature blood cells. The leukemic cells are released from the bone marrow into the peripheral blood and may accumulate in vital organs such as the spleen, liver, skin, central nervous system and lymph nodes. Chronic leukemias arise form hyperproliferation without a clear maturation arrest. In children, chronic leukemias are rare, and most cases are classified as acute leukemias. (Pui, *et al* 2011) Acute leukemias can be further subdivided in acute lymphoblastic leukemias (ALL, either from precursor T- or B-cells), and in acute myeloid leukemias (AML, either from red blood cell precursors, platelet precursors, or granulocytic or monocytic precursors). In children, approximately 80% of cases are ALL, and 15-20% AML. There is a peak in the incidence of AML in infants under one year of age, after which the incidence is low throughout childhood. (Creutzig, *et al* 2010a, Kaspers and Zwaan 2007) AML may even be present in newborn babies. (Bresters, *et al* 2002) In adolescents the incidence of AML starts to rise and rises further throughout adult life (1-3 per 10^5 each year in childhood, rising to 15 per 10^5 in early adulthood to 35 per 10^5 at the age of 90 years). (Ries, *et al* 1999)

AML may either arise de novo or occur following underlying diseases such as myelodysplastic syndrome, which is much more frequent in elderly patients with AML than in children. Other underlying diseases may be chromosomal-breakage syndromes such as Fanconi anemia. (Tonnies, *et al* 2003) Moreover, AML may be secondary to previous exposure to irradiation or to chemotherapy, including both alkylating chemotherapy and epipodopyllotoxins. (Sandler, *et al* 1997, Weiss, *et al* 2003) A specific type of AML arises in children with Down syndrome. (Zwaan, *et al* 2008) Exposure to environmental factors has also been described as a potential cause of AML. (Smith, *et al* 2011) Infrequently, families with an unexplained high risk of AML have been described which suggests that germ-line mutations such as *RUNX1* and *CEBPA* may play a role in leukemogenesis. (Owen, *et al* 2008)

1.1 Clinical presentation

AML has a variable clinical presentation. The history of a child with AML is often relatively short and at most a few weeks. Children with AML usually present with signs of inadequate production of normal blood cells, such as pallor and tiredness or feeding problems due to anemia, spontaneous bleeding due to al low platelet count, and fever/infections due to low white blood cells. High white counts can give rise to hyperviscosity and sludging and hence

to pulmonary complaints (dyspnea) or central nervous system related symptoms (lowered consciousness, coma, convulsions). Bone pain due to high intra-osseous pressure often occurs. Extramedullary disease due to infiltration of leukemic cells has been reported in 4-10 percent of all cases, and may either present as skin infiltrates (referred to as 'blue-berry muffin' skin lesions) or solid leukemic masses, also referred to as chloromas. Organs prone for accumulation of leukemic cells and subsequent organomegaly are the spleen, liver, gingiva and lymph nodes. Leukemia in the central nervous system may occur either as liquor pleiocytosis or as solid tumors in the central nervous system. A specific type of AML, acute promyelocytic leukemia (APL), often presents with serious life threatening bleeding disorders, which is due to abnormal coagulation factors, and not just to thrombocytopenia. (Creutzig, *et al* 2010c)

2. Diagnostics

2.1 Morphology and immunophenotyping

The first step to diagnose leukemia is to study the morphology of the peripheral blood and the bone marrow aspirate using light microscopy. A classical morphological feature distinguishing AML from ALL are the so-called Auer rods (see Figure 1), which are mainly seen in leukemias derived from granulocytic precursors. However, differentiation between AML and ALL is nowadays usually done with flow cytometry. Typically, AML blasts are positive for CD13 or CD33, and negative for lymphocyte markers such as CD3/CD7 (T-cells) or CD19/CD20/CD2 (B-cell precursors). Myeloperoxidase (MPO) staining can be used to differentiate AML from ALL, although MPO-positivity is mainly confined to granuclocytic leukemias. Esterase staining is helpful to identify monocytic types of leukemia.

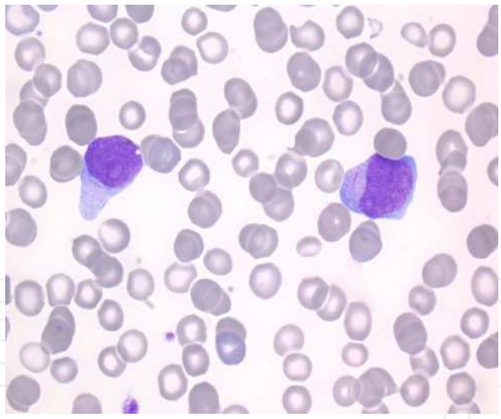


Fig. 1. Auer rods present in the 2 AML blasts visible in a peripheral blood smear.

The morphological classification of AML is referred to as the French-American-British or FAB-classification (see table 1), and is based on the cell-line of origin. (Bennett, *et al* 1985a, Bennett, *et al* 1985b, Bennett, *et al* 1991) Certain morphological subtypes need confirmation with flowcytometry, such as minimally differentiated AML (FAB M0) and acute megakaryoblastic leukemia (FAB M7). (Bennett, *et al* 1985a, Bennett, *et al* 1991) Morphological assessment should also focus on the occurrence of myelodysplasia, and differentiation between AML and advanced myelodysplastic syndromes (MDS) may be difficult. In adults, a blast threshold of 20% is used to differentiate between these 2 diseases,

but in children we still use the 30% cut-off. (Hasle, *et al* 2003) Other characteristics may also be helpful: AML-specific translocations, organomegaly, rapid progression and CNS-localization are indicative or AML rather than MDS.

FAB type	Name	Relationship with specific cytogenetic abnormalities
M0	minimally differentiated acute myeloblastic leukemia	
M1	acute myeloblastic leukemia, without maturation	
M2	acute myeloblastic leukemia, with granulocytic maturation	t(8;21)(q22;q22), t(6;9)(p23;q34)
M3	promyelocytic, or acute promyelocytic leukemia (APL)	t(15;17)(q22;q12)
M4	acute myelomonocytic leukemia	
M4Eo	myelomonocytic together with bone marrow eosinophilia	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)
M5	acute monoblastic leukemia	*MLL*-gene rearrangements
M6	acute erythroid leukemias	
M7	acute megakaryoblastic leukemia	t(1;22)(p13;q13)

Table 1. FAB-classification of AML, and relationship between FAB-types and specific cytogenetic abnormalities. (Bennett, *et al* 1985a, Bennett, *et al* 1985b, Bennett, *et al* 1991). *MLL*=mixed-lineage leukemia

2.2 Cytogenetics and molecular genetic screening

AML is a genetically very heterogeneous disease. Genetic aberrations in AML can be subdivided in type 1 and type 2 aberrations, based on the Gilliland hypothesis that at least two different collaborative types of abnormalities are needed in the pathogenesis of AML. Kelly, L.M. & Gilliland, D.G. (2002a) Genetics of myeloid leukemias. *Annu.Rev.Genomics Hum.Genet.*, 3, 179-198. Type 1 abnormalities mainly induce proliferation, and consist for instance of mutations in tyrosine kinase receptors such as the *FLT3*-gene(Zwaan, *et al* 2003a) or *KIT*-mutations(Goemans, *et al* 2005, Pollard, *et al* 2010), and type 2 abnormalities induce maturation arrest and mainly result from genetic aberrations in hematopoietic transcription factors, either resulting from translocations, or from mutations in genes such as *NPM1*, *GATA1* and *CEBPA*. (Ahmed, *et al* 2004, Hollink, *et al* 2011, Hollink, *et al* 2009c) Evidence for this model is supported by several factors: 1) AML-specific translocations can already be demonstrated in cord-blood (Wiemels, *et al* 2002), and may only cause AML several years later, 2) fusion transcripts may be demonstrated using sensitive techniques in patients in long-term clinical remission of AML (Leroy, *et al* 2005), 3) *FLT3* mutations induce a myeloproliferative disorder in mice but lack the maturation arrest typical of full-blown AML (Kelly, *et al* 2002b), and 4) certain type I and II genetic aberrations cluster together in a non-random fashion.

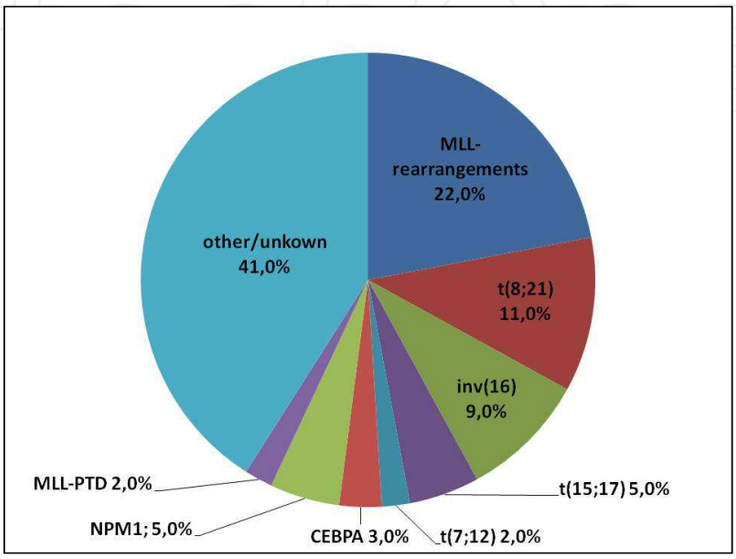
Conventional karyotyping may identify AML-specific abnormalities, which are not only of use in diagnosis and the correct classification of the leukemia, but may also provide prognostic information used for risk-group stratification of pediatric AML. (Harrison, *et al* 2010, von Neuhoff, *et al* 2010) One of the recurrent aberrations in pediatric AML is the group of 'core binding factor (CBF)' leukemias, including t(8;21)(q22;q22) and

Major categories	**Subdivided in the following categories:**
Acute myeloid leukemia with recurrent genetic abnormalities	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* t(15;17)(q22;q12); *PML-RARA* t(9;11)(p22;q23); *MLLT3-MLL* t(6;9)(p23;q34); *DEK-NUP214* inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(1;22)(p13;q13); *RBM15-MKL1* *Provisional entity: AML with mutated NPM1* *Provisional entity: AML with mutated CEBPA*
Acute myeloid leukemia with myelodysplasia-related changes	
Therapy-related myeloid neoplasms	
Acute myeloid leukemia, not otherwise specified	AML with minimal differentiation AML without maturation AML with maturation Acute myelomonocytic leukemia Acute monoblastic/monocytic leukemia Acute erythroid leukemia Pure erythroid leukemia Erythroleukemia, erythroid/myeloid Acute megakaryoblastic leukemia Acute basophilic leukemia Acute panmyelosis with myelofibrosis
Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	

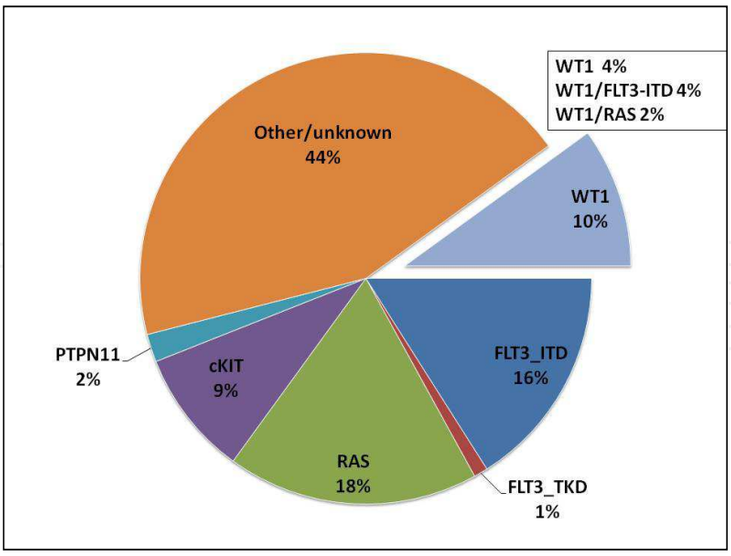
Table 2. The new WHO-classification of AML (Vardiman, *et al* 2009)

inv16/t(16;16)(p13/p13;q22), which are considered as good-risk abnormalities by most collaborative groups. (Creutzig, *et al* 1993a, Grimwade, *et al* 1998) CBF-AML is present in approximately 20-25% of pediatric AML cases, which is a higher frequency than found in adults. Rearrangements of the *Mixed Lineage Leukemia (MLL)*-gene, localized at chromosome 11q23, are associated with >50 different fusion partners, and are considered as intermediate or poor risk. *MLL*-gene rearrangements are usually screened for with fluorescent in-situ hybridization (FISH), which does not identify the translocation partner. However, prognosis may depend on the translocation partner, and therefore certain translocation partners need to be specifically searched for with reverse-transcriptase polymerase chain reaction (RT-PCR), such as the t(1;11)(q21;q23), t(6;11)(q27;q23) and t(10;11)(p12;p23). (Balgobind, *et al*

2009) Other abnormalities involve deletion of chromosome 7q or monosomy 7, which are generally considered as poor risk abnormalities. (Hasle, *et al* 2007) Some abnormalities are only found in pediatric AML, such as t(7;12)(q36;p13) and t(1;22)(p13;q13), which both occur in infants with AML. (Bernard, *et al* 2009, von Bergh, *et al* 2006) On the other hand, certain abnormalities such as inv(3)(q21q26.2), which is associated with poor clinical outcome, are rare in children and more frequently found in adults. (Balgobind, *et al* 2010a)



Type 2 abnormalities in pediatric AML



Type 1 abnormalities in pediatric AML.

Fig. 2. Genetic abnormalities in pediatric AML, subdivided as type 1 and type 2 abnormalities. WT1 mutations were included in this graph as type I aberrations, please see text for comments.

In the revised WHO-2008 classification of myeloid neoplasms (Table 2), the category of AML with recurrent genetic abnormalities was further expanded and *NPM1* and *CEBPA* mutated AML were added as provisional categories. (Vardiman, *et al* 2009)
Apart from cytogenetic aberrations, AML is characterized by various gene mutations. Some of these mutations cluster in cytogenetically-normal AML, which is found in 20-25% of pediatric AML cases, which is a lower frequency than in adults, where approximately 50% of cases do not have cytogenetic abnormalities. (Balgobind, et al 2011a, Marcucci, et al 2011) *NPM1* and *CEBPA* gene mutations confer good clinical outcome, whereas mutations in the *FLT3* and *WT1*-genes confer poor clinical outcome. (Ho, et al 2009, Ho, et al 2010b, Hollink, et al 2011, Hollink, et al 2009a, Hollink, et al 2009c, Meshinchi, et al 2006, Zwaan, et al 2003a) Figure 2 shows the distribution of type 1 and 2 abnormalities, as identified in >400 cases of pediatric AML. We have arbitrarily included the WT1 mutations as type I aberrations, however, their role in AML still has to be elucidated. (Hollink, et al 2009a, Yang, et al 2007) Moreover, they are not mutually exclusive with some other typical type I aberrations, as shown in the graph.

2.3 Gene expression profiling as a diagnostic tool

Recently, in pediatric AML, several gene expression profiling studies have been performed with the aim to study their diagnostic potential, and whether they could replace the current diagnostics mentioned above. In a seminal study of 130 *de novo* pediatric AML patients, Ross and colleagues discriminated successfully between acute lymphoblastic leukemia (ALL) and AML by gene expression signatures. (Ross, *et al* 2004) Likewise, the major prognostic AML subclasses, i.e. t(15;17), t(8;21), inv(16), and t(11q23)/*MLL*, as well as cases classified as acute megakaryoblastic leukemia were correctly predicted with an overall classification accuracy greater than 93% using supervised learning algorithms. (Ross, *et al* 2004) This was confirmed by Balgobind et al. in an independent study of 237 children with pediatric AML (specificity and sensitivity for discovery of the indicated cytogenetic subclasses was 92% and 99%, respectively). (Balgobind, *et al* 2011b) However, in the latter study no general predictive gene expression signatures were found for the molecular genetic aberrations *NPM1*, *CEBPA, FLT3*-ITD, *or KIT*. This may have been caused either by a low frequency of certain mutations, but also by underlying cytogenetics or cell line of origin. For instance, distinct gene expression signatures were discovered for *FLT3*-ITD in patients with normal cytogenetics and in those with t(15;17)(q21;q22)-positive AML. (Balgobind, *et al* 2011b) Therefore, the value of gene expression profiling for use in routine diagnostics is limited to the 40% of cases with clearly discriminative profiles.

3. Current treatment of pediatric AML

3.1 Chemotherapy

Chemotherapy treatment for pediatric AML can be subdivided in several treatment phases: a) induction chemotherapy – which typically consists of 2 courses of intensive chemotherapy; b) consolidation chemotherapy, which may again consist of 2 or 3 courses of chemotherapy; and c) maintenance therapy, which is currently only applied by some groups; and d) hematopoietic stem cell transplantation, which is subject to debate, and is discussed in more detail in paragraph 5.2. Almost all modern protocols include risk-group stratification based on a combination of cytogenetics (defining a good-risk group consisting

of CBF-AML and acute promyelocytic leukemia or FAB M3) and early response to therapy (either day 15 bone marrow results, or CR after course 1, or minimal-residual disease status after course 1, which is discussed further in paragraph 6 below).

The former protocols of the Children's Cancer Group (CCG-2891) were based on 'timed sequential induction chemotherapy', which involved a 4-day cycle of five different chemotherapeutic agents, with the second cycle administered either 10 days after the first cycle, despite low or dropping blood counts (intensive timing), or 14 days or later from the beginning of the first cycle, depending on bone marrow status (standard timing). (Woods, *et al* 1996) This concept, however, was inferior to results obtained with other regimens in that era from the MRC and BFM-AML groups(Gibson, *et al* 2005, Stevens, *et al* 1998), and hence this was abandoned. One explanation for the differences in outcome between the CCG 2891 study and the MRC and BFM protocols may have been differences in ethnicity between the populations enrolled on these studies, as Hispanic and black children have poorer outcome compared to white children on CCG 2891, and are over represented in the CCG compared to the Northern-European protocols. (Aplenc, *et al* 2006)

Most protocols nowadays use a typical '3+10 day induction course' (3 days of anthracyclines + 10 days of cytarabine ± a third drug) followed by a second '3+7 or 3+8 course' (3 days of anthracyclines plus 7 or 8 days of cytarabine ± a third drug). The NOPHO group uses a different format which resembles the aforementioned CCG-approach, but is response based. (Abrahamsson, *et al* 2011) The first induction course in their protocols lasts 6 days and contains only 4 days of cytarabine. The timing of the 2nd course then depends on the bone marrow response at day 15. All patients with <5% blast are allowed hematological recovery, all others start with the 2nd course at day 15. The total CR rate was 92% after 2 courses, which is very similar to the CR rates with MRC or BFM approaches. (Creutzig, *et al* 2010b, Gibson, *et al* 2005) Most protocols nowadays consist of a total of 4-5 courses of intensive chemotherapy, although the optimal number of cycles has not been established. (Creutzig, *et al* 2005b, Gibson, *et al* 2005, Kaspers and Creutzig 2005, Kaspers and Zwaan 2007) In protocol MRC AML 12 this question was addressed (see Table 4). Maintenance therapy in AML is subject to debate, but there are several studies showing that if any effect it leads to worse retrieval at relapse, and is therefore probably not índicated. (Perel, *et al* 2002, Wells, *et al* 1994)

Chemotherapy for AML is intensive and consists of a cytarabine/anthracycline backbone to which other drugs may be added, for instance epipodophyllotoxins (i.e. etoposide) or anti-metabolites (i.e. 6-thioguanine). In some protocols asparaginase is applied, which seems mainly effective against monoblastic leukemias (Zwaan, *et al* 2002a), and is usually given in combination with cytarabine (also referred to as the Capizzi regimen). (Capizzi, *et al* 1988, Zwaan, *et al* 2002b) Some protocols use 2-chlorodeoxyadenosine as nucleoside analog instead of cytarabine. Other protocols aim at potentiating cytarabine by combining it with fludarabine (often combined with GCSF and then referred to as a FLAG course) or 2-chlorodeoxyadenosine, which leads to increased Ara-CTP levels (the active metabolite). (Burnett, *et al* 2011, Creutzig, *et al* 2010b, Rubnitz, *et al* 2009) In more recent studies gemtuzumab ozogamicin has been evaluated together with standard chemotherapy in induction and consolidation, but results for children have not been reported as yet. (Burnett, *et al* 2011) In older protocols, steroids were sometimes included, but steroids may (at least in-vitro) induce proliferation of AML cells, and hence are no longer applied. (Zwaan, *et al* 2002b)

Prevention of CNS-relapse is mainly based on intrathecal chemotherapy, which is given on top of intensive IV cytarabine courses. There is no evidence that low numbers of blasts in the

Study	Randomized comparison	Era	CR rate	EFS	OS	Ref
AML-BFM 2004	Liposomal DNR 3x80 mg/m² vs. idarubicin 3x12 mg/m²	2004-2010	NA	L-DNR 60% vs. Ida 54% (p=0.17)	L-DNR 78% vs. Ida 70% (p=0.15)	(Creutzig, *et al* 2010b)
St Jude AML02	High-dose vs. low dose cytarabine (18 vs. 2 gr/m²)	2002-2008	MRD-positivity high 34% vs. low 42%, p=0.17	High: 60.2% vs. low 65.7%, p=-p.41	High 68.8% vs. low 73.4%, p=0.41	(Rubnitz, *et al* 2010)
MRC-AML 12	DNR 3x50 mg/m² vs. Mitoxantrone 3x12 mg/m²	1995-2002	DNR 92% vs. Mitox 90%, p=0.3	NA	DNR 65% vs. Mitox 70%, p=0.1	(Gibson, *et al* 2005)
POG-9421	Standard dose (100 mg/m²x7 days) versus high dose (1 gram/m²/x7 days) cytarabine	1995-1999	Standard 87.9% vs. high 91%, p=0.23	Standard 35% vs. high dose 40%, p=0.28	NA	(Becton, *et al* 2006)
AML-BFM 1993	DNR3x60mg/m² vs. idarubicin 3x12 mg/m²	1993-1998	>5% blasts in day 15 BMA: Ida 17% vs DNR 31%, p=0.01	Ida 51 *vs* DNR 50%, p=0.72	Ida 60% *vs* DNR 57, p=0.55	(Creutzig, *et al* 2001)
CCG 2891	Standard versus intensive timing	1989-1995	Standard 70% vs. intensive 75%, p=0.18	Standard 27% vs. intensive 42%, p=0.0005	Standard 39% vs. intensive 51%, p=0.07	(Woods, *et al* 1996)
MRC-AML 10	6-thioguanine 75 mg/m², 12-h, d1-10 vs. etoposide 100 mg/m² IV day 1-5	1988-1995	6-TG 90% vs Etoposide 93%, p=0.3	6-TG 48% vs Etoposide 45%, p=0.3	6-TG 57% vs Etoposide 51%, p=0.5	(Gibson, *et al* 2005)

CR=complete remission, EFS=event free survival, OS=overall survival, Ref=reference, DNR=daunorubicn, Ida=idarubicin, Mitox=mitoxantrone, 6-TG=6-thioguanine, NA=not available, BMA=bone-marrow aspirate, MRD=minimal residual disease.

Table 3. Randomized induction questions in pediatric AML studies.

cerebrospinal fluid (CNS-2 status) are clinically relevant in AML, and hence additional intrathecal therapy is not needed in case of CNS-2. (Abbott, *et al* 2003) Most groups do not apply prophylactic CNS-irradiation in pediatric AML patients, apart from the BFM-group. In their AML-BFM 87 study, which was initially set-up as a randomized study but failed due to non-compliance with this randomization, it was found that irradiated patients had fewer bone marrow relapses, and hence prophylactic irradiation was continued. (Creutzig, *et al* 1993b) Patients with clear CNS-involvement (CNS-3) are given irradiation in most treatment protocols, although this may be replaced by frequent intrathecal injections in younger children, with the aim to avoid late effects or cranial irradiation on neurocognitive development.

Several randomized studies have been performed addressing either induction or consolidation chemotherapy questions over the past few years. Table 3 summarizes the

induction randomizations that were performed. As can be seen most randomizations were negative, although it remains difficult to interpret the results for the anthracyclines, as it is not known whether the randomized dosages are in fact dose-equivalent. Considering consolidation, the randomized questions are summarized in Table 4, and again most of these do not provide statistically significant results.

Study	Era	Randomized comparison	EFS	OS	Ref.
AML-BFM 2004	2004-2010	Cytarabine/idarubicin ± 2-chlorodeoxyadenosine (2-CDA)	2-CDA 51% vs. no 2-CDA 51%, p=0.98	2-CDA: 75% vs. no 2-CDA 65%, p=0.18	(Creutzig, *et al* 2010b)
AML-BFM 98	1998-2004	6-week consolidation vs. 2 short cycles	6-week 51% vs 2 cycles 50%, p=0.66		(Creutzig, *et al* 2006)
AML-BFM 93	1993-1998	Early HAM course in consolidation versus late	Early: 49% vs. Late 41% (p=non-significant)	Early: 57% vs. Late 54% (p=non-significant)	(Creutzig, *et al* 2005b)
POG-9421	1995-1999	Ciclosporin A (CsA) added to consolidation chemotherapy	DFS: CsA 40.6% vs. no CsA 33.9%, p=0.24	NA	(Becton, *et al* 2006)
MRC-AML12	1995-2002	4 versus 5 courses (MIDAC vs. MIDAC plus CLASP)	NA	4 courses 81% vs. 5 courses 78%, p=0.5	(Gibson, *et al* 2005)

EFS=event free survival, OS=overall survival, Ref=reference, NA=not available, DFS=disease free survival

Table 4. Chemotherapy-based consolidation randomizations in pediatric AML (excluding stem-cell transplant related questions).

3.2 Stem-cell transplantation

The principle of stem-cell transplantation is to eradicate minimal residual disease using high-dose chemotherapy and/or total body irradiation. (Bleakley, *et al* 2002, Niewerth, *et al* 2010) Allogeneic SCT also has an immunological effect, as the graft may induce a 'graft-versus-leukemia effect (GVL)', and hence may be able to prevent leukemia relapse. Autologous SCT has also been used in pediatric AML, but there is basically no evidence that this is superior to intensive chemotherapy consolidation. (Aplenc, *et al* 2006, Pession, *et al* 2005) Two reviews have addressed the issue of allo-SCT versus chemotherapy in pediatric AML, and both conclude that although allo-SCT reduces relapse risk this is counterbalanced by increased procedure-related mortality and by poorer retrieval at relapse. (Bleakley, *et al* 2002, Niewerth, *et al* 2010) Hence, in most studies overall survival does not improve. It should also be emphasized that 'older' studies may show more benefit from SCT than more recent studies, given that the beneficial effect of SCT is likely to be greater with less intensive induction chemotherapy. (Creutzig and Reinhardt 2002, Woods, *et al* 2001) In most current protocols SCT in 1st complete remission is therefore only recommended for selected high-risk cases, although there is little evidence that this in fact improves outcome in these cases. (Creutzig and Reinhardt 2002, Reinhardt, *et al* 2006) In first relapse, most patients are transplanted after achieving a 2nd CR. (Kaspers, *et al* 2009) There is limited evidence that pre-emptive therapy post-SCT may be effective in reducing the frequency of overt relapse. (Bader, *et al* 2004)

3.3 Supportive care

The current intensity of pediatric AML treatment is only possible with rigorous supportive care, including (but not limited to) blood transfusions, antibiotic and antifungal prophylaxis, viral surveillance, early diagnostics of fungal infections with high-resolution CT-scans, prevention of nephropathy using rasburicase in hyperleucocytosis, GCSF use in life-threatening infections, tube feeding and total parenteral nutrition. (Goldman, *et al* 2001, Inaba, *et al* 2011, Lehrnbecher, *et al* 2009, Lehrnbecher, *et al* 2004, van de Wetering, *et al* 2005) In fact, a substantial part of the progress in pediatric AML over the last decades is due to improvements in supportive care. Despite this progress, a a significant number of patients still do not survive as a result of early death or due to treatment related mortality, as summarized in Table 5. Therefore, further intensification of AML studies is currently not considered feasible. This was also demonstrated in a French study from the LAME group, who tried to further intensify induction therapy by a timed-sequential approach, but this pilot was stopped given the time needed for hematological recovery until consolidation, which was median 98 days in the timed-sequential approach versus 76 days using their regular 2 induction courses. (Perel, *et al* 2005)

	Early death	Treatment related mortality	Cumulative incidence of death	References
DCOG 83, 87 and 92/94 studies	13.1%	4.4%	NA	(Slats, *et al* 2005)
BFM 93- and 98 studies	3.5%	8%	NA	(Creutzig, *et al* 2004)
St Jude	NA	NA	7.6%	(Rubnitz, *et al* 2004)
NOPHO 84, 88 and 93 studies	3%	10%	NA	(Molgaard-Hansen, *et al* 2010b)

NA=not available

Table 5. Summary of early death and treatment related deaths in pediatric AML studies.

4. Outcome of pediatric AML

4.1 Newly diagnosed pediatric AML

The outcome of newly diagnosed pediatric AML has increased significantly over the past decades. Contemporary studies show survival rates in the range of at least 65-75%, as detailed in Table 6.

4.2 Relapsed AML

The cumulative incidence of relapse is around 30% with modern intensive chemotherapy protocols used in newly diagnosed disease. (Creutzig, *et al* 2005b, Gibson, *et al* 2005, Sander, *et al* 2010) Relapsed AML is usually treated with similar chemotherapy as given upfront, hence intensive cytarabine/anthracyline based chemotherapy. Following a second remission induction patients are usually transplanted. A summary of studies in relapsed pediatric AML is provided in table 7. As can be seen, outcome is poor, and the largest and most recent study of the International BFM-Study Group reported 35% overall survival. (Kaspers, *et al*

2009) Outcome for patients with late relapse and/or good risk cytogenetics is better, as well as for patients who have not been transplanted in CR1 and for those achieving CR2 with re-induction chemotherapy. (Sander, *et al* 2010, Webb 1999) Patients with refractory first relapse or with second relapse are considered candidates for experimental therapy. (Zwaan, *et al* 2010b)

Study Group	**Years**	**No of patients**	**EFS (5yrs)**	**OS (5yrs)**	**References**
LAME 91	1991-1998	262	47%	61%	(Perel, *et al* 2005)
AIEOP LAM 92	1992-2001	160	54%	60%	(Pession, *et al* 2005)
GATLA AML 90	1993-2000	179	31%	41%	(Armendariz, *et al* 2005)
EORTC 58921	1993-2000	177	49%	62%	(Entz-Werle, *et al* 2005)
MRC AML 12	1994-2002	455	56%	66%	(Gibson, *et al* 2005)
POG 9421	1995-1999	565	36% (3-year EFS)	54% (3-year OS)	(Becton, *et al* 2006)
AML PPLLSG 98	1998-2002	147	47%	50%	(Dluzniewska, *et al* 2005)
BMF 98	1998-2003	473	49%	62%	(Creutzig, *et al* 2006)
AML 99 Japan	2000-2002	240	62%	76%	(Tsukimoto, *et al* 2009)
SJCRH AML	2002-2008	230	63%	71%	(Rubnitz, *et al* 2010)
NOPHO AML 2004	2004-2009	151	57% (3-year EFS)	69% (3-year OS)	(Abrahamsson, *et al* 2011)
AML-BFM 2004	2004-2010	566	54%	72%	(Creutzig, *et al* 2010b)

Table 6. Overall outcome data for pediatric AML studies started from 1990 onwards.

Study Group	**Years**	**No of patients**	**DFS (5yrs)**	**EFS (5yrs)**	**OS(5yrs)**	**Ref**
TACL institutions	1995-2004	99	43%	24%	29%	(Gorman, *et al* 2010)
LAME group	Relapse following LAME 89/91	106	45%	NA	33%	(Aladjidi, *et al* 2003)
MRC group	Relapse following MRC AML-10	125	44%	NA	24% (3 yrs)	(Webb, *et al* 1999)
BFM-group	Relapse following AML-BFM 87, 93 and 98	379	NA	NA	23%	(Sander, *et al* 2010)
I-BFM	2002-2009	360	NA	NA	35% (3-year OS)	(Kaspers, *et al* 2009)

Table 7. Studies in relapsed pediatric AML.

4.3 Late effects of treatment

The major long-term toxicity in AML patients treated without stem cell transplantation is long-term cardiac toxicity. (Creutzig, *et al* 2007, Temming, *et al* 2011) This is associated with higher cumulative dosages of anthracyclines. (Nysom, *et al* 1998) The use of liposomal formulations may be an option to reduce cardiac toxicity, as discussed below in paragraph 7.2. Stem cell transplantation is associated with many late effects, mainly depending on the type of conditioning regimen (type of chemotherapy and/or total body irradiation), and the occurrence of graft-versus-host disease. Toxicities include growth arrest, infertility, other endocrine abnormalities, secondary cancers and cataracts. (Leung, *et al* 2000, Leung, *et al* 2001) Neurocognitive sequelae may be anticipated in patients receiving cranial irradiation, depending on dose and age of radiotherapy administration. (Reinhardt, *et al* 2002b, Temming and Jenney 2010) A quality-of-life study form the NOPHO group showed that self-reported health was considered excellent or very good in 77% of ex-patients, and comparable to that of siblings, with a median follow-up of 11 years. (Molgaard-Hansen, *et al* 2010a)

5. Specific subgroups in pediatric AML

5.1 Children with Down syndrome

Children with Down syndrome have an increased risk (approximately 150-fold) of developing myeloid leukemia, which is often preceded by a so-called 'transient leukemia (TL)' in neonatal life. (Hasle, *et al* 2000, Zwaan, *et al* 2008) This Down syndrome associated myeloid-leukemia (ML-DS) is a unique disease entity characterized by occurrence at young age (before the age of 4 years), a smoldering disease course, megakaryocytic features, and mutations in the *GATA1* transcription factor gene localized on the X-chromosome. (Ahmed, *et al* 2004, Creutzig, *et al* 2005a, Hitzler, *et al* 2003, Lange, *et al* 1998, Zwaan, *et al* 2008) Interestingly, ML-DS is a highly curable disease, when reduced-intensity treatment protocols are used, avoiding excessive treatment-related mortality. (Creutzig, *et al* 2005a, Gamis, *et al* 2006) This is probably due to enhanced sensitivity to chemotherapy, as was determined with in-vitro cell-kill assays. (Ge, *et al* 2004, Zwaan, *et al* 2002b) This also implicates that these patients should not be transplanted in CR1, and that longer intervals between courses are necessary and acceptable if the patient needs to recover from a prior course of chemotherapy. TL occurs in approximately 10% of children with DS, and is probably derived from trisomy 21 induced expansion of fetal liver megakarocyte precursors, which become 'leukemic' once a *GATA1* mutation occurs. (Chou, *et al* 2008, Klusmann, *et al* 2008, Tunstall-Pedoe, *et al* 2008) In most cases (~80%) TL resolves spontaneously without development of ML-DS later in life, however, in 20% of children TL is followed by ML-DS between 1-4 years of age (Figure 3). (Hasle, *et al* 2008) It is currently unknown whether ML-DS may also occur without preceding TL, although it is perhaps unlikely. Moreover, it is unknown which factors exactly drive clonal evolution to ML-DS in these 20% of children, although research is ongoing to unravel this. (Chen, *et al* 2010, Klusmann, *et al* 2010a, Klusmann, *et al* 2010b) Of interest, a recent paper shows that lower protein expression of GATA1s predicts a higher chance of ML-DS development after TL. (Kanezaki, *et al* 2010) Current efforts in TL are focused on 2 aspects: 1) Treatment of children with symptomatic TL to avoid TL-related deaths, which may occur from either fluid overload, organomegaly and high WBC, or from liver failure which is believed to result from cytokines produced by the leukemic blasts infiltrating the liver. (Klusmann, *et al* 2008) Treatment can consist of

(repetitive) courses of low dose cytarabine (Al Ahmari, *et al* 2006), and 2) the potential to avoid clonal evolution to ML-DS by treating children with low clearance of TL as assessed by MRD measurements at pre-defined time-points. Results from the latter studies are not yet available, and hence this cannot be considered standard of care as yet.

5.2 Infants with AML

There is a peak in the incidence of AML in children below the age of 1 year. These leukemias have a different genetic profile compared to older children with AML, as approximately 50% of these cases are characterized by *MLL*-rearrangements. (Creutzig, *et al* 2010a, Vormoor, *et al* 1992) Moreover, certain specific chromosomal aberrations are only found in children below one year of age, such as the *OTT-MAL* fusion gene found in young children with megakaryoblastic leukemia and t(1;22)(p13;q13)(Reinhardt, *et al* 2005), and the t(7;12)(q36,p13), which is characterized by very poor clinical outcome. (von Bergh, *et al* 2006) Clinically, children below the age of one year more often present with high WBC, organomegaly and CNS-involvement. (Pui, *et al* 2000, Vormoor, *et al* 1992) In ALL, outcome of infants is worse compared to older children, which led to the introduction of specific treatment protocols, but there is no evidence that this is the case in AML. (Creutzig, *et al* 2010a, Pieters, *et al* 2007) Most protocols advise dose-reduction in infants with AML, and chemotherapy is usually calculated on a mg/kg basis rather than using body surface area.

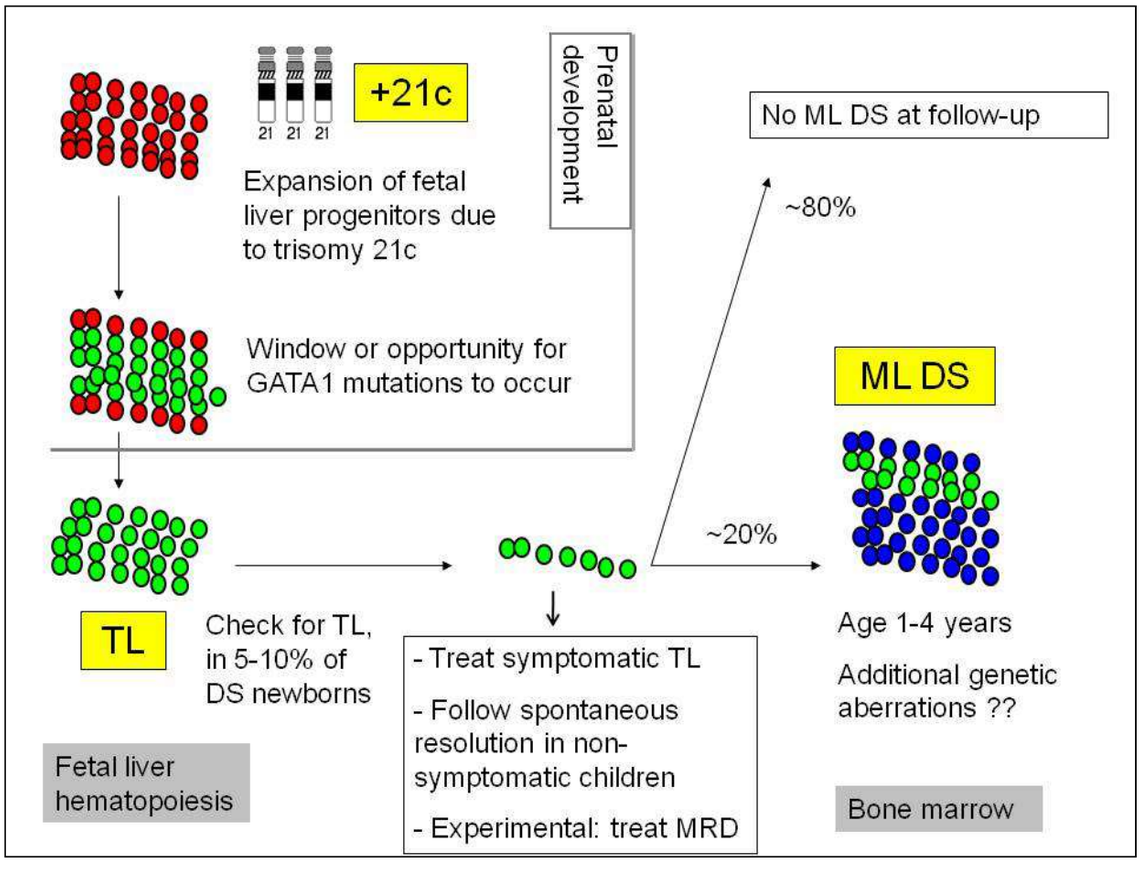


Fig. 3. Development of ML-DS from transient leukemia.

5.3 Adolescents and young adults with AML

In ALL, it appeared that adolescents and younger adults fared much better on pediatric treatment protocols than on adult treatment regimens. (Boissel, *et al* 2003, de Bont, *et al* 2004) Subsequently, this was also investigated for AML. Creuztig et al. could not find differences in outcome between patients treated on a pediatric and an adult treatment protocol. (Creutzig, *et al* 2008) In an Australian study, for cases diagnosed between 2000 and 2004, there was no difference in outcome for children, adolescents and young adults (20-29 years). (Pinkerton, *et al* 2010) This is probably due to a greater similarity between pediatric and adult AML protocols, whereas there are major differences between pediatric and adult ALL protocols. Prognosis however declines with age, as a consequences of a reduction of good-risk cytogenetic abnormalities, and reduced host-tolerance to chemotherapy.

5.4 Cytogenetically normal AML

In children, approximately 15-20% of AML cases present without karyotypic abnormalities, which is a much lower frequency than in adults. (Balgobind, *et al* 2011a, Harrison, *et al* 2010, von Neuhoff, *et al* 2010) Over the past few years many gene mutations or overexpression of specific genes have been identified in CN-AML, with clear prognostic impact. (Hollink, *et al* 2009b) This includes typical type II aberrations such as *NPM1* mutations in ~20%, *CEPBA* double mutations in ~15-20% of cases. (Balgobind, *et al* 2011a) The *NPM1* and *CEBPA* double mutations confer good clinical outcome, allowing risk-stratification with the "good risk" cytogenetic subgroups. (Brown, *et al* 2007, Ho, *et al* 2009, Hollink, *et al* 2011, Hollink, *et al* 2009c) In addition, the following type-1 mutations were identified: *FLT3*-internal tandem duplications (*FLT3*-ITD), found in ~30-40% of cases, *FLT3*-tyrosine kinase domain mutations (*FLT3*-TKD) in ~2% and *N*- or *K-RAS* mutations in ~15-20% of CN-AML cases. (Balgobind, *et al* 2011a, Goemans, *et al* 2005, Meshinchi, *et al* 2006) *WT1* mutations were found in 20-25% of pediatric CN-AML cases, in approximately half of the cases together with a *FLT3*-ITD, and in a quarter together with a *RAS*-mutation. (Balgobind, *et al* 2011a, Ho, *et al* 2010b, Hollink, *et al* 2009a) In 20-25% of cases no type-I aberration can be detected so far. The Children's Oncology Group published similar data, although they could not confirm the poor outcome of patients with *WT1* mutations. In adults, specific prognostic paradigms are being developed for CN-AML, which is not yet the case in children, in part because numbers are small. (Damm, *et al* 2011, Mrozek, *et al* 2007)

5.5 MLL-rearranged AML

MLL-rearrangements are typically found in younger children with AML. The true incidence of *MLL*-rearrangements in pediatric AML is considered to be in the range of 15-25% according to the latest trials, since cryptic *MLL*-rearrangements were not always identified in the past with conventional karyotyping only. (Harrison, *et al* 2010, von Neuhoff, *et al* 2010) In the past, *MLL*-rearranged AML has been related to poor outcome despite intensive chemotherapy. However recent studies showed that outcome in *MLL*-rearranged AML is dependent on different factors, e.g. translocation partner, age, WBC and additional cytogenetic aberrations. (Balgobind, *et al* 2009) Cases with a t(1;11)(q21;q23) have an excellent outcome and may benefit from less intensive treatment, whereas cases with a t(6;11)(q27;q23) or t(10;11)(p21;q23) have a poor outcome and do need adjusted and alternative treatment strategies to improve outcome. This means that these abnormalities need to be specifically screened for, as suggested in Figure 4. Although cooperating events

are a hallmark of developing AML, additional genetic aberrations in *MLL*-rearranged AML are hardly identified. Roughly 50% of the *MLL*-rearranged AML cases harbor a known type-I mutation, and most of these mutations were identified in genes involved in the RAS-pathway, including mutations in *NRAS*, *KRAS*, *PTPN11* and *NF1*. (Balgobind, *et al* 2008) Recently, novel aberrantly expressed genes have been identified that are involved in MLL-gene rearranged AML leukemogenesis, such as *IGSF4*, *BRE* and *EVI1*. (Balgobind, *et al* 2010a, Balgobind, *et al* 2010b, Kuipers, *et al* 2011) Upregulation of *HOX* genes is one of the most important hallmarks of *MLL*-rearranged leukemias, and may be a target for epigenetic therapy. (Krivtsov, *et al* 2008)

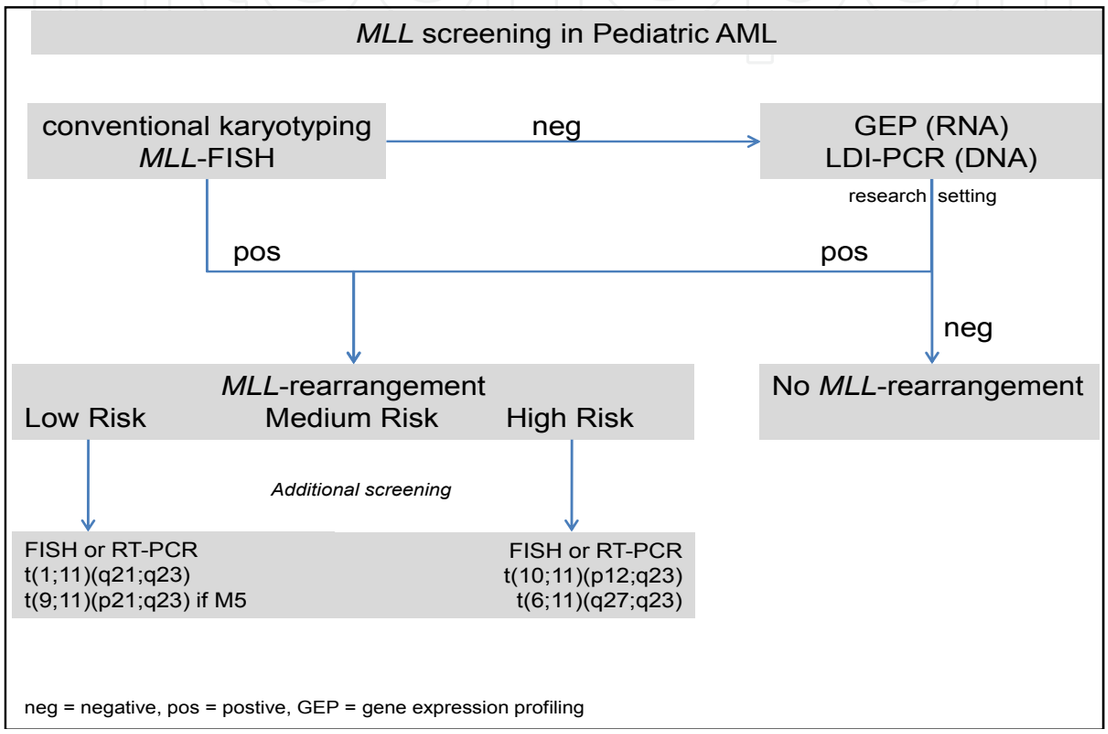


Fig. 4. Screening for *MLL*-rearrangements in pediatric AML.

5.6 Acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is a distinct pathological entity that occurs in only 4-8% of all AML cases in children. The disease is characterized by a specific morphological subtype (FAB M3), although in a small percentage morphology is different, referred to as 'microgranular variant morphology (M3V)'. (Tallman, *et al* 2010) Furthermore, APL is characterized by the presence of the chromosomal translocation t(15;17)(1q22;q21), which results in the *PML-RARa* fusion transcript, and its reciprocal product *RARa-PML*. (Sanz, *et al* 2009) In a minority of cases (<5%), *RARa* is fused to an alternative partner, most commonly *NPM1* resulting from a t(5;17)(q35;q21) or *NuMA* in t(11;17)(q13;q21). (Grimwade, *et al* 2000) The diagnostic white blood cell count is the most important prognostic factor in APL. The hallmarks of the disease is the sensitivity for all-trans-retinoic acid (ATRA), which is now considered standard of care for APL in induction and in maintenance in combination with chemotherapy, or arsenic trioxide (ATO), which is mostly used in salvage treatment.

(Soignet 2001) Both drugs induce differentiation and apoptosis of leukemic cells, and have reduced the incidence of early fatal bleeding complications that APL is associated with. (Sanz, *et al* 2009, Stein, *et al* 2009) Currently, overall survival rates in children with APL are in the range of 80-90% (see table 8). (Creutzig, *et al* 2010c, Testi, *et al* 2005) Based on these results, the International-BFM Group has launched a 'standard of care' protocol for children with APL (the ICC APL study 01). The main aim of this study is to lower the cumulative dose of anthracyclines used in the treatment of APL, which is very high in some adult protocols that pediatric regimens were based upon. (Testi, *et al* 2005) Given the risk of severe long-term cardiac toxicity, the ICC APL 01 study combines a lower dose of anthracyclines with cytarabine and ATRA, as has been used previously by the BFM group. (Creutzig, *et al* 2010c)

Study Group	Years	No of patients	EFS (5yrs)	OS(5yrs)	References
AML-BFM SG	1993-2010	81	73%	89%	(Creutzig, *et al* 2010c)
GIMEMEA-AEIOPAIDA	1993-2000	107	76%	89%	(Testi, *et al* 2005)
North-American Intergroup Trial*	1992-1995	53	NA	69%	(Gregory, *et al* 2009)
AML-99 M3 (Japan)	1997-2004	58	91%	93%	(Imaizumi, *et al* 2011)

* ATRA was not given to all patients

Table 8. Outcome results in APL in children.

Several adult studies have now also introduced arsenic trioxide in newly diagnosed patients, either in combination with chemotherapy, or as single-agent, or in combination with ATRA. (Hu, *et al* 2009, Mathews, *et al* 2010, Powell, *et al* 2011) Using arsenic alone, Mathews et al. reported durable responses with almost 70% event-free survival. (Mathews, *et al* 2010) This has also been piloted in 11 children, with similar encouraging findings. (George, *et al* 2004) When this is confirmed in larger studies treatment of APL without chemotherapy may be feasible, especially when no long-term toxicities from arsenic treatment emerge.

6. Minimal Residual Disease

In acute lymphoblastic leukemia risk group stratification is based on assessment of minimal residual disease (MRD) in modern treatment protocols, as this is superior to any of the classical prognostic factors (age, WBC, cytogenetics, immunophenotype). (Flohr, *et al* 2008, Van Dongen, *et al* 1998) In ALL, this can either be done using flow cytometry, or by using quantative polymerase chain reaction of immunoglobulin or T-cell receptor rearrangements. (van der Velden and van Dongen 2009) In AML, MRD assessment is more complicated. (Goulden, *et al* 2006) Flow cytometry is used by several investigators, and leukemia-specific aberrant immunophenotypes can be detected in the majority of patients. (van der Velden, *et al* 2010) However, flow cytometry may not always have sufficient sensitivity. For instance, investigators from the AML-BFM SG analysed MRD in their AML-98 study. (Langebrake, *et al* 2006) Using 4-color immunophenotyping, they could not show that MRD was superior to

the traditional BFM-risk group classification (based on cytogenetics at diagnosis and morphological assessment of bone marrow blasts at day 15 and 28) to predict clinical outcome. However, other groups have reported independent prognostic significance of MRD assessment. Van der Velden et al. have monitored MRD in the context of the MRC12 protocol, and showed that 3-year relapse-free survival was 85% for MRD-negative patients (MRD<0.1%) and 64% for MRD-low-positive patients (0.1%<or=MRD<0.5%) and only 14% for MRD-high-positive patients (MRD>or=0.5%; P<0.001). (van der Velden, *et al* 2010) In the AML02 study from St Jude Children's Research Hospital MRD was used for patient stratification. (Rubnitz, *et al* 2010) High MRD at the end of induction was the only independent risk-factor for survival, with a cut—off level for MRD-positivity of 0.1%. In conclusion, there is an increasing amount of evidence that flow cytometry based MRD stratification is superior to using more conventional parameters to risk-stratify patients. Molecular MRD assessment in pediatric AML has been based on the quantative assessment of fusion-genes using RQ-PCR. Only rising MRD values are clinically relevant, as it is known that for instance *AML1-ETO* and *CBF*beta-*MYH11* can still be detected with sensitive methods in patients in long-lasting continuous complete remission. (Leroy, *et al* 2005, Miyamoto, *et al* 1996, Perea, *et al* 2006, Viehmann, *et al* 2003) Using fusion genes as MRD targets has the limitation that only a subset of patients (approximately 40-50%) can be studied. However, the newly discovered molecular mutations, such as *NPM1* or *GATA1* mutations, may also be suitable MRD-targets. (Pine, *et al* 2005, Schnittger, *et al* 2009) Some of these targets, such as *FLT3* mutations, may not be stable between diagnosis and relapse, and this may result in false-negative results(Bachas, *et al* 2010), which may also occur in flow-cytometry based MRD assessment due to immunophenotypic shifts. (Langebrake, *et al* 2005) Another important issue is the frequency of required sampling post-treatment, as leukemias may differ in the lag-time between molecular and overt relapse, which appears to be translocation/molecular marker dependent. (Ommen, *et al* 2010) Given this heterogeneity a more ubiquitously expressed MRD target would be more practical, and several investigators have chosen *WT1*-expression as a suitable MRD-target, given that *WT1* is overexpressed in the majority of pediatric AML patients. (Cilloni, *et al* 2009, Lapillonne, *et al* 2006, Willasch, *et al* 2009) Despite all these technical advantages, MRD in pediatric AML is still mainly an area of research rather than a standardized approach implemented as standard of care in clinical treatment protocols, in contrast to pediatric ALL. The one exception in AML is acute promyelocytic leukemia, where MRD-follow-up is nowadays considered standard, and where it has been shown that pre-emptive therapy of molecular relapse may prevent the occurrence of overt relapse. (Grimwade, *et al* 2009, Testi, *et al* 2005)

7. New treatment options

7.1 Gemtuzumab ozogamicin

Gemtuzumab ozogamicin (GO) is a conjugated antibody in which an anti-CD33 antibody is linked to the anti-tumor antibiotic calichemicin. (Sievers, *et al* 1999, Zwaan, *et al* 2003b) After binding to CD33 the complex is internalized and calicheamicin is spliced off and exterts its cytotoxic activity. In studies in adults, the main side-effects of GO were hematological and liver toxicity, referred to as sinusoidal obstruction syndrome (SOS). (Rajvanshi, *et al* 2002, Sievers, *et al* 2001) Although the initial development in adults concerned single-agent high-dose GO (2 dosages of GO 9 mg/m² IV given with a 14 day-interval), combination studies showed that dosages in the range of 3-5 mg/m² could be incorporated in existing AML

chemotherapy regimens. (Kell, *et al* 2003) In AML in adults, several large randomized studies were performed. This includes the addition of GO in induction therapy in the MRC-AML 15 study, which showed an improvement in survival mainly for patients with good-risk cytogenetics. (Burnett, *et al* 2011) Löwenberg et al. gave 3 cycles of GO (6 mg/m2 at 4 week intervals) as post-remission treatment in elderly AML patients, which failed to show a benefit in this population. (Lowenberg, *et al* 2010a)

In children, phase I studies showed that 6-7.5 mg/m^2 was the maximum tolerated dose. (Arceci, *et al* 2005) Several phase II studies have been performed, either as single-agent or in combination with cytarabine, showing response rates in the range of 30-40%. (Brethon, *et al* 2008, Zwaan, *et al* 2010b) GO seems better tolerable in children, in that lower frequencies of SOD were seen. Aplenc et al. published safety data of GO in combination with either cytarabine and mitoxantrone or cytarabine and asparaginase in relapsed pediatric AML patients, and showed that the MTD for the 1st combination was 3 mg/m^2 of GO, versus 2 mg/m^2 for the latter combination. (Aplenc, *et al* 2008) The results of a study in newly diagnosed AML patients as conducted by the Children's Oncology Group are awaited. Rubnitz et al. gave GO in combination with induction chemotherapy to slow early responders (non-randomized). (Rubnitz, *et al* 2010) Given the results of the phase II studies mentioned above, the International-BFM AML group will perform a randomized study in relapsed/refractory AML patients in which standard chemotherapy is given with or without one infusion of GO. Considering its use in pediatric AML the current phase II results suggest better activity and less side-effects than in adults, but no randomized studies have been performed as yet. The current registration status of GO is a major obstacle in its use, as it is only licensed for use in Japan, and hence is not commercially available in Europe or the US. Its prior accelerated approval in the US was withdrawn in 2010 after a follow-up study in adults with relapsed AML (study SWOG S0106) was interrupted as it did not show sufficient benefit and caused safety concerns. (FDA 2010)

7.2 Liposomal drugs

A major concern in children is the development of long-term cardiac toxicity following exposure to high dosages of anthracyclines. (Creutzig, *et al* 2007, Lipshultz and Adams 2010, van Dalen, *et al* 2006) It is hypothesized that liposomal daunorubicin (DNX) has less cardiac toxicity, as the liposomal formulation prohibits its accumulation in cardiac tissue. A cardio-protective effect has been shown for liposomal doxorubicin in solid tumors,(van Dalen, *et al* 2010) however no long-term follow-up studies are available for liposomal daunorubicin to show that it is indeed cardioprotective as well. In adults, a randomized trial between 80 mg/m^2 DNX compared to 45 mg/m^2 of daunorubicin showed a survival advantage for the DNX-arm because of a reduction in late relapses, despite increased treatment related deaths in the DNX-arm. (Latagliata, *et al* 2008) In children, DNX was piloted by the BFM-group in the relapsed AML-98 trial, and was used in all subsequent relapse studies. (Reinhardt, *et al* 2002a) Population pharmacokinetic data showed a lower volume of distribution and lower clearance compared to free daunorubicin. (Hempel, *et al* 2003) DNX is currently considered standard of care in relapsed pediatric AML, given the results of the I-BFM Relapsed AML 2001/01 randomized study showing a significant benefit in terms of early treatment response in patients randomized to the FLAG plus DNX arm (60 mg/m^2 on day 1, 3 and 5), versus those randomized to FLAG alone. (Kaspers, *et al* 2009) Moreover, in the AML-BFM SG upfront studies, DNX was introduced in the 2004 protocol at a dose of 80 mg/m^2 and randomized against idarubicin. (Creutzig, *et al* 2010b) Patients randomized to DNX had

better outcome, although the results were not statistically significant. DNX appeared somewhat less toxic than idarubicin, which included less cases of acute cardiac toxity. (Creutzig, *et al* 2010b) Perhaps further dose-escalation of DNX is possible given the improved therapeutic index for acute cardiac and other toxicity(Creutzig, *et al* 2010b, Kaspers, *et al* 2009), as it is expected that a higher anthracycline dose will translate in better survival, as recently demonstrated in a randomized study in elderly patients with AML (45 versus 90 mg/m^2 for 3 days in induction). (Lowenberg, *et al* 2009)
A new liposomal formulation (CPX-351) combines bot cytarabine and daunorubicin in a 5:1 ratio. (Feldman, *et al* 2011) Recently, a phase I study in adults with relapsed/refractory AML was completed, showing responses in approximately 25% of patients. The recommended phase II dose was 101 U/m^2, following toxicities including hypertensive crisis, congestive heart failure, and prolonged cytopenias at higher dosages.

7.3 Nucleoside analogs

2-Chlorodeoxyadenosine (2-CDA) is a synthetic nucleoside analog that inhibits ribonucloetide reductase and increases the activity of deoxycitidine kinase. In vitro, the drug was more potent than cytarabine, and especially monoblastic leukemias appeared sensitive to this compound. (Hubeek, *et al* 2006) This nucleoside analog has mainly been incorporated in studies from St Jude Children's Research Hospital, showing clear anti-leukemic efficacy against relapsed and newly diagnosed AML. (Krance, *et al* 2001, Santana, *et al* 1991, Santana, *et al* 1992) In later studies it was combined with cytarabine to potentiate the efficacy of cytarabine, and enhanced cytarabine-triphosphate levels (the active metabolite of cytarabine) were demonstrated in patients treated with the combination. (Crews, *et al* 2002, Rubnitz, *et al* 2009) The AML-BFM SG has randomized 2-CDA in consolidation in high risk patients in their AML-BFM 2004 study and compared activity to cytarabine, and no significant difference was found. (Creutzig, *et al* 2010b)
Clofarabine is a new nucleoside analog, which was synthesized to improve the properties of its ancestors fludarabine and cladribine. The phase I study in children showed that the maximum tolerated dose was 52 mg/m2, once daily for 5 consecutive days. (Jeha, *et al* 2004) Liver toxicity and skin rash were the main dose-limiting toxicities. Based on its activity in relapsed pediatric ALL, this drug was approved for this indication in 2004. A phase II study in pediatric AML showed mainly partial responses, perhaps reflecting the resistant phenotype of the leukemias that were included. (Jeha, *et al* 2009) However, in adults with AML clofarabine appears to be an active agent. (Burnett, *et al* 2010) Several phase II studies in pediatric AML are currently ongoing which combine clofarabine with standard AML drugs such as cytarabine, anthracyclines and/or etopside aiming at the development of a new treatment block that could be randomized against other AML blocks. (Jeha, *et al* 2006) A head-to-head comparison to cytarabine or to a FLAG-course should demonstrate whether clofarabine has indeed superior activity, and is not available at the moment.
Elacytarabine is a lipophilic fatty acid derivative of cytarabine, which is in phase II development in adults, and may retain activity in cells with deficient nucleoside membrane transport, and hence be able to overcome cytarabine resistance. Currently, no pediatric studies have been performed. (O'Brien, *et al* 2009)

7.4 Signal transduction inhibitors

7.4.1 FLT3-inhibitors

Several activated tyrosine kinase pathways are described in pediatric AML, which have led to the development of targeted therapy options. Most of the attention has been focused on

FLT3 mutations and small molecule inhibitors, and pediatric development in general follows adult development programs. There are several *FLT3*-inhibitors available on the market, with different selectivity against *FLT3*. This includes for instance the relatively selective inhibitors AC220 and sorafenib, the intermediate selective inhibitor sunitinib, and the less selective inhibitors such as midostaurin and lestaurtinib. In vitro, comparing the properties of these compounds, Pratz et al. reported that in newly diagnosed samples the less selective inhibitors appeared more effective in terms of cytotoxicity, but it is unknown whether this assay is a reliable predictor of clinical responses. (Pratz, *et al* 2010) Moreover, they showed that the presence of dephosphorylation not always predicted cytotoxicity, which may be explained by the lack of oncogenic addiction in some AML cases despite an activation of this pathway, or the activation of parallel pathways at the same time.

Several of these compounds are currently being evaluated in children with leukemia. There is an ongoing phase I study with midostaurin in patients with relapsed pediatric AML and an activating *FLT3*-mutation (NCT00866281). This study builds on the results of studies in adults, which showed moderate activity as a single-agent. (Fischer, *et al* 2010) However, a randomized trial of midostaurin in combination with chemotherapy is ongoing. Sorafenib is evaluated in children with de novo or relapsed *FLT3*-mutant AML, and preliminary results in 15 children are reported. (Inaba, *et al* 2010) In this study most children are treated with combination therapy together with sorafenib, and hence it is difficult to draw conclusions regarding its activity. At 200 mg/m2 twice daily for 20 days 3/6 children had DLTs, but no DLTs were observed on the next lower dose-level of 150 mg/m2 twice daily. Several reports are available on the use of sorafenib in adults with AML. Metzelder et al. observed responses using single-agent sorafenib on compassionate use basis. (Metzelder, *et al* 2009) Ravandi et al performed a phase I/II study of sorafenib in conjunction with chemotherapy. (Ravandi, *et al* 2010) In the phase I portion they escalated sorafenib to 400 mg twice daily together with idarubicin 12 mg/m2 for 3 days and cytarabine 1.5 gram/m2 for 4 days. They found a 93% CR rate in the phase II part of the study for the 15 *FLT3*-mutated patients, versus 66% in *FLT3*-wild type patients. Serve et al. reported initial results of a placebo-controlled trial in elderly AML patients in combination with standard chemotherapy. (Serve, *et al* 2010) No beneficial effect of sorafenib was found, also not in the small subset of patients with a *FLT3*-mutation (n=28 of the 197 patients in the total study). Lestaurtinib is evaluated in children and younger adults with relapsed/refractory AML (NCT00469859), but no results have been presented as yet. In an adult trial in *FLT3*-mutant AML in 1st relapse patients were treated with chemotherapy alone plus or minus lestaurtinib during aplasia between courses and/or following chemotherapy. (Levis, *et al* 2011) Patients treated with lestaurtinib did not achieve better responses, and survival was not prolonged. Of interest, only 58% of patients had sufficient target inhibition in the lestaurtinib arm. This was considered due to the unfavorable pharmacokinetic properties of lestaurtinib, but also to increasing*FLT3*-ligand levels after intensive chemotherapy. (Sato, *et al* 2011) Especially the latter might be a problem that may cause resistance to all *FLT3*-small molecule inhibitors. Other resistance-mechanisms may consist of secondary mutations in the *FLT3*-gene, that impair with binding of the inhibitors.

7.4.2 KIT-inhibitors

Dasatinib may be of use for inhibition of KIT, especially as it also has activity against the D816V mutant, and hence is an option in core-binding factor leukemias which are

frequently associated with these mutations. (Goemans, *et al* 2005, Pollard, *et al* 2010) There is an ongoing study in adults with CBF-AML and dasatinib, and no results have been reported to date. In the pediatric phase I study with dasatinib no responses were observed in AML-patients, but none of the included patients was *KIT*-mutated. (Zwaan, *et al* 2006)

7.5 Others

Tosedostat is a compound with a new mechanisms of action, i.e. it is an orally available aminopeptidase inhibitor. In a phase II study in adult relapsed/refractory AML, using the 130 mg/m2 dose level for 28-days blocks, an overall response rate of 27% was noted. (Lowenberg, *et al* 2010b) There are, to the best of our knowledge, no pediatric studies ongoing at this moment.

8. Genome-wide approaches in AML

Genome-wide approaches proved to be a powerful tool to further dissect AML, providing insight in the heterogeneity of AML, and directing the development of *novel* treatment strategies. The use of high resolution array-based comparative genome hybridization (A-CGH) and single nucleotide polymorphism arrays (SNP-A) led to the identification of recurrent copy number aberrations (CNAs) and regions with loss of heterozygosity. However, the frequency of CNAs in AML appeared to be relatively low, which suggests that AML is a genomically stable disease. (Bullinger, *et al* 2010, Radtke, *et al* 2009) However, using such techniques, aberrations in the tumor suppressor gene *TET2* were discovered in 26% of adult MDS patients, as well as in AML. (Delhommeau, *et al* 2009, Langemeijer, *et al* 2009) Pediatric data show that this mutation is rare *in children with AML*. (Langemeijer, *et al* 2011) Also, the *WT1* mutations and *NF1*-mutations described in pediatric AML were detected with genomic profiling. (Balgobind, *et al* 2008, Hollink, *et al* 2009a)

The development of high-throughput sequencing methods aims at identifying new mutations involved in AML. The sequencing of the first AML genome led to the identification of repetitive *IDH1*-mutations, although again they appeared to be rare in pediatric AML. (Ho, *et al* 2010a, Mardis, *et al* 2009) Moreover, *DNMT3A* mutations (encoding DNA methyltransferase 3A) were identified in this way, which appeared highly recurrent and associated with poor clinical outcome. (Ley, *et al* 2010, Yan, *et al* 2011) Recently, Greif et al. sequenced all transcriptionally active genes in another AML genome. (Greif, *et al* 2011) Five mutations specific to the tumor sample were found.

Novel information on the molecular pathogenesis underlying paediatric AML, can also be found by gene-expression profiling. For example, *NPM1*-mutated AML was associated with deregulation of homeobox genes, different from *HOX* gene deregulation in *MLL*-rearranged paediatric AML, thereby suggesting for the first time different routes of perturbed *HOX* gene expression in paediatric AML subclasses. (Mullighan, *et al* 2007) In addition *novel* genes involved in the pathogenesis of MLL-gene rearranged pediatric AML were identified, such as the *IGSF4* and *BRE* genes. (Balgobind, *et al* 2010b, Kuipers, *et al* 2011) Insights into the function of leukemia-associated antigens were recently gained from investigating the expression levels of the *PRAME* (Preferentially Expressed Antigen of MElanoma) gene in paediatric AML, showing cases with *PRAME*-overexpression to also harbour an increased expression of genes encoding ABC transporters such as multidrug resistance (MDR) proteins, and a decreased expression of genes encoding apoptotic proteins. (Goellner, *et al* 2006)

9. Conclusion and perspectives

In conclusion, pediatric AML is a heterogeneous disease, which currently can be cured in approximately 70% of children. Despite the heterogeneity most cases of AML are treated on uniform treatment protocols, as a result of the historical division between lymphoblastic and non-lymphoblastic leukemia. Improvement in prognosis may have reached a plateau as further intensification of therapy is not considered feasible, due to the relatively high rate of treatment-related deaths. Therefore, further improvements should come from understanding the underlying biology of pediatric AML and the development of more targeted therapy options. For many of the new therapeutic developments we are dependent on data obtained in adults, given the small number of available patients for studies. Nonetheless, pediatric safety studies should always be performed, as children are not small adults when it comes to drug development, especially given the risk of long term toxicity on growth and development. (Zwaan*, et al* 2010a) In the end this will require large international collaboration, especially for smaller subgroups characterized by specific genetic abnormalities, such as *FLT3*-mutated or *KIT*-mutated AML. That this is feasible is shown by current available treatment protocols specifically for Down syndrome AML and APL.

10. References

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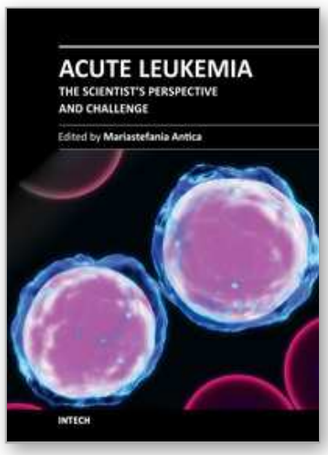

Acute Leukemia - The Scientist's Perspective and Challenge

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This book provides a comprehensive overview of he basic mechanisms underlying areas of acute leukemia, current advances, and future directions in management of this disease. The first section discusses the classification of acute leukemia, taking into account diagnoses dependent on techniques that are essential, and thankfully readily available, in the laboratory. The second section concerns recent advances in molecular biology, markers, receptors, and signaling molecules responsible for disease progression, diagnostics based on biochips and other molecular genetic analysis. These advances provide clinicians with important understanding and improved decision making towards the most suitable therapy for acute leukemia. Biochemical, structural, and genetic studies may bring a new era of epigenetic based drugs along with additional molecular targets that will form the basis for novel treatment strategies. Later in the book, pediatric acute leukemia is covered, emphasizing that children are not small adults when it comes to drug development. The last section is a collection of chapters about treatment, as chemotherapy-induced toxicity is still a significant clinical concern. The present challenge lies in reducing the frequency and seriousness of adverse effects while maintaining efficacy and avoiding over-treatment of patients.

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