Pediatric acute myeloid leukemia: towards high-quality cure of all patients

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ABSTRACT

Prognosis of childhood acute myeloid leukemia (AML) has improved significantly over the past decades, from nearly no child surviving to a present probability of cure of approximately 60%. However, this can only be achieved using very intensive chemotherapy which results in relatively high rates of treatment related deaths and significant late effects. This review summarizes current and future classification of pediatric AML, ongoing phase III studies, and subgroup-directed treatment. In addition, the possibilities for more precise risk-group stratification which would allow more tailored and further refined subgroup-directed treatment are discussed. These include minimal residual disease monitoring, pharmacogenomics and the detection of AML-specific molecular abnormalities. Finally, we discuss the opportunities for innovative therapy in pediatric AML, such as the use of novel analogues, monoclonal antibody-mediated drugs, and receptor tyrosine kinase inhibitors. Given the enormous increase in our understanding of the underlying biology of AML, and the development of many new targeted drugs, it should be possible to achieve high-quality cure in nearly all children and adolescents with AML within the next few decades.

Key words: acute myeloid leukemia, childhood, quality of life, prognosis, clinical trials, risk-group classification, molecular biology.

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The prognosis of children and adolescents with acute myeloid leukemia (AML) has improved significantly over the past decades. Nowadays, up to 65% of pediatric AML patients experience long-term survival.[1] This has been achieved not only by the more effective use of anti-leukemic agents, but also by improvements in supportive care and by better risk-group stratification. Current risk-group classification is mainly based on cytogenetics and early response to treatment. Such early response is measured either by minimal residual disease (MRD) or, more often, by bone marrow response during or after the 1st course of chemotherapy. Therapy nowadays consists of a limited number of intensive courses of chemotherapy based on cytarabine and an anthracycline. While most European pediatric AML groups are abandoning stem cell transplantation in first complete remission,[2,3] the Children's Oncology Group (COG) and other groups still advocate its use in most patients up-front, except in good risk patients with t(8;21) or inv(16) (*personal communication, Dr. A. Gamis, June 28, 2006*). An important problem in the treatment of pediatric AML remains the high frequency of treatment related deaths as well as the long term side-effects.[4-6] This also hampers further therapy-intensification, and most investigators therefore feel that we have reached a plateau in the number of patients that can be cured with current chemotherapy regimens. Our efforts should, therefore, focus on clarifying the biology of pediatric AML. This knowledge can be used for novel classification and risk-group stratification. In addition, it creates the potential for targeted, i.e. more leukemia-specific, therapy. It is anticipated that such therapies will increase the cure-rate and also decrease the toxicity of treatment of children with AML. A large number of new agents are currently under development, mainly in adults. Only the most promising of these new drugs should be adopted for pediatric studies, since the possibility of testing new agents in pediatric oncology is limited because of the small number of available patients. However, international collaboration between the various collaborative pediatric AML treatment groups does enable both drug development (through the ITCC consortium: *Innovative therapies for children with cancer*, www.itccconsortium.org),

and phase III clinical studies. New intergroup phase III protocols have been developed for rare distinct subtypes of AML, such as myeloid leukemia of Down syndrome and acute promyelocytic leukemia (APL). This review summarizes the most important areas in which progress is being made, with an emphasis on classification, current phase III clinical studies, subgroup-directed therapy, minimal residual disease monitoring and innovative drug treatment of AML.

AML classification: what's new?

Traditionally, AML is classified according to morphology, which is described in the so-called FAB (French-American-British) classification, as summarized in Table 1.[7] In the more recent additions to this classification, describing FAB M0 and M7, immunophenotyping is considered essential to the correct diagnosis of these subtypes.[8,9]

More recently, karyotyping has become extremely important for the classification of AML, since karyotypes were found to be predictive of prognosis. The recent World Health Organization (WHO) classification, which is also summarized in Table 1, is therefore mainly based on cytogenetics.[10] This classification is not yet routinely implemented in pediatric hematology/oncology. This may be explained at least in part by the fact that several factors specific for pediatric AML are not addressed in this classification. First of all, to allow a diagnosis of AML, the threshold for the percentage of blasts was lowered from 30 to 20%. Therefore, pediatric cases formerly classified as myelodysplasia, i.e. refractory anemia in excess of blasts in transformation (RAEBt), are now formally classified as AML. However, it has not been demonstrated in well-designed clinical trials that such patients benefit from intensive AML chemotherapy preceding stem cell transplantation, and infact, the data from the European Working Group on Myelodysplastic Syndrome (EWOG-MDS) even suggest that this may not be the case.[11] As many cases of MDS in children are hypoplastic, intensive chemotherapy may result in long-lasting aplasia and infectious complications. A more practical approach to differentiate between AML and MDS, rather than a definition based on strict blast percentages, is to assess disease progression with a wait-and-see policy, and to look for signs indicative of AML such as hepato- and/or splenomegaly and non-random genetic abnormalities.[12] Secondly, the WHO-classification does not recognize rare but important subgroups in pediatric AML, such as infants with AML FAB M7 and a translocation (1;22). In addition, children with myeloid leukemia of Down syndrome are not mentioned as a separate entity in the WHO classification for AML or myelodysplastic syndrome.[12] Neither the WHO- or the FAB-classification uses age criteria to classify AML. However, although the underlying biology of certain well-defined cytogenetic subgroups may not differ between adults and children, there are striking differences between the various age-groups in AML: (i) prognosis declines with increasing age, from 50-70% survival in children,[3,13-15] to approximately 40-50% for younger adults, and only 10% for older adults;[16,17] (ii) this may be due to a different distribution of risk-factors, since children have higher frequencies of the good-risk cytogenetic subgroups defined as the core binding factor (CBF) leukemias with either t(8;21) or inversion(16), and acute promyelocytic leukemia (APL). Children also have less frequently myelodysplasia, preceding AML and have a lower frequency of P-glycoprotein overexpression;[18,19] (iii) host factors differ extensively. Children usually tolerate chemotherapy better and treatment doses can be higher. Even within the pediatric age group there may be differences in the distribution of AML subtypes, such as for FAB M5, which is the predominant FAB-type in infants.

Recent data suggest that, apart from the translocations that interfere with transcription factors (referred to as type 2 abnormalities), other genetic abnormalities are of interest in AML. For instance, mutations in receptor tyrosine kinases, tyrosine phosphatases and in oncogenes such as RAS, may be important as they confer a proliferative advantage to these leukemias (referred to as type 1 abnor-

Table 1. FAB (French-American-British) and WHO (World-Health-Organization) classification of acute myeloid leukemia.[7-10]

FAB classification	
M0	AML with minimal differentiation
M1	Myeloblastic leukemia without maturation
M2	Myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M5	Acute monoblastic leukemia
M6	Acute erythroblastic leukemia
M7	Acute megakaryoblastic leukemia

WHO classification	
AML with recurrent cytogenetic translocations	
	AML with t(8;21)(q22;q22), AML1(CBF-α)/ETO
	Acute promyelocytic leukemia
	AML with t(15;17)(q22;q12) and variants; *PML/RAR*α
	AML with abnormal bone marrow eosinophils: inv(16)(p13;q22) or t(16;16)(p13;q22); CBF-β/MYH1
	AML with 11q23 (*MLL* gene) abnormalities
AML with multilineage dysplasia	
	With prior MDS
	Without prior MDS
AML with myelodysplastic syndrome, therapy related	
	Alkylating agent related
	Epipodophyllotoxin related
	Other types
AML not otherwise categorized	
	AML minimally differentiated
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monocytic leukemia
	Acute erythroid leukemia
	Acute megakaryocytic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis

malities, see Figure 1).[20-24] In pediatric AML, the frequencies of these abnormalities again differs from adult AML. For instance, the frequency of FLT3 internal tandem duplications (FLT3/ITD) is 10-15% in children and 20-30% in adults.[22,25] The type 2 abnormalities are interrelated with morphology and conventional cytogenetics, and certain interesting new data emerge form these observations: (i) the pediatric CBF leukemias have a high frequency of *KIT*-mutations in exon 8 and 17 (40-50%).[20] The true frequency may even be higher, as recently ITDs in *KIT* have been described in exon 11 and 12;[26] (ii) FLT3/ITD can be found in 20-25% of pediatric cases with an otherwise normal karyotype, and in 35% of children with APL, but is rare in CBF-leukemias and in AML M5;[22,24] (iii) PTPN11 mutations seem to occur in approximately 20% of AML M5 in pediatric patients from Southern Europe, but only 7% in Northern Europe.[23,27]

Recently, novel mutations of nucleophosmin (*NPM1*) have been discovered. *NPM1* is involved in the arf-p53 tumor suppressor pathway, and *NPM1* mutations can be found in 5-10% of pediatric AML cases, but up to 20-30% in the subgroup with a normal karyotype.[28-30] This is a lower frequency than that is found in adults, where *NPM1* mutations can be found in 50-60% of normal karyotype patients and confer a favorable prognosis.[31] Children with AML usually present with *NPM1* mutations in their leukemic cells (mainly type B mutations) that differ from those found in adults (mainly type A mutations). This may indicate differences in leukemia pathogenesis between adults and children.[32] *NPM1* mutations are frequently associated with mutations in the FLT3 gene, and loose their favorable prognostic impact when a *FLT3* mutation is present in the same sample.[31,33] Pediatric data from the COG show that mutated patients did not have an improved outcome, although there was a trend for better prognosis in the *normal karyotype* subgroup.[30] Combined FLT3 and *NPM1* pediatric data are not yet available. Apart from *NPM1* mutations and *FLT3*/ITDs, several new genetic abnormalities have been identified in normal karyotype AML, such as mutations in *CEPBα*, which occur in up to 20% of adult normal karyotype AML and are associated with favorable prognosis.[34] Other abnormalities, all associated with poor outcome, include the MLL-partial tandem duplication,[35] and overexpression of the *ERG*[36] and BAALC genes.[37] However, for most of these abnormalities only very limited pediatric data are available.

Clearly, much progress has been made in understanding the genetic abnormalities underlying the various subtypes of AML, and new classification schemes will have to consider this new information.[38,39]

Ongoing phase III trias in pediatric AML

Recently published results of pediatric phase III trials are summarized in Table 2. In these studies, mainly performed in the previous decade, most groups achieved survival rates of between 40 and 60%, with the best outcome reported by the MRC group (5-year overall survival of

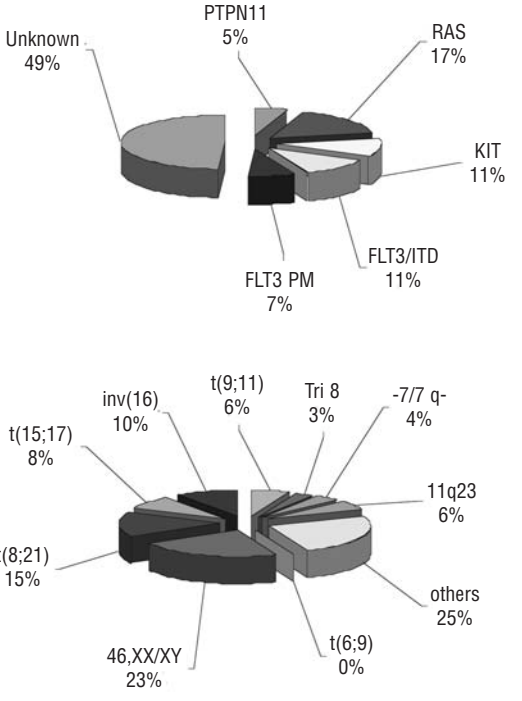

Figure 1. Distribution of the various type-1 above and type-2 genetic abnormalities in pediatric acute myeloid leukemia, based on data from the literature.[20,21,27,138,139]

68%).[3] However, the MRC AML 10 and 12 studies applied a relatively high cumulative dosage (roughly 550 mg/m^2, when utilizing the most arbitrary conversion factor of 1:5 to convert dosages of idarubicin and mitoxantrone to the cumulative dosage of anthracyclines) of anthracyclines, and cumulative dosages above 300 mg/m^2 are well-known for their increased risk of cardiac toxicity.[40] Therefore, it would be interesting if late cardiac toxicity data became available from patients treated in the MRC studies, since this may allow us to re-evaluate the excellent anti-leukemic results that were reported using these protocols.[40] In the POG-9421 study, the concept of MDR-reversal by adding cyclopsorin A was tested but did not show better responses. This was possibly due to the low expression of P-glycoprotein in pediatric AML.[18,19] The ongoing phase III clinical studies in pediatric AML address several important new issues, as summarized in Table 3. Several conclusions can be drawn from an analysis of these studies. First of all, three different and relatively new drugs are being investigated in phase III collaborative group studies, i.e. gemtuzumab ozogamicin (GO, Mylotarg®), 2-chlorodeoxyadenosine (2-CDA, Cladribine®) and liposomal daunorubicin (DNX, DaunoXome®). Interestingly, GO is studied in all 3 phases of treatment, i.e. in induction, consolidation and in a minimal residual disease setting. Secondly, some of the aims reflect not just an attempt to increase anti-leukemic efficacy, but also to reduce toxicity, especially late cardiac toxicity. Both the current randomized MRC-consolidation question and the randomized use

of liposomal daunorubicin in the AML-BFM study and the international Relapsed AML 2001/01 study are examples of this. Finally, the concept of subgroup-directed therapy is applied by administering 2-CDA in high risk patients in the AML-BFM study, as well as in the St. Jude trials. Although relatively small numbers are involved, it has been reported that FAB M5 AML blasts in particular are significantly more sensitive to 2-CDA, both *in vitro* and *in vivo*.[41,42]

Tailored and subgroup therapy in pediatric AML risk groups

Most pediatric collaborative study groups use risk-stratified therapy, based on a combination of cytogenetics and early treatment response. Early treatment response is usually determined using the day 15 bone marrow, or by achieving complete remission after 1 course of chemotherapy. This does not apply to patients with APL, as they are being treated with ATRA which induces differentiation and blasts disappear relatively slowly.[43] The MRC studies showed that, in contrast to other subgroups, slow early response in the CBF-leukemias does not compromise overall survival, and therefore does not need to be considered in these studies.[3]

An overview of current risk group classification used in the various collaborative groups is given in Table 4, demonstrating similarities but also discrepancies in risk-group classification. In the cytogenetic classification, the CBF leukemias and APL are generally considered a favorable risk.[3,44] In addition, some study groups, i.e. the Nordic Society for Pediatric Hematology and Oncology (NOPHO) and St. Jude Children's Research Hospital, consider the subgroup of AML patients with a t(9;11) as favorable.[45,46] Although patients with t(8;21) are generally considered good-risk, their relapse rate is actually at best average[1], and a good outcome is more likely to be explained by a high salvage-rate after relapse.[47,48] Children with monosomy 7 or del(7q) are generally considered to have a poor prognosis, although a recent retrospective pediatric intergroup analysis confirmed the earlier finding in adults and children reported by Grimwade *et al*. that patients with del(7q) in fact have an intermediate prognosis.[49,50] Myeloid leukemia of Down syndrome is considered a favorable AML subgroup and is discussed separately below.

There is clear evidence that *FLT3* length mutations are associated with a poor prognosis in children with AML.[21,22] Based on these data, several groups have decided to stratify patients with a *FLT3*/ITD to the high-risk group. However, recent data suggest that the presence of a *FLT3*/ITD by itself does not indicate an unfavorable prognosis in pediatric AML, but rather the allelic ratio (AR) between mutant and wild-type FLT3.[51] Meschinchi *et al*. reported that patients with an AR below or equal to 0.4 had a similar prognosis to patients without *FLT3*/ITD, while patients with an AR>0.4 had very poor outcome. Interestingly, the point-mutations which occur in the kinase domain of the *FLT3* gene in almost 7% of patients have not been associated with poor clinical outcome.[51] So far, no studies have been reported in which flt3 inhibitors have been tested in pediatric AML patients.

Recent studies suggest that *C-KIT* mutations also confer poor outcome, especially within the subgroup of core-binding factor leukemias, although Boissel *et al*. report that *KIT*– mutations were not predictive in the inv(16) subgroup.[20,52,53] So far this has not been applied to risk-group classification, and larger and prospective studies in pediatric AML are needed to confirm the prognostic significance of *KIT*– mutations.

Table 2. Recently published results of mature phase III clinical trials in pediatric AML.

Study group	*Protocol*	*n*	*Time period*	*Follow-up time*	*pEFS*	*pOS*	*Ref.*
AEIOP	AIEOP LAM 92	160	1992-2001	5 years	54%	60%	Pession *et al.*[140]
AML-BFM SG	AML-BFM 93	471	1993-1998	5 years	51%	60%	Creutzig *et al.*[141]
CCG	CCG 2891	294	1989-1995	3 years	27%	39%	Woods *et al.*[134]
	Standard timing			8 years	–	34%	
	CCG 2891	295	1989-1995	3 years	42%	51%	
	Intensive timing			8 years	–	49%	
DCOG	AML-92/94	78	1992-1998	5 years	42%	42%	Kardos *et al.*[13]
EORTC	EORTC 58921	177	1993-2000	5 years	49%	62%	Entz-Werle *et al.*[142]
LAME	LAME 89/91	309	1988-1996	6 years	48%	60%	Perel *et al.*[143]
MRC	AML12	529	1995-2002	5 years	58%	68%	Gibson *et al.*[3]
NOPHO	AML 93	219	1993-2000	7 years	49%	64%	Lie *et al.*[144]
POG	POG 9421	565	1995-1999	3-years	36%	54%	Becton *et al.*[18]
PPLLSG	AML 98	104	1998-2002	5-years	47%	50%	Dluzniewska *et al.*[145]
St. Jude Children's Research Hospital	AML 91	62	1991-1997	5-years	44%	57%	Ribeiro *et al.*[146]
Tokyo CCSG	AML13/14	216	1991-1998	5-years	56%	62%	Tomizawa *et al.*[147]

AIEOP: Associazone Italiana di Ematologia e Oncologia Pediatrica; AML-BFM SG: AML Berlin-Frankfurt-Münster Study Group; CCG Children's Cancer Group (now with POG the Children's Oncology Group); DCOG: Dutch Childhood Oncology Group; EORTC: European Organization of Research and Treatment of Cancer; LAME: Leucémie Aiquë Myéloblastique Enfant; MRC: Medical Research Council; NOPHO: Nordic Society of Pediatric Hematology and Oncology; POG: Pediatric Oncology Group (now with CCG the Children's Oncology Group); PPLSG: Polish Pediatric Leukemia/Lymphoma Study Group.

Myeloid leukemia of Down syndrome

Children with Down syndrome have an increased risk of developing leukemias,[54] not only myeloid leukemia but also acute lymphoblastic leukemia (ALL). The myeloid leukemias differ from regular pediatric AML and are considered a single entity.[55] They are therefore referred to as *Myeloid Leukemia of Down syndrome*.[12] They are characterized by (i) a predominance of the FAB types M0, M6 and mainly M7, (ii) onset before the age of 5 years, (iii) a low white blood cell count at diagnosis, (iv) the presence of mutations in the *GATA1* gene, which encodes a hematopoietic transcription factor β and (5) a frequent pre-phase with thrombocytopenia or myelodysplasia.[56,57] This pre-phase needs to be differentiated from the transient leukemia which may be diagnosed in children with Down syndrome in the neonatal period.[58] This transient leukemia disappears spontaneously in most infants, but approximately 20% of them present later with myeloid leukemia of Down syndrome.[59] Furthermore, some children with transient leukemia die from disease-related complications.[60] An important new question is whether the progression from transient leukemia to later AML can be prevented with chemotherapy prophylaxis. Several studies have been set up in the pediatric community to investigate this further. In the past, children with myeloid leukemia of Down syndrome were often not offered curative treatment. However, studies performed in the eighties showed that these patients were curable with chemotherapy.[61,62] *In vitro* studies by us and others demonstrated an enhanced sensitivity to anticancer drugs of AML blasts from children with Down syndrome.[63,64] Because children with Down syndrome also have an increased risk of treatment related mortality, treatment intensity needs to be carefully balanced against toxicity. Currently, excellent results have been obtained with moderate intensity treatment protocols without stem-cell transplantation.[57] This also led to the initiative of an *International Pediatric AML Group* protocol for children with myeloid leukemia and Down syndrome which will start enrolling patients in the near future.

Acute promyelocytic leukemia

Low-risk and high-risk APL patients can be distinguished by white blood cell count at initial diagnosis.[43,65] APL is the point of reference for targeted treatment in hematologic malignancies, as all-trans retinoic acid (ATRA) induces differentiation of APL cells by targeting pml-rara.[66,67] ATRA is usually added to chemotherapy in induction because, this reduces early mortality, especially by decreasing the bleeding tendency which is typical for APL.[68] In the case of high white blood cell counts, early chemotherapy in addition to ATRA decreases the incidence of the ATRA syndrome. This syndrome is characterised by fever, weight gain, respiratory distress and pleural and pericardial effusions, and occurs in approximately 10% of children with APL treated with ATRA.[43] It is currently unknown whether prolonged use of ATRA will further improve the prognosis for children with APL.[43]

High cumulative dosages of anthracyclines are very effective in APL, and in adults it has been debated whether APL can be treated with ATRA and anthracycline monotherapy.[69] However, it is unknown whether this can be applied to

Table 3. Clinical study questions and/or specific treatment in certain phases in ongoing, actively recruiting phase III clinical trials in pediatric AML (excluding acute promyelocytic leukemia and myeloid leukemia of Down syndrome).

Phase of treatment	*Collaborative group*	*Question*
Induction	BFM	Randomized comparison of idarubicin versus liposomal daunorubicin
	COG	Randomized addition of GO to induction regimen
	MRC/DCOG	Randomized comparison of FLAG-Ida versus ADE
	St. Jude	Randomized comparison between low and high dose cytarabine during induction. Poor responders are treated with a 2nd block containing GO
Consolidation	BFM	Randomized addition of 2-CdA to consolidation, in high-risk patients only
	COG	Addition of GO to consolidation chemotherapy (extension of initial randomization, meaning patients either get GO (at both induction and consolidation) or no GO at all
	MRC/DCOG	Randomized comparison of anthracycline based consolidation versus high-dose cytarabine courses, and the addition of a 5th course of chemotherapy (the latter by the MRC only)
	NOPHO	Randomized post-consolidation addition of GO in minimal residual disease setting, for all non-SCT patients
	St. Jude	MRD stratified consolidation with GO for MRD-positive patients and 2-CdA for inv(16) and t(9;11) cases.
	Several groups	Non-randomized risk-group stratified chemotherapy
CNS-directed therapy	BFM	Randomized comparison of 12 versus 18 Gy cranial irradiation
Maintenance	BFM	All patients to receive 1 year of maintenance therapy
	ELAM	IL-2 in patients without allo-SCT
	Other groups	No maintenance
Stem cell transplantation	Several groups	Genetic assignment to MSD- or MUD-SCT for intermediate and/or high-risk patients
	AIEOP	Genetic assignment of autologous versus allogeneic SCT in all HR patients

Information was provided by several colleagues representing their study groups, as mentioned in the acknowledgements. GO: gemtuzumab ozogamicin; ADE: cytarabine, daunorubicin and etoposide; FLAG-Ida: fludarabine, cytarabine, granulocyte colony stimulating factor and idarubicin; 2-CdA: 2-chloro-deoxyadenosine; SCT: stem cell transplant; MRD: minimal residual disease; APL: acute promyelocytic leukemia; MSD: matched sibling donor; MUD: matched unrelated donor.
For collaborative group names: see Tables 2 and 4.

pediatric APL, especially since we want to avoid higher dosages of anthracyclines (>300 mg/m^2) which may result in significant cardiotoxicity.[40,70] The so-called *International Consortium for childhood APL* recently developed an intergroup protocol for children with APL. ATRA will be used in all phases of treatment, and the cumulative doses of anthracyclines is limited to 355 mg/m^2 in low risk, and 405 mg/m^2 in high-risk patients. Gemtuzumab ozogamicin will be used in the salvage regimen.[71]

Quantitative molecular monitoring of minimal residual disease is recommended in APL, and molecular persisting or residual disease should be treated before full-blown relapse occurs.[72,73] There is no clear-cut clinical evidence to support this, as it is unknown whether early treatment in an MRD-setting leads to a better outcome than treatment at frank relapse. However, there is sufficient evidence that molecular persisting disease after consolidation or rising RQ-PCR levels indicating molecular relapse will evolve to frank disease, and it makes sense to treat APL before clinical problems such as coagulation disorders become evident. Initiating treatment when there is still a relatively low tumor burden also reduces the risk of secondary mutations and clonal evolution. Several studies suggest the effectiveness of ATRA combined with arsenic trioxide without conventional chemotherapy.[74] However, experts recently reported that it is too early to conclude that this should replace current ATRA and conventional chemotherapy-based protocols, until randomized studies are available.[75] As far as children are concerned we need to have more data regarding safety and efficacy in adult AML before routinely introducing arsenic in up-front APL protocols.

Table 4. Current risk group stratification in several pediatric AML collaborative group treatment protocols (excluding acute promyelocytic leukemia and myeloid leukemia of Down syndrome), and percentages of the total group of patients per risk-group.

Protocol	*Standard risk (SR)*	*% of patients*	*Medium risk (MR) in SR*	*% of patients*	*High risk (HR) in MR*	*% of patients in HR*
AIEOP-LAM 2002/01	t(8;21) or inv(16)/t(16;16)# and CR after course 1	18%	–	–	All other patients	82%
BFM-AML 2004	FAB M1/M2 with Auer rods or FAB M4Eo$^+$ or t(8;21) or inv(16)* and blasts on day 15 <5% and absence of *FLT3*/ITD	30%	–	–	All patients with *FLT3*/ITD, and all patients who are not standard risk	70%
COG AAML0531	t(8;21), inv(16) or t(16;16)	25%	All others	57%	-7, -5, 5q-; bone marrow M3 (>15% of blasts) after course 1, except for those with good risk cytogenetics	18%
ELAM 2002	t(8;21)* (not eligible for SCT in CR1)	14%	All others	81%	-7, 5q-, t(9;22), t(6;9)	5%
JPLSG AML-05	t(8;21), inv(16), or t(16;16)"	40%	All others	40%	-7, 5q-, t(9;22), t(16;21), *FLT3*-ITD, no CR after course I	20%
MRC/DCOG AML15	t(8;21) and inv(16)/t(16;16)*, irrespective of marrow status after 1st course or the presence of other genetic abnormalities	30%	All other patiënts	55%	>15% blasts after the 1st course, or adverse cytogenetics [-5, -7, del(5q), abn(3q), t(9;22), complex karyotype$^@$]	15%
NOPHO-AML 2004	< 15% blasts after the 1st and CR after the 2nd course, or t(8;21), inv(16), t(16;16), t(9 ;11)* and CR after the 2nd course	80%	–	–	11q23 abnormalities other than t(9;11) or >15% blasts day 15 or lack of remission after 2 coursOes of chemotherapy	20%
St. Jude AML-2002	t(8;21), inv(16), t(9;11)*	35%	All other patients	40%	Cytogenetic abnormalities [-7, t(6;9), *FLT3*/ITD], or FAB M6 or M7, or therapy-related AML, or secondary AML after MDS, or lack of remission after 2 courses	25%

**As detected by karyotyping and/or molecular methods, independent of secondary abnormalities; $^@$5 or more structural karyotypic abnormalities; #as isolated structural abnormality, detected by karyotyping and/or molecular methods "As detected by karyotyping, and/or PCR but in case of the latter only it must be confirmed by FISH/FAB-classification: morphological classification of AML; MRC, Medical Research Council study group; BFM, Berlin-Frankfurt-Münster study group; NOPHO, Nordic Society for Pediatric Hematology and Oncology; St. Jude, St Jude Children's Research Hospital, Memphis, USA; AIEOP, Associazione Italiana Ematologia Oncologia Pediatrica; ELAM, Enfant Leucémie Aiquë Myéloblastique; COG, Childhood Oncology Group; JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group; DCOG: Dutch Childhood Oncology Group.*

Minimal residual disease monitoring

In ALL, measurement of minimal residual disease (MRD) by leukemia-specific PCR-based quantitative techniques has emerged as a very powerful prognostic factor,[76] and several groups are currently using MRD-levels to stratify treatment. In AML, progress has been less striking. MRD monitoring of fusion gene transcripts is made difficult by the heterogeneity of AML, and because it has been observed that persisting low levels of fusion genes (especially for the CBF-leukemias) may exist in the absence of relapse.[77] However, this drawback may be overcome by the development of quantitative PCR-technology which may be predictive of prognosis.[78-80]

Several collaborative AML groups currently focus on MRD monitoring by flow cytometry.[81] Only a few studies demonstrated the clinical significance of MRD in pediatric AML.[82-84] MRD measurements by flow cytometry are based on leukemia-specific aberrant antigen expression and can be applied in the vast majority of AML patients. One problem is that immunophenotypic shifts between diagnosis and relapse occur in most patients.[82] Also, the sensitivity of MRD by flow cytometry in AML is still too limited. While it became clear that in ALL it is important to be able to detect at least 1 in 10^4 cells, flow cytometry in AML currently has a sensitivity in the range of 0.1-0.01%.[82] However, the technical possibilities are improving rapidly, and 8- to 12-color flow cytometry is now possible. This will undoubtedly make the technique more sensitive although more complex. Therefore, standardization of flow-based MRD technology is urgently required. Currently, only St. Jude Children's Research Hospital is using MRD for treatment-stratification, and most other groups still have to perform trials to confirm its prognostic significance and define their cut-off values for further prospective studies.

Newly detected genes may be more promising as MRD targets. For instance, overexpression of the Wilms tumor gene 1 was found to be an independent predictor of relapse, although wt1 is also expressed by normal hematopoietic progenitors which may hamper its specificity at low MRD-levels.[81,85] Alternatively, FLT3/ITDs may be used as MRD markers, although clonal instability has been described.[86] *NPM1* may be another candidate, although the frequency is relatively low in pediatric AML.[87] However, most of these markers still need to be confirmed in larger and prospective clinical trials in pediatric AML before they can be used.

Pharmacogenomics

Recent studies have analyzed the influence of host-factors on outcome in pediatric AML. CCG studies have shown that Hispanics and black children have a poorer outcome than white children. This may be because of pharmacogenetic differences.[88] Interestingly, black children also had fewer HLA-identical sibling donors available.

There have been no larger prospective studies linking drug-metabolizing polymorphisms to outcome in pediatric AML.[89] So far, mostly single gene polymorphisms have been studied. Davies *et al.*, for example, reported that children who lacked glutathion s-transferase theta 1 (gstt1) had greater toxicity and reduced survival after chemotherapy for AML compared with children with at least one *GSTT1* allele.[90] However, polymorphisms in the gene encoding for XPD, which is involved in DNA-repair, did not affect the etiology or outcome of pediatric AML.[91]

Innovative therapies and drug development studies in pediatric AML

Drug development studies in pediatric AML are made more difficult by the low number of patients, as well as by the fact that most patients are heavily pretreated. This creates the problem that potentially effective new drugs may be abandoned because of lack of efficacy, when in fact this is caused by the resistance phenotype of the leukemias rather than lack of efficacy of a new drug. Another problem is that the market is too small to interest pharmaceutical companies to carry out pediatric studies. Since 1997, this has been addressed in the USA by creating specific regulations regarding medicinal products for pediatric use and the extension of market exclusivity (*the Pediatric Rule*). In Europe, a similar law (*Better Medicines for Children*) is in the last stages of implementation by the Agency for the Evaluation of Medicinal Products (EMEA, *www.emea.eu*). We discuss here the results of several phase I/II studies in pediatric AML. In addition, we briefly discuss drugs that are being explored in adults, and that may become of interest to the pediatric population in the near future.

2-chlorodeoxyadenosine (cladribine)

Resistance to cytarabine is a major cause of treatment failure in AML, and new analogues have been designed to overcome this resistance. Like cytarabine, cladribine is phosphorylated into its triphosphate form and incorporated into the DNA of cycling cells, resulting in cell death. However, cladribine may also induce apoptosis in non-dividing cells, and is resistant to inactivation by deamination.[41] Of interest, *in vitro*, cladribine was the only analogue that was significantly more cytotoxic towards pediatric AML than ALL cells among an in-vitro panel of more than 10 drugs.[41] Clinical studies with continuous infusion of cladribine showed 59% of relapsed pediatric AML patients responded, with a CR rate of 27%.[92] In *de novo* AML, single-agent cladribine induced CR in 42% of pediatric patients after 2 courses.[42] However, acute monoblastic leukemia (FAB M5) was seen to be more sensitive than non-FAB type M5 cases (n=20, p=0.002) with a CR rate of 71%.[42] Subsequently, cladribine was combined with cytarabine, and the combination appeared to be more effective if cytarabine was given by continuous infusion rates than by a 2-hour infusion, with a CR rate after 1 course of 63% vs. 32% respectively in pediatric AML patients.[93] The BFM-group has currently also included cladribine in the BFM-AML 2004 study for high-risk children, which includes most FAB M5 patients.

Clofarabine

Clofarabine is a designer nucleoside analog. It is orally bioavailable and combines the most favorable pharmacokinetic properties of fludarabine and cladribine. This results in a drug that potently inhibits DNA polymerases and DNA synthesis as well as ribonucleotide reductase. In relapsed/refractory pediatric AML, however, only limited efficacy was found, with only 1 complete remission (with insufficient platelet recovery) and 8 partial remissions out of 35 children.[94] However, in elderly patients who were not considered fit to undergo intensive multi-agent chemotherapy, clofarabine 30 mg/m^2 for 5 days per course with a maximum of 5 courses was well tolerated, and 59% of patients achieved complete remission after 1 course.[95] Clofarabine has now been registered by the FDA and the EMEA for use in relapsed/refractory pediatric ALL, based on data by Jeha *et al*.[96] Several pediatric studies with clofarabine in combination with other chemotherapeutic agents, such as cytarabine and cyclophosphamide plus etoposide, are ongoing. Ideally, a randomized study should confirm the benefit of novel nucleoside analogs such as clofarabine as compared with cytarabine or the combination of fludarabine, cytarabine and G-CSF (FLAG).

Liposomal daunorubicin

Liposomal daunorubin was mainly known for its use in Kaposi sarcoma. Among a cohort of nearly 1,000 adult patients treated with liposomal daunorubicin at cumulative doses of up to 1,700 mg/m^2, only 1 patient developed clinically apparent cardiotoxicity.[97] In general, liposomal anthracyclines cause less cardiotoxicity than conventional anthracyclines.[98] This may be explained by a preferential release of daunorubicin in tumor cells. In a mouse study, low incorporation of liposomal daunorubicin in heart muscle was found when compared with tumor cells.[99] Several other animal studies demonstrated a lack of cardiotoxicity of liposomal anthracyclines, while other *in vitro* and animal studies showed that at an equivalent daunorubicin dose, liposomal daunorubicin had more anti-tumor effect than conventional daunorubicin.[100,101] These findings stimulated the use of liposomal daunorubicin in AML because the use of anthracyclines is limited by acute and long-term cardiotoxicity.[40,70] In one study, liposomal daunrobicin was combined with cytarabine in 69 children with pediatric relapsed/refractory AML. This was feasible in terms of toxicity and induced a 2nd remission in 67% of children.[102] The BFM group is currently randomizing between liposomal daunorubicin and idarubicin in induction for pediatric *de novo* AML. The international study Relapsed AML 2001/01 randomizes liposomal daunorubicin on a basis of FLAG (fludarabine, cytarabine and G-CSF). This will provide data on both efficacy and long-term cardiotoxicity. So far, acute cardiotoxicity has not been a problem in these studies.

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin (GO) is an anti-CD33 directed monoclonal antibody which is linked to a potent cytotoxic agent, calicheamicin.[103] After binding to CD33, the drug is internalized and the calicheamicin is released, resulting in apoptosis by inducing DNA double strand breaks. Although GO was thought to be highly leukemia specific, at least 2 major side-effects have occurred that were not anticipated, maybe due to CD33 expression on the cells that are involved in these complications. The first is the occurrence of sinusoidal obstruction syndrome (SOS), and the second is slow platelet recovery.[104,105] In pediatric AML, a phase I study was performed which showed that the MTD was 2 infusions at 6 mg/m^2 with a 14-day interval, with SOS as dose-limiting toxicity at the 9 mg/m^2 dose-level.[106] All patients had myelosuppression, and other toxicities included grade 3-4 hyperbilirubinemia (7%) and elevated hepatic transaminases (21%). However, the incidence of grade 3-4 mucositis (3%) and sepsis (24%) was low. The remission rate was 28%. Thirteen patients were transplanted within 3.5 months post re-induction with GO, of which 6 (40%) developed SOS during this procedure. In an earlier report, 15 children were reported, treated on compassionate use basis with GO 4-9 mg/m^2, up to 3 infusions.[107] Eight children had no evidence of leukemia, of which 5 were classified as CRp (complete remission with insufficient platelet recovery). Toxicity consisted of veno-occlusive disease (n=1), grade 3 hyperbilirubinemia (n=1), grade 3 transaminase elevation (n=1) and grade 3 hypotension during GO administration (n=1). No infections or mucositis occurred. Versluys *et al*. reported on 5 children with AML, and suggested that defibrotide may play a role in the prevention of SOS at subsequent stem-cell transplantation after re-induction with GO.[108] In another compassionate use series, 12 children (including 9 AML cases) were treated with GO, 3-9 mg/m^2 for 1-5 infusions.[109] There was a 25% response rate, and no SOS occurred. In general, GO seems to be an active agent in these very resistant patients. The toxicity profile is acceptable apart from the risk of SOS. In adult AML studies, GO has been combined at induction and consolidation with conventional chemotherapy.[110] This study showed that low dose GO (3 mg/m^2) was very well tolerated when incorporated in such regimens (although not in consecutive courses), and that combination with thioguanine was not possible due to hepatotoxicity. In pediatrics, GO has been combined with cytarabine in relapsed/refractory AML.[111] Currently, several pediatric study groups have also incorporated GO in their upfront treatment protocols (Table 3). Several study groups are investigating which role GO can play and in which patient-groups, including the MRC and COG. The recent MRC AML15 study in *de novo* and secondary AML has shown improved disease-free survival with GO, although not a significantly improved overall survival.[112] Prolonged follow-up will show if survival also improves with GO. GO should become available for larger clinical studies in pediatric AML, but the

current lack of registration of GO in Europe is a problem still to be resolved.

Potential new drugs for pediatric AML that are being tested in adults

The impressive results obtained with imatinib mesylate in chronic myeloid leukemia have increased interest in inhibitors of type 1 genetic abnormalities in AML.[113] Apart from activity against bcr-abl, imatinib also inhibits wild-type c-kit which is normally expressed on AML cells. Given this, Kindler *et al*. performed a phase II study in which 21 patients were treated with 600 mg imatinib once daily.[114] Two patients had a complete hematologic remission and one other patient showed no evidence of leukemia after treatment. None of the patients were *KIT* mutated. Whether dasatinib will prove to be a more potent inhibitor of kit still needs to be seen.[115] A potential advantage of dasatinib over imatinib is that it also inhibits the D816V mutation which is relatively frequent in pediatric AML.[20,115] Another flt3 and c-kit inhibitor is PKC412. This is of clinical interest given the mutually exclusive mutations in either C-KIT or FLT3 in up to 30% of pediatric AML patients.[20] PKC412 has not yet been studied in children, but a phase II study in adults showed clinical activity.[116] Various other flt3-inhibitors have been tested in phase I/II clinical trials in adults.[117,118] In general, these inhibitors result in relatively short-lived reductions in peripheral blood or bone-marrow blast counts.[116-118] This is similar to the experience with imatinib in Philadelphia-positive acute lymphoblastic leukemia, and probably reflects the fact that AML and Ph^+ ALL are genetically multi-hit diseases.[119] Current studies focus on the addition of these compounds to regular chemotherapy. A recent in-vitro study of *MLL*-gene rearranged MLL suggests that flt3 inhibitors are best given directly after exposure to chemotherapy.[120] Schedule dependency has also been observed for imatinib in Philadelphia chromosome positive ALL.[121] Whether a newly developed antibody against flt3 will be more effective than the small molecules has to be awaited.[122] A trial with SU5416, which is an inhibitor with activity against multiple targets relevant in AML (flt3, kit and vegf), also showed only modest activity with 5% partial responses in 55 patients.[123] A phase I study with another multi-targeted tyrosine kinase inhibitor, sunitinib (SU11248, Sutent®),[124] obtained responses in all *FLT3*-mutated AML patients (n=4), as compared with 2 out of 7 non-mutated AML patients, although the responses were short-lived.[125] Sunitinib is now registered for use in gastro-intestinal stroma cell tumors and metastatic renal cancer.[126] Farnesyltransferase inhibitors (FTI) is a novel class of anti-cancer agents that interfere with the farnesylation of several proteins, such as ras and rhoB.[127] Tipifarnib, which is one of the FTIs, has shown promising activity in a phase II study of previously untreated elderly AML or MDS patients, with a complete response rate of 14% and an overall response rate of 23%.[128] However, in pre-treated patients, activity was very limited.[129] Currently, no data on tipifarnib in pediatric AML are available. Clearly, many new compounds are available which may be of interest for pediatric AML. Only the most promising can be adopted, given the low numbers of patients available to test these compounds, and selection must be guided by preliminary results in adults. Furthermore, international collaboration is essential for most if not all early clinical studies with targeted agents.

Allogeneic bone marrow transplantation

Allogeneic stem cell transplantation (allo-SCT) aims at reducing the risk of relapse by administering high-dose anti-leukemic therapy, and by inducing a graft-versus-leukemia (GvL) response which matches that of graft-versus-host disease (GvHD). To assess the potential benefit of allo-SCT, many studies focus on the reduction of relapse risk only. However, treatment related mortality should be taken into account, and therefore benefit should be expressed as improvement in overall survival rather than the cumulative incidence of relapse only. Autologous SCT has not been shown to be superior to chemotherapy-based consolidation.[130,131] However, several studies in pediatric AML have shown the superiority of allo-SCT compared to chemotherapy, as summarized by Bleakley *et al*.[132] When interpreting these data, however, it should be recognised that the actual reduction of relapse risk is highly dependent on the efficacy and intensity of the control chemotherapy arm.[133] In current studies, from for example, the MRC and BFM groups, the role of SCT in 1st CR seems very limited given the relatively good results obtained with chemotherapy only.[2,3,133] Recent studies from the US however, still advocate allo-SCT in most pediatric AML patients in first complete remission.[134] Most if not all groups consider allo-SCT to be indicated in relapsed AML, ideally after achieving a subsequent complete remission. However, there are no randomized studies to prove that allo-SCT is better than intensive chemotherapy alone in that setting. More experience is being acquired from the use of matched unrelated donors and mismatched family donors for patients in 2nd remission who lack an HLA-identical sibling donor.[102] Given that a GvL effect is demonstrable in pediatric AML, another option would be to use a reduced-intensity rather than a myeloablative conditioning regimen.[135,136] However, the anti-leukemic efficacy in such transplants is highly dependent on the induction and extent of GvHD. This has major limitations in children because of its side-effects.[137] A similar immunologic approach can be tried in patients who show increasing mixed chimerism in the post-allo-SCT setting. These patients experience a poor outcome, but early immunologic intervention with donor lymphocyte infusions and rapid tapering of immunosuppresion was able to rescue some patients.[135]

Concluding remarks and future perspectives

Remarkable progress has been made in the treatment of pediatric AML over the past decades, and the overall prob-

ability of survival in newly diagnosed pediatric AML is now above 60%. However, we may have reached a plateau in the cure rate with conventional chemotherapy, given the treatment-related mortality rates and the long-term side-effects associated with intensive chemotherapy and stem-cell transplantation in selected patients.

Improvements may come from improved risk-group stratification, based either on novel genetic abnormalities, or on the monitoring of minimal residual disease. For instance, the development of specific subgroup-directed protocols for children with myeloid leukemia of Down syndrome and APL may further improve their outcome and reflects differences in the underlying biology of the disease. Further investigation into the genetic aberrations of pediatric AML cells may provide the knowledge needed to develop compounds directed against leukemia-specific targets. Treatment of APL with ATRA, as well as gemtuzumab ozogamicin, are examples of such a targeted approach. So far, the small molecularly targeted molecules have not shown an impressive efficacy in AML, and it still needs to be seen whether combination studies with chemotherapy will be more successful. However, subgroup-directed and rationally targeted therapy does offer possibilities for improved care of patients with AML, but will also have implications for the design of clinical trials. With more and more subgroups, sample sizes become smaller. In the long term, this may make large randomized trials including all children with AML impossible, but may be replaced with international subgroup specific protocols. Fortunately, platforms for international collaboration enabling the study of new agents in pediatric AML have been established, and it is therefore to be expected that high-quality cure can be achieved in the future for many if not most children and adolescents with AML.

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Authors' contributions

GJLK has designed the review and wrote parts of the manuscript, based on literature, intellectual knowledge and personal communication with colleagues from the fiels (see acknowledgements). He revised the manuscript regarding parts written by CMZ. He approved the final version of the paper to be published; CMZ has helped in designing the review and wrote parts of the manuscript, based on literature and intellectual knowledge; revised the manuscript regarding parts written by GJLK, and approved the final version of the paper to be published.

Conflict of Interest

The authors reported no potential conflicts of interest.

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