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Paediatric Update

Acute Myeloid Leukaemias

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INTRODUCTION

THE ACUTE myeloid leukaemias (AML) are a group of heterogenous haematological malignancies with a similar morphology both in children and in adults [1]. AML accounts for only 15–20% of newly diagnosed leukaemias in children and adolescents.

Although the majority of AMLs seem to be more resistant to currently available cytotoxic drugs as compared with childhood ALLs, significant progress in improving outcome for children with AML has been achieved over the past 20 years [2–5]. This can be attributed to intensification of chemotherapy both for remission induction and postremission treatment, to marked improvement in supportive care, especially for children during long-lasting bone marrow aplasia and to the increased use of bone marrow transplantation (BMT) in first or second remission.

With currently available intensive polychemotherapy, 75–90% of children achieve a complete remission (CR), which translates into a long-term event-free survival (EFS) of 40–50% for children given different types of postremission therapy. Thus, 30–50% of children with AML will have an unmaintained remission and the vast majority will eventually be cured of their leukaemia with current treatment strategies [6–8]. Further 10–20% of children who relapse will have a long-lasting second remission with a chance of cure in second remission [9].

Despite this progress, the majority of children and adolescents with newly diagnosed AML will eventually die of their leukaemia today, thus demonstrating that the currently available treatment strategies are still suboptimal. This may be true for cytotoxic treatment, the appropriate integration of allogeneic or autologous stem cell transplantation and especially for appropriate treatment of infections during bone marrow aplasia.

AETIOLOGY AND PATHOGENESIS

A number of predisposing factors and inciting agents have been described for childhood AML (Table 1). Prior exposure to chemotherapeutic agents has emerged as a possible risk factor for the subsequent development of AML. Treatment with akylating agents is associated with an increased incidence of MDS (myelodysplastic syndromes)/AML (treatment-associated MDS/AML). These leukaemias may initially present as MDS. Their peak-incidence occurs within 4–6 years after initial therapy with a decreasing risk after 9–12 years [10, 11]. Chromosomal deletions involving the long arms of chromosomes 5 and 7 are particularly common in these leukaemias [12, 13]. The development of AML after prolonged exposure to epipodophyllotoxin is now well established. This has been demonstrated in children who received etoposide (VP-16) for the treatment of ALL [14]. Epidophyllotoxin-associated secondary AML is most commonly of the French-American-British (FAB classification) subtype M4 or M5 and is characterised by chromosome 11q23 abnormalities [14, 15].

Children with Down's syndrome have an approximately 20-fold increased risk of developing leukaemia. The types of leukaemia follow the usual distribution of childhood leukaemia, except during the first 3 years of life, when AML—especially of the megakaryoblastic (FAB M7) subtype—is more likely to occur. In addition neonates with trisomy 21 may show a transient myeloproliferation, which is morphologically and clinically indistinguishable from congenital leukaemia [16, 17]. In contrast to congenital leukaemia, this myeloproliferative syndrome regresses spontaneously within 1–3 months, but up to 30% of children with this transient myeloproliferative disorder (TMD) subsequently develop true AML during the next 3 years of life [18].

CLINICAL CHARACTERISTICS

Signs and symptoms of AML in children are usually identical to ALL. Extramedullary leukaemic infiltrations may affect liver, spleen and lymph nodes and occur in approximately 35% of the children, especially within the subgroups FAB M4 and FAB M5. Infiltration of the skin and the gum occurs especially in the subtype FAB M5 (acute monoblastic leukaemia). CNS involvement (≥ 5 leukaemic blasts in the HCSF and/or clinical or radiological signs of intracranial infiltration) is found in 5–10% of children with AML. In children with the life-threatening hyperleukocytosis (WBC > 100 000/μl) leukostasis syndrome microcirculation is impaired, especially in the CNS and the lungs [19]. A complex coagulation/fibrinolysis may occur in children with an elevated white

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Table 1. *Predisposing factors associated with the development of childhood AML*

Genetic factors	Down's syndrome
	Fanconi anaemia
	Bloom syndrome
	Kostmann syndrome
	Diamond Blackfan anaemia
	Paroxysmal nocturnal haemoglobinuria
	Li-Fraumeni syndrome
	Neurofibromatosis
Chemicals	Benzene
	Alkylating agents
	Nitroso-ureas
	Epipodophyllotoxins
Radiation	
Myelodysplastic syndromes	

blood cell count (WBC) and in most children with the M3 subtype (acute promyelocytic leukaemia). The WBC at presentation is variable with approximately 30% of children with a peripheral blast count exceeding 100 000/μl.

Myelomonoblastomas, also described as chloromas or granulocytic sarcomas, are solid tumours of myeloid blasts or monoblasts, most often occurring in the epidural and retro-orbital area or the subcutis. The differentiation between myelomonoblastoma and Non-Hodgkin's Lymphoma may be difficult even for the experienced pathologist. Thus, imprint preparation of suspicious lesions for cytological examinations are of upmost importance.

CLASSIFICATION

The widely used FAB classification system [20–23] allows the distinction between ALL and AML blasts (Table 2). Furthermore, it allows in its present version as of 1991 [23] the differentiation of eight AML subtypes (Table 3). The

Table 2. *Distinctive features of ALL and AML blasts*

	ALL	AML
Morphology	No granules No Auer rods	Usually granules (except in M_0, M_5, M_7) Auer rods may be present
Cytochemistry		
Myeloperoxidase	Negative	Positive in M_1, M_2, M_3, M_4
Non-specific esterase	Negative	Positive in M_4, M_5
Immunophenotype	CD19, CD10, CD79, CD20, CD22, HLA-DR, CD34 (B-precursor ALL) CD2, CD7, CD5, CD3, CD1, CD4/8 (prec. T/T-ALL)	CD13, CD33, CD65, CD34, CD11c, CD14 (M_0–M_5) CD41, CD42, CD61 (M_7) Glycophorin A (M_6)
Cytogenetics	Hyperdiploidy in ~35% of cases t(9;22) B-precursor ALL t(8;14) B-ALL t(2;8) B-ALL t(8;22) B-ALL t(4;11) pro-B-ALL, AHL t(11;14) T-ALL t(7;9) T-ALL	Hyperdiploidy rare t(8;21) M_1, M_2 t(15;17) M_3 t(16;16) M_{4eo} inv(16) M_{4eo} 11q23 translocations M_5 eg t(9;11) -7;7q$^-$ sec. AML -5;15q$^-$ sec. AML

Table 3. *Classification of the acute myeloid leukaemias*

FAB subtype	Abbreviation	Cytochemistry	Frequency, AML-BFM 87 (%)
M_0 Acute myelogenous leukaemia	AML (without maturation)	MPO$^-$ EST$^-$	6
M_1 Acute myelogenous leukaemia	AML (with minimal maturation)	MPO$^+$ EST$^-$	10
M_2 Acute myelogenous leukaemia	AML (with significant maturation)	MPO$^+$ EST$^-$	27
M_3 Acute promyelocytic leukaemia	APL	MPO$^+$ EST$^-$	5
M_4 Acute myelomonocytic leukaemia	AMML	MPO$^+$ EST$^+$	21
M_{4eo}	(with atypical eosinophilic maturation)		12
M_5 Acute monoblastic leukaemia	AMoL	MPO$^-$ EST$^+$	22
M_{5a}	poorly differentiated		20
M_6 Acute erythroleukaemia	AEL	Erythroblasts PAS$^+$	3
M_7 Acute megakaryoblastic leukaemia	AMegL	MPO$^-$ EST$^-$	6

MPO, myeloperoxidase; EST, non-specific esterase; PAS, periodic acid schiff (glycogen).

Table 4. Chromosomal and molecular genetic abnormalities in the acute myeloid leukaemias

Chromosomal abnormality	Genes involved	Protein class	FAB types	Frequency (%)
t(8;21)(q22;q22)	*AML1*, *ETO*	Transcription factor	M_1, M_2	10–15
inv(16)(p13;q22) and t(16;16)(p13;q22)	*SMMHC*, *CBFβ*	Muscle protein Transcription factor	M_{4eo}	10–15
t(15;17)(q22;q21)	*RML*, *RARα*	Nuclear protein Hormone receptor	M_3	5–10
t(11;17)(q23;q21)	*PLZF*, *RARα*	Transcription factor Hormone receptor	M_3	1
t(9;11)(p22;q23)	*AF9*, *MLL*	Homeobox	M_4, M_5	10–15
t(11q23 to various partners)	*MLL*	Homeobox	M_4, M_5	frequent in sec. AML type II
t(21q22 to various partners)	*ERG*	Transcription factor		
t(1;22)(p13;q13)	uk	uk	M7	< 1
t(6;9)(p23;q34)	*DEK*, *CAN*	Transcription factor Nuclear protein	M2, M4 with basophilia	< 1
t(8;16)(p11;p13)	uk	uk	M5 with phagocytosis	< 1
t(9;22)(q34;q11)	*BCR*, *ABL*	Tyrosine kinase Serine-threonine kinase	M1, M2	< 1
t(3;21)(q26;q22)		Transcription factor	M2	sec. AML (rare)
-5;5q-	uk	uk	all	frequent in sec. MDS/AML type I
-7;7q-	uk	uk		

sec., secondary; uk, unknown.

subtypes FAB M1 to M6 can be recognised by morphology and cytochemistry alone, whereas for appropriate diagnosis of subtypes M0 and M7 immunophenotyping has to be used.

The differentiation of AML (> 30% blasts in the bone marrow aspirate) and MDS is sometimes difficult, especially in the rare M6 subtype [24, 25]. Thus in doubtful cases, a second bone marrow aspiration within 1–2 weeks is recommended to clarify the situation. However, even then the differentiation may be sometimes arbitrary [26]. In cases of difficult bone marrow aspiration (dry tap), which may be due to bone marrow fibrosis or necrosis and is a typical finding in the M7 subtype in children with or without Down's syndrome [26, 27], a trephine biopsy including imprint preparations is required.

For the detection of immunological markers and haematopoetic cells, monoclonal antibodies (MAbs) are now widely used. An international nomenclature committee has grouped the various MAbs into clusters of differentiation (CD), which detect identical CD molecules (antigens; epitops) on haematopoetic cells. From five leucocyte typing conferences, 130 CD codes have now been established [28].

Most myeloid precursor cells and virtually all cells of the granulocytic and monocytic cell lineages express one or more of the panmyeloid markers CD13, CD33, CD65 and myeloid peroxidase (MPO). Monocytic cells express the CD14 antigens, whereas macrophages are positive for the CD68 antigen. During granulopoiesis the CD15 antigen is expressed. During erythropoiesis glycophorin A and the H-antigen are expressed. CD41, CD42 and CD61 are used as megakaryocytic-platelet markers.

Precursor cells of lymphopoiesis and myelopoiesis generally express the CD34 antigen and some of them also the CD117 antigen. TdT is expressed in most lymphoid cells and in a fraction of precursor myeloid cells.

Together with morphology and cytochemistry, immunophenotyping allows the appropriate classification of $\geq 95\%$ of childhood leukaemias as either ALL or AML [29, 30]. 4–25% of ALLs coexpress at least one myeloid antigen [31], whereas 11–38% of AMLs coexpress at least one lymphoid antigen [32]. Only 1–2% of children with acute leukaemias have either two distinct populations of lymphoblasts and myeloblasts or are true hybrid leukaemias, i.e. demonstrate co-expression of lineage specific myeloid and lymphoid markers within the same cell [33].

The development of high-resolution chromosome banding techniques which can demonstrate clonal chromosomal abnormalities in the majority of cases are the basis of the morphological, immunological and cytogenetic (MIC) working classification of acute myeloid leukaemias [34]. The most frequently detected chromosomal abnormalities found in childhood AML are listed in Table 4. Some chromosomal abnormalities are restricted to a particular subtype of AML, such as t(15;17), which is exclusively detected in acute promyelocytic leukaemia (FAB M3). Other abnormalities, such as those involving the *MLL* gene on chromosome band 11q23 can not only be detected in a variety of AML subtypes, but have been detected in ALLs as well.

TREATMENT OF NEWLY DIAGNOSED AML

The goal of any treatment regimen for childhood AML is to obtain a long-term remission that eventually translates into cure. Traditionally, leukaemia treatment is divided into different treatment phases (Table 5), although this is somewhat artificial, since the results of early treatment phases will influence the results of later phases. With the increasing intensity of antileukaemic regimens, appropriate supportive care from the very beginning is of utmost importance to

Table 5. Phases of treatment in childhood AML

Remission induction therapy
Postremission therapy
Consolidation therapy
Intensification therapy
CNS-directed treatment
High-dose radiochemotherapy with subsequent support by autologous or allogeneic
Haematopoietic stem cell infusion (autologous or allogeneic bone marrow/peripheral stem-cell transplantation)
Maintenance therapy

minimise infectious and bleeding complications during phases of long-lasting bone marrow aplasia. Thus, treatment of childhood AML should be undertaken only in specialised centres.

AML in childhood often presents as an oncological emergency, thus detection, prevention or treatment of life-threatening complications, such as bleeding, infection, tumour lysis syndrome and the hyperleukocytosis/leukostasis syndrome are a prerequisite before cytotoxic treatment is instituted. Bleeding is usually due to thrombocytopenia and platelet transfusion is recommended for all children with a platelet count $< 20\,000/\mu l$. Clinical and laboratory evidence of a severe coagulopathy, which resembles partly disseminated intravascular coagulation, is often seen in acute promyelocytic leukaemia (M3 and M3v). This coagulopathy frequently worsens once cytotoxic treatment is instituted. Coagulation factors should be consequently replaced during remission induction therapy. The role of heparin is still a matter of debate in this situation [35]. The use of all-*trans* retinoic acid (ATRA) significantly shortens the time at risk of this life-threatening coagulopathy in children with M3 and M3v [36].

Children with fever at diagnosis should receive early empiric antibacterial and antifungal treatment after appropriate cultures have been obtained [37]. Children with a high tumour burden (hyperleukocytosis $\geq 100\,000/\mu l$; enlarged liver, spleen and lymph nodes) should be treated with careful hydration to ensure a continuous urine flow, with close monitoring of serum electrolytes, uric acid and serum creatinine. Either allopurinol together with intravenous (i.v.) bicarbonate or urate oxydase should be given to prevent hyperuricaemia with subsequent renal failure.

The brain and the lungs are most commonly affected by the hyperleukocytosis/leukostasis syndrome [19]. Prompt initiation of cytotoxic treatment with low-doses of Ara-C (1 to 2 mg/kg/day) together with hydroxyurea, leukapheresis or exchange transfusion is recommended in this life-threatening situation [19, 38, 39].

The aim of induction therapy is to eradicate the leukaemic cell clone below detectable levels and to restore normal haematopoiesis. This can be achieved only by intensive multiagent chemotherapy causing prolonged bone marrow aplasia. The introduction of cytosine-arabinoside (Ara-C) in combination with an anthracycline for induction treatment was a major breakthrough in the successful treatment of AML, both in children and adults [44–55].

Cytosine-arabinoside

Although progress has been made in the understanding of pharmacokinetics and pharmacodynamics of Ara-C [40, 41], optimal dosing and scheduling of Ara-C during remission induction treatment remains controversial. Because of the short plasma half-life of Ara-C and the importance of maintaining intracellular Ara-CTP levels, continuous infusion of Ara-C is principally preferable to bolus injection or short-time infusion, as first demonstrated by a CALGB study [42]. Ara-C at conventional doses of 100–200 mg/m^2/day is usually given for 7 days [43]. Prolonging the Ara-C infusion up to 10 days [42] or increasing the dose from 100 to 200 mg/m^2/day did not improve remission rate or duration in adults. Because of these studies, conventional dose Ara-C continuous infusion combined with an anthracycline has become the gold-standard in the treatment of childhood AML [44–51].

Intermediate ($> 400\,mg/m^2$/day) and high-dose ($\geq 1.000\,mg/m^2$/day) doses of Ara-C have the goal of saturating Ara-CTP formation by providing excessive amounts of Ara-C for cellular uptake and phosphorylation and thus overcoming resistance to Ara-C. A randomised study in adults did not reveal an increased remission rate in the high-dose Ara-C group, due to a significantly higher treatment-related mortality. However, the probability of disease-free survival (DFS) of 5 years was 41% in the high-dose and 23% in the standard dose group [52]. High-dose Ara-C ($3.000\,mg/m^2$/12 h for six doses) has also been investigated as part of the double induction strategy, used by the German AML cooperative group in adults. The remission rate and the 5-year DFS were slightly increased in the group treated with HD-Ara-C [53].

HD-Ara-C together with daunorubicin was used as induction treatment also in children with AML by the Boston group [54]. Early results were promising, however the original induction regimen had to be modified because of severe CNS toxicity [55].

Anthracyclines

Anthracyclines are a fundamental element of induction therapy of AML, as has been demonstrated by the randomised POG Study AML 8101, comparing DAT (daunorubicin, Ara-C and 6-thioguanine) with VADx (vincristine, Ara-C, dexamethasone): the VADx arm had to be discontinued because of a lower response rate with 61% CRs compared with 82% in the DAT arm [56]. Daunorubicin is the most commonly used anthracycline in the treatment of childhood AML, since doxorubicin appeared to cause more gastrointestinal toxicity [57, 58]. A comparison of $3\times30\,mg/m^2$ with $3\times\,45\,mg/m^2$ showed a higher remission rate particularly for younger patients receiving the higher-dose [58]. In some recent paediatric AML trials, an even higher-dose of daunorubicin ($3\times50\,mg/m^2$ [59] or $3\times60\,mg/m^2$ [44]) has been used.

The main problem with anthracyclines is their cardiotoxicity, which is correlated with the cumulative dose [60]. However, other factors such as young age, female gender and the rate of administration have also to be considered [61]. In order to find new anthracyclines with similar antileukaemic efficacy but reduced cardiotoxicity idarubicin and mitoxantrone have recently been introduced to AML trials. Initial randomised studies in adults demonstrated the superiority of $12\,mg/m^2$/day idarubicin compared with $50\,mg/m^2$/day daunorubicin, both given on days 1–3 in combination with Ara-C [62–64]. Idarubicin has also been introduced into paediatric trials [65, 66].

Mitoxantrone combined with high-dose Ara-C (HAM) is currently being evaluated for double induction and post-remission therapy in both adults [53] and children [67].

Liposomal formulations of daunorubicin with apparently less cardiotoxicity [68] but so far unknown antileukaemic efficacy have recently been introduced in trials for refractory AML both in children and adults.

Additional drugs such as etoposide (VP-16) and 6-thioguanine (TG) have been added to Ara-C plus an anthracycline with the aim of further improving the remission rate and duration. The most commonly used induction regimens are DAT (daunorubicine, cytosine-arabinoside, thioguanine) [69] ADE (cytosine arabinoside, daunorubicin, etoposide) [44], DCTER (dexamethasone, Ara-c, thioguanine, etoposide, daunorubicin) [49] and VAPA (vincristine, doxorubicin,

prednisone, Ara-C) [70]. However, so far there have been no randomised trials in childhood AML indicating that any of these regimens is superior to 3 days of daunorubicin and 7 days of Ara-C. A recent large British trial (MRC-10) including children and younger adults, comparing ADE with DAT demonstrated no significant differences between these two regimens [51].

Dosing of polychemotherapy for children younger than one year of age is often calculated according to weight (mg/kg) instead of surface area (mg/m^2) often with additional dose reduction under the assumption of a reduced tolerance, especially of the GI tract to cytotoxic drugs in this age group. Although this is clearly indicated for anthracyclines [71], considering the high-risk of anthracycline-induced cardiotoxicity and GI toxicity in infants, other drugs, such as etoposide show similar pharmacokinetics in children above and those below one year of age [72]. Correct dosing of cytotoxic drugs depends on volume of distribution, metabolic activation/elimination and renal clearance which all undergo rapid changes during the neonatal period and infancy. Pharmacokinetic and pharmacodynamic monitoring should therefore be implemented in childhood AML studies to optimise treatment. Using these parameters a dose-adaption for high-dose Ara-c has been suggested for children below 2 years of age [73, 74].

Recently, attempts have been made to increase the dose intensity of induction polychemotherapy. Results of a CCG trial indicated an increased DFS for patients whose induction was intensified by early delivery of a second induction block (double induction) [50]. An increased DFS was found in all children irrespectively of postremission treatment (autologous BMT, allogenous BMT, intensive polychemotherapy) confirming results of the German AML Cooperative Group in adults [53].

Since the leukaemic initiating cell in AML has similar biological properties as the haematopoetic stem cell, eradication of leukaemic stem cells is always followed by severe and prolonged bone marrow aplasia, leading to a high therapy-related mortality, which exceeds 10% in some studies. Thus, treatment of AML in children with myeloablative multiagent chemotherapy should be undertaken only in specialised centres that have clinical experience with intensive polychemotherapy and diagnostic facilities for successfully treating these children. This includes early diagnosis and early empirical treatment of bacterial and fungal infections [75]. Some special aspects of supportive care in childhood AML are shown in Table 6.

Table 6. Supportive care in AML during phases of bone marrow aplasia

Single room care
Restricted visitors' access to the oncological ward
Use of CMV negative blood products
Exclusion of any but filtered, irradiated blood products
Pre-emptive/prophylactic platelet transfusion to maintain platelet count $\geq$ 20,000/μl
Selective (Gram negative bacteria, fungi) decontamination of the alimentation tract
Pneumocystis carinii prophylaxis
Surveillance cultures, monitoring of CRP
Pre-emptive/prophylactic antifungal and antibacterial treatment of invasive fungal and bacterial infections in high-risk patients
Prophylactic use of penicillin after high-dose-Ara-C
Prophylactic use of acyclovir in severe mucositis
Standardised guidelines for placement and use of central lines
Standardised treatment of febrile neutropenia

POSTREMISSION TREATMENT

Successful remission induction results in a reduction of the total body leukaemic cell burden from 10^{12} to less than 10^9 cells. Without further treatment 90% of patients will eventually relapse due to the significant leukaemic cell burden (minimal residual disease). Thus postremission therapy is needed in all children in whom the aim is to eradicate the residual leukaemic cells. The intensity and duration of postremission therapy remains controversial. An early German pilot study in adults could clearly establish the need of postremission therapy after TAD induction [76]. In another early study, children and adults were treated with 14 months of high-dose postremission therapy using sequential courses of different drugs (VAPA) for children and adults, demonstrating that 45% of the responders remained in long-term continuous complete response [77]. Subsequent paediatric AML trials have noted a similar long-term survival advantage after intensive postremission chemotherapy [69, 78, 79].

More recent studies have confirmed that the intensity of postremission chemotherapy correlates with long-term survival. High-dose (HD)-Ara-C seems to play a key-role in intensification of postremission chemotherapy and adult patients t(8;21) and inv(16) appear to profit from this treatment, in particular [80–82]. Most recent paediatric trials have also applied HD-Ara-C in postremission, but the efficacy has been less clear than in adults [17, 45, 49]. In study AML-BFM-87 two blocks of intensification with HD-Ara-C and VP-16 were introduced following induction and consolidation therapy. So far, there has been only a tendency towards a slight reduction of relapses in the subgroup of high-risk patients receiving cranial irradiation compared with historical controls [45]. Thus, adding HD-Ara-C to children which had already received intensive induction and early postremission chemotherapy has so far only a limited effect in further reducing relapse rates in children with AML. The introduction of intensive postremission chemotherapy, including HD-Ara-C, led to significant toxicity with a mortality up to 9% during these intensification courses [49, 51].

RISK-ADAPTED THERAPY

A retrospective analysis of study AML-BFM-83 allowed the identification of prognostic factors predicting relapse-free survival [44, 83]. Standard-risk patients were those with the FAB types M1/M2 with auer rods, M3, and M4 eo, responding to induction therapy ($\leq$ 5% blasts within the bone marrow on day 15, except for M3); all other children (approximately 70%) being high-risk patients. To improve outcome for these high-risk patients, the ongoing study AML-BFM-93 adopted a risk-adapted approach including a further block of HD-Ara-C plus mitoxantrone (HAM) which had shown a high antileukaemic activity in both children [84] and adults [85].

MAINTENANCE THERAPY

Long-term maintenance therapy with conventional dose Ara-C combined with TG, daunorubicin or cyclophosphamide has been demonstrated to improve long-term survival in an early randomised German trial in adults [76], which was confirmed by the ECOG [86]. Thus maintenance therapy

was introduced into many paediatric trials. In the current BFM trial, maintenance treatment with daily oral TG combined with subcutaneous Ara-C every 4 weeks is given for a total treatment duration of 18 months. With increasing intensity of remission induction and postremission induction therapy, long-term maintenance may become less important. A recent CCG trial suggests that after 8 months of intensive treatment further long-term maintenance therapy may become unnecessary [49, 87]. However, certain subgroups of children with more slowly proliferating disease, responding slowly to therapy, as demonstrated by a persistent positivity for minimal residual disease, may need prolonged chemotherapy.

CNS-DIRECTED THERAPY

Preventive CNS-directed therapy usually consists of intrathecal doses of Ara-C, MTX, or triple drug including hydrocortisone, with or without cranial irradiation. An early study had demonstrated that up to 20% of children with AML will relapse in the CNS without CNS-directed therapy [88]; this was prevented by cranial irradiation. The first VAPA study which did not include CNS prophylaxis, demonstrated that 36% of all relapses involved the CNS; this high incidence was reduced by intrathecal therapy in the subsequent study 80-035 [89–91]. Therefore, some form of CNS-directed treatment is included in all paediatric AML trials. Because of the late effects of cranial irradiation as observed in long-term survivors in children with ALL, controversy exists whether cranial irradiation should be included for all children with AML or should be retained for those with overt CNS involvement. Data from the AML-BFM-87 study demonstrated a significant higher relapse rate both within the bone marrow and within the CNS in children, who had not received cranial irradiation [45]. These data suggest that the CNS presents a sanctuary for leukaemic cells in childhood AML. Another speculative interpretation of these unexpected results could be that local irradiation may exhibit some systemic antileukaemic effect. Thus, within the current AML-BFM trial, cranial irradiation was reintroduced for all children with AML.

BONE MARROW TRANSPLANTATION

Allogeneic bone marrow transplantation

The role of allogeneic BMT in first remission is still unclear. Although the antileukaemic efficacy of allogeneic BMT is established in AML [92], donor availability and transplantation related mortality (TRM) limit its use. Furthermore, the severe long-term sequelae, such as growth impairment, gonadal and thyroid dysfunction, chronic GvHD (graft versus host disease) and the increased risk for carcinogenesis pose a particular problem for paediatric patients [93].

Early studies from the CCG and the Pediatric Association of Italian Haematology Oncology (AIEOP) suggested that allogeneic BMT may be superior to postremission chemotherapy used at that time in preventing relapse and prolonging overall survival in children with AML [46, 94]. However, with intensification of postremission chemotherapy, the difference between allogeneic BMT and chemotherapy diminished [95, 96]. Similar results came from the MRC-AML-10 trial, which failed to show any significant survival differences between children receiving intensive postremission chemotherapy and those undergoing BMT [59]. Furthermore, a matched-pair analysis of patients of study AML-BFM-83 and -87 demonstrated equal treatment results for children with or without BMT [97].

The decision for or against allogeneic BMT in first remission should, therefore, depend on the predicted outcome of the individual child under the conditions of the given protocol. In the ongoing BFM study, allogeneic BMT is offered only to children within the high-risk group, having an HLA-identical sibling donor. Children in the standard risk group with a probability of an EFS of 70% after 7 years are unlikely to benefit from BMT in first complete remission [98, 99].

Autologous BMT

Postremission therapy can be further intensified by autologous BMT, which allows myeloablative chemotherapy (conditioning) with or without total body irradiation (TBI) followed by reinfusion with autologous bone marrow or peripheral blood stem cells. Several recent studies in adults have shown a low relapse rate and a 3-year DFS of 50–60% after autologous BMT [100, 101].

One limitation of autologous BMT is the possibility of reinfusing leukaemic cells. Gene-marking studies have shown that leukaemic cells from the autograft can contribute to relapse [102]. Thus different purge strategies have been developed to eliminate residual leukaemic cells from the autograft [103, 104], but the clinical value of current purging methods is still a matter of controversy. Three recent prospective clinical trials by the Pediatric Oncology Group (POG) [105], the CCG [50] and the MRC [59] compared autologous BMT with intensive postremission polychemotherapy in children with AML in first remission. Early results from the POG study have so far failed to show an advantage of autologous BMT over intensive chemotherapy [105]. Early results of the CCG trial showed a higher relapse rate in children undergoing autologous BMT early in remission, thus demonstrating the importance of intensive polychemotherapy (*in vivo* purging) [50]. Thus, autologous BMT is currently not considered as a treatment option for children with AML in first remission in the ongoing BFM trial.

The randomised comparison in the MRC-10 trial, which reported the highest complete response and clinical complete remission rates, has shown that autologous BMT may reduce the risk of relapse, but this did not translate into any long-term survival advantage [59].

In Table 7 an overview of five recent multicentre studies is given, demonstrating considerable differences in complete remission rates, end-results, number of children undergoing allogenous or autologous BMT in first remission and supportive failures (death in aplasia, death in remission). The reasons for these astonishing differences are so far unknown and may be clarified by retrospective intergroup analyses (meta-analyses).

TREATMENT OF RELAPSE

The prognosis of children with relapsing AML depends largely on the time-point on which the relapse occurs. Early relapse had a significantly poorer outcome in a recent BFM trial compared with late relapse [9]. After reinduction with mitoxantrone/etoposide followed by HD-Ara-C and mitoxantrone, allogeneic BMT ($n = 27$) autologous BMT ($n = 23$) or further chemotherapy ($n = 10$) was applied. The estimated probability of survival after 5 years is 40% (SEM 10%) in children relapsing more than 18 months after the initial diagnosis. Thus, children with late relapses may have a significant second chance of long-term survival according to these early results.

Table 7. Treatment results of five recent multicentre childhood AML trials

	CCG-2891 [50]	POG-8821 [105]	MRC-10 [59]	BFM-87 [9]	NOPHO-88§
Trial period	1989–1994	1988–1993	1988–1995	1987–1992	1988–1992
N	558	649	341	307	118
Early death	42 (7.5%)	26 (4%)	15 (4.4%)	28 (9%)	14 (12%)
Resistant disease	109 (19.5%)	71 (11%)	12 (3.5%)	49 (16%)	4 (3%)
Complete remission (CR)	407 (73%)	552 (85%)	314 (92%)	230 (75%)	100 (85%)
N allogeneic BMT	105	89	63	17	15
N autologous BMT	107	115	60	6	25
Death in CR	n.a.	19	30	8	10
Estimated probability of event-free survival at 5 years	43 ± 6%	n.a.	48 ± 2%	43 ± 3%	42 ± 2%
Estimated probability of disease-free survival at 5 years	46 ± 6%	37 ± 6%	54 ± 2%	55 ± 3%	49 ± 2%
Overall survival	n.a.	42% (3 years)	58% (5 years)	49% (5 years)	n.a.
Comments	*	†	†	‡	

*A short interval between the first two induction cycles improved the end result in all branches. †No difference in the end results of the different branches. ‡Cranial irradiation reduces the risk of systemic relapse. §Data not shown.

LATE EFFECTS

Late effects in children after successful treatment of AML do not differ from those seen in children with ALL [106, 107]. These late effects depend largely on the given treatment: polychemotherapy, cranial irradiation, allogeneic or autologous BMT, total body irradiation. Since higher cumulative doses of anthracyclines are given in most AML protocols, a higher incidence of late cardiomyopathy has to be expected in children cured of their AML compared with ALL. Thus, careful life-long observation of children after successful treatment for AML is mandatory.

FUTURE CONSIDERATIONS

Since AML is a heterogenous disease, further improvement of treatment results may lie in further individualisation according to the predicted risk of relapse (pretherapeutic biological and clinical risk factors), the careful monitoring of early response to the given treatment and further optimisation and standardisation of supportive care, which is of upmost importance during myeloablative therapy.

Adaptation of therapy intensity according to risk factors and according to response within a given protocol has the aim of treating the individual child as intensively as necessary to cure the leukaemia and to avoid unnecessary toxicity and long-term sequelae. A prerequisite of this aim is the definition of prognostic parameters which predict the risk of relapse for the individual child within a given protocol. As an example, the ongoing AML-BFM-93 study offers further intensification of postremission therapy with HAM and allogeneic BMT only to children in the high-risk group, defined by pretherapeutic features and response to therapy. Treatment of APL with ATRA is the first example of biology-adapted AML therapy [108]. A better understanding of the molecular events underlying other subtypes of AML will hopefully lead to more specific treatment approaches.

Early response to treatment can now be monitored by detecting minimal residual disease (MRD) by PCR and multiparameter flow cytometry [109, 110]. With increasing evidence that children with slow early response to treatment as measured by MRD have a higher probability of relapse, future studies have to evaluate if prognosis can be improved by early intensification of therapy in MRD positive patients.

The increasing knowledge of the pharmacokinetics and pharmacodynamics of cytotoxic drugs have the potential for further individualisation of treatment protocols [111].

New drugs, which are currently being evaluated in childhood AML include 2-CDA and fludarabine. A pilot study demonstrated a high antileukaemic efficacy of 2-CDA as a single drug in newly diagnosed childhood AML [112]. Fludarabine, which has been shown to enhance Ara-CTP formation [113], is presently tested in combination with Ara-C, idarubicin and G-CSF (IDA-FLAG) in the treatment of children with refractory AML by the international BFM study group.

In vitro drug sensitivity testing may also give important information of leukaemic cell behaviour under special *in vitro* conditions. Using the MTT test, early studies found significant differences in *in vitro* drug resistance between different FAB types in childhood AML [114]. Using the same assay it could be demonstrated that blasts of children with AML who required two or more cycles of induction therapy were more resistant to Ara-C compared with patients who achieved complete remission after one cycle of therapy [115].

Standardisation and further optimisation of supportive care, including the optimal use of haematopoetic growth factors such as G-CSF to shorten the duration of therapy-induced neutropenia [116] and the prevention and early empiric treatment of invasive fungal infections [75], may hopefully further reduce therapy-related morbidity and mortality, thus allowing the timely application of polychemotherapy cycles, which has been demonstrated to be of upmost importance for both increasing complete remission rates and the probability of clinical complete remissions [50]. If transplantation-related mortality and long-term sequelae can be reduced, allogeneic BMT may play a significant role in further improving survival in children with AML with an HLA matched donor. More patients may benefit from autologous BMT, if effective purging strategies can be developed.

In summary, there is still much room for further improving current treatment strategies with the realistic aim of curing the majority of children with AML.

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Commentary

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THE MANAGEMENT of acute myeloid leukaemia (AML) in young people has been one of the greatest cancer success stories. Prior to the early 1970s there were very few survivors and thereafter no more than 1 in 10 survived until the advent of more intensive therapy and bone marrow transplantation later in that decade. During the 1980s some progress was made but even in the childhood age group, wherein the cure rates had always been higher, only approximately a third were cured.

Professor Ritter's update clearly documents the last 10 years during which survival rates have nudged over the 50% mark. A good risk group of patients with chromosome t(8; 21), t(15; 17) translocations and inversion of chromosome 16 have survival rates equivalent to the better risk groups with acute lymphoblastic leukaemia (ALL). The survival rates of young infants with ALL is worse than those with AML.

This progress has been achieved because supportive care, in the form of indwelling venous catheters, total parenteral nutrition, antibiotics, antifungals and intensive care have allowed the use of extremely dosage-intensive regimens. There really is little evidence that so-called 'maintenance' or continuation therapy works in AML as opposed to ALL and the Medical Research Council studies have shown, in my view, that cranial radiation has little role to play. The central nervous system relapse rate is very low with the use of simple intrathecal chemotherapy which has less long-term toxicity than cranial irradiation.

I remain very sceptical about the value of autologous bone marrow rescue from high-dose therapy and am unconvinced that marrow purging mill make a tangible difference. The real challenge for the future is to design even more successful chemotherapy regimens which preferably do not contain anthracyclines because of the looming problem of cardiotoxicity. In that vein, I believe that current evidence for one anthracycline being better than another is weak and that what we should be doing is large randomised trials of cardio-protective agents. We are already seeing long-term survivors whose hearts are damaged enough to require heart transplant and we must aim for cure at least cost within the next decade. In that context, I would agree that fludarabine and a cytokine-containing regimen must be explored in randomised clinical trials, along with high-dose cytarabine and possibly asparaginase-containing regimens.

Increased success has led to a greater ability to predict the outcome, based mainly upon good and poor (the latter being chromosomes 5, 7, 3 and complex changes) cytogenetic features. This certainly helps with planning therapy but we must resist the temptation to tailor individual treatment until we know more about how different prognostic groups respond to different therapies. However, significant numbers of patients can be cured without resort to bone marrow transplantation and as chemotherapy improves the hope is that it will mainly find use as a salvage therapy for patients with resistant disease and early relapse. Patients with a poor risk AML do badly with any type of therapy at present and less than 1 in 5 is cured and, thus, we must continue to search for better chemotherapeutic options.