Acute myeloid leukemia in children: Current status and future directions

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Abstract
Acute myeloid leukemia (AML) accounts for 25% of pediatric leukemia and affects approximately 180 patients annually in Japan. The treatment outcome for pediatric AML has improved through advances in chemotherapy, hematopoietic stem cell transplantation (HSCT), supportive care, and optimal risk stratification. Currently, clinical pediatric AML studies are conducted separately according to the AML subtypes: de novo AML, acute promyelocytic leukemia (APL), and myeloid leukemia with Down syndrome (ML-DS). Children with de novo AML are treated mainly with anthracyclines and cytarabine, in some cases with HSCT, and the overall survival (OS) rate now approaches 70%. Children with APL are treated with an all-trans retinoic acid (ATRA)-combined regimen with an 80–90% OS. Children with ML-DS are treated with a less intensive regimen compared with non-DS patients, and the OS is approximately 80%. HSCT in first remission is restricted to children with high-risk de novo AML only. To further improve outcomes, it will be necessary to combine more accurate risk stratification strategies using molecular genetic analysis with assessment of minimum residual disease, and the introduction of new drugs in international collaborative clinical trials.

Key words acute myeloid leukemia, acute promyelocytic leukemia, clinical trial, Down syndrome.

Acute myeloid leukemia (AML) accounts for approximately 25% of pediatric leukemia, and affects approximately 180 patients annually in Japan.1 The prognosis for pediatric AML has improved, and with recent advances in chemotherapy, hematopoietic stem cell transplantation (HSCT), and supportive care, the long-term survival rate now approaches 70%. Considering that overall survival (OS) rates for pediatric cancer patients are now approaching 80%, however, there is considerable room for further improvement. Currently, for patients with newly diagnosed AML, clinical studies are conducted separately according to the three disease subtypes: de novo AML; acute promyelocytic leukemia (APL); and myeloid leukemia with Down syndrome (ML-DS).

In this review, the current status of pediatric AML (de novo AML, APL and ML-DS) in Japan, including the history of clinical trials and comparisons with other developed countries, are presented. Future directions for the diagnosis and treatment of pediatric AML are also discussed.

De novo AML

History of Japanese clinical trials for pediatric AML

ANLL91 study
This trial was the first multicenter prospective study for pediatric de novo AML in Japan, supported by a grant from the Ministry of Health and Welfare.2 All patients received etoposide 150 mg/m² for 5 days followed by cytarabine 200 mg/m² (12 h infusion) for 7 days and mitoxantrone 5 mg/m² for 5 days (ECM induction therapy). The patients with an HLAmatched family donor received allotopic HSCT in first complete remission (CR). The other patients received eight additional courses of intensification therapy including continuous or high-dose cytarabine (HDCA) or autologous HSCT. In total, 157 patients were enrolled, and CR, 7 year event-free survival (EFS), and OS rates were 91%, 55%, and 62%, respectively. In the successor study conducted by the Tokyo Children’s Cancer Study Group (TCCSG M96-14), similar EFS (51% in 5 years) and OS rates (58% in 5 years) were observed, despite the reduction of total chemotherapy courses to seven courses compared with nine courses in the ANLL91 study.2

AML99 study
The AML99 study was conducted based on the ANLL91 study by the Japanese Childhood AML Cooperative Study Group (consisting of the TCCSG, Japan Association of Childhood Leukemia Study [JACLS], and Kyushu Yamaguchi Children’s Cancer Study Group [KYCCSG]).3 This study consisted of a risk-oriented regimen by treatment response to induction therapy, and chromosomal abnormalities of leukemic cells. The regimen consisted of six chemotherapy courses including continuous or HDCA. The patients with intermediate-risk (IR) and an HLAmatched family donor, and all the high-risk (HR) patients received allotopic HSCT in first CR. From 1999 to 2003, 240 patients were enrolled in total. CR, 5 year EFS and OS rates were 94%, 61%, and 75%, respectively, which was one of the best reported outcomes among developed countries.3

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CCLSG AML9805 study

In parallel to the AML99 study, the Japanese Childhood Cancer and Leukemia Study Group (CCLSG) performed another prospective childhood AML study, termed AML9805, from 1998 to 2003. The aim of this study was to improve the outcome of children with AML by morphological response-based risk stratified therapy. Remission induction therapy consisted of two courses of pirarubicin, vincristine, and continuous-dose cytarabine (AVC1). The patients who achieved CR were treated with either of the two consolidation therapies according to the French-American-British (FAB) classification system. The patients who did not respond to the initial courses of AVC1 underwent salvage therapy. Of the 101 patients registered, 74 achieved CR with the first AVC1 course. The EFS and OS rates at 5 years were 53.4% and 74.2%, respectively.

Japanese Pediatric Leukemia/Lymphoma Study Group AML-05 study

Following the excellent outcomes of the AML99 study, a nationwide multicenter study (termed the AML-05 study, UMIN000000511) was conducted by a new national collaboration established in 2003, the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), to further optimize risk-stratified therapies for childhood AML; in which the four existing pediatric leukemia study groups (TCCSG, JACLS, KYCCSG, and CCLSG) were merged.

In the JPLSG AML-05 study, patients were stratified into three risk groups according to specific cytogenetic characteristics and morphological treatment responses after two courses of common induction therapy. Low-risk (LR) children were defined as those with t(8;21) or inv16 (core binding factor, CBF), and a good bone marrow response to the first induction course. HR children were those with abnormalities of monosomy 7, 5q-, t(16;21)(p11;q22), t(9;22), fms-related tyrosine kinase 3 internal tandem duplication (FLT3-ITD), and/or poor response to the first induction course. IR children were those who were neither LR nor HR. Only patients designated HR were candidates for HSCT in first CR in AML-05. Patients in CR after two courses of induction therapy received a further three courses of consolidation chemotherapy, which were intensified using HDCA, whereas four courses of consolidation therapy were given in AML99. In particular, the cumulative doses of anthracyclines and etoposide were reduced, aiming to decrease the risk of late complications, such as anthracycline-induced cardiotoxicity for the LR group.

Between November 2006 and December 2010, 443 eligible patients were registered in the AML-05 study. The 3 year EFS and OS rates were 54.2% and 73.1%, respectively, which was similar to the outcomes of the AML99 study. The key findings of the AML-05 study were as follows: (i) the EFS for CBF leukemia was worse than in the AML99 study due to excessive treatment reduction, especially with anthracyclines; (ii) the outcome for non-CBF AML was similar to that in the AML99 study, even with the reduction of treatment courses and restriction of HSCT indication at first remission; (iii) serious pulmonary complications in infants frequently occurred during induction therapy and dose reduction would be needed for this group; (iv) the outcome for AML with myelodysplastic syndrome (MDS)-related changes was poor; and (v) the outcome for FLT3-ITD-positive AML could not be improved even with escalation to HR because of poor treatment response to induction therapy before HSCT.

Therapy according to risk stratification

It is important to provide appropriate risk stratification for AML patients in order to design optimal treatment strategies, including HSCT, because treatment-related mortalities and late complications would be increased by uniform therapeutic intensification. Like the JPLSG AML-05 study described in the previous section, chemotherapy for AML consists of one or two courses of induction therapy, followed by post-remission therapy including HSCT with risk stratification based on chromosomal abnormalities of leukemic cells, and response to initial induction therapy.

The outcomes of recent clinical trials, risk stratification and indication for HSCT, cumulative doses of anthracyclines and cytarabine for de novo AML in children are summarized in Tables 1–3, respectively.

Induction therapy

The treatment of pediatric AML consists of multi-agent chemotherapy, especially with cytarabine and anthracyclines. In addition, a third class of chemotherapeutics, such as etoposide, is often used, although it is unclear if this provides additional benefits. The regimen for induction therapy is based on a “3 plus 7” system, consisting of continuous infusion of cytarabine 100–200 mg/m² for 7 days and daunorubicin (DNR) 45–60 mg/m² for 3 days, which was established in the 1970s. The ADE regimen (cytarabine 200 mg/m² [i.v., q12 h] for 10 days combined with DNR and etoposide), became the standard for children with AML in the UK and USA due to its effectiveness in the MRC AML10 study.

In Japan, the ECM regimen has been used in the ANLL91, AML99 and JPLSG AML-05 studies and is established as the standard for pediatric AML.

Post-remission induction therapy (Intensification therapy)

Post-remission induction therapy, including allogeneic HSCT, is stratified by risk group according to specific cytogenetic characteristics and response to induction therapy.

For patients with CBF leukemia, who are considered to have a good prognosis, only chemotherapy is performed. For patients with poor response to induction therapy, or with HR cytogenetics such as monosomy 7, and 5q- among others, who are thought to have poor prognosis, allogeneic HSCT in first remission is indicated. For non-CBF-AML patients without HR features, allogeneic HSCT is still controversial, but there is a trend towards omitting HSCT in line with recent improvements in chemotherapy and the potential acute and late complications of HSCT. In addition to the conventional cytogenetic abnormalities, recent progress in molecular genetics has identified various novel genetic abnormalities such as mutations of CEBPA or NPM1, which are reported to be good prognostic factors. The prognostic significance of many of the other newly identified mutations, however, is still controversial. For example, cKIT mutation was reported to be a poor prognostic indicator for relapse in Japanese studies (AML 99 and AML-05), but not in the Children’s Oncology Group (COG) or European
Thus, the prognostic impact of novel genetic abnormalities should be carefully evaluated before inclusion in risk stratification systems.

Similar to induction therapy, intensification therapy for pediatric AML consists of multi-agent chemotherapy with cytarabine and anthracyclines, usually consisting of four to six courses including induction therapy.

Since the 1990s, the use of HDCA in intensification courses has been a standard for AML treatment. It is proven that HDCA has contributed to an improved survival rate for CBF leukemia, especially in children and young adults.20–22 HDCA was used in three of five post-remission courses in the IR group and in four of five courses in the LR group for intensification therapy in the AML99 study. Intensive use of HDCA in the AML99 study seems to have

Table 1  Outcome of recent clinical trials for pediatric de novo AML

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>n</th>
<th>Age (years)</th>
<th>HSCT (%)</th>
<th>3 year EFS (%)</th>
<th>3 year OS (%)</th>
<th>RR (%)</th>
<th>TRM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML993</td>
<td>2000–2002</td>
<td>240</td>
<td>0–18</td>
<td>Allo 17, Auto 2</td>
<td>61 (SR 71, IR 60, HR 57) (5 years)</td>
<td>75 (SR 86, 72, HR 57) (5 years)</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>AML-055</td>
<td>2006–2010</td>
<td>443</td>
<td>0–18</td>
<td>12</td>
<td>54 (LR 69, IR 57, HR 53)</td>
<td>73 (SR 93, IR 73, HR 69)</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>SJCRH-AML028</td>
<td>2002–2008</td>
<td>216</td>
<td>0–21</td>
<td>25</td>
<td>63</td>
<td>71</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>NOPHO-AML 2004</td>
<td>2004–2009</td>
<td>151</td>
<td>0–15</td>
<td>15</td>
<td>57</td>
<td>69</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>MRC-AML1210</td>
<td>1995–2002</td>
<td>564</td>
<td>0–15</td>
<td>11</td>
<td>54 (10 years)</td>
<td>63 (LR 83, IR 70, HR 39)</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>BFM 200411</td>
<td>2004–2010</td>
<td>521</td>
<td>0–18</td>
<td>NA</td>
<td>55 (SR71, HR 46) (5 years)</td>
<td>74 (SR 89, HR 65) (5 years)</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>AIEOP AML2002/0112</td>
<td>2002–2011</td>
<td>482</td>
<td>0–18</td>
<td>Allo 29, Auto 21</td>
<td>55 (SR 63, HR 53) (8 years)</td>
<td>67 (LR 83, HR 64) (8 years)</td>
<td>24</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2  Risk stratification and indication for HSCT in recent clinical trials for de novo AML

<table>
<thead>
<tr>
<th>Study</th>
<th>Low (standard) risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
<th>Indication HSCT in 1st CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML993</td>
<td>t(8; 21) and WBC &lt;50000/μL, inv(16) and CR after Ind-1, or, age &lt;2 years without HR features</td>
<td>No LR or HR features</td>
<td>−7, 5q-, t(16;21)(p11;q22), Ph1, or, non-CR after Ind-1</td>
<td>All HR and IR with MFD</td>
</tr>
<tr>
<td>AML-055</td>
<td>All t(8; 21), inv(16) and, CR after Ind-1, and, absence of FLT3-ITD</td>
<td>No LR or HR features</td>
<td>−7, 5q-, t(16;21)(p11;q22), Ph1, or FLT3-ITD or, non-CR after Ind-1</td>
<td>All HR</td>
</tr>
<tr>
<td>SJCRH-AML028</td>
<td>t(8; 21), inv(16), t(9; 11)</td>
<td>No LR or HR features</td>
<td>−7, FLT3-ITD, t(6; 9), AMKL, t-AML, AML from MDS</td>
<td>SR and HR with MSD</td>
</tr>
<tr>
<td>NOPHO-AML 2004</td>
<td>No HR features, t(8; 21) and inv(16) with CR after Ind-2</td>
<td>No LR or HR features</td>
<td>≥15% blasts after Ind-1 or non-CR after Ind-2, or MLL rearrangement</td>
<td>HR with donor</td>
</tr>
<tr>
<td>MRC-AML1210</td>
<td>t(8; 21), inv(16) and CR after Ind-1</td>
<td>No LR or HR features</td>
<td>&gt;15% blasts after Ind-1 or −7, − 5, 5q, abn(3q), complex (≥ abnormalities)</td>
<td>IR and HR with MSD</td>
</tr>
<tr>
<td>BFM 200411</td>
<td>FAB M1/M2 with Auer rods, M4eo or t(8; 21) and inv(16) and &lt;5% BM blasts on day 15 and absence of FLT3-ITD</td>
<td>No LR or HR features</td>
<td>No SR features</td>
<td>HR with MSD</td>
</tr>
<tr>
<td>AIEOP AML2002/0112</td>
<td>All t(8; 21), inv(16) and, CR after Ind-2</td>
<td>No LR or HR features</td>
<td>−7, 5q- or &gt;15% blasts after Ind-1 or FLT3-ITD-HAR</td>
<td>HR with donor</td>
</tr>
<tr>
<td>COG AAML0531†</td>
<td>All t(8; 21), inv(16) and, CR after Ind-1 and absence of FLT3-ITD-HAR</td>
<td>IR: no LR or HR features</td>
<td>−7, − 5, 5q- or &gt;15% blasts after Ind-1 or FLT3-ITD-HAR</td>
<td>All HR</td>
</tr>
</tbody>
</table>

†Patients with no MFD, eligible for auto-HSCT. AML, acute myeloid leukemia; CR, complete remission; GO, gemtuzumab ozogamicin; HR, high-risk group; HSCT, hematopoietic stem cell transplantation; IR, intermediate-risk group; LR, low-risk group; NA, not evaluated; OS, overall survival; SR, standard-risk group; RR, relapse rate; TRM, treatment-related mortality.
Table 3  Cumulative dose of anthracyclines and cytarabine in recent clinical trials for pediatric de novo AML

<table>
<thead>
<tr>
<th>Study</th>
<th>Anthracyclines</th>
<th>Cytarabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type</td>
<td>Cumulative dose (mg/m²)</td>
</tr>
<tr>
<td>AML99 LR³</td>
<td>MIT, IDA</td>
<td>295–300</td>
</tr>
<tr>
<td>AML99 IR/HR³</td>
<td></td>
<td>370–375</td>
</tr>
<tr>
<td>AML05 LR⁵</td>
<td>MIT, IDA</td>
<td>225</td>
</tr>
<tr>
<td>AML05 IR/HR⁵</td>
<td></td>
<td>375</td>
</tr>
<tr>
<td>SJCRH AML02D</td>
<td>DNR, MIT</td>
<td>450–550</td>
</tr>
<tr>
<td>NOPHO-AML, 2004⁴</td>
<td>MIT, IDA</td>
<td>480</td>
</tr>
<tr>
<td>MRC AML12¹⁰⁴</td>
<td>DNR, MIT</td>
<td>300–610</td>
</tr>
<tr>
<td>BFM 2004 SR¹¹</td>
<td>IDA, L-DNR, MIT</td>
<td>350–410</td>
</tr>
<tr>
<td>BFM 2004 HR¹¹</td>
<td></td>
<td>450–510</td>
</tr>
<tr>
<td>AIEOP AML2002/01¹²⁴</td>
<td>IDA, MIT</td>
<td>460</td>
</tr>
<tr>
<td>COG AAML0531 (GO arm)¹³</td>
<td>DNR, MIT</td>
<td>540</td>
</tr>
</tbody>
</table>

¹Calculated relative to the amount of daunorubicin using a conversion rate of 5:1 for daunorubicin to mitoxantrone/idarubicin.
AML, acute myeloid leukemia; DNR, daunorubicin; GO, gemtuzumab ozogamicin; IDA, idarubicin; L-DNR, liposomal daunorubicin; MIT, mitoxantrone.

contributed to the superior outcome, although the indication of HSCT at first remission was relatively low.³

**Indication for HSCT**

Since the 1980s, HSCT from an HLA-matched related family donor has been widely performed for pediatric AML at first remission, but there are no randomized clinical studies comparing chemotherapy and allogeneic HSCT. To date, the only studies available have compared chemotherapy and allogeneic HSCT by familial donor availability and a mendelian/genetic randomization with intent-to-treat analysis.

A few reports showed superior outcomes for HSCT from an HLA-matched family donor over chemotherapy, but most of the recently conducted studies in the USA and Europe found no advantage of HSCT.²³–²⁷ Thus, considering recent improvements in chemotherapy, and the potential risk of acute and late toxicities of HSCT, there is a trend towards restricting HSCT at first remission to HR patients only. Currently, a clinical study evaluating the role of reduced-intensity conditioning in HSCT for de novo AML (FLAMEL-15) is planned by the JPLSG SCT committee.

**Relapsed AML**

The outcomes for children with newly diagnosed AML are improving, but once they relapse, their prognosis remains poor, with reported OS rates of 24–36%²⁸–³¹ In Japan, 71 patients who relapsed following first-line treatment under the AML99 protocol were analyzed retrospectively.³⁵ Sixty-six patients received reinduction chemotherapy and 33 (50%) achieved CR. Twenty-nine CR2 patients and 35 non-CR2 patients underwent allogeneic HSCT. The 5-year OS rate after relapse was 37%. The 5-year OS rate was significantly higher in patients who underwent HSCT in CR2 compared with those in non-CR2. On multivariate analysis early relapse and FLT3-ITD positivity were adverse prognostic factors for survival.³⁵ Given that outcome for relapsed AML patients treated with conventional chemotherapy with or without allogeneic HSCT is poor, the introduction of novel and more effective chemotherapeutics is urgently required.

**Future for pediatric de novo AML**

As mentioned here, EFS and OS rates for childhood AML are approaching 60% and 70%, respectively. This has been achieved with intensified multi-drug chemotherapy with cytarabine and anthracyclines, optimal indication for HSCT by risk stratification, and advances in supportive care. For further improvement, the development of a more definitive risk stratification system, the intensification of current AML chemotherapy, and the introduction of new treatment options, including molecular targeted drugs are necessary.

New genetic abnormalities have been discovered as a result of recent progress in molecular genetics. Presently, the prognostic impact of these newly found abnormalities is controversial. Once their significance is more clearly established, however, it is likely that they will have a major influence on future risk stratification of pediatric AML.

Recently, much attention has been focused on minimal residual disease (MRD) as a prognostic factor for children with AML. The detection of MRD involves searching for chimeric transcripts, or specific gene abnormalities on polymerase chain reaction (PCR) and/or specific surface antigens on flow cytometry of residual leukaemic cells at morphological remission. For AML patients the assessment of MRD on PCR is problematic because only 45–70% of the MRD of candidate patients can be detected and the residual chimeric transcripts, such as RUNX1-RUNXIT1 and CBF-MYH11, do not always correlate with risk of relapse. In contrast, recent studies from St Jude Children’s Research Hospital (St Jude), the UK, and COG showed the prognostic impact of flow-based MRD detection,³⁶–³⁸ and it is already used for risk stratification in the current St Jude and COG studies. But, given that the prognostic impact of MRD clearly correlates with prior treatment, the role of flow cytometry-based MRD detection is under evaluation in the current ongoing JPLSG AML-12 study, which commenced in 2014.

Intensification of current AML chemotherapy, especially increased use of cytarabine and anthracyclines, would be another key strategy to improve the outcome of pediatric AML. Intensification of anthracyclines in the induction phase clearly improved outcome in adult studies.³⁹,⁴⁰ Anthracycline intensification, however,
may lead to an increase in late cardiotoxicity, which would not be acceptable for children with AML because they have a higher susceptibility to anthracyclines, and may experience significant life-long sequelae.

Intensification of cytarabine, especially the use of HDCA, is another consideration. As mentioned here, the use of HDCA during intensification has contributed to improved outcome, especially in CBF leukemia, but the effectiveness of its use in the induction phase is still controversial.41-46 Currently, the JPLSG AML-12 study (UMIN000013288), a randomized controlled study of ECM versus HDCA-based induction therapy, is underway in Japan.

Finally, the general consensus in the field is that only limited improvement in outcome will be achieved with intensification of conventional chemotherapy with or without HSCT, highlighting the necessity for the introduction of new drugs based on AML biology. Several candidate drugs are currently in development for adult and pediatric AML: including clofarabine, a new purine nucleoside analog;47 FLT3 inhibitors;48 KIT inhibitors;49 Polo-like kinase inhibitors;50 proteasome inhibitors;51 epigenetic modifiers, such as demethylating agents and histone deacetylase inhibitors;52 and novel immunotherapies targeting AML antigens such as bi-specific T-cell engager (BiTE) antibodies for CD33 and chimeric antigen receptor (CAR), and T-cell therapy targeting CD33, CD123, and others.53,54 The development of novel drugs to treat childhood malignancy, however, remains a major challenge in Japan because under the Japanese universal health-care system, use of off-label drugs is prohibited; thus, it is crucial to develop promising agents with the aim of obtaining approval for marketing authorization. Unfortunately, company-initiated trials are rarely undertaken due to the small number of children with cancer, and lack of incentives encouraging pharmaceutical companies to develop drugs for childhood malignancy. Meanwhile, investigator-initiated drug development, as well as fund raising for pediatric trials, are urgently required.

**Acute promyelocytic leukemia**

**Overview**

Acute promyelocytic leukemia is a subtype of AML, characterized by a differentiation disorder at the promyelocyte stage. It is classified as M3 or M3v in the FAB system and APL with t(15;17) (q22;q12); and PML-RARA according to the World Health Organization 2008 classification.55-58 APL in children accounts for 10–15% of AML cases, and it is estimated that approximately 10 patients per year develop pediatric APL in Japan. The clinical features and biology of childhood APL are considered to be the same as those in adults. APL blasts have a translocation of chromosome 15 and 17, and the product of this translocation, the PML-RARA fusion protein, inhibits transcription by competitively inhibiting the binding of the normal RARA transcriptional activator protein to DNA, resulting in defective myeloid differentiation. It is known that patients with APL often have complex presentations, with disseminated intravascular coagulation (DIC), which is often fatal at the onset or during initial induction therapy of APL.

In 1988, the effectiveness of ATRA for the treatment of APL was reported from China, and the effect was subsequently demonstrated to be the result of induced differentiation of APL cells. Introduction of ATRA enabled patients with APL to achieve CR without developing organ bleeding due to DIC. The duration of remission on ATRA alone, however, was short, and recently combination chemotherapy with ATRA and other anti-leukemic agents has been used nationwide in developed countries.

The treatment strategy for childhood APL is similar to adults. Approximately 95% of children with APL achieved CR and the EFS and OS rates were 80–90% and approximately 90%, respectively. HSCT for children and adults is not indicated for patients at first remission, but especially autologous HSCT is indicated for patients after recurrence. Treatment using new agents such as arsenic trioxide (ATO) and/or gemtuzumab ozogamicin (GO) have been used for patients with ATRA resistance.

Treatment strategies based on ATRA induction therapy and anticancer drugs, intensification therapy mainly by anthracyclines, maintenance therapy with ATRA alone, or ATRA with other anticancer drugs have been established in several developed countries.59-60 Recent clinical trials for children with APL are summarized in Table 4.61-65 The International consortium for childhood APL (ICC-APL) was organized by the International BFM group; and the ICC-APL01 study, as an arm in the AIEOP study including MRD intervention, is ongoing. PETHEMA (Spain) is carrying out the ongoing LPA2005 study with adults,66 and COG has been performing the AAML1331 study, following the original AAML0631 study.

**History of Japanese clinical trials for pediatric APL**

**AML99-M3 study**

A multi-institutional prospective study, AML99-M3, undertaken by the Japanese AML cooperative study group, enrolled 58 patients from 1999 to 2004.61 The treatment regimen included ATRA and anthracyclines combined with cytarabine in both the induction and consolidation phases, and intermittent ATRA alone for 1 year for maintenance. Although two patients died of hemorrhage by DIC in induction, the remainder (n = 56) achieved CR. Two patients who achieved CR relapsed in the bone marrow after 15 and 19 months, respectively. The 7 year EFS and OS rates were 91.4% and 93.1%, respectively, similar to recent clinical trials in the USA and Europe.

**JPLSG AML-P05 study**

The result of the AML99-M3 study was excellent, but severe hemorrhage due to DIC during the induction phase, and prolonged neutropenia with a relatively high incidence of sepsis because of more intensive consolidation chemotherapy compared with other studies, were problematic issues. On the basis of these results, a nationwide prospective study in Japan for childhood APL by JPLSG was performed from 2006 (UMIN000000645). All patients received at least 3 day ATRA monotherapy, followed by cytarabine and daunorubicin as the first induction therapy. The second induction therapy and the subsequent three courses of consolidation therapy consisted of ATRA, either high- or intermediate-dose cytarabine,
dose in this study was converted to 280 mg/m² of doxorubicin. The criteria for anthracycline equivalents, the cumulative anthracycline abnormalities did not in

period was 4.47 years (range, 0.745 years).

Eighty-five percent. Neither cardiac adverse events nor treatment-related death were observed during consolidation and maintenance therapies. Three patients relapsed during or after maintenance therapy, and the overall CR rate was 85.7%. Neither cardiac adverse events nor treatment-related death were observed during consolidation and maintenance therapies. Three patients relapsed during or after maintenance therapy, and the other of infection in the second course. Two patients died during induction therapy: one of coagulopathy in the first course, and the other

measurement of remission status and prediction of relapse. As a result of recent progress described here and previous Japanese trials, a new prospective trial, named the JPLSG AML-P13 study (UMIN000015348), is currently being carried out. In this study, induction therapy is the same as in the previous AML-P05 study, but all three courses of intensification consist of ATO only. The patients who could not achieve CR will be treated with ATO and/or GO. Moreover, MRD is measured routinely, and for the patients with positive MRD after intensification, reinduction therapy including GO will be initiated.

Myeloid leukemia with Down syndrome

Overview

Although exact numbers are not available, it is estimated that 20–30 patients per year develop ML-DS in Japan. ML-DS has unique characteristics: a predominance of acute megakaryoblastic leukemia; tendency to occur during the first 4 years of life; and higher sensitivity to chemotherapeutic agents. The latter translates into a good treatment response, with the drawback of increased treatment-related toxicities compared with non-DS children with AML. As a result, in recent clinical studies in several countries, ML-DS children were treated separately and less intensively than non-DS AML children.

Recent clinical trials for ML-DS are summarized in Table 5. In Europe, the ML-DS 2006 study by the International BFM group, which is based on the BFM98 protocol for de novo AML, is ongoing. This protocol consists of four courses with an HDCA-containing regimen. The US AAML0431 study, conducted from 2007 to 2011 by the COG, which also included an HDCA regimen, showed excellent outcomes (n = 204; 3 year EFS and OS rates were 90%, and 92.7%, respectively).73

History of Japanese clinical trials for ML-DS

AML99 Down study

A multi-institutional prospective study, designated the AML99 Down study, enrolled 72 patients from 2000 to 2004 and was conducted by the Japanese AML Cooperative Study Group. The study evaluated a slightly modified regimen from a previous trial using pirarubicin instead of daunorubicin, and a reduced total number of treatment courses from six to five. The 3 year EFS and OS rates

Table 4  Outcome of recent clinical trials for pediatric APL

<table>
<thead>
<tr>
<th>Group</th>
<th>Study</th>
<th>Period</th>
<th>n</th>
<th>Cumulative dose of anthracyclines (mg/m²)</th>
<th>CR rate (%)</th>
<th>5 year EFS (%)</th>
<th>5 year OS (%)</th>
<th>TRM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>AML99-M3</td>
<td>1997–2004</td>
<td>58</td>
<td>352</td>
<td>96.6</td>
<td>91.4 (7 years)</td>
<td>93.1 (7 years)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>AML-P05</td>
<td>2006–2011</td>
<td>43</td>
<td>280</td>
<td>85.7</td>
<td>83.6 (3 years)</td>
<td>90.7 (3 years)</td>
<td>2</td>
</tr>
<tr>
<td>European</td>
<td>APL93</td>
<td>1993–98</td>
<td>31</td>
<td>495</td>
<td>97</td>
<td>71</td>
<td>90</td>
<td>3</td>
</tr>
<tr>
<td>AIEOP</td>
<td>AIDA0493</td>
<td>1993–2000</td>
<td>107</td>
<td>650</td>
<td>96</td>
<td>76</td>
<td>89</td>
<td>4</td>
</tr>
<tr>
<td>PETHHEMA</td>
<td>LPA96/99</td>
<td>1996–2004</td>
<td>66</td>
<td>650-750</td>
<td>92</td>
<td>77</td>
<td>87</td>
<td>8</td>
</tr>
<tr>
<td>BFM</td>
<td>AML93/98/2004</td>
<td>1993–2007</td>
<td>81</td>
<td>300-410</td>
<td>95</td>
<td>65 (10 years)</td>
<td>82 (10 years)</td>
<td>7</td>
</tr>
<tr>
<td>COG</td>
<td>C9710</td>
<td>1999–2005</td>
<td>56</td>
<td>400</td>
<td>91</td>
<td>53 (3 years)</td>
<td>87 (3 years)</td>
<td>5</td>
</tr>
</tbody>
</table>

*Calculated relative to the amount of daunorubicin: conversion rate of 5:1 for daunorubicin to mitoxantrone/idarubicin, 0.5:1 for daunorubicin to pirarubicin, 0.4:1 for daunorubicin to aclorubicin. APL, acute promyelocytic leukemia; CR, complete remission; EFS, event-free survival; OS, overall survival; TRM, treatment-related mortality.
were 83% and 84%, respectively, and treatment-related mortality was only 1.4%. In this study, failure to achieve M1 marrow after initial induction was a poor prognostic factor.

CCLSG AML9805 Down study

The CCLSG performed a prospective study using continuous or high-dose cytarabine combined chemotherapy for patients with ML-DS.79 Of the 24 patients enrolled from 1998 to 2006, 21 achieved CR, and three died during remission induction therapy due to serious infection. All but one patient maintained CR without serious complications. The 5 year EFS and OS rates were 83.1% and 87.5%, respectively.

JPLSG AML-D05 study

As shown in these previous studies, the majority of ML-DS patients could be cured with relatively mild chemotherapy compared with AML in non-DS children,77 but patients are rarely salvageable once they relapse.82 On the basis of these results, a nationwide prospective study in Japan for ML-DS was conducted by JPLSG (UMIN000000989).80 Between January 2008 and December 2010, patients with ML-DS were enrolled. The patients received one course of induction therapy with daunorubicin, intermediate-dose cytarabine, and etoposide (CET), which was the same as the induction in the AML-D05 study. Moreover, new therapeutic regimen, was observed. The 3 year EFS and OS rates were 83.3 ± 4.4% and 87.5 ± 3.9%, respectively. No patients with secondary cancer or severe cardiotoxicity were observed, and therapy-related mortality for this study was only 1.4%. Age at diagnosis <2 years old was a significant favorable prognostic factor on both univariate and multivariate analysis. Other factors, including sex, high WBC count (>20 000/μL), FAB morphologies (non M7), chromosomal abnormalities (sole trisomy 21 or monosomy 7), and no GATA1 mutation did not adversely affect the risk of relapse.

Future for ML-DS

The Japanese trials described here investigated less intensive chemotherapy for ML-DS compared with those conducted in Western countries. Treatment outcomes were similar despite the dose reduction of chemotherapeutic agents compared with previous studies, and the overall outcomes were good. Combined with the results from the Toronto group with an ultra-low-dose cytarabine-based regimen,77 further dose reduction might be possible for specific subgroups. In contrast, most relapses occurred in the SR group defined by morphological treatment response, and relapsed patients are rarely salvageable, even in those receiving stem cell transplantation.82 In terms of treatment outcome, ML-DS is a heterogeneous disease, so risk-oriented therapy is a reasonable strategy. Unexpectedly, risk stratification by morphological treatment response in the AML-D05 study did not work well, because there were few HR patients. To find a more accurate method for the identification of the subgroup with poor prognosis, we are currently analyzing the role of MRD with various methods (flow cytometry, PCR, WT1 expression, and GATA1 mutation) in the ongoing JPLSG AML-D11 study (UMIN 000007237), which has a treatment protocol that is the same as the AML-D05 study. Moreover, new therapeutic

Table 5  Outcome of recent clinical trials for myeloid leukemia with Down syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>n</th>
<th>Daunorubicin (mg/m²)</th>
<th>Cytarabine (mg/m²)</th>
<th>Etoposide (mg/m²)</th>
<th>TRM (%)</th>
<th>EFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFM98 for DS72</td>
<td>1998–2003</td>
<td>67</td>
<td>220–240</td>
<td>23–29 000</td>
<td>950</td>
<td>5</td>
<td>89 (3 years)</td>
<td>91</td>
</tr>
<tr>
<td>NOPHO AML9373</td>
<td>1988–2002</td>
<td>41</td>
<td>300</td>
<td>48 600</td>
<td>1600</td>
<td>5</td>
<td>85 (8 years)</td>
<td>NA</td>
</tr>
<tr>
<td>MRC AML10/1274</td>
<td>1989–2002</td>
<td>46</td>
<td>670</td>
<td>10 600</td>
<td>0</td>
<td>15</td>
<td>74 (5 years)</td>
<td>74</td>
</tr>
<tr>
<td>CCG 2861/289175</td>
<td>1989–1999</td>
<td>160</td>
<td>320</td>
<td>15 800</td>
<td>1600</td>
<td>4</td>
<td>77 (6 years)</td>
<td>79</td>
</tr>
<tr>
<td>COG A297176</td>
<td>1999–2003</td>
<td>132</td>
<td>320</td>
<td>27 200</td>
<td>0</td>
<td>3</td>
<td>79 (5 years)</td>
<td>84</td>
</tr>
<tr>
<td>LD-cytarabine77</td>
<td>1990–2003</td>
<td>34</td>
<td>0</td>
<td>7400</td>
<td>0</td>
<td>0</td>
<td>67 (5 years)</td>
<td>77</td>
</tr>
<tr>
<td>AML99 DS78</td>
<td>2000–2004</td>
<td>72</td>
<td>(250)</td>
<td>3500</td>
<td>2250</td>
<td>1</td>
<td>83 (4 years)</td>
<td>84</td>
</tr>
<tr>
<td>JCCLSG 9805DS79</td>
<td>1998–2006</td>
<td>24</td>
<td>(190)</td>
<td>12 600</td>
<td>200</td>
<td>12.5</td>
<td>83 (5 years)</td>
<td>88</td>
</tr>
<tr>
<td>JPLSG AML D0580</td>
<td>2008–2010</td>
<td>72</td>
<td>(250) (SR)</td>
<td>3500 (SR)</td>
<td>1350 (SR)</td>
<td>(1)</td>
<td>83 (2 years)</td>
<td>88</td>
</tr>
</tbody>
</table>

DS, Down syndrome; EFS, event-free survival; HR, high-risk group; OS, overall survival; SR, standard-risk group; TRM, treatment-related mortality.

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approaches using new drugs such as Wee 1 inhibitor, Aurora kinase inhibitor and histone deacetylase inhibitors will be needed for relapsed/treatment-refractory patients.

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Disclosure
The authors declare no conflict of interest.

References


The authors further describe the outcomes in children with acute myeloid leukemia treated with various therapies, including high-dose cytarabine and other chemotherapeutic agents. They highlight the importance of developing effective treatment strategies for this disease.

The text concludes with a section on the outcomes of the AML in children and the importance of ongoing research and clinical trials to improve treatment options for these patients.


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