

## REVIEW

# Hematopoietic stem cell transplantation for childhood malignancies of myeloid origin

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**Myeloid malignancies in children include *de novo* acute/chronic myeloid leukemia (AML/CML) and secondary malignancy due to genetic predisposition or previous therapy. Generations of clinical trials for childhood myeloid disorders have resulted in improved disease characterization and outcome, and defined therapeutic strategies combining chemotherapy, biologic response modifiers and immunotherapy. With advancement in molecular genetics and the development of sensitive techniques to detect response, residual disease and relapse, therapy can be tailored in a risk-based manner using clinical and biological/molecular parameters and several 'good-risk' myeloid malignancies enjoy high cure rates with targeted therapy. However, hematopoietic stem cell transplant remains the best method of treatment intensification for poor-risk disorders such as relapsed/secondary AML, myelodysplastic syndrome and juvenile myelomonocytic leukemia. Indications for transplant and outcomes of previous clinical studies, and novel transplant strategies designed to improve safety and efficacy of the procedure are reviewed.**

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**Keywords:** childhood; myeloid disorders; stem cell transplant; review of outcomes

## Introduction

Survival rates in children with myeloid malignancies have improved over recent years as a result of rigorous clinical trials. Generations of trials within cooperative pediatric cancer groups have paved the way for standardization of basic therapy and provided an opportunity to study new

agents and strategies to improve outcomes. Table 1 shows outcomes of the most recent generation of trials in children with acute myeloid leukemia (AML) focusing on important lessons learnt in relation to hematopoietic stem cell transplantation (HSCT). These trials have also helped in disease characterization according to risk factors, biology, morphology, cytogenetics and molecular analyses. Patients with good outcome can receive 'tailored chemotherapy' sparing children with low-risk disease from being exposed to intense treatment regimens.

## Prognostic markers in AML

Biological studies have simultaneously identified several good (for example, *inv*(16), *t*(8;21)) and poor prognostic markers (for example, *-7*, *-5/-5q*, FLT3 mutation/high allelic ratio) in AML. The latter result in poor outcomes and 'high-risk' patients. Several signal-transduction pathways and cytogenetic abnormalities (for example, *11q23* translocations) are under review for further risk stratification.<sup>1</sup> AML can be subclassified using prognostic indicators (Table 2). Patients with AML who have established high-risk features require more than conventional therapy to improve outcomes. Newer protocols continue to ask therapeutic questions in a risk-stratified manner. High-risk patients with *de novo* AML may benefit from treatment intensification such as HSCT during frontline therapy; this approach is under investigation. Patients with relapsed or resistant disease, and therapy-related/secondary AML are also high-risk patients; salvage with chemotherapy alone is almost impossible due to drug resistance. Innovative clinical trials using targeted therapy with HSCT may improve outcomes in relapsed/resistant disease.

## Autologous HSCT for AML

Intensification of therapy by autologous HSCT following complete remission decreases relapse rates. An 8-year disease-free survival (DFS) of 47% was reported by the Children's Cancer Group (CCG) study 2891 in patients with an initial WBC <50 000/ $\mu$ l transplanted in first complete remission (CR1).<sup>2</sup> However, autologous HSCT

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**Table 1** Treatment outcomes in pediatric AML—HSCT lessons learnt

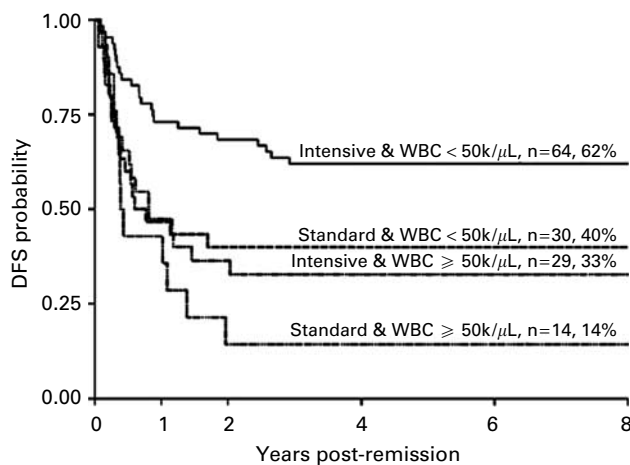
Trial	Patient number	OS, % (years)	DFS, % (years)	Conclusions from outcome analysis of serial trials
Medical Research Council (MRC 12) (1995–2002) <sup>4</sup>	564	66 (5)	61 (5)	No advantage to five courses; four-course therapies sufficient. Allogeneic HSCT only for standard or high-risk AML
AML-97 (St Jude) (1997–2002) <sup>32</sup>	40	47.5 (5)	58.3 (5)	HSCT was limited to high-risk patients
Pediatric Oncology Group (POG 9421) (1995–1999) <sup>33</sup>	624	55.6 (3) (EFS)	41.2 (3) (EFS)	Patients who had allogeneic HSCT fared better than those who received chemotherapy alone
NOPHO-AML 93 (Nordic) (1993–2001) <sup>34</sup>	243	65 (5)	52 (5)	HSCT not necessary at first remission
AML-BFM 93 (Germany) (1993–98) <sup>35</sup>	471	57 (5)	61 (5)	HSCT did not provide a survival advantage in first remission
Children's Cancer Group (CCG 2891) (1989–95) <sup>36</sup>	886	45 (5)	45 (5)	Intensively timed sequential chemotherapy and allogeneic HSCT improved survival
EORTC CLG 58921 (1992–2002) <sup>37</sup>	177	62 (5)	58 (5)	Survival was dependent on prognostic cytogenetic features
LAME 91 (French) (1991–98) <sup>38</sup>	262	60.6 (5)	52.1 (5)	Allogeneic BMT did not improve outcomes in good-risk patients
LAM-92 (Italy) (1992–2001) <sup>39</sup>	160	59.5 (5)	60.4 (5)	75% underwent HSCT (auto or allo) following stratification into risk groups; better survival results than previous trials

Abbreviations: DFS = disease-free survival; EFS = event-free survival; OS = overall survival; HSCT = hematopoietic stem cell transplantation.

**Table 2** Potential prognostic features affecting outcomes in pediatric AML<sup>1</sup>

Category	Good outcome	Intermediate	Poor outcome
Age			> 10 years
Leukocyte count			$\geq 50 \times 10^9/l$
Patient characteristics			Over- or under-weight African-American/Hispanic Treatment-related AML Duration of CR1 < 1 year
Morphology (FAB classification)	M3 M4	M1 M2 M5	M0 M6 M7
Cytogenetics	Constitutional trisomy 21 inv(16) t(15;17) t(8;21)		Monosomy 5 or 7
Mutations in signal transduction			FLT3 ITD-AR > 0.4
Response to therapy			> 15% marrow blasts after first induction
Minimal residual disease			+ by flow cytometric assays after clinical remission

Abbreviation: ITD-AR = internal tandem duplication-allelic ratio.



**Figure 1** Disease-free survival based on initial WBC count and induction timing: CCG study 2891. Neudorf S *et al. Bone Marrow Transplant* 2007; 40(4): 313–318 (reproduced with permission).

as performed in CCG-2891 was not superior to chemotherapy administered in the post-remission phase (Figure 1). Another retrospective registry review of autologous HSCT showed 3-year DFS of 54% in CR1 and 60% in CR2, but only if relapse occurred > 12 months following CR1. DFS was only 23% in patients with a short CR1.<sup>3</sup> Thus, the benefit of autologous HSCT was apparent only in 'better-risk' cases. Of note, autologous HSCT in CR1 resulted in poor response to second-line therapy following relapse.<sup>4</sup> However, certain poor prognosis subgroups such as children with M7 disease in the absence of Down's syndrome and without the luxury of a matched family donor may benefit from autologous transplantation in CR1.<sup>5</sup>

### Allogeneic HSCT for AML

Allogeneic HSCT (allo-HSCT) provides a method of treatment intensification in patients with AML who have

poor outcomes due to intermediate- or high-risk characteristics, and refractory disease or relapse. Treatment intensification is provided not only by the conditioning regimen used but also by harnessing immunologic mechanisms for a graft-versus-leukemia (GVL) effect. Allo-HSCT, however, is offset by complications such as graft-versus-host disease (GVHD), infections, organ toxicity, treatment-related morbidity and mortality especially in the unrelated donor setting. Hence, HSCT is not a planned therapeutic intervention during frontline therapy for good-risk patients with AML even when a healthy HLA-matched family donor is available. In the event of relapse in good-risk patients, salvage rates with HSCT during CR2 are equivalent to transplant as frontline therapy. However, in the presence of a matched sibling donor, HSCT has an advantage over chemotherapy alone if there are no good-risk features at presentation.<sup>6</sup> Thus, the decision to transplant is based primarily on risk group and secondarily on the availability of a donor. Outcomes following allo-HSCT for childhood AML are summarized in Table 3.

Several transplant-related lessons are evident from HSCT for AML. The development of acute GVHD decreased relapse risk in AML in more than one trial supporting a GVL effect, although the correlation is not quite as strong as in chronic myeloid leukemia (CML).<sup>6,7</sup> The timing of relapse after initial therapy was critical—survival was 21% after early (<1 year) and 48% after late relapse.<sup>8</sup> Although not prospectively studied, a retrospective registry review reported similar outcomes in young children (<18 months) following HLA-matched sibling or unrelated donor transplantation in CR1 (3-year survival 54 and 49% respectively).<sup>9</sup> When deemed necessary, HSCT should be considered in young children from suitable family or unrelated donors. The stem cell source (bone marrow versus cord blood) did not influence outcomes as strongly as disease status at transplant; chemotherapy-resistant disease had poor outcomes with <30% survival.<sup>10</sup> However, it is notable that a third of patients transplanted in relapse survive their disease, unlike lymphoid malignancies.<sup>8</sup> Transplant outcomes listed in Table 3 in patients with relapsed disease reflect survival after HSCT but do not take into account patients who died during salvage therapy and did not make it to transplant. Finally, the necessity for second transplants due to recurrent disease within 6 months of previous transplants resulted in higher subsequent relapse rates (80 versus 25%). For second transplants performed after 6 months, recipients of prior allo-HSCT were harder to salvage with second transplants than those receiving a prior autologous transplant.<sup>11</sup>

### Acute promyelocytic leukemia

Acute promyelocytic leukemia (APL) is a rare subtype in children; many features distinguish APL from other AML subtypes. APL blasts result from a PML–RAR $\alpha$  (promyelocytic leukemia–retinoic acid receptor- $\alpha$ ) fusion transcript. These cells are able to undergo differentiation with all-*trans* retinoic acid (ATRA) used in induction and maintenance therapy. Excellent outcomes are reported in adults with arsenic trioxide (induces apoptosis in APL blasts). Unlike

other AML subtypes, 3-year DFS exceeds 75% in good-risk patients. Unfavorable prognostic features in adults include older age (for example, >30 years), high initial WBC count (for example, WBC >10 000/mm<sup>3</sup>) and the bcr3 isoform of the PML–RAR $\alpha$  fusion transcript.<sup>12</sup> The influence of the FLT3 internal tandem duplication mutation on prognosis is unclear in APL. HSCT is considered only in the event of relapse. There are few data for HSCT in childhood APL due to the rarity of the disorder. In adults, autologous transplants have low mortality (6%) and 7-year DFS was 79% when performed following molecular remission.<sup>13</sup> Allogeneic transplants are reserved for patients without molecular remission and 7-year DFS was 92%. As expected, morbidity and mortality following allo-HSCT are higher and event-free survival was 52%. Strategies to decrease toxicities of allo-HSCT will benefit this population further.

### Down's syndrome and AML

Children with Down's syndrome are at risk for developing myeloproliferative disorders and acute leukemia. AML develops at a median age of 1.8 years and is predominantly of the megakaryocytic subtype (FAB M7). In CCG-2891, children with Down's syndrome had an 8-year event-free survival of 77%.<sup>14</sup> Event-free survival decreased considerably when Down's syndrome children were >4 years of age (28%); the incidence of remission failure was 14% (Figure 2). In the Medical Research Council 10 and 12 trials, overall survival (OS) for children with Down's syndrome was 74% at 5 years.<sup>15</sup> Patients were more susceptible to toxicities of chemotherapy, resulting in several early treatment-related deaths. The current recommendation for the treatment of children with Down's syndrome is the use of non-intensive chemotherapy without HSCT, even when an HLA-matched related donor is available.

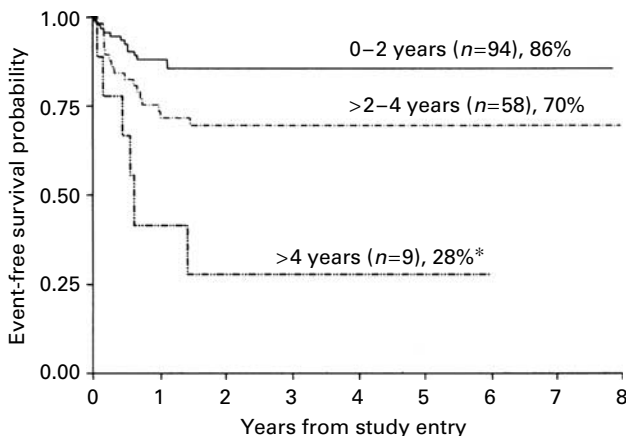
### Juvenile myelomonocytic leukemia

This rare childhood myeloproliferative disorder results in organ infiltration, thrombocytopenia and immunosuppression. Juvenile myelomonocytic leukemia (JMML) is fatal in 90% of children without allo-HSCT. Clinical manifestations include bleeding, splenomegaly, eczema and failure to thrive. Laboratory parameters include an absolute monocytosis, increased Hb F and leukocytosis. It is characterized by genetic mutations mainly inhibitory to Ras pathway signaling; some patients have monosomy 7. As a result of disruption of inhibitory pathways, myeloid precursors are hypersensitive to GM-CSF. Traditional chemotherapy does not improve JMML outcomes. HSCT is the only intervention that can control the disease long-term. A retrospective National Marrow Donor Program registry analysis of 46 JMML patients revealed only 24% DFS at 2 years with a relapse probability of 58%; the development of chronic GVHD was beneficial.<sup>16</sup> The European Blood and Marrow Transplantation and the European Working Group on Childhood MDS reported on 100 children with JMML

**Table 3** Outcomes of allogeneic HSCT for childhood AML

Author	No. of recipients/ conditioning regimen	Recipient details	Donor source	OS, % (years)	DFS, % (years)	aGVHD, % (grade)	cGVHD (%)	TRM (%)
Willemze <i>et al.</i> <sup>7</sup>	55 AML/majority fractionated TBI + Cy	CR1	MSD bone marrow	74 (5)	73 (5)	6 (2–4)	8	6
Neudorf <i>et al.</i> <sup>6</sup>	150/BU 16 + CY 200	CR1	Related bone marrow	67 (6)	57 (6)	9 (3–4)	21	17
Abrahamsson <i>et al.</i> <sup>8</sup>	64/NR	CR2/PR2	MUD BM MFD BM	62 (5)	57 72	NR	NR	20 11
Michel <i>et al.</i> <sup>40</sup>	95/BU or TBI based	CR1 20 CR2 47 AL 28	URD UCB	49	59 50 21 (2)	35	NR	20
Meshinchi <i>et al.</i> <sup>11</sup>	25/TBI + CY	Second HSCT	21 related 4 unrelated BM	48 (10)	44 (10)	76 (2–4)	47	20
Oyekunle <i>et al.</i> <sup>41</sup>	25 AML; 19 ALL/BU or TBI based	Refractory disease	MFD or MUD BM or PB	28 (5)	26 (5)	48 (1–4)	32	37

Abbreviations: AL = acute leukemia; BM = bone marrow; DFS = disease-free survival; MFD = matched family donor; MSD = matched sibling donor; MUD = matched unrelated donor; NR = not reported; OS = overall survival; PB = peripheral blood; TRM = treatment-related mortality; URD = unrelated donor; UCB = umbilical cord blood.



**Figure 2** Probability of event-free survival in children with AML and Down's syndrome classified by age: CCG study 2891. Gamis AS *et al.* *J Clin Oncol* 2003; **21**(18): 3415–3422 (reproduced with permission).

who were transplanted following a preparative regimen of BU, CY and melphalan.<sup>17</sup> This has been the most successful treatment approach reported to date with 5-year OS of 64% and event-free survival of 52% (Figure 3). Younger children fared better in this study. Of those who had disease recurrence, 7 of 15 patients who underwent a second HSCT following total body irradiation survived disease-free. Responses were noted to donor leukocyte infusions (DLI) but only from unrelated donors, suggesting that disease control was proportional to allogeneicity.<sup>18</sup>

### HSCT for myelodysplastic syndrome

Myelodysplastic syndrome (MDS) is rare in childhood and is frequently associated with monosomy 7 and del(7q). Transformation to AML, and association with additional cytogenetic abnormalities such as inv(3) –5/del(5q) or +21

is associated with poor survival rates (<5%). MDS associated with good prognostic cytogenetic markers (Table 2) had a higher survival rate (75%), showing that the latter had a stronger influence on outcome. Survival in the absence of additional cytogenetic markers in monosomy 7 patients was low (46%). Allo-HSCT is the only known curative therapy for this group of disorders.<sup>19</sup>

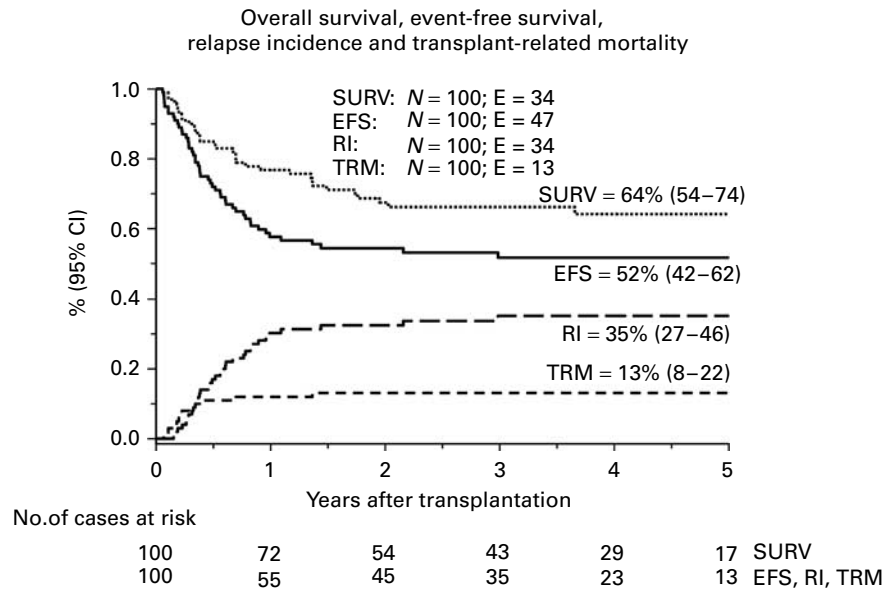
Therapy-related secondary AML or MDS is aggressive, hard to treat and associated with poor outcome. DFS is reported between 15 and 38% with high treatment-related mortality (27–59%).<sup>20</sup> Reduced-intensity immunosuppressive regimen using fludarabine and/or ATG in combination with low-dose chemo/radiotherapy may be better tolerated due to previous therapy-related toxicities, poor performance status, infections, and so on, although this is an area of ongoing investigation. Relapse rates were significantly lower in the presence of chronic GVHD (70 versus 15%), another attestation to the potential effect of GVL on myeloid malignancies.<sup>21</sup>

### HSCT for myeloid stem cell disorders

Several rare pediatric disorders such as severe congenital neutropenia, Shwachman–Diamond syndrome and Fanconi anemia, involving dysregulated myeloid hematopoiesis, are predisposed to aggressive MDS/AML with poor outcome. Survival is improved by HSCT.<sup>22,23</sup> Graft rejection rates and treatment-related mortality increase with age and progression to AML, suggesting that HSCT should be considered prior to progression to malignancy.<sup>24</sup>

### Chronic myeloid leukemia

Allo-HSCT from HLA-matched related or unrelated donors was previously the curative treatment of choice for children with CML. Outcomes were best when HSCT



**Figure 3** Survival and mortality following hematopoietic stem cell transplant for juvenile myelomonocytic leukemia. Locatelli F *et al. Blood* 2005; **105**(1): 410–419 (reproduced with permission).

was performed less than 1 year from diagnosis and in chronic-phase disease.<sup>25</sup> Several HSCT trials have attempted to lower toxicity in children by using approaches such as reduced-intensity conditioning (RIC), low-dose DLI, and so on.<sup>26</sup> The development of imatinib and subsequently other tyrosine kinase (TK) inhibitors that are successful at obtaining long-term cytogenetic response has changed therapeutic strategies for CML. However, TK inhibitors have not proven to be curative and HSCT still remains the only proven curative approach to children with CML.

In a recently published prospective study of 354 younger (<60 years) adult patients with newly diagnosed CML, following a median observation time of 8.9 years, survival was superior with oral drug therapy than with related donor HSCT, especially for low-risk disease but was equivalent after 8 years, stressing the need for even longer follow-up for better comparison.<sup>27</sup> Major causes of death included blast crisis (42.5%) and transplant-related mortality (26.1%). Five- and 10-year survival in all patients (72%/46% in low-risk patients; 62%/36% in intermediate-risk patients; 49%/26% in high-risk patients, respectively) highlights the dropout rate. A subset of patients develop imatinib-resistant clones with BCR-ABL kinase domain mutations. Although over 77 such mutations are described, only the T315I mutation (15% of imatinib-resistant patients) is resistant to all newer TK inhibitors.<sup>28</sup>

With the ability to follow remission status, best treatment practice in adult CML patients includes TK inhibitor therapy at diagnosis; allo-HSCT is indicated for patients who have poor response, and/or those who recur/progress on therapy. The decision and timing to proceed to HSCT in children given the requirement of life-long therapy and mutagenesis in BCR-ABL remain uncertain. Pre-HSCT imatinib did not influence or worsen HSCT outcomes.<sup>29</sup> In some countries, the cost of life-long expensive drug therapy may support a decision to proceed with HSCT as a curative option.

### Innovative strategies to improve transplant outcomes in myeloid malignancies

Although HSCT is not necessary for all patients with myeloid disorders, it is a useful approach to improve DFS in specific situations, and sometimes the only effective therapeutic intervention. In general, if HSCT is considered necessary, allo-HSCT is the treatment of choice to harness GVL barring a few indications for autologous transplants (APL in second molecular remission). Table 4 has a list of myeloid disorders, where a consideration for allo-HSCT may be entertained. Group 1 patients have little hope of long-term survival without transplant, whereas safe and effective HSCT will benefit group 2 patients.

Transplant techniques have evolved over recent years to improve outcomes. Areas of improvement have included RIC regimen, better donor availability and HLA-matching techniques (between donors and recipients), graft source manipulation such as partial T-cell depletion and improved methods of cord blood collection and storage, advanced techniques to detect minimal residual disease, post transplant immunotherapy, progress in supportive care, GVHD prophylaxis and therapy, and detection and treatment of infections.

Monitoring minimal residual disease levels either by multiparameter flow cytometry or real-time PCR is a sensitive way of monitoring for disease response or early relapse after chemotherapy and before and after HSCT.<sup>30</sup> Minimal residual disease is rapidly becoming the most sensitive predictor of disease status and can pave the way for strategizing therapy such as the decision to proceed to transplant after chemotherapy. Disease-specific markers such as Flt3 mutations/allelic ratio, BCR-ABL (CML), PML/RAR $\alpha$  (APL) are applicable for minimal residual disease analyses.<sup>31,32</sup> Protocols based on careful measurement of minimal residual disease allow for a more individualized treatment approach and will form the crux of new generation trials.<sup>33</sup>

**Table 4** Indications for allogeneic HSCT in myeloid disorders of childhood

Strong consideration	<ol style="list-style-type: none"> <li>1. AML CR2</li> <li>2. MDS-RAEB</li> <li>3. Refractory AML, primary induction failure</li> <li>4. APL in CR2 without molecular remission</li> <li>5. JMML</li> <li>6. CML</li> <li>7. Secondary AML</li> </ol>
Consider	<ol style="list-style-type: none"> <li>1. Intermediate-risk AML in CR1 with matched family donor</li> <li>2. High-risk AML in CR1</li> </ol>
Relative contraindication	<ol style="list-style-type: none"> <li>1. Good-risk AML in CR1</li> <li>2. APL in CR1</li> </ol>

Abbreviations: APL = acute promyelocytic leukemia; HSCT = hematopoietic stem cell transplant; JMML = juvenile myelomonocytic leukemia.

Several strategic innovations are undergoing trials to further improve allo-HSCT outcomes. An upcoming Children's Oncology Group (COG) HSCT trial for AML is designed to test the feasibility of reconstituting genotypically mismatched killer immunoglobulin-like receptors (KIR) on donor natural killer cells by typing donor KIR and recipient ligand pretransplant and evaluating reconstitution post transplant. Donor-recipient KIR mismatching in the presence of T-cell depletion can facilitate natural killer reconstitution and harness donor natural killer cell-mediated cytotoxicity against leukemia cells. Significantly, improved leukemia-free survival was found retrospectively with KIR incompatibility with haploidentical T-depleted and allo-HSCT following donor T-cell depletion with ATG.<sup>34</sup> The COG trial will help to prospectively evaluate benefits of this mechanism in children with high-risk AML. Another trial conducted by the Bone Marrow Transplant Clinical Trials Network (BMT CTN) is prospectively evaluating the benefits of infusing two partially matched cord blood products in HSCT for childhood hematologic malignancies in an effort to improve engraftment and survival.<sup>35</sup> Since cord blood grafts have equivalent outcomes to bone marrow grafts in leukemia even with mismatching at 1–2 HLA loci, this strategy, if successful, could improve donor availability and outcomes.<sup>10</sup> Pre- and post transplant immunological/molecular/signal-transduction pathway interventions are another area of active investigation targeting transplant modulation.

### Late effects of HSCT

The intensity of conditioning and timing of HSCT in childhood can result in toxicities and late effects that need monitoring and intervention. Children and adolescent transplant recipients are at significant risk of developing late emotional, social and adjustment problems.<sup>36,37</sup> Growth impairment has been associated with myeloablative conditioning regimens especially with irradiation.<sup>38</sup> Additional late complications include second malignancies, sterility, cataract, motor impairment, hearing and vision

loss, diabetes/hypertension, bone necrosis and chronic pain particularly associated with unrelated donor HSCT and cGVHD.<sup>39–42</sup> Post transplant lymphoproliferative disorders occur within the first year post-HSCT; the cumulative probability of developing a solid tumor at 10 years post-HSCT is 6.1% and continues to rise with time; HSCT-related hematological malignancies and MDS can occur but are rare.<sup>43</sup> Relative mortality decreases with time from HSCT, but remains significantly elevated compared to the general population even 15 years after transplant for the above reasons.<sup>44</sup>

### Reduced-intensity conditioning

Efforts to reduce early and late transplant toxicities have resulted in trials of RIC targeted at harnessing the GVL effect to achieve disease control instead of myeloablation. Patients targeted to receive RIC HSCT have initially been either the elderly or those with comorbidities. RIC regimen uses combinations of immunosuppressive agents such as fludarabine, lympholytic agents such as alemtuzumab or antithymocyte globulin, and lowered dose alkylating agents (melphalan, CY or treosulfan) or radiation. Early results in adult patients suggest better tolerance (that is, reduced early toxicity), and equivalent early survival with comparable GVHD rates.<sup>45–47</sup> However, disease relapse remained the commonest cause of treatment failure in the first 24 months, especially in patients with persistent disease at the time of transplant, questioning the efficacy of this approach in high risk and refractory disease settings.<sup>48</sup> RIC in children is currently best reserved for patients in complete remission and those with comorbidities limiting myeloablative regimen until follow-up studies establish long-term efficacy of this approach.

### Summary

Therapy for childhood myeloid malignancies has come a long way since the advent of combination chemotherapy, resulting in a steady increase in OS rates. The role of HSCT in disorders with poor outcomes such as relapsed/secondary AML, MDS and JMML is better defined in terms of indications and timing, but remains ill defined for intermediate- and high-risk AML. HSCT is not indicated for good-risk AML and APL in first remission. As targeted therapy for myeloid disorders continues to improve outcome, indications for HSCT are likely to narrow down further in a focused manner. Continued clinical trials of interventions designed to increase efficacy and decrease HSCT-related complications will assist in improving outcomes following transplant.

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