

EDITORIAL

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Stem Cell Transplantation to Treat Acute Myeloid Leukemia in Children

Przeszczepianie komórek macierzystych w leczeniu ostrej białaczki szpikowej u dzieci

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Introduction

Acute myeloid leukemia (AML) is heterogeneous disorder of the myeloid lineage. The biology is with minor exceptions (infant leukemia, Down syndrome and myeloid leukemia) similar in children and adults. Although AML is much more resistant to chemotherapy than acute lymphoblastic leukemia (ALL), treatment results in childhood AML have considerably improved during the last 15 years. Leading collaborative groups report remission rates of 80–90%, and 5-year survival over 40% in children and young adults.

These improved response and survival rates have largely resulted from the intensification of chemotherapy combined with good supportive care, but have been associated with a treatment-related mortality rate of up to 15% [1]. Relapse still remains the main cause of treatment failure, and occurs in 30–40% of those who achieve a complete remission.

Chemotherapy

Chemotherapy starting with intensive induction treatment, designed to cause marrow aplasia is far more intensive compared to childhood ALL. The primary objective in treating patients with AML is to induce remission and thereafter prevent relapse. Treatment is conventionally divided into two phases: induction and consolidation (postremission therapy). Daunorubicin and cytosine arabinoside (AraC) have been the backbone of treatment to induce remission. Complete remission can be routinely induced in 80 to 90% of children.

There is some evidence that the addition of etoposide can further increase remission rates. Three options are available for consolidation therapy in the younger patients: allogeneic stem cell transplantation (SCT), autologous SCT, or chemotherapy. There is a suggestion that more is better; the optimal number of courses has not yet been determined, except that more than one is necessary to achieve cure [2]. Patients who received initial intensive-timing chemotherapy had a significantly improved outcome regardless of the type of postremission intensification [3]. Data of several studies revealed lower relapse rate in children and adults after the introduction of highly intensive therapy with high-dose AraC (HD-AraC) in postremission treatment. Patients with high-risk AML who received additional intensification with high-dose AraC (HD-AraC) and mitoxantrone in the context of BFM protocol had improved outcome [4].

Prognostic Factors

Genetic subtype and early treatment response are the most important prognostic factors in childhood AML. Overall incidence of clonal chromosomal abnormalities is over 70% in children [5]. British MRC AML-10 study divides children in three risk groups according to genetic subtype and early treatment response. Good, standard and poor-risk children constituted 28%, 52% and 20% of the population, respectively [6, 7]. Good-risk patients are those with favourable cytogenetic abnormalities t(15;17), t(8;21), or inv(16) mutation or molecular evidence of these abnormalities.

These children have high rates of complete remission (more than 85%) and relatively low risk of relapse. Poor-risk patients are those not in either complete remission (CR) or partial remission (PR) after first course of therapy or with adverse cytogenetic abnormalities – monosomy of chromosomes 5 or 7, del 5q-, abnormalities of 3q or complex karyotype (more than four abnormalities). To the standard-risk group belong all others. Outcome of patients stratified to these 3 risk groups is showed in Table 1.

Table 1. Effect of risk group on response to therapy

Endpoint	Risk group			
	good	standard	poor	p value
Deaths in CR1 (%)	9	1	10	0.5
RFS (% at 7 years)	65	62	36	< 0.001
Survival from relapse (% at 3 years)	61	17	0	< 0.001
Survival from CR (% at 7 years)	78	60	33	< 0.001

CR1 = first complete remission, RFS = relapse free survival.

Different treatment results inside the same genetic subgroup can be partly explained by the presence of additional chromosomal abnormalities. Recently identified activating mutations in the FLT3 receptor are associated with poor outcome [8]. No current approach to the poor-risk group – including transplantation – is satisfactory.

Allogeneic SCT in First Complete Remission

There has not been a conventional, randomized, controlled trial to definitively test the role of allogeneic SCT in patients with AML. All studies have been based on a genetic or biologic randomization; patients who have an appropriate family donor have been assigned to receive a SCT. The value of allogeneic SCT can be assessed unbiasedly comparing patients whose siblings are HLA-compatible with those who are not [9].

Meta-analysis of six prospective cohort studies comparing the outcome of pediatric AML patients with and without matched sibling donor showed that allocation to SCT reduced risk of relapse and improved DFS and OS. Data were insufficient to determine whether this is true for all subgroups of AML [10].

Allogeneic SCT is the most active antileukemic treatment currently available. The risk of relapse among patients in CR1 is generally less than twenty

percent. The reduced relapse rate is the result not only of the use of marrow-ablative high dose cytotoxic therapy before SCT, but also of the graft-versus-leukemia effect [11]. The best timing of allogeneic SCT in CR1 is unknown. The outcome of children transplanted after two, three or four chemotherapy courses was comparable [6, 12, 13].

In recent years, the use of more intensive regimens of chemotherapy has improved the results in children enough so in some studies there was no overall survival benefit for the group with donors, despite the fact that there was a lower risk of relapse [6, 14, 15]. SCT is not necessary in children with acute promyelocytic leukemia who are treated using separate protocols that include molecularly targeted therapy with ATRA. Children with Down syndrome and distinct type of leukemia (M7) have an excellent prognosis when treated by reduced intensity AML type chemotherapy only [16].

SCT is probably also unnecessary in other low-risk patients in first remission. Overall survival of the young patients transplanted after first relapse would be the same even though SCT may be less effective after relapse. Patients cured by chemotherapy alone would be spared the potential morbidity of the transplant procedures. High-risk patients do less well after transplantation than those at low or moderate risk, and the limited comparative data available do not show a benefit after allogeneic SCT [15, 17]. The results of HR patients with or without SCT are prospectively evaluated in a European cooperation (I-BFM-SG and the EBMT Working Party for Pediatric Diseases). The goal is to achieve sufficient number of patients for the analysis in the short period of time. A common feature of studies in which no benefit of allogeneic SCT was shown was that the chemotherapy group received at least one course of high-dose Ara-C. There is a strong evidence of a dose-response effect of AraC in patients with AML – even in high risk patients.

Pretreatment cytogenetics retains its prognostic significance in the context of SCT in first CR.

Poor-risk patients constitute a group with a disease that is unresponsive to any of the currently available therapeutic options [17]. Whether SCT from alternative donors might improve the outcome of patients with monosomy 7,5q-or poor response to induction therapy remains to be determined.

Autologous SCT in CR1

Many studies reported a reduced risk of relapse among adults who underwent autologous SCT in CR1. In spite of higher mortality rate dis-

ease free survival was also improved. Overall survival did not differ significantly because salvage therapy with transplantation after relapse was possible in the case of some patients in the chemotherapy group. A typical feature of all these trials was that only minority of patients who were in remission and could have undergone transplantation actually did so [6, 18]. There is only one non-randomized single-institution study demonstrating excellent results of autologous SCT as a consolidation therapy in children with AML [13]. Relapse remains a problem because of the presence of residual disease in the absence of GVL effect and contamination of the autograft with leukemic cells. There are no comparative clinical data to confirm that techniques employed to purge the autograft *ex vivo* are effective. Autologous SCT using myeloablative regimen adds additional risk of late toxicity (gonadal functions) to patients already exposed to high doses of chemotherapy.

Although less toxic than allogeneic SCT due to eliminated risk of GVHD autologous SCT proves to be less effective with the possible risk of reinfusion of leukemic stem cells. Up to now autologous SCT alone does not seem to improve cure rates in childhood AML [10].

Conditioning Regimen

Busulfan and cyclophosphamide is preferred type of conditioning regimen before allogeneic SCT in CR1 in children due to decreased late toxicity in comparison with total body irradiation (TBI)-based regimens. In patients with more advanced disease there is trend to more intensive conditioning regimens. TBI is combined with cyclophosphamide or melphalan, busulfan and cyclophosphamide with melphalan or VP-16. There is no documented advantage of one type of pretransplant myeloablative therapy over others in reduction of posttransplant relapse. There is limited experience with reduced-intensity pretransplant regimens in children.

Minimal Residual Disease

The lack of widely expressed molecular markers in AML cells precludes the systematic study on MRD by PCR. Therefore, correlative studies between MRD and treatment outcome have been performed only in selected groups of patients. Detection of MRD by flow cytometry in AML also presents some specific difficulties which may reduce the sensitivity [19]. Studies demonstrating similar importance of pre transplant MRD level for post transplant outcome like in ALL, are lacking.

Using RT-PCR assays for the PML/RARA transcript with a sensitivity level 10^{-3} to 10^{-4} , it has now been clearly shown that serial PCR negative tests after completion of therapy are associated with prolonged remission, whereas patients who remain or convert to PCR positivity after consolidation were very likely to relapse within a short period of time.

If minimal residual disease (MRD) continues to be positive after 6–8 months of therapy and matched family donor is available SCT is indicated in M3 leukemia. Clinician has the opportunity to offer patients in molecular relapse salvage treatment before the onset of hematological relapse composed of ATRA followed by consolidation chemotherapy and autologous or allogeneic SCT [20].

Studies of the use of RT-PCR for detecting residual disease in AML with t(8;21) or inv [16] have yielded discrepant results. Persistence of residual disease has also been reported after both autologous and allogeneic SCT. Serial quantitative RQ-RT-PCR monitoring of MRD in patients with t(8;21) is very useful in identifying patients at high risk of relapse. There may be a window of opportunity of up 4 months during which an early therapeutic intervention including SCT may be carried out in an attempt to prevent hematological relapse [20, 21]. Another promising and rapid approach for monitoring of MRD is RQ-RT-PCR-based analysis of WT1 gene expression [22].

Secondary AML

Secondary AML may develop in patients with a hematologic disorder (e.g. severe congenital neutropenia) or an inherited disease (e.g. Bloom's syndrome and Fanconi anemia), in patients who have had myelodysplastic syndrome for at least three months, or in those who have been exposed to leukemogenic agents, often as a component of the therapy for an unrelated neoplasm. For example AML can be expected to develop in 3 to 10 percent of patients who receive alkylating agents as part of their therapy for Hodgkin's disease or non-Hodgkin's lymphoma. The risk of this complication peaks 5 to 10 years after the start of chemotherapy. Such a course is often associated with deletions of chromosomes 5 and 7. The prognosis of these patients is considerably worse than that for patients with primary AML. In contrast to alkylating agent-induced secondary AML second distinct subtype of therapy-induced AML develops after a relatively short latency period (two to three years) as a complication of treatment with topoisomerase II inhibitors, such as the epipodophyllotoxins. This type of secondary AML is

not preceded by MDS, and is frequently associated with 11q23 chromosomal abnormalities. Results of chemotherapy and SCT are disappointing in these patients due to high toxicity of the procedure and risk of relapse [23]. According to the experience of the EWOG-MDS, SCT should be performed as soon as possible, once the diagnosis of secondary AML has been established. Preparative regimen consisting of busulfan, cyclophosphamide and melphalan seems to be reasonable option [24].

Relapse

Despite improvements in therapy, a high proportion of patients with AML still relapse. Since the treatment results of relapsed patients have been poor, the highest priority should be to prevent the first relapse.

Over 90% of relapses involve the bone marrow, whereas CNS relapse is very uncommon following regimens with limited or even no intrathecal chemotherapy. Most relapses are early, with 60% occurring in the first year from complete remission and few if any occurring after 4 years. Whether these patients should first receive induction therapy or immediately undergo transplantation has not been settled. Current policy in treating AML relapse is the introducing of two to three courses of chemotherapy following intensification with an autologous or allogeneic SCT. Some patients may not enter a second remission and are therefore candidates for the experimental therapy. Gemtuzumab ozogamicin (immunoconjugate, consisting of humanized anti-CD33 antibody linked to the antitumor antibiotic calicheamicin) has clinical activity in these children [25]. Successful reinduction of CR is possible in a substantial proportion of patients who relapse, with second CR rates of 40–60% achieved with combination chemotherapy or SCT in many studies. Similar results have been achieved with a variety of intensive regimens, most commonly combining anthracyclines with AraC. Currently survival rate after either autologous or allogeneic SCT for patient with AML in first relapse or second remission is about 30% [26]. Experience with the use of transplants from matched unrelated or partially matched related donors is still limited. Long-term survival could be achieved with chemotherapy alone in some patients. At present there are not data which unequivocally demonstrate that overall survival is improved in transplanted patients compared to those given chemotherapy alone as treatments following relapses have been non-randomized. Survival after extramedullary relapses is pos-

sible following chemotherapy and local irradiation without recourse to SCT.

Further relapse remains a major cause of treatment failure following SCT, occurring in 10–40% of cases. There is evidence for higher relapse rate following autologous compared with allogeneic SCT, but this is counterbalanced by a lower treatment-related mortality for autologous procedures, especially in children.

Time until relapse reflecting the duration of first remission is the only variable correlating CR and survival rates. Defining early relapse as less than 1.5 years from diagnosis to relapse resulted in 5-year survival of 10% for early relapses and 40% for late relapses in German relapse studies in children [27]. Time until relapse predicted long-term survival in pediatric patients whether treated with SCT or chemotherapy alone. Patients with late relapse have the same chance of achieving complete remission as those with de novo AML. Results of treatment in relapsed AML may largely depend on the inclusion of late or early relapse patients in the study.

MRC experience in treating children with first relapse of AML is shown on the Table 2.

Table 2. Effect of length of first remission on response to further treatment

Time to relapse	CR rate %	Survival %
< 6 months	14	10
6–12 months	43	13
12–24 months	67	37
24–48 months	88	88

Some independent effect for survival maintains initial risk group. Poor-risk patients on AML 10 trial had uniformly bad outcome following retreatment with intensive regimens irrespective of the length of first remission [28].

Relapse treatment is highly dependent on previous treatment, especially if a patient has received SCT in first remission, and moreover the type of SCT that is performed. Second transplant is experimental option connected with high morbidity and mortality. Feature associated with poor outcome after second SCT include an interval between procedures less than 1 year. Non-myeloablative conditioning seems especially attractive for this group of patients. Donor lymphocytes may be more effective if used in the setting of CR and MRD, suggesting that reinduction therapy should be administered prior to DLI in patients with frank relapse. The dose of DLI employed in these cases varied, and there is a time interval of several weeks before an optimum effect is achieved, a fur-

ther reason for prior retreatment with chemotherapy. Pediatric AML patients with increasing mixed chimerism are at highest risk for relapse and the early immunological intervention can prevent relapse in these patients [29].

Conclusion

AML continues to be a major challenge in pediatric oncology. Despite very intensive chemo-

therapy almost half of children relapse with disease. Treatment causes prolonged bone marrow aplasia and modern supportive care play extremely important role in the management of the disease. For the majority, who relapse within 1 year of achieving first remission, the outlook is very poor with only the occasional survivors following further intensive chemotherapy. Despite a higher rate of second relapse than is found following allografting, autologous SCT is also useful in this group.

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