Current Indications of Bone Marrow Transplantation (BMT) in Pediatric Malignant Conditions; a Review

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Abstract

Hematopoietic stem cell transplantation (HSCT) has been practiced for more than 30 years. Hematological malignancies are the main indications for this treatment. However, its indications in adults are different from children. Advances in chemotherapy and target therapy have improved treatment outcome of some of the very high risk cancers, and changed indications of HSCT in children. Multi-center clinical trials evaluating outcome of childhood cancers using different therapeutic protocols are needed to precisely define the role of HSCT. A review on the current literature about HSCT indications in pediatric cancers is presented in this manuscript.

Keywords: Hematopoietic stem cell transplantation, Cancer, Pediatrics.

Introduction

Hematopoietic stem cell transplantation (HSCT) has been practiced for more than 30 years mainly indicated for hematological malignancy. In 2006, more than 18600 allogeneic HSCT were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The most common diseases for which allogeneic HSCT is indicated include acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), and other hematological malignancies. Non-malignant conditions such as severe aplastic anemia or hereditary diseases in children constitute only a small percentage of allogeneic HSCTs. The indication of HSCT in children is different from adults. ALL in adults is always associated with poor prognosis and HSCT is commonly performed, but pediatric ALL has a much better prognosis with chemotherapy. Chronic myeloid leukemia (CML) and lymphoma are common indications for HSCT in adults but much less common in children. Autologous HSCT is commonly performed in adults. The most common condition requiring autologous HSCT in North America is multiple myeloma which is not seen in children. Neuroblastoma is the most common indication for autologous HSCT in children, but the indication of HSCT for other pediatric solid tumors is less well defined. Over the past decades, we observed changes in the indication of HSCT in children. The indication for HSCT is now getting more refined. With the large multi-center studies on chemotherapy of childhood leukemia, oncologists gain better understanding of prognostic factors predicting treatment failure, in both first complete remission and subsequent relapses. Better understanding of genetic abnormalities of leukemia also identified some of the important prognostic factors. The indication for HSCT is based on the risk-benefit ratio of conventional treatment and HSCT. Factors to be considered include treatment-related mortality, disease-free survival (DFS), and late complications. With more studies on the long term outcome of HSCT in children, late complications are reported such as growth and intellectual impairment, and of greater concern is secondary malignancy. Type and availability of stem cells such as related or unrelated donor, bone marrow or peripheral blood stem cell (PBSC) or umbilical cord blood (UCB) also has .

impact on the decision to perform HSCT. The introduction of new target therapy such as imatinib and monoclonal antibodies produces promising early results; however the long term benefit is still under investigation

Acute lymphoblastic leukemia (ALL)

ALL is the most common childhood malignancy. With improvement of chemotherapy regimens, the disease free survival (DFS) has improved to 80% in most recent reported trials such as Children Oncology Group (COG) and the German BFM Group studies.[1,2] Thus most children can now be cured with chemotherapy without HSCT at the first complete remission (CR1). Only 20% or less of ALL patients fail the first line treatment but they may still be salvaged with another course of chemotherapy. HSCT in paediatric ALL should be confined to a small proportion of children who have low chance of cure with chemotherapy, either in the first complete remission, or second remission or beyond.

Indication for HSCT in the first complete remission (CR1)

Previously, high white blood cell count (WBC) and T-cell ALL were considered as the poor prognostic factors and indication for HSCT in children. With improvement in chemotherapy, chemotherapy outcome in these patients is now approaching the standard risk patients, and high WBC count and T-cell ALL are no more included as indications for HSCT. Cytogenetic abnormalities are found to be predictive of relapse. Philadelphia chromosome (Ph) occurs in 3-5% of all childhood ALL and is associated with poor prognosis. Ph ALL with poor prednisone response is particularly at high risk of induction failure or relapse. Most transplant centers accept CR1 Ph ALL as indication for transplant, including both related and unrelated HSCT. Recent studies showing that combination of imatinib and intensive chemotherapy can achieve a 3-year DFS of 80% necessitate redefining need for HSTC in patients with Ph ALL in CR1.[3]

Early treatment response is also highly predictive of subsequent relapse. Poor prednisone response (PPR) on day 8 of steroid prephase treatment was found to be a poor prognostic factor in BFM and other studies.[4] However, intensive chemotherapy can now achieve 60% DFS in patients with PPR only, but patients with other poor prognostic factors should be considered for transplant in CR1. Infant ALL with mixed lineage leukemia (MLL) gene rearrangement and PPR has particularly poor prognosis, and HSCT in CR1 is more acceptable for them.[5] Induction failure after 4-5 weeks of modern intensive induction chemotherapy is another poor prognostic factor. Some of these patients may never enter into CR1 and they do not benefit from HSCT while still having active leukemia. Even if remission is achieved with further intensive chemotherapy, risk of relapse is still high and thus HSCT in CR1 in late responders is also accepted. Another important early response marker is the minimal residual disease (MRD) after induction chemotherapy or early consolidation treatment. Flowcytometry or polymerase chain reaction (PCR) for leukemia specific clone or gene rearrangement is now included in many clinical trials for risk stratification. High MRD level is associated with high chance of relapse and thus some centers now include MRD as an indication for HSCT in CR1.[6,7] However, the critical level of MRD for HSCT is variable as it depends on the type of chemotherapy used and also the timing of MRD assessment.

Most transplant centers now accept the following indications for transplant in CR1 in ALL: (1) Induction failure after 4-5 weeks of standard induction chemotherapy, (2) high risk Ph+ ALL such as poor steroid response, (3) high minimal residual disease (MRD) at 1-3 months after start of chemotherapy, although the assessment method and critical level of MRD varies according to study groups. Infants with MLL rearrangement constitute another group of patients with poor outcome after chemotherapy; however the value of HSCT is controversial.

Indication for HSCT in relapsed ALL

In the past, relapsed ALL was always considered an indication for HSCT. The BFM studies of treating relapsed ALL patients using uniform protocols identified the risk factors predicting treatment failure. T-cell ALL or Ph ALL with relapse are very difficult to be cured with chemotherapy, therefore HSCT should be considered. Timing and sites of relapse are other important prognostic factors for DFS in relapsed ALL.[8,9] Those with early bone marrow relapse within 30 months (especially those within 18 months) from diagnosis have very poor prognosis. HSCT should be arranged in these patients early, as the second remission is not durable and patients may develop second relapse within a short period. For unknown reasons, those

with combined bone marrow and extramedullary relapse would fare better with chemotherapy treatment.[10] The MRD level after re-induction treatment is now also included in the risk stratification for HSCT. Patients with late bone marrow relapse have a good chance of cure with second course of chemotherapy if they can achieve a very low MRD after the induction chemotherapy; HSCT may not be indicated for this group of patients. Some patients may have second relapse, then HSCT is always indicated once they can get into another remission. If patients cannot get into complete remission, HSCT is not successful to maintain a long term DFS and should not be considered until a consolidated remission is achieved. Isolated extramedullary relapse is seldom indicated for HSCT, as local therapy such as cranial irradiation with further systemic reinduction chemotherapy is successful to achieve cure in a high percentage of patients.

Acute myeloid leukemia (AML)

AML in CR1

Acute myeloid leukemia (AML) still has less favorable outcome compared with ALL. With the modern aggressive chemotherapy treatment, the overall DFS is now reported to be 50-60% in recent reports.[11,12] Studies have now identified a favorable cytogenetic group that can be treated with chemotherapy and achieve a good outcome, namely t(15;17), t(8;21), and inv (6). The DFS of this 'good risk' group is over 60% and most centers do not consider this group as an indication for HSCT in CR1. COG and UKMRC studies confirmed that sibling donor HSCT in favorable cytogenetic group does not confer superior outcome compared with chemotherapy arms. Acute promyelocytic leukemia (APL) now has 80% chance of long-term DFS when transretinoic acid is included as part of the chemotherapy protocol. Even if relapse occurs in APL patients, arsenic trioxide can successfully maintain a prolonged second remission.[13] Thus APL is now seldom included for HSCT in most clinical studies. For the non-good risk patients, they may be considered for HSCT if HLA-identical sibling donor is available. Early treatment response as determined by blast percentage (15% to 25%) after 2-4 weeks of induction is also an important prognostic factor. Some studies will consider the late remitters or those with slow responses for HSCT in CR1. Unfavorable cytogenetic features such as monosomy 5, and 7 have poor treatment outcome, and HSCT in CR1 is always indicated. Anti-CD 33 monoclonal antibody is now included in the upfront treatment of AML, the long-term outcome needs to be evaluated.

Relapsed AML

Relapsed AML is always associated with poor prognosis except APL. Most of the relapses occur in bone marrow. It is a common indication for HSCT in most studies. However, a small percentage of patients with late relapse with CR1> 1 year may now be salvaged with chemotherapy with or without anti-CD33 treatment.

Other Leukemia Types

Juvenile myelomonocytic leukemia (JMML) has poor response to intensive chemotherapy, and most centers recommend early HSCT without attempting intensive treatment to achieve remission. A small proportion of JMML patients, especially those without monosomy 7 or abnormal cytogentic features, may remain in long-term remission with mild chemotherapy. Therefore, an initial trial of chemotherapy may be justified in this group of patients. Indication of HSCT in myelodysplastic syndrome (MDS) is more difficult to define in children as the condition is heterogeneous and rare. Severe neutropenia and thrombocytopenia are important factors to make decision for HSCT.

Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) was previously considered as an absolute indication for HSCT including matched unrelated donor (MUD). With the introduction of imatinib and other tyrosine kinase inhibitors (TKI), adult hematologists now will not perform HSCT in CML adults and all patients will be treated with medical treatment first. Only those patients who do not respond to TKI or develop blastic phase are considered for HSCT. The situation in children is very different; the outcome of HSCT in children with CML is better than adults, moreover the long term side effects of TKI in children are unknown. Thus, CML patients with an HLA identical sibling may also be considered for transplant in chronic phase.

Lymphoma

Non-Hodgkin Lymphoma and Hodgkin lymphoma in children can mostly be cured by chemotherapy with or without radiotherapy. HSCT in CR1 is not accepted by most centers. For patients with relapse, especially those with bone marrow relapse, allogeneic HSCT will be considered for salvage therapy. Hodgkin disease without bone marrow involvement may benefit from autologous HSCT. However the data of HSCT for lymphoma is rather scarce and it is difficult to draw a definite conclusion on the indication of transplant, when and how.

Autologous HSCT for solid tumors in children

Autologous HSCT is not considered for childhood leukemia except those with late relapse AML. Some studies may also consider early extramedullary relapse ALL for autologous HSCT, but this should be part of a clinical trial. In fact, most cases of the autologous HSCT in children are performed for solid tumors. The value of HSCT in solid tumors in children is best defined in advanced stage neuroblastoma (NBL).[14] Stage IV NBL had been studied in well designed CCG trial and autologous HSCT was shown to improve DFS. Nowadays most centers will include megatherapy with stem cell rescue as the last consolidation treatment in NBL. N-myc amplification is an important prognostic factor in NBL, stage III patients with N-myc amplification should also be treated with the most aggressive treatment regimens including autologous HSCT. Chemosensitive brain tumors such as medulloblastoma and CNS non-germinomatous germ cell tumors have been studied in clinical trials with autologous stem cell transplant as part of the consolidation therapy, but mostly only limited to the high risk subgroups of the above tumors. Some studies included medulloblastoma patients below 3 years of age for intensive chemotherapy and autologous HSCT as the consolidation treatment, and hope that these young children may be spared from the cranio-spinal irradiation.[15] Ewing's sarcoma is another chemo-sensitive tumor that may benefit from autologous HSCT; randomized study is now under investigation. The value of autologous HSCT in other tumors such as rhabdomyosarcoma is very controversial.

Conclusion

With the advances in chemotherapy and target therapy, some of the very high risk cancers may now be cured with non-HSCT approach. However, long-term results of the new treatments are still not available. Properly conducted clinical trials studying the early and long term outcome are necessary. In view of the rarity of childhood cancers requiring HSCT, multi-centre collaborative studies may provide concrete results.

References

1 . Möricke A, Reiter A, Zimmermann M, Gadner H, Stanulla M, Dördelmann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood, 2008; 111: 4477-98.

2 . Matloub Y, Lindemulder S, Gaynon PS, Sather H, La M, Broxson E, et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. Blood, 2006; 108:1165-73.

3 . Schultz KR, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, et al. Improved early event-free survival with Imatinib in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: a Children's Oncology Group Study. J Clin Oncol, 2009; 27:5175-81.

4 . Manabe A, Ohara A, Hasegawa D, Koh K, Saito T, Kiyokawa N, et al. Significance of the complete clearance of peripheral blasts after 7 days of prednisolone treatment in children with acute lymphoblastic leukemia: the Tokyo Children's Cancer Study Group Study L99-15. Haematologica, 2008; 93:1115-60.

5 . Pieters R, Schrappe M, De Lorenzo P, Hann I, De Rossi G, Felice M, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. Lancet, 2007; 370: 240-50.

6 . Coustan-Smith E, Sancho J, Behm FG, Hancock

ML, Razzouk BI, Ribeiro RC., et al. Prognostic importance of measuring early clearance of leukemic cells by flow cytometry in childhood acute lymphoblastic leukemia. Blood, 2002; 100:52-8.
7 . Borowitz MJ, Devidas M, Hunger SP, Bowman WP, Carroll AJ, Carroll WL, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group Study. Blood, 2008; 111:5477-85.
8 . Ko RH, Ji L, Barnette P, Bostrom B, Hutchinson R, Raetz E, Seibel NL, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: A therapeutic advances in childhood leukemia Consortium Study. J Clin Oncol, 2009; 27: 648-54.
9 . Raetz EA, Borowitz MJ, Devidas M, Linda SB, Hunger SP, Winick NJ, et al. Reinduction platform for children with first marrow relapse of acute lymphoblastic leukaemia: A Children's Oncology Group Study. J Clin Oncol, 2008; 26:3971-8.
10. Einsiedel HG, von Stackelberg A, Hartmann R, Fengler R, Schrappe M, Janka-Schaub G, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Miüster Group 87. J Clin Oncol, 2005; 23: 7942-50.
11. Creutzig U, Zimmermann M, Ritter J, Reinhardt D, Hermann J, Henze G,, et al. Treatment strategies and long-term results in paediatric patients treated in four consecutive AML-BFM trials. Leukemia, 2005; 19: 2030-42.
12. Lange BJ, Smith FO, Feusner J, Barnard DR, Dinndorf P, Feig S, et al. Outcomes in CCG-2961, a Children's Oncology Group Phase 3 Trial for untreated pediatric acute myeloid leukemia: a report from the Children's Oncology Group. Blood, 2008; 111:1044-53.
13. Wang Z.Y., Chen Z. Acute promyelocytic leukemia: from highly fatal to highly curable. Blood, 2008; 111:2505-15.
14. Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, et al. Long-term results for children with high-risk neurobloastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-Retinoic acid: a Children's Oncology Group Study. J Clin Oncol, 2009; 27:1007-13.
15. Dhall G, Grodman H, Ji L, Sands S, Gardner S, Dunkel IJ, McCowage GB, et al. Outcome of children less than three years old at diagnosis with non-metastatic medulloblastoma treated with chemotherapy on the "Head Start" I and II protocols. Pediatr Blood Cancer, 2008; 50:1169-75.