# Indications for hematopoietic stem cell transplantation in the treatment of pediatric disorders

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Osgood et al[1] found that patients with aplastic anemia could be cured by transfusion of bone marrow from siblings in 1939 and Jacobson et al[2,3] found in experiments that normal hematopoietic function could be recovered in lethally irradiated mice shielding the spleen or bone marrow from the normal same strain of mice transfused. Later, hematopoietic stem cells (HSCs) were observed in the splenic nodules and bone marrow, and the compatibility of the major and minor histocompatibility complex (MHC) between human recipients and donors, i.e., human leukocyte antigen (HLA)[4] was found to be closely related to the success of allogeneic transplantation of HSCs, the severity of graft-versus-host response (GVHR), and the effects of graft-versus-leukemia (GVL). In the early 1960s, Ronald Thomas from University of Washington, Seattle, USA successfully treated patients with advanced leukemia, aplastic anemia by allogeneic bone marrow transplantation (Allo-BMT). The successful rate or the cure rate of Allo-BMT could result in a complete remission (CR) in patients with acute leukemia. Lots of evidence from experiments *in vitro* and *in vivo* suggested that HSCs not only exist in bone marrow, but also in granulocyte-colony stimulation factor (G-CSF) mobilized peripheral blood and cord blood.[5-7] Thus, the scope of HSC transplantation has been greatly expanded and the lives of many patients could be saved. This great contribution enabled Ronald Thomas to be the first winner of Nobel Prize.

Since HSC transplantation has been successful in the treatment of adults with leukemia, clinical trials on HSC transplantation in the treatment of children with hematological malignancies and non-malignant disorders have been carried out with promising results. The spectrum and biological characteristics of hematological malignancies are significantly different between children and adults, even in those with the same disease, such as acute lymphoblastic leukemia (ALL). Their response to chemotherapy may be varied. The long-term event-free survival (EFS) can be approached to 90% of children with ALL after combined chemotherapy[8-11] but only 20% of adults with ALL. Hence, the indications for HSC transplantation in children vary greatly. To improve the successful rate of the operation, reduce transplantation-related mortality (TRM) and long-term sequelae, and guarantee the growth and development of children, it is pivotal to standardize the indications for HSC transplantation in children according to physiological and biological characteristics of the diseases.

In high-risk patients with ALL in $CR_1$,[12-14] CR could not be achieved after initial induction therapy. Over $10^{-2}$ minimal residual disease (MRD) remains after induction therapy, and Ph' chromosome or the Bcr-AbL fusion gene is still positive. In infants aged less than one year with t (4:11) and the $MLL/AF_4$ fusion gene, intermediate and standard-risk ALL may relapse with $CR_2$. High-risk acute myelogenous leukemia (AML) includes $M_4$, $M_5$, $M_6$, $M_7$ subtypes in FAB classification in $CR_1$, Ph' chromosome (+) AML in $CR_1$, 5q, 7q deletion in $CR_1$, and Flt3-ITD mutation in $CR_1$.[15,16] Moreover, CR could not be achieved after one or two courses of standardized induction therapy. The WBC count is over $100\times10^9$/L initially in $CR_1$. $CR_2$ AML or secondary AML is due to MDS transformation and $CR_1$ in treatment-related AML (t-AML). Chronic myelogenous leukemia is in chronic phase, and patients in accelerated or blast transformation phase have been transformed back to the chronic phase after therapy. In juveniles, it is called juvenile chronic myelogenous leukemia (JCML).

Patients with Hodgkin's lymphoma in stage IV sized over 10 cm in diameter have initial B symptoms

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and $CR_1$ after treatment.[17] The tumor may be in progress with induction therapy, or relapse after combined chemotherapy with or without local radiation. The high-risk population of non-Hodgkin's lymphoma (NHL)[17,18] includes patients with T-cell-NHL stage III-IV, and $CR_1$ can be achieved after induction therapy or the tumor may relapse after $CR_1$. As TRM is very high for allo-HSC transplantation and the response rate in patients with NHL is similar to that of the autologous HSC transplantation, HSC transplantation is just left for clinical trial. Myelofibrosis, myelodysplastic syndrome (MDS), familial hemophagocytic lymphohistiocytosis should be considered as the candidate for HSC transplantation.

Congenital non-malignant disorders include severe combined immunodeficiency diseases (SCID), chronic mucocutaneous candidiasis, and Wiskott-aldrich syndrome. Hematologic disorders include hemoglobinopathies, sickle cell anemia, β-thalassemia with HLA compatible donor and age of patient less than 17 years, Fanconi's anemia, Schwachman-diamond syndrome, Kostman's agranulocytosis, congenital dyskeratosis, thrombocytopenia absent radii syndrome (TAR), chronic granulomatosis disease (CGD), Chediak-Hegashi syndrome, $CD_{11/19}$ deficiency (leukocyte adhesion deficiency), and neutrophil actin defects. Others are storage disease (Gaucher's disease), lysosomal disease (Lash-nyhan syndrome), mucolipidoses (metachromatic leukodystrophy), mucopolysaccharidoses (Hurler's syndrome, Hanter disease), and infantile osteopetrosis.

Acquired non-malignant disorders include severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, and radiation accident.

In the treatment of acute leukemia or ALL and AML, cryopreserved HSC harvested in $CR_1$ stage is used for autologous HSC transplantation. The disadvantage is that MRD still exists in the transplant, when it is transfused back, relapse may be induced. It is only used in clinical trial, but some derivatives from cyclophosphamide such as tetrahydroxide cyclophosphamide, etc can be co-incubated with auto-HSC to purge MRD. The main shortcomings of such procedure include a high rate of HSC loss, and toxic effects of derivatives from cyclophosphamide on normal HSC. Thus, the recovery rate of HSC will be greatly reduced with no "GVL" for autologous HSC transplantation. Further investigation is necessary to see whether it works. In the treatment of chronic leukemia mentioned above. Autologous HSC transplantation is feasible when patients with Hodgkin's lymphoma in IV stage have the following features: tumor size over 10 cm in diameter; progressive tumor or tumor cells detected by biopsy after initial combined chemotherapy; tumor relapsed after multi-drug chemotherapy and local radiation or CR or partial remission (PR) achieved after comprehensive chemotherapy before autologous HSC transplantation; non-Hodgkin's lymphoma in high risk[16,18] including those with T-cell NHL stage IV. When CR or PR can be achieved after induction chemotherapy, relapse may occur in these cases. The efficacy of autologous HSC transplantation is confirmed after CR is regained.

In the treatment of neuroblastoma stage III-IV,[19] when CR or good partial remission (GPR) (The size of primary tumor shrunk over 50% with the metastatic lesions disappeared) can be obtained after combined chemotherapy plus resection of primary tumor and no tumor cell could be found in bone marrow or $CD_{34}$ positive selection is made to remove MRD, autologous HSC transplantation can be done with good results. As to Ewing sarcoma and peripheral primary neuroectodermal tumor (PNET) in III-IV stage, their size is reduced by over 50% or CR is achieved after 3-6 courses of combined chemotherapy. Rhabdomy sarcoma (especially for Embryoniform) stage III-IV is treated with 3-6 courses of combined aggressive chemotherapy plus complete resection or partial resection of the tumor, which could be followed by autologous HSC transplantation. Germ cell tumor in III-IV stages is treated after CR or GPR plus complete resection or radical resection of the tumor, which could be followed by autologous HSC transplantation. Brain tumors,[20] especially infratentorial astrocytoma, cerebellar medulloblastoma and ependymoma can be partially resected, followed by local radiation and 3-6 courses of combined chemotherapy. Testicular cancer in stage III-IV is dealt with complete resection of primary tumor plus chemotherapy.

Patients with autoimmune disorders such as scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis, dermatomyositis, mixed connective tissue disorders, refractory idiopathic thrombocytopenia, autoimmune hemolytic anemia, and pure red cell aplasia (Diamond-Blackfan anemia) can be successfully treated by autologous HSC transplantation.[19] As to auto-reactive lymphocytes especially T-lymphocytes, clonal and monoclonal propagations resulting in producing auto-antibodies and cytotoxic effect on self-tissues have proved to be the pathogenesis of auto-immune disorders. Taking advantage of the $CD_{34}$ antigen expression on the surface of HSC and T-, B-lymphocytes without such antigen expression, auto-reactive lymphocytes can be separated with the magnetic beads conjugated with $CD_{34}$ monoclonal antibody from the G-CSF mobilized

peripheral hematopoietic stem cell transplant (PHSCT), then conditioning regimen is given to remove auto-reactive T-lymphocytes as much as possible. Then these purified HSCs are transfused back to protect hematopoietic functional failure of bone marrow from the conditioning regimen and to reduce the number of auto-reactive T-lymphocytes as much as possible. Thus, the condition of patients with refractory autoimmune disorders can be greatly improved. This is an advance in clinical application of autologous HSC transplantation. In addition, it can be used in gene therapy of molecular diseases.

In conclusion, HSC transplantation is indicated for different disorders according to their physiological and biological characteristics in children. The lives of patients can be saved with low cost and less side-effects such as TRM, long-term sequelae, secondary malignancies and underdevelopment and growth.

**Funding:** None.
**Ethical approval:** Not needed.
**Competing interest:** None.
**Contributors:** WYP wrote this article.

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*Received June 22, 2005*
*Accepted after revision November 19,2005*