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REVIEW ARTICLE

Autologous hematopoietic stem cell transplantation (auto-HSCT) in children in Poland: 2021 indications and practice

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Abstract

Unlike in adults, the number of pediatric autologous hematopoietic stem cell transplants (HSCT) has decreased in last years. This is because of changing indications for this type of treatment and new therapies available in recent years. Polish pediatric HSCT centers have followed the published recommendations of the Polish Pediatric Hematopoietic Stem Cell Transplantation Group, which are generally based on European Society for Blood and Marrow Transplantation indications. Differences are observed in obtaining autologous hematopoietic stem cells from children compared to adults in terms of the timing of the scheduled harvest and technical aspects of the harvesting procedure. As a result, stem cell harvesting in pediatric populations involves more medical professionals, and requires more time and more financial resources compared to adults. Pediatric autologous stem cell transplantation in neuroblastoma and Ewing's sarcoma has confirmed efficacy. Autologous cell harvesting in young children established in autologous transplant procedure is now increasingly used in apheresis of lymphocytes for approved CAR-T cell therapies in relapsed/resistant leukemia and lymphoma. Recent studies suggest that cell-based immunotherapy is a potential treatment for refractory or relapsed pediatric solid tumors.

Key words: autologous stem cell transplantation, children, stem cell harvest

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Specificity of auto-HSCT in children

Since 1990, the European Blood and Marrow Transplantation Society (EBMT) has collected data about hematopoietic stem cell transplantations performed in Europe. Currently, of about 700 accredited and annually reporting centers, only 122 are dedicated solely to children, and 128 declare that they treat children and adults. Out of 28,714 autologous hematopoietic stem cell transplants (HSCTs) performed in 2019 (59% of all procedures), pediatric patients comprise only 1,199 reported cases. Unlike in adults, the number of pediatric autologous hematopoietic stem cell transplants has decreased in recent years [1]. This is because of changes in indications for this type of treatment and new therapies becoming available.

Indications and qualifications

Polish pediatric HSCT centers follow the recommendations of the Polish Pediatric Hematopoietic Stem Cell Transplantation Group (PPGTKK, *Polska Pediatryczna Grupa ds. Transplantacji Komórek Krwiotwórczych*), which are generally based on EBMT indications. Current indications for auto-HSCT in children according to PPGTKK [2] and EBMT [3] are set out in Table I.

Course of procedure

Important differences are observed in obtaining autologous hematopoietic stem cells in children compared to adults in terms of the time of scheduled harvest. Current treatment protocols of neuroblastoma and Ewing's sarcoma indicate a time of apheresis early in treatment course i.e.

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Table I. Indications for autologous hematopoietic stem cell transplants (auto-HSCT) in children

Indication	PPGTKK	EBMT
Leukemia, myelodysplastic syndrome, myeloproliferative disorders	Not recommended	Not superior to chemotherapy
Hodgkin lymphoma	Progression during first line treatment and relapse in intermediate and high-risk group	Primary refractory disease and chemosensitive first relapse
Non-Hodgkin lymphoma	Pre-B and pre-T lymphomas in isolated relapse (except CNS) >12 months after diagnosis Primary mediastinal large B-cell lymphoma with residual tumor with live tumor cells after resection	Pediatric indications not specified
Neuroblastoma	In 1st CR — HR patients, >1 CR — all children not transplanted in first CR	First-line high-risk NBL >18 months at diagnosis, metastatic disease or any age with MYCN-amplified tumors
Ewing's sarcoma	In 1st CR — poor histological response for chemotherapy, large tumor volume or metastatic disease, all chemosensitive relapses not transplanted in first CR	In 1st CR — poor histological response for chemotherapy, large tumor or metastatic disease, all chemosensitive relapses not transplanted in first CR
Other solid tumors	As clinical studies or individual consult with national coordinator	High risk medulloblastoma, recurrent germ cell tumor in biological remission
Autoimmune disease	Juvenile rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, systemic sclerosis or Crohn's disease not responding to conventional, biological and low doses cytostatic drug therapies	Multiple sclerosis, systemic sclerosis or Crohn's disease not responding to conventional and biological drug therapies

PPGTKK (*Polska Pediatryczna Grupa ds. Transplantacji Komórek Krwiotwórczych*) — Polish Pediatric Hematopoietic Stem Cell Transplantation Group; EBMT — European Blood and Marrow Transplantation Society; CNS — central nervous system; CR — complete remission; HR — high-risk; NBL — neuroblastoma

2–3 months after diagnosis, and several months before auto-HSCT.

The common practice is implantation, for apheresis purpose, of a temporary double lumen catheter in the vast majority of pediatric patients. Peripheral veins as well as permanent catheters, pre-implanted for chemotherapy, are believed to have a flow rate not sufficient for harvest. However, a recently published report from three German pediatric centers demonstrates comparable efficacy and safety of apheresis using permanent catheters. This is leading to reconsideration of this common practice [4].

The second important technical difference is related to the low body weight of children: in patients weighing below 10–12 kg, priming with red blood cells and continuous infusion of calcium is necessary to avoid short term complications [5]. For these reasons, stem cell harvesting in pediatric populations involves more medical professionals, and requires more time and more financial resources compared to adults.

Megachemotherapy protocols in pediatric patients are based on busulfan, treosulfan, melphalan or thiotepa at maximum tolerated doses in main indications. Due to the low rate of co-morbidities in children, procedure-related deaths and life-threatening complications are rare, even in highly pretreated patients. Most treatment failures are related to disease relapse or progression, and therefore the remission status and optimal timing of auto-HSCT in children continues to be the most important prognostic factor for outcomes [6, 7].

Auto-HSCT in children — practice in Poland

Hematopoietic stem cell transplantation in dedicated pediatric centers in Poland began in 1989, but the first auto-HSCT was not performed until 1994. Until 2016, autologous procedures comprised 31% of all reported transplants in five Polish pediatric centers, very close to the 33% rate performed in European centers dedicated for children [8].

The current practice in auto-HSCT in Poland in the last two years compared to previous data is presented in Table II. Neuroblastoma and Ewing's sarcoma continues to be the leading indication for autologous HSCT, and these procedures are no longer performed in children for acute leukemia or non-Hodgkin lymphoma.

Auto-HSCT prospects in the near future

Pediatric autologous stem cell transplantation in neuroblastoma and Ewing's sarcoma has confirmed efficacy. A combination of this method with specific immunotherapy, differentiating agents or meta-iodobenzyl guanidine therapy (MIBG) can improve the outcome of patients in the future [10, 11].

Table II. Changes in practice of autologous stem cell transplantation (auto-HSCT) in children in Poland (data from Prof Jacek Wachowiak, personal communication)

Cause of auto-HSCT	1993–2016 [9] N =788	2018–2019 N =96
Leukemia (ALL or AML)	96 (12%)	0
Hodgkin lymphoma	42 (5%)	4 (4%)
Non-Hodgkin lymphoma	100 (13%)	0
Neuroblastoma	326 (42%)	46 (48%)
Ewing's sarcoma	111 (14.5%)	17 (18%)
CNS tumors	26 (3%)	5 (5%)
Other solid tumors	82 (10.5%)	14 (15%)

ALL — acute lymphocytic leukemia; AML — acute myeloid leukemia; CNS — central nervous system

Autologous cell harvesting in young children established in transplant procedure is now increasingly used in apheresis of lymphocytes for approved CAR-T cell therapies in relapsed/resistant leukemia and lymphoma [12]. EBMT data confirms that this type of cellular therapy is increasingly used in EBMT centers (adult and pediatric): from 151 procedures in 2017 to 1,111 (824 in non-Hodgkin lymphoma/ /Hodgkin lymphoma, 232 in acute lymphocytic leukemia, and 55 in other malignancy) in 2019 [13]. Recent studies suggest that CAR-T cell-based immunotherapy has potential also for the treatment of refractory or relapsed pediatric solid tumors [14].

Author'scontributions

KD — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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