

ORIGINAL ARTICLE

**CLINICAL PROFILE OF CHILDREN UNDERGOING
HEMATOPOIETIC STEM CELL TRANSPLANTATION***

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ABSTRACT

Objective: to identify the clinical profile of children in the hematopoietic stem cell post-transplant period.

Method: quantitative, cross-sectional, retrospective study, performed in a transplantation service of the South of Brazil, with data from the medical records of children less than 12 years of age, who had undergone transplantation. Measures of central tendency, dispersion and frequency were used for the analysis and the chi-squared and Fisher's tests to associate variables.

Results: the mean age was 6.2 years, males, with 92 (66.7%), the diagnosis of Fanconi anemia, with 42 (30.4%), and unrelated allogeneic transplantation, with 71 (51.4%), were predominant. Hospital discharge occurred within 30 days after transplantation for 85 (61.6%) patients and 48 (34.8%) were readmitted. Catheter failures occurred in 11 children (8.0%) and the main outpatient clinical intercurrents were pain, cough, runny nose and fever. Viral infection was associated with the unrelated transplant and graft-versus-host disease.

Conclusion: the profile identified corroborates the care planning for this population, contributing to the nursing practice.


DESCRIPTORS: Hematopoietic stem cell transplantation; Health profile; Nursing care; Oncological nursing; Pediatric Nursing.


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PERFIL CLÍNICO DE CRIANÇAS SUBMETIDAS A TRANSPLANTE DE CÉLULAS-TRONCO HEMATÓPOIÉTICAS**RESUMO**

Objetivo: identificar o perfil clínico de crianças em pós-transplante de células-tronco hematopoéticas.

Método: pesquisa quantitativa, transversal, retrospectiva, em serviço transplantador do Sul/Brasil, com dados de prontuários de crianças com 12 anos incompletos, submetidas a transplante. Para análise utilizaram-se medidas de tendência central, dispersão, frequências e testes do qui-quadrado e Fisher para associar variáveis.

Resultados: a média de idade foi de 6,2 anos, predomínio do sexo masculino 92 (66,7%), diagnóstico Anemia de Fanconi 42 (30,4%) e transplante alogênico não aparentado 71 (51,4%). A alta hospitalar aconteceu em até 30 dias pós-transplante para 85 (61,6%) e 48 (34,8%) foram reinternadas. As perdas do cateter acometeram 11 crianças (8%) e as principais intercorrências clínicas ambulatoriais foram dor, tosse, coriza e febre. Infecção viral esteve relacionada ao transplante não aparentado e doença do enxerto contra hospedeiro.

Conclusão: o perfil identificado corrobora o planejamento de cuidados a esta população, contribuindo com a prática de enfermagem.

DESCRIPTORES: Transplante de células-tronco hematopoéticas; Perfil de saúde; Cuidados de enfermagem; Enfermagem oncológica; Enfermagem Pediátrica.

PERFIL CLÍNICO DE NIÑOS SOMETIDOS A TRASPLANTE DE CÉLULAS MADRE HEMATOPOYÉTICAS**RESUMEN**

Objetivo: identificar el perfil clínico de niños tras realización de trasplante de células madre hematopoyéticas.

Método: investigación cuantitativa, trasversal, retrospectiva, en servicio trasplantador de Sur/Brasil, con datos de prontuarios de niños con 12 años sin cumplir, sometidos a trasplante. Para análisis, se utilizaron medidas de tendencia central, dispersión, frecuencias y prueba chi cuadrada y Fisher a fin de asociar variables.

Resultados: el promedio de edad fue de 6,2 años, predominio del sexo masculino, 92 (66,7%), diagnóstico Anemia de Fanconi 42 (30,4%) y trasplante alógeno sin parentesco 71 (51,4%). El alta hospitalario ocurrió en hasta 30 días tras el trasplante para 85 (61,6%) y 48 (34,8%) se reingresaron. Las pérdidas del catéter atingieron 11 niños (8%) y las principales complicaciones clínicas ambulatorias fueron dolor, tos, secreción nasal y fiebre. Infección viral fue asociada al trasplante sin parentesco y enfermedad del injerto contra huésped.

Conclusión: el perfil identificado corrobora el planeamiento de cuidados a esa población, contribuyendo con la práctica de enfermería.

DESCRIPTORES: Trasplante de células madre hematopoyéticas; Perfil de salud; Cuidados de enfermería; Enfermería oncológica; Enfermería Pediátrica.

INTRODUCTION

Hematopoietic Stem Cell Transplantation (HSCT) represents a cure prospect for malignant and non-malignant diseases and is considered to be effective in increasing survival due to the return of the correct spinal function⁽¹⁻²⁾. In Europe, more than 40,000 HSCTs were performed in 2016, of which 40.4% were allogeneic and 4,400 pediatric, representing an increase of 80% over the previous 15 years⁽³⁾. In Brazil, between January and September 2016, 1,577 HSCTs were reported, of which 36.4% were allogeneic. In Paraná, 224 HSCTs were performed in the year 2015, of which 56.3% were allogeneic⁽⁴⁻⁵⁾.

Over the years, HSCT has achieved better results due to approaches to improve donor cell grafting, infection mortality, organ dysfunction, and Graft-versus-Host Disease (GVHD). Appropriate donor selection, choice of conditioning regimens with fewer side effects, adequate immunosuppression, and improved supportive care are among the approaches cited⁽⁶⁻⁷⁾. These approaches allow HSCT to also be performed with debilitated patients, those with comorbidities, incompatibilities in the human leukocyte antigen (HLA) and with older patients.

Thus, there was an increase in the number of indications, leading to a greater need for clinical evaluation in the post-transplantation period, especially in relation to early hospital discharge and/or risk of complications. If discharge is too early, in terms of medullary recovery or preparation for care, the patient may be at greater risk.

It should be highlighted that there is a high risk of early morbidity and mortality⁽⁸⁻⁹⁾ inherent to the procedure, especially in the first 100 days post-transplantation, when the patient is in medullary recovery and outpatient/home care. The 100 days comprise the immediate post-transplant phase, characterized by the control of complications; in this stage recovery of the T cells has not yet occurred and immunity is not effective⁽¹⁰⁾.

Thus, the risk of complications, clinical interurrences, readmissions and death increases. Studies have indicated complications in the post-HSCT period, such as GVHD and recurrence of the disease, with infection being one of the main causes of death^(2,11-12). Such complications may be responsible for clinical interurrences presented and can interfere in the recovery, in which preparation of the patient and caregiver for home care is required.

The study proposed here evaluated this outpatient/home care period, when the identification of signs and symptoms of possible complications and their prevention is also performed by the caregiver, in addition to the health team. In terms of complications and nursing care in the post-HSCT period, a greater focus on the period of hospitalization, rather than the outpatient care period, can be observed in the scientific publications⁽¹³⁻¹⁴⁾. There is still a gap in these publications, children and adults are usually investigated together⁽¹⁵⁻¹⁶⁾, with few studies directed toward the pediatric specificities.

It is believed that identifying the clinical profile of children submitted to HSCT after hospital discharge will allow targeted health actions to be planned and implemented, contributing to advances in nursing care. Accordingly, this study sought to identify the clinical profile of children in the immediate post-HSCT period, in outpatient care.

METHOD

This was a quantitative, cross-sectional, retrospective study. The choice of this type of study was due to the option of investigating clinical interurrences within a specific time frame, from hospital discharge to 100 days after transplantation.

The study site was an outpatient clinic of the Bone Marrow Transplantation Service (BMTS) of a large hospital in the southern region of Brazil, which is a Brazilian referral center, treats adults and children and performs all types of HSCT. It has had the modality of hospital day care since 2013, attending patients of greater complexity and those who are

discharged within a few days after the transplantation.

The data were collected from the medical records between January and July 2015, and the inclusion criteria were: children aged, on the date of the HSCT, 0 to 11 years, 11 months and 29 days, this being the age limit for children, according to the Statute of the Child and Adolescent,⁽¹⁷⁾ and that underwent the transplant from January 2009 to December 2013. The choice of starting the collection in 2009 was due to this being the year in which more transplants were performed in the service. All the patients were monitored in the outpatient clinic after the hospital discharge, therefore the inclusion criteria were applied to all the children in the prescribed time period, producing a total of 165 medical records.

The exclusion criteria were medical records of children who died during the hospitalization, who were discharged after 100 days from the HSCT or who were transferred during the hospitalization to other services. Records with incomplete information about the HSCT were also excluded from the final sample. Thus, of the 165 medical records, 138 were evaluated.

A structured instrument was used for the data collection, with previous definition of the criteria for classification of the variables, completed by one of the researchers, with knowledge of the BMTS routines and the organization of the medical records. Among the variables studied, the following should be highlighted: age, weight, height, origin, type of HSCT, HLA compatibility, conditioning, degree of mucositis, catheter presence and antibiotic use, among others.

Data analysis was performed through descriptive statistics using the Statistical Package for the Social Sciences (SPSS) 19.0®, in which the data were double entered and stored. The results were expressed as measures of central tendency and dispersion for the numerical variables and absolute and relative frequencies for the categorical variables. For the evaluation of the association between categorical variables, the chi-squared test and Fisher's exact test were applied, with p-values <0.05 being considered significant.

The study was approved by the Research Ethics Committee of the Sector of Health Sciences of the Federal University of Paraná, authorization No. 742.621, of August 2014.

RESULTS

Of the 138 medical records that composed the sample of this study, the mean age was 6.2 years, minimum zero and maximum 11 years (standard deviation – SD 3.5). A total of 92 children were male (66.7%); 94 children (68.1%) were white, 17 (12.3%) were from the metropolitan region of Curitiba, 33 (23.9%) were from the state of Paraná and 88 (63.8%) from other states, of whom, 28 (31.8%) were from the Northeast. It was found that 71 children (51.4%) were students prior to the transplantation.

Of the medical diagnoses, Fanconi anemia predominated, with 42 cases (30.4%), as presented in Table 1.

Table 1 - Comparison between medical diagnosis and time of diagnosis prior to transplantation. Curitiba, PR, Brazil, 2015

Medical Diagnosis	Diagnosis Time Interval (months)													
	< 11		12 to 23		24 to 35		36 to 47		48 to 59		> 60		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
FA	11	8.0	5	3.6	8	5.8	3	2.2	3	2.2	12	8.7	42	30.4
SAA	7	5.1	5	3.6	4	2.9	4	2.9	1	0.7	---	---	21	15.2
ALL	3	2.2	6	4.3	1	0.7	4	2.9	2	1.4	3	2.2	19	13.8
AML	4	2.9	1	0.7	2	1.4	1	0.7	1	0.7	---	---	9	6.5
CML	1	0.7	---	---	---	---	---	---	---	---	---	---	1	0.7
MDS	---	---	---	---	1	0.7	1	0.7	---	---	---	---	2	1.4
IMD	10	7.2	5	3.6	2	1.4	1	0.7	---	---	1	0.7	19	13.8
MPS	3	2.2	---	---	---	---	---	---	---	---	---	---	3	2.2
DBA	---	---	---	---	2	1.4	---	---	---	---	1	0.7	3	2.2
ADL	1	0.7	---	---	1	0.7	1	0.7	---	---	---	---	3	2.2
Other	7	5.1	1	0.7	2	1.4	4	2.9	---	---	2	1.4	16	11.6
Total	47	34	23	17	23	17	19	14	7	5.1	19	14	138	100

p=0.238

Legend: FA - Fanconi anemia; SAA - Severe aplastic anemia; ALL - Acute Lymphoid Leukemia; AML - Acute Myeloid Leukemia; CML - Chronic Myeloid Leukemia; MDS - Myelodysplasia; IMD - Immunodeficiency; MPS - Mucopolysaccharidosis; DBA - Diamond-Blackfan anemia; ADL - Adrenoleukodystrophy.

The source of stem cells most used was bone marrow, with 111 cases (80.4%), followed by umbilical cord blood, with 27 (19.6%). All the HSCT were allogeneic, with 71 (51.4%) unrelated and 16 (12.3%) with incompatible related donors, including haploidentical donors; unrelated donors totaled 72 (52.2%); 96 (69.6%) patients were transplanted with compatible HLA and 70 (50.7%) received reduced intensity conditioning.

Between 21 and 30 days post-transplantation, 85 children (61.6%) were discharged from the hospital; 48 (34.8%) children needed to be readmitted for up to 100 days, the main cause being fever in 33 (23.9%).

Central venous catheter use was identified in 136 children (98.6%) and the loss of functionality in 11 (8%), 5 (3.6%) being due to infection. The mean number of days for programmed catheter removal was 84 (SD 12.13, minimum 56 days and maximum 100). The use of nasogastric/nasoenteral tubes in situations of nutritional deficiencies and medication ingestion difficulties was observed in 16 children (11.6%).

The therapeutic use of antibiotics occurred in 94 children (68.1%). The most prevalent causes of use were fever, in 60 children (43.5%), and diarrhea, in 24 (17.4%). Regarding antiviral medications, 71 (51.4%) children used these therapeutically, with 63 (45.7%) due to Cytomegalovirus reactivation.

The main clinical complications presented after hospital discharge are described in Table 2.

Table 2 - Clinical intercurrents in the children with hospital discharge up to 100 days post-transplantation. Curitiba, PR, Brazil, 2015

Clinical Intercurrences	(n)	%
Pain	84	60.9
Cough	79	57.2
Coryza	65	47.1
Fever	65	47.1
Vomiting	64	46.4
Diarrhea	54	39.1
Viral Infection	51	37.0
Nausea	49	35.5
Skin Rash	45	32.6
Inapetence	38	27.5
Graft-versus-Host Disease	37	26.8
Neutropenia	33	23.9
Fungal Infection	22	15.9
Bacterial Infection	17	12.3
Other Causes	61	44.2

Viral infection was associated with unrelated HSCT ($p=0.008$); of the children who underwent related transplantations, 67 (25.4%) presented viral infection, while 71 (47.9%) of those that underwent unrelated transplantations presented infection. There was an association between viral infection and GVHD ($p=0.034$).

Viral infections occurred in 51 children (37.0%), including herpes viruses (Herpes Simplex Virus, Human Herpesvirus 6), Epstein-Barr (EBV), Rhinovirus, Coronavirus, Influenza, Parainfluenza and Respiratory Syncytial Virus (RSV).

Of the total, 59 (42.8%) underwent up to five transfusions (platelet concentrate and red blood cells); 12 (8.6%) developed a transfusion reaction, such as body pruritus in 5 (3.6%) and hyperthermia in 3 (2.2%).

DISCUSSION

It was found that the children in the immediate post-transplantation period in outpatient care were mostly male, which corroborates data from the literature,⁽¹⁸⁻¹⁹⁾ with a mean of 6.2 years, which leads to reflections on the impact on their education, due to the school interruption necessary with the treatment. Furthermore, there was a predominance of children with white skin color, and those that came from outside Paraná, which reaffirms the transplant center as a national referral center.

Regarding the clinical profile of this population, although the most common diagnosis in the literature in children undergoing HSCT is leukemia,⁽²⁰⁾ in the present study a higher prevalence of Fanconi anemia was found, which can be explained by the fact that the center is a referral center for the treatment for this diagnosis. This may also be a justification for the diagnosis being late in many situations, since, in health centers, there is a lack of

specific diagnostic methods capable of detecting the genetic alterations characteristic and confirmatory of the disease⁽¹⁰⁾.

Although it is known that the time elapsed prior to the HSCT is one of the main risk factors for the outcome presented by the patient,^(2,21) no association was identified between the medical diagnosis and time to the HSCT ($p=0.238$).

Bone marrow was the predominant stem cell source, as the greater risk of chronic graft-versus-host disease causes stem cells from peripheral blood to be less suitable for children^(10,21).

Regarding the type of HSCT, unrelated allogeneic HSCT was predominant. A worldwide trend in the development of allogeneic HSCT⁽³⁾ can be seen due to improvements in donor/recipient compatibility, an increase in the number of unrelated donors registered and improvements in the understanding of stem cell biology⁽²⁰⁾. In a recent study, there were no significant differences in survival between HSCT recipients with unrelated donors and those with sibling donors, considering children with leukemia⁽²²⁾. This trend corroborates the data found here, in which unrelated donors were prevalent, characterizing the demand of the transplant center. However, it should be highlighted that transplants with these donors may result in a greater risk of complications, justifying the clinical intercurrents found.

Almost one third of the children (30.4%) underwent transplantation with incompatibilities in the HLA, which is related to deficient reconstitution of the immune system, increased GVHD and rejection⁽²⁰⁾. Thus, the team is required to give more attention to the post-transplantation clinical evolution.

In terms of conditioning, myeloablative is highly toxic, increasing morbidity and mortality^(10,20), which may have contributed to the use of reduced intensity conditioning, as well as the greater number of nonmalignant diseases. The agents and doses used in this type of conditioning have a relatively low risk of side effects, reducing toxicity⁽⁶⁾.

Characteristics of this clinical profile that are relevant for nursing care should be highlighted, specifically; the results demonstrate the presence of a central venous catheter, which results in greater safety for the child and the nursing team compared to the use of the peripheral endovenous route, since there are complications related to extravasation/infiltration of medications, with risk of severe necrosis of the skin, involvement of nerves and tendons, and phlebitis⁽²³⁾. A low percentage of loss of functionality of the device was observed, suggesting effectiveness in the nursing care, evidenced also by the length of permanence of the catheter.

In addition, nursing care related to the use of nasoenteral/nasogastric tubes should be considered, since their use can be beneficial in children with high weight losses during hospitalization, difficulties in food acceptance and rejection of medication ingestion. Due to their fragility, transplant children should be evaluated regarding the necessity for these devices and for nutritional therapies.

As far as the hospital discharge is concerned, its precocity has been a trend, since it is possible to treat a greater number of patients and reduce the waiting time for transplantation⁽²⁴⁾. The data of this study do not allow the precocity of the discharge to be evaluated, however, the BMTS of the study operates day hospitalization, a fact that increased the number of patients in simultaneous post-discharge monitoring, as well as the demand for care. In this situation, the patients have more needs at the time of hospital discharge and may not be prepared for home care, increasing the risk of complications.

The main clinical intercurrent was pain, located in the abdomen, lower limbs, joints, oral cavity and upper limbs. Abdominal pain may be related to GVHD intestinal involvement,⁽²⁵⁾ therefore this represents a nursing care alert, needing to be carefully monitored.

The patient also needs care to avoid respiratory infections; in accordance with the present results, in another study which evaluated respiratory infections in children undergoing HSCT, cough (79.8%), fever (67.4%), and coryza (38.2%) were common symptoms⁽²⁶⁾. This care can reduce morbidity and mortality in the post-transplant period and should include: mask use; hand washing; social isolation; preventive respiratory isolation from suspected cases until confirmation and isolation of confirmed cases⁽²⁶⁾.

As previously mentioned, unrelated allogeneic HSCT is a risk factor for the development of some post-transplant infections, which may have contributed to the higher rate of viral infections in the children of this sample. Viral infection, such as Cytomegalovirus and Human Herpes Virus 6, carries with it a risk of graft failure⁽⁶⁾, hence the relevance of its evaluation in transplant patients.

Viral infections have been associated with GVHD, which is one of the most serious post-transplant complications, as it predisposes to the appearance of infections due to delay in the reconstitution of the immune system^(20,27). In the literature it is possible to find studies showing a higher GVHD frequency than the one found here⁽¹⁵⁻¹⁶⁾. A possible justification is that peripheral blood stem cells, which have a greater potential to cause GVHD, were not used in the transplantations of this study⁽²⁷⁾. Regardless of this, it is a serious complication, in which clinical signs and symptoms need to be identified and therapy instituted.

Another intercurrent is the transfusion reactions, which are significant considering the usual need for the use of blood components by HSCT patients. Regarding the use of blood components, in addition to transfusion reactions, the increase in institutional costs due to the processes necessary prior to the transfusion in immunocompromised patients must be considered. In a study with adults after autologous HSCT, the mean number of transfusions was three units of red blood cells and four units of platelet concentrates⁽²⁴⁾. In the present study the mean was five blood transfusions, however, because it deals exclusively with HSCT in children, it is difficult to compare this with the literature, which does not prioritize this group of patients.

The number of transfusion reactions identified was low, which can be attributed to the processing of blood components performed by the study hospital and to the use of prophylactic medications. Patients in the post-HSCT period receive blood components that have been irradiated and filtered or washed in special situations. In the transplantation center of this study a blood bank is responsible for performing these processes, however, this is not a common reality in many centers throughout Brazil, and should be reconsidered in public health policies.

Regarding hospital readmission, the scarcity of comparative literature makes it impossible to compare this number. However, post-HSCT patients are critical and rehospitalization is a possibility. Hospital discharge, if not scheduled and prepared, may increase the risk of intercurrents and complications, especially if satisfactory medullary recovery has not occurred.

Considering the profile identified, the nursing actions for the transplant child should involve the inclusion of the caregiver in the care; assessment of the adaptation to the provisional residence for performance of the care; daily assessment of bodily systems, with special attention to fever and neutropenia, as well as nutritional losses; evaluation of the medullary attachment; and prevention of rehospitalization by monitoring the clinical evolution, conducting and guiding the care. These actions contribute to the achievement of better results and to the nursing care in this context.

It has been clarified that HSCT in children presents more success than in adults⁽²¹⁾. Therefore, investments in therapeutics and studies are necessary considering the evolution and chances of a cure, in addition to the care specificities presented by this population⁽²⁸⁾.

The investigation of the clinical profile of children undergoing HSCT in outpatient/home care contexts contributes to the development of care strategies, the creation of protocols and the preparation of the team for the care. It should be highlighted that the

adequate insertion of the patient and caregiver into the home corroborates the early recognition of signs and symptoms, since they become co-authors in the care⁽²⁹⁾.

The following limitations for this study should be considered, a lack of information in the medical records, including nursing procedures, the transversal time period, which does not allow causal relationships to be established, and the data referring to only one institution, making generalizations impossible. However, the number of patients evaluated and the performance of the study in a referral center are important aspects.

CONCLUSION

This study achieved the proposed aim of identifying the clinical profile of children in the immediate post-HSCT period, in outpatient care. These are children who are vulnerable due to the condition of dependency or ineffectiveness of the immune system. When performing unrelated HSCT with incompatibilities, a high risk of complications is assumed, possibly requiring longer hospitalization, bed availability for readmissions, adequate preparation for hospital discharge and evaluation of the clinical evolution.

It is possible to establish healthcare strategies aimed at the prevention and early identification of intercurrents and complications. The clinical intercurrents evidenced may require more nursing care, implying a risk of rehospitalization, complications and death. In the immediate post-HSCT period, monitoring the appearance of signs and symptoms in children is essential care for nurses. Simultaneously, these professionals are responsible for providing adequate guidance and supervision of the home care performed by the caregiver.

It is believed that this study corroborates the knowledge of the post-transplant clinical evolution in children, however, the need is emphasized for further studies in pediatric populations, with haploidentical HSCT and in patients requiring hospital readmission after transplantation, as well as longitudinal studies, to corroborate the findings indicated and the healthcare.

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