

# Clinical Characteristics and Complications of the Haploidentical Transplantation with Post-Transplant Cyclophosphamide: Implications for Nursing

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*Características Clínicas e Complicações do Transplante Haploidentico com Ciclofosfamida Pós-Transplante: Implicações para a Enfermagem*

*Características Clínicas y Complicaciones del Trasplante Haploidentico con Ciclofosfamida Post-Transplante: Implicaciones para la Enfermería*

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## Abstract

**Introduction:** Haploidentical Transplantation (haplo) has been growing in numbers and becoming a viable alternative for patients without compatible donors. Qualified nursing care is also very important for its success. Therefore, it becomes necessary to acquire knowledge and skills about the subject. **Objective:** To describe clinical characteristics and complications of haplo with post-transplant cyclophosphamide and discuss its implications for nursing care. **Method:** Integrative literature review published from 2014, searched in the bases of the “Biblioteca Virtual em Saúde” with the descriptor “haploidentical transplantation” and selected with predefined criteria. **Results:** Twenty-five texts were reviewed, all of them of the medical area and consisting mainly of retrospective cohort studies with small samples. Among the most prevalent characteristics, the following were outstanding: the mother as the main donor for children (5/7 studies); non-myeloablative regimen (52%) and peripheral blood graft (56%). In addition to graft versus host disease and rejection, the most described complications were: BK virus hemorrhagic cystitis (56%) and reactivation of cytomegalovirus (48%); and the ones with the highest variations in frequencies were mucositis (8% to 100%) and non-infectious fever (22% to 100%). The main causes of mortality were relapse of the disease (3% to 35%) and infections (3% to 32%). **Conclusion:** This review warned about the necessity of improving the care in the administration of post-cyclophosphamide, the support to donors and management of non-infectious fever, viral infections and hemorrhagic cystitis to improve the quality of life of patients and reduce haplo-related morbidity and mortality.

**Key words:** Transplantation, Haploidentical/adverse effects; Cyclophosphamide; Nursing Care.

## Resumo

**Introdução:** O transplante haploidentico (haplo) vem crescendo em números e se tornando uma alternativa viável para pacientes sem doadores compatíveis. Uma assistência de enfermagem qualificada também é muito importante para o seu sucesso. Portanto, torna-se necessário adquirir conhecimentos e habilidades no assunto. **Objetivo:** Descrever as características clínicas e complicações do haplo com ciclofosfamida pós-transplante e discutir suas implicações para a assistência de enfermagem. **Método:** Revisão integrativa da literatura publicada a partir de 2014, pesquisada nas bases da Biblioteca Virtual em Saúde com o descritor “haploidentical transplantation” e selecionada com critérios pré-definidos. **Resultados:** Vinte e cinco textos foram revisados; todos da área médica e compostos principalmente de estudos de coorte retrospectivos com amostras pequenas. Entre as características mais prevalentes, destacaram-se: a mãe como principal doadora para crianças (5/7 estudos); regime não mieloablativo (52%); e enxerto de sangue periférico (56%). Além da doença enxerto versus hospedeiro e da rejeição, as complicações mais descritas foram: cistite hemorrágica por vírus BK (56%) e reativação do citomegalovírus (48%); e as com maiores variações nas frequências foram mucosite (8% a 100%) e febre não infecciosa (22% a 100%). As principais causas de mortalidade foram a recaída da doença (3% a 35%) e as infecções (3% a 32%). **Conclusão:** Esta revisão alertou para a necessidade de aprimoramento da assistência na administração da ciclofosfamida pós-transplante, no suporte aos doadores e no manejo da febre não infecciosa, das infecções virais e da cistite hemorrágica, para que haja melhora na qualidade de vida dos pacientes e diminuição na morbidade e na mortalidade relacionadas ao haplo.

**Palavras-chave:** Transplante Haploidentico/efeitos adversos; Ciclofosfamida; Cuidados de Enfermagem.

## Resumen

**Introducción:** El diagnóstico precoz del riesgo nutricional puede mejorar el pronóstico de los pacientes onco-hematológicos. **Objetivo:** Describir el estado nutricional en los pacientes onco-hematológicos y evaluar los factores asociados al riesgo nutricional en los pacientes onco-hematológicos de un Hospital Universitario Terciario de Fortaleza - Ceará. **Método:** Estudio transversal que incluyó a 127 pacientes adultos internados. Los datos de diagnóstico clínico y demográfico fueron recolectados a través de análisis de prontuarios. El estado nutricional fue evaluado por el índice de masa corporal (IMC), circunferencia braquial (CB) y por la aplicación de la herramienta de clasificación de riesgo nutricional - NRS-2002. **Resultados:** Diferentes parámetros, hubo divergencias en el estado nutricional. La mayoría de la muestra presentaba riesgo nutricional de acuerdo con la evaluación de la NRS-2002 70,1% (n=89), seguida por la CB 33,9% (n=43) y por IMC 8,7% (n=11). Se observó una correlación positiva significativa entre el IMC y la edad [ $r=0,313$ ,  $p<0,001$ ] y CB [ $r=0,846$ ,  $p<0,001$ ]. Se observó una asociación significativa NRS-2002 $\geq 3$ , e IMC $<18,5$  kg/m<sup>2</sup> ( $p=0,023$ ) y CB desnutrida ( $p=0,001$ ). Hubo asociación significativa entre IMC $<18,5$ kg/m<sup>2</sup> y CB desnutrida ( $p=0,001$ ), y entre residir en zona urbana y presentar CB adecuado ( $p=0,023$ ). **Conclusión:** Alta prevalencia de riesgo nutricional, así como una asociación significativa entre riesgo nutricional y bajos valores de IMC y CB, y residir en zonas rurales. Hay la necesidad de utilizar una combinación de indicadores para diagnosticar de forma más precisa y precoz el estado nutricional de estos pacientes.

**Palabras clave:** Trasplante Haploidentico/efectos adversos; Ciclofosfamida; Atención de Enfermería.

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## INTRODUCTION

The first attempts with haploidentical transplantation (haplo) occurred in the years 1970. The results were quite poor because of the high rates of rejection of the graft or of the high rates of incidence of severe graft versus host disease (GVHD), which resulted in great mortality related to the treatment. It was clear, however, that new techniques to overcome the barrier of compatibility among the human leukocyte antigens – HLA were necessary. The studies and experiments continued but only two decades ago, with the development of differentiated platforms of immunosuppression, haplo is growing in numbers and in importance and becoming a viable alternative for patients without compatible donors<sup>1,2</sup>.

Haplo is defined by the descriptors of the Virtual Health Library (BVS) as a “transplantation among individuals that share a partial correspondence of haplotypes”<sup>3</sup>. An identical copy of only one of the chromosomes 6 where the genes that codify the system HLA are encountered. For this to happen, it is necessary that the donors are relatives of first or occasionally second degree. However, they still can share with the patient a series of other genes located in the other nonidentical chromosome 6, resulting, in most of the cases, in more than 50% of compatibility<sup>1</sup>.

To control the challenge imposed by the partial incompatibility, that results in an intense alloreactivity of lymphocyte T either of the patient or the donor, currently three platforms of immunosuppression are adopted. The first consists in the manipulation of the graft for total depletion or selective of cells T, *in vitro*, with infusion of megadoses of stem-cells. The second adopts non manipulated grafts with the administration of antithymocyte globulin – ATG. Its most known protocol is GIAC, mainly utilized in China. It consists of the mobilization of the donor with stimulating factor of colonies of granulocytes (G); intensified immunosuppression (I) post transplantation with cyclosporine, methotrexate and mycophenolate of mofetil; inclusion of ATG (A) in the conditioning and a combined graft (C) of bone marrow and peripheral blood<sup>1,2</sup>.

The third option of immunosuppression, also for non-manipulated grafts, consists in the administration of high doses of cyclophosphamide, 50 mg/kg/day, generally in days +3 and + 4 post-transplantation and the objective is to make, *in vivo*, a depletion of alloreactive cells T in bidimensional form. At the same time, the drug inactivates cells T of the receptor, diminishing the probability of graft rejection and inactivates cells T of the donor, diminishing the incidence and severity of acute and chronic GVHD<sup>1,2</sup>.

Currently, this is the platform of immunosuppression

for haplo most utilized worldwide. First, because it works, and cyclophosphamide is a potent immunosuppressor. Second, because it does not need technology and specialized team as in the expensive processes of depletion of cells T *in vitro* and, for this, is cheaper and can be adopted in sites without many resources<sup>2</sup>. Third, the drug has great availability and all the teams that perform hematopoietic stem-cells transplantations (HSCT) are quite familiarized with the management of its adverse events.

The results of haplo with cyclophosphamide post-transplantation have been compared to the results of standard compatible related HSCT and of the unrelated alternative, umbilical cord blood and haplos that adopt the other two platforms of immunosuppression previously described. Overall, with some exceptions, similar results among them have been encountered, in relation to global survival. Haplo tends to have lower mortality related to the treatment; but, in counterpart, high rate of relapse when protocols of reduced intensity are adopted. However, the essential difference is in the incidences of acute GVHD and mainly of the chronic that, in haplo with cyclophosphamide post-transplantation have been showing significantly lower<sup>1</sup>.

These findings are relevant and encouraging, since GVHD is one of the complications who affect most negatively the quality of life of the patients transplanted. They also corroborate, increasingly, haplo as a viable alternative for HSCT. However, in despite of the optimism, caution and more controlled studies are necessary because its long-term effects are yet totally unknown, and most of the current studies present significant limitations as retrospective analysis, non-randomized comparisons and small samples.

Similar as for all types of transplantation, a qualified nursing assistance is very important for the success of haplo. For such, it is necessary that the team acquires knowledge and skills related to this alternative of transplantation<sup>4</sup>.

During a HSCT, the main focuses of nursing attention are: education and preparation of the patients, donors and relatives; execution of operational procedures with compliance; administration of regimens of conditioning and immunosuppression; infusion of graft and control of immediate, early and late complications related to the treatment. In haplo, because it is a relatively new modality, it is essential to pay attention to its characteristics and specific complications to improve care and consequently, enhance better results<sup>4</sup>.

Based in these considerations, this integrative literature review had the objective of describing clinical characteristics and complications of haplo with

cyclophosphamide post-transplantation and discuss its implications for nursing assistance.

## METHOD

The evidences-based practice has generated an increase of the production of systematic literature review and meta-analysis that, although present strong levels of evidences, fail to respond to important questions of nursing related to the care and/or impact of the disease or the treatment in the quality of life of the patients and their relatives. In this aspect, the integrative review is a more amplified methodological approach that allows the inclusion of data of theoretical, empirical, experimental or not literature and even of unpublished material in order to offer a more consistent knowledge and grounded in concepts, theories or health problems relevant for the profession<sup>5</sup>.

This integrative review was based in the method proposed by Souza et al.<sup>5</sup> and developed in the following stage: formulation of the guiding question; search and selection of literature; data extraction, analysis of the studies; discussion of the results and presentation of the review.

Considering the current scenario of haplo and main focus of attention of nursing in HSCT, the following question was formulated: “What are the main clinical characteristics and complications of haplo with cyclophosphamide post-transplantation and how they can impact the nursing assistance?”

In May 2019, it was conducted search and selection of studies in the following databases of BVS Brazil: LILACS; MEDLINE and BDENF. The descriptor utilized was “*haploidentical transplantation*” and the combination of this with “*nursing*” or “*nursing care*” through Boolean connectors “*AND*” and “*OR*” in advanced search.

The inclusion of the studies was made through the application of the following filters of BVS itself: descriptor in the title of the article; complete text available; cyclophosphamide as main subject; limit in humans; Spanish, English or Portuguese as languages and publications from 2014 (last 5 years). After reading the titles and abstracts, or full texts, the review studies, case reports, paid articles and those which did not match the objectives of this review were excluded (Figure 1).

After the selection, the data about the studies, the clinical characteristics of the samples, the results and the complications were extracted according to an adaptation of the instrument validated by Ursi (apud Souza et al.<sup>5</sup>). The frequencies of the variables were managed in a spreadsheet in Microsoft Windows Excel 10.0. Percent not explicit in the results of the studies were calculated, based in the sample size of haplo with cyclophosphamide

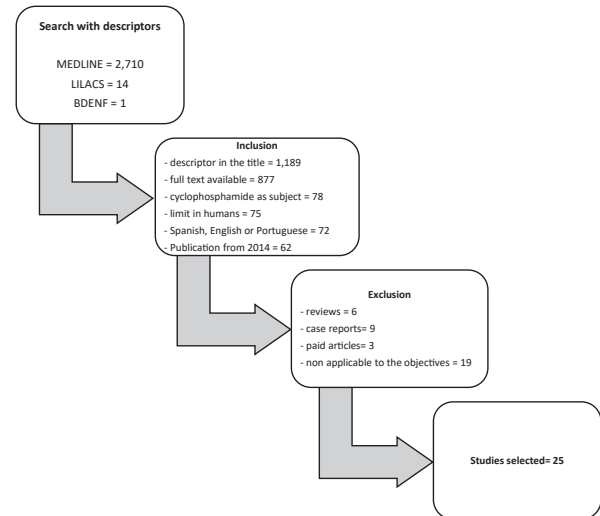


Figure 1. Flowchart of search and selection of studies

post-transplantation, regardless of comparisons with other types of HSCT or other type of immunosuppression. In order to improve the reliability of the data, the information extracted about the characteristics and complications were revised by the author in a second moment.

In order to groundwork the discussion of this review, it were considered as evidences the frequencies of the clinical characteristics and the complications that were described in five (20%) or more studies. The levels of evidences were hierarchized according to the classification proposed by Stetler et al.<sup>6</sup>. They are: 1 - meta-analyzes of multiple controlled clinical cases; 2 – individual experimental studies; 3 – nearly experimental studies or pairwise case control studies; 4 - non-experimental descriptive studies, qualitative studies or series of cases; 5 – case or experience reports; and 6 - opinions of experts or committees of specialists, regulations or legislations.

## RESULTS AND DISCUSSION

All the 25 articles selected were from the medical area published in English whose source was MEDLINE. Fifteen (60%) were retrospective, cohort observational studies, level of evidence 4; and four (16%) were clinical studies, level 2. Twenty-three (92%) were original articles and two (8%) were letters to the editor. Seven (28%) were originated in the United States, and three of them from the University/Hospital Johns Hopkins of Baltimore; this group developed and consolidated in 2008 the pioneer platform of cyclophosphamide post-transplantation for haplo<sup>2</sup>. Six (24%) were from a cooperation between France and Italy; three (12%) only from Italy; two (8%) from Spain; and one (4%) from a cooperation between

the United States and Colombia. Brazil, Colombia, India, Japan, Mexico and Uruguay contributed with one study (4%) each.

According to the data presented in Table 1<sup>7-31</sup>, the sample size (N) varied from 16 to 687 patients, and in 14 (56%) studies, N was lower than 50. The age varied from 1 to 78 years. Seven (28%) studies were formed by children, adolescents and young adults and two (8%) were elderly with 50 years or more. Male gender was the principal in 15/25 samples. Most part of the diagnosis was of onco-hematologic diseases, with higher frequency of acute myeloid leukemia (44%). One study described the results in pediatric solid tumors<sup>28</sup> and another, in Fanconi anemia<sup>23</sup>.

Haplo was adopted as first, second and even third transplantation. The stages of the disease were the most different as possible: low, medium and high risk; complete, partial remission, in relapse or in progression; refractory; localized or extensive. Exclusively, in one of the studies, haplo was evaluated as rescue therapy for relapse after completely compatible transplantation<sup>16</sup>.

As for the donors, 40% of the studies did not specify them; in the samples of adults and elderly, siblings and children were more frequent; in the pediatric samples, mother was the main donor in 5/7 studies. The regimen of non-myeloablative conditioning was the most frequent in 52% of the studies and the near totality of these were based in the Baltimore platform, represented in Table 2. The graft of peripheral blood was the only or principal in 56% of the samples. In four (16%), haplo was performed in hospital-day regimen; two of these described that 60% and 84% of the patients needed hospitalization for control of complications.

Twenty-two studies (88%) had as primary outcomes the estimates of survival, mortality, relapse, grafting and GVHD. The mean period of follow up varied from seven to 48 months; the global survival, in the greatest time estimated, varied from 21% to 73%; the cumulative incidence of relapse of 15% to 81% and the mortality related to treatment, of 6% to 36%. The mean neutrophil engraftment varied from 13 to 21 days and of platelets, from 14 to 35 days. In the other three studies, the primary outcomes were, in each one of them, fever<sup>12</sup>, infections<sup>21</sup> and viral hemorrhagic cystitis<sup>30</sup>.

The incidence of GVHD was investigated in 92% of the studies. The frequency of acute GVHD grades II-IV varied from 14% to 70%; acute GVHD grades III-IV of 2% to 33%; and chronic GVHD from 4% to 67%. The primary rejection (failure) of the graft was investigated in 72% of the studies and its incidence varied from <1% to 15%. The other complications described, presented in Table 3, were by toxicity of the treatment or infectious, the

most described were reactivation of the cytomegalovirus (CMV) and hemorrhagic cystitis by virus BK (initials of the name of the first patient where the virus was isolated).

The main causes of mortality were the relapse of the disease with a variation of 3% to 35%; the infections from 3% to 32%; GVHD from 1% to 17% and multiple or single organ failure from 3% to 7%.

GVHD and the rejection of the graft were, as concerning outcomes in incompatible transplantations, the complications most investigated in the studies reviewed. However, with the platform of cyclophosphamide post-transplantation, these do not appear to be great problems in haplo<sup>1</sup>. Mucositis also presented high frequency in some studies<sup>14,23</sup>, but the use of non-myeloablative regimens have reduced its severity. These are the complications most discussed in the literature of HSCT and have defined protocols or guidelines of control.

In addition to the own cyclophosphamide post-transplantation, other characteristics and complications were also more described and/or presented higher frequencies. Therefore, it were considered also significant and emerged as themes for discussion. Since the search and selection process did not result in any specific nursing study about haplo, in addition to the data presented, this discussion was also based in the integration with some literature about HSCT in general and with the personal experience of the author.

The pioneer platform with cyclophosphamide post-transplantation of Baltimore produced satisfactory effects in the prevention of GVHD and is being replicated in several studies and institutions. However, it has been undergoing modifications in the last years as intensification of the regimen of conditioning, use of graft of peripheral blood *in lieu* of bone marrow and administration of inhibitors of calcineurin and mycophenolate prior to cyclophosphamide. It is also no more exclusive for haplo and has been investigated as sole or combined immunosuppressor in the HSCT totally compatible and even experimented in joint transplantations of kidney with bone marrow<sup>1,8,11,15,17</sup>.

To be effective in the prevention of graft rejection and GVHD, it is recommended that the first dose of cyclophosphamide is administered in an interval of two to three days after the infusion of graft. More precisely, in operational terms, between 60 and 72 hours after. Studies with animals have demonstrated that, in this period, mature T cells are in frank process of cellular division and in the peak of DNA synthesis, when the drug is more active. If administered before 24 hours or after 96 hours, its inductive effect of allogeneic tolerance can be compromised<sup>1,20</sup>. Therefore, nursing must concur with pharmacy and prepare the patient to receive the drug within this time frame.

Table 1. Clinical characteristics in the studies reviewed

Number	Characteristics of the study: author/origin country/type	Characteristics of the Sample	Characteristics of the haplo
1	Castagna et al. <sup>7</sup> , 2014 France and Italy ROCS bicentric	N = 69 Age <sup>a</sup> = 44 (19-68) Gender = NS Diag. <sup>b</sup> = HL (42%)	Donor <sup>b</sup> = NS Regimen <sup>b</sup> = NMA (100%) Graft <sup>b</sup> = BM (67%)
2	Sugita et al. <sup>8</sup> , 2015 Japan Multicenter PCS	N = 31 Age = 48 (21-65) Gender M/F = 22/9 Diag. = AML (55%)	Donor = son (45%) Regimen = RI (100%) Graft = PB (100%)
3	Kasamon et al. <sup>9</sup> , 2015 USA ROCS unicentric	N = 271 Age = 61 (50-75) Gender M/F = 184/87 Diag. = NHL (47%)	Donor = NS Regimen = NMA (100%) Graft = BM (100%)
4	Cieri et al. <sup>10</sup> , 2015 Italy Unicentric PCS	N = 40 Age = 55 (21-78) Gender M/F = 23/17 Diag. = AML (55%)	Donor Son (55%) Regimen = MA (100%) Graft = SP (100%)
5	Bacigalupo et al. <sup>11</sup> , 2015 Italy Unicentric OCS	N = 148 Age = 47 (17-74) Gender = NS Diag. = AML (32 %)	Donor NS Regimen = MA (100%) Graft = BM (100%)
6	Arango e Combariza <sup>12</sup> , 2017 Colombia Unicentric retrospective case studies series	N = 40 Age = 18 (1-59) Gender = NS Diag. = ALL (50%)	Donor Father (55%) Regimen = NMA (60%) Graft = PB (100%)
7	González-Llano et al. <sup>13</sup> , 2016 Mexico ROCS unicentric	N = 25 Age = 10 (1-21) Gender M/F = 17/8 Diag. = ALL (72%)	Doador = Mother (80%) Regimen = NS Graft = PB (100%)
8	Jaiswal et al. <sup>14</sup> , 2016 India PCS unicentric	N = 20 Age = 12 (2-20) Gender M/F = 12/8 Diag. = AML (65%)	Donor = Mother (70%) Regimen = MA (100%) Graft = PB (100%)
9	Devillier et al. <sup>15</sup> , 2017 France and Italy NS bicentric	N = 46 Age = 61 (50-73) Gender = NS Diag. = NHL (35%)	Donor = NS Regimen = NMA (100%) Graft = PB (100%)
10	Gorgeis et al. <sup>16</sup> , 2016 USA ROCS unicentric	N = 20 Age = 54 (21-66) Gender M/F = 13/7 Diag. = AML (35%)	Donor = NS Regimen = NMA (85%) Graft = PB (55%)
11	Rashidi et al. <sup>17</sup> , 2016 USA ROCS unicentric	N = 62 Age = 54 (19-73) Gender M/F = 30/32 Diag. = AML (100%)	Donor = NS Regimen = RI (56%) Graft = PB (100%)
12	Devillier et al. <sup>18</sup> , 2016 France and Italy ROCS bicentric	N = 60 Age = 57 (22-73) Gender = NS Diag. = AML (68%)	Donor = NS Regimen = RI (67%) Graft = PB (80%)
13	Dufort et al. <sup>19</sup> , 2016 Uruguay ROCS unicentric	N = 23 Age = 15 (1-26) Gender M/F = 13/10 Diag. = ALL(52%)	Donor = Mother (74%) Regimen = MA (70%) Graft = PB (100%)
14	Berger et al. <sup>20</sup> , 2016 Italy ROCS multicenter	N = 33 Age = 12 (1-21) Gender M/F = 20/13 Diag. = ALL (45%)	Donor = Mother (54 %) Regimen = NMA (57 %) Graft = BM (91 %)

to be continued

Table 1. continuation

Number	Characteristics of the study: author/origin country/type	Characteristics of the Sample	Characteristics of the haplo
15	Slade et al. <sup>21</sup> , 2017 USA ROCS unicentric	N = 104 Age = 50 (19-73) Gender M/F = 57/47 Diag. = AML (67 %)	Donor = NS Regimen = NMA (59%) Graft = PB (100%)
16	Castagna et al. <sup>22</sup> , 2017 France and Italy ROCS multicenter	N = 30 Age = 56 (31-65) Gender M/F = 13/17 Diag. = MM (100%)	Donor = Son (63%) Regimen = MA (53%) Graft = BM (60%)
17	Bonfim et al. <sup>23</sup> , 2017 Brazil OCS unicentric	N = 30 Age = 10 (4 - 16) Gender M/F = 22/8 Diag. = Fanconi Anemia (100%)	Donor = Mother (67%) Regimen = NMA (100%) Graft = MO (100%)
18	Castagna et al. <sup>24</sup> , 2017 France and Italy NS	N = 62 Age = 31 (19-68) Gender M/F = 36/26 Diag. = HL (100%)	Donor = Brother (55%) Regimen = NMA (81%) Graft = BM (63%)
19	Srouf et al. <sup>25</sup> , 2017 USA and Colombia ROCS multicenter	N = 109 Age = 32 (18-66) Gender = 64/45 Diag. = ALL (100%)	Donor = Brother (49%) Regimen = MA (64%) Graft = PB (54%)
20	Bashey et al. <sup>26</sup> , 2017 USA OCS prospective multicentric	N = 687 Age = 47 (18-76) Gender M/F = 394/293 Diag. = AML (44%)	Donor = NS Regimen = NMA (72%) Graft = BM (72%)
21	Klein et al. <sup>27</sup> , 2017 USA ROCS unicentric	N = 40 Age = 20 (1-25) Gender M/F = 28/12 Diag. = HL(35%)	Donor = Father (50%) Regimen = NMA (95%) Graft = BM (95%)
22	Llosa et al. <sup>28</sup> , 2017 USA PCS unicentric	N = 16 Age = 18 (3-26) Gender M/F = 8/8 Diag. = RMS (38%)	Donor = Father (94%) Regimen = RI (100%) Graft = BM (100%)
23	Esquirol et al. <sup>29</sup> , 2017 Spain ROCS multicenter	N = 81 Age = 53 (18-70) Gender M/F = 40/41 Diag. = AML (36%)	Donor = Son (47%) Regimen = MA (100%) Graft = PB (62%)
24	Rimondo et al. <sup>30</sup> , 2017 France and Italy ROCS bicentric	N = 161 Age = 53 (19-73) Gender = NS Diag. = NS	Donor = NS Regimen = NMA (69%) Graft = MO (52%)
25	Kwon et al. <sup>31</sup> , 2017 Spain ROCS multicenter	N = 36 Age = 38 (21-65) Gender M/F = 21/15 Diag. AML (100%)	Donor = Brother (36%) Regimen = MA (100%) Graft = PB (97%)

**Captions:** <sup>a</sup> – mean age and variation; <sup>b</sup> – most frequent type; ROCS – retrospective observational cohort study; PCS – prospective clinical study; OCS – observational cohort study; N – sample size; M/F – male/female; NS – non specified; Diag. – diagnostic; AML – acute myeloid leukemia; ALL – acute lymphoblastic leukemia; HL – Hodgkin lymphoma; NHL – Non-Hodgkin Lymphoma ; MM – multiple myeloma; RMS – rhabdomyosarcoma; MA – myeloablative; NMA – non-myeloablative; RI – reduced intensity; BM – bone marrow; PB – peripheral blood.

For being of high dose, cyclophosphamide post-transplantation can cause chemical hemorrhagic cystitis. Hyper hydration during and until at least 24 hours after the administration of the drug and forced diuresis with diuretic, if necessary, are the main measures of prevention of complication. In

the studies reviewed, it was also frequent the use of the uroprotective medication mesna<sup>8-11,13,18,22,28,29</sup>. Nursing is responsible for administering rigorously in the defined time, before and until 12 to 24 hours after cyclophosphamide, according to the institutional protocol<sup>32</sup>.

**Table 2.** Platform of cyclophosphamide post-transplantation of Baltimore, USA

Drugs, irradiation and doses	Days in the transplantation queue
Cyclophosphamide 14.5 mg/kg/day	-6 and -5
Fludarabine 30 mg/m <sup>2</sup> /day	-6 to -2
Total body irradiation 200 cGy	-1
Infusion of the graft of bone marrow	0
Cyclophosphamide 50 mg/kg/day	+3 and +4
Filgrastim 5 mcg/kg/day	+5 until medullar grafting
Mycophenolate 15 mg/kg, 3 times/day	+5 until +35
Tacrolimus 0,015 mg/kg, 2 times/day	+5 until +180

Source: Adapted from Klein et al.<sup>27</sup>.

**Table 3.** Complications described in the studies reviewed

Complications	Frequency in the studies %	Variation of the frequency in the samples % <sup>Ref.</sup>
1- Hemorrhagic cystitis by virus BK and others	56	77, <sup>30</sup> to 50 <sup>23</sup>
2- Viremia or reactivation of CMV	48	33 <sup>22</sup> to 75 <sup>23</sup>
3- Disease by CMV	32	3 <sup>22</sup> to 15 <sup>10,21</sup>
4- Fungic infections in general	32	5 <sup>14</sup> to 25 <sup>3,28</sup>
5- Viremia, reactivation or disease by EBV	28	3 <sup>20,31</sup> to 23 <sup>24</sup>
6- Viremia or disease by other viruses	24	3 <sup>20</sup> to 65 <sup>10</sup>
7- Bacterial infections in general	24	13 <sup>10</sup> to 62 <sup>21</sup>
8- Sinusoidal obstruction syndrome	24	1 <sup>29</sup> to 17 <sup>19</sup>
9- Mucositis	20	8 <sup>13</sup> to 100 <sup>14</sup>
10- Infectious fever and febrile neutropenia	20	18 <sup>7</sup> to 87 <sup>21</sup>
11- Non-infectious fever	20	22 <sup>28</sup> to 100 <sup>8</sup>

Captions: CMV – cytomegalovirus; EBV – Epstein-Barr virus.

Other measures are to stimulate mictions in short and frequent periods; monitor the aspect and volume of diuresis; collect urine sample for tests in case of suspicious signs and symptoms and follow up the levels of electrolytes and kidney function. The orientation to the patient for administration of cyclophosphamide and

the importance of reporting promptly the symptoms of cystitis is essential for the application of early interventions for its control<sup>32</sup>.

Another measure also recommended is that it should be avoided the administration between days -1 and +5, of glyccorticoids. They can compromise the immunosuppressor effect of cyclophosphamide and must only be adopted in emergency cases and at the physician's discretion<sup>1,8,12</sup>.

The mother as main donor for children characterizes an ambivalent role: caretaker and donor. In the hospitalization, it is the mother who appears as main caretaker of the child. In the day of the transplantation, she goes to the surgical room or apheresis sector to donate stem-cells. When she returns, she is taken care by the team. In the next day, when she is discharged and should go home to recover from the donation process, she remains with the child, assuming or at least trying to assume its role as caretaker. In addition to all the problems she already has, there is also the pain, fatigue and limitations imposed by the donation. However, for being a mother and even that there are other persons providing support, she does not want to waive the care to her child. For her, the gesture of donating can be the symbolism of giving his child life for the second time and she may feel responsible for the results of the transplantation<sup>33</sup>.

The child as main character of this context is suffering physical, emotional, cognitive and social adverse events of the transplantation and, consequently, compromise its quality of life. It can even experience symptoms of depression and anxiety as result of the complexity of the treatment but also uses to express concerns with the well-being of its mother. There is a strong relation of this last aspect with the adaptation of the child to the process of HSCT and the health team needs to be alert about this<sup>33</sup>.

Nursing, *a priori*, may have some more work in the administration of medications and dressings, but also many concerns, because it is a "second" patient in the room with risks of infections, fall and bleeding<sup>33</sup> and, according to the study of Halter et al.<sup>34</sup>, a minimum, but actual, risk of serious adverse events and even death. These complications support the importance of a thorough previous evaluation and follow up of donors in the periods immediate, early and late after the donation. Therefore, special attention must be given to this mother during the whole period of follow up of the child.

Still in this context, it must be considered that because of the limitations, she can also request or even demand that exceptions are made to the rules of the service. This may require routine changes and conflicts with the nursing team. In addition, in the situations where the evolution of the transplantation is unfavorable, as for instance, failure

of the graft, the mother can feel guilty and the tension in the ambient can build up<sup>33</sup>.

In order to control, when possible, these problems, nursing must attempt to prepare the patient as adequately as possible and its family for haplo. It is of great utility when they are present in the educational meetings, attend the nursing consultation and can know in advance the unit of hospitalization with clarifications about the procedure and routines<sup>33</sup>.

Other essential actions would be to refer the family to social workers, psychology and spiritual support and keep the interdisciplinarity with them; help the mothers in their needs, create empathy, be patient and nice, listen attentively, with interest and tolerance and attempt to understand and accept her. The creation of a therapeutic relationship of the health team with this mother can alleviate its anxiety, her fear of uncertainty and its emotional toll and, consequently, reduce the stress of all the players involved<sup>33</sup>.

A high fever, that can vary from 38° to more than 40° C, associated or not to tremors and chills and that manifests since hours after the infusion of the graft until around day +5, or extend until day +14, can be the results not of an infectious process, but alloreaction of lymphocytes T, either of the patient or the donor. This process releases in the blood flow a series of inflammatory cytokines, mainly interleukina-6 (IL-6), characterizing the called cytokine release syndrome (CRS)<sup>35</sup>.

This syndrome is graduated and varies from symptoms of mild risk as fever, nausea, fatigue and malaise; goes through hypotension and respiratory disorder, changes of the liver and kidney functions and can evolve to cardiac, neurological alterations, failure of multiple organs and death<sup>35</sup>. It uses to be more incident in cases that were grafted with peripheral blood, since this type of graft has more quantity of cells T than those of bone marrow<sup>29,35</sup>.

The milder grade can have high prevalence: 83% in the study of Arango e Combariza<sup>12</sup> and 100% in the study of Sugita et al.<sup>8</sup>, but the severest grades, yet less frequent, can offer a bad prognosis to the patients<sup>35</sup>. However, the majority of the patients often has the fever reduced few days after the administration of cyclophosphamide post-transplantation, since it treats the cause of the syndrome inactivating the lymphocytes T and interrupting the release of cytokines<sup>12</sup>.

The importance for nursing is that, in case of fever, either by CRS or not, the protocol for febrile neutropenia was and should be created to prevent sepsis<sup>11,31</sup>. Even if the patient presents with signs of inflammation, the use of glyccorticoids should not be done until day +5, except at medical discretion<sup>1,8,12</sup>. The monitoring of the cardiac, respiratory, kidney, hepatic and neurological functions in febrile patients through systematic verification of vital

signs, oxygen saturation, hydric control, body weight and level of conscience must be constant and any alteration promptly reported to the medical team.

The literature and the results of this review show that the infection is the second isolated cause of death in the allogeneic HSCT, remaining behind only of disease relapse. Nursing has a crucial role in its control and in order to contribute to reduce the statistics, must implement educative actions and operational routines to prevent infections in hospital environment<sup>36</sup>.

According to pre-clinical studies, cyclophosphamide does not act in cells that are in rest. Therefore, this platform spares young non-alloreactive lymphocytes, lymphocytes T of memory and regulating lymphocyte T, which is essential for the immune reconstitution of the patient after haplo. More important still is that it does not affect hematopoietic stem-cells. They contain a great quantity of aldehyde dehydrogenase enzyme and this makes them resistant to the action of the drug. Therefore, the hematologic recovery is not compromised<sup>1</sup>.

In the studies of this review, the near totality of the patients recovered the neutrophils in a mean of 13<sup>14</sup> to 21<sup>18</sup> days post-transplantation. However, the study of Rashidi et al.<sup>17</sup> discussed the neutrophilic grafting and the cellular immunology recovery and humoral of haplo can be slower because of the incompatibility of HLA and of the differentiated platforms of immunosuppression. Therefore, even after grafting and until the later phases, as in all types of HSCT, they remain subject to infections by a series of bacteria, fungi, protozoa and respiratory and intestinal viruses seasonal or not<sup>36</sup>.

Although EBV, adenovirus, herpes simplex, human herpes 6 and other viruses have been reported in the reviewed studies, CMV and BK were the most described in 48% and 56% of the samples, respectively. These pathogens can cause pneumonia and lethal visceral diseases, in addition to prolonged hemorrhagic cystitis and of difficult control<sup>32,36</sup>.

The study of Slade et al.<sup>21</sup>, with 104 patients showed that the infection was the primary cause of death in 12% of them and the secondary in 41%. In addition to bacterial and fungic infections, it were encountered 54 (76%) reactivations of CMV in 71 seropositive patients. Of these, 15% presented visceral disease: seven intestinal, six pulmonary and two in both locations. The virus BK was reactivated in 33 patients and, of these, 20 (19% of the total) presented hemorrhagic cystitis. It also occurred reactivations of herpes virus in seven patients and 16 cases of infections by seasonal respiratory viruses.

Another example is the Brazilian study of Bonfim et al.<sup>23</sup> with 30 patients with anemia of Fanconi submitted to haplo, where 75% reactivated CMV and 50%,



presented hemorrhagic cystitis. The great majority of these complications occurred in the phase post-grafting. Interstitial pneumonia by CMV, toxoplasmosis and disseminated adenoviruses contributed for death in three cases.

Nursing must intensify its educational actions with the patients and family in relation to control measures of infections, mainly, proper hands washing and signs and symptoms that must be reported promptly in case they occur<sup>36</sup>. Reminding that patients of haplo may have been discharged from hospital, professionals working in wards or hospital-day should keep a thorough approach and a differentiated view over this patient in relation to these complications.

Anamnesis must investigate objectively respiratory, intestinal, urinary alterations with direct questions about cough, tiredness with effort, expectorations and its characteristics, dysuria, pollakiuria, hematuria, abdominal pain, diarrhea etc. The physical examination must address the respiratory pattern, oxygen saturation and presence of adventitious rumors or abolished in the pulmonary auscultation<sup>36</sup>. These alterations must be promptly reported to the medical team and respiratory physiotherapy.

Samples of bronchial secretions, stools and urine must be collected for research of virus in symptomatic cases. Of great importance is the weekly collection of blood for polymerase chain reaction – PCR viral and/or antigenemia for CMV and nursing must be attentive to this monitoring. Virus detection before the patient becomes symptomatic can guide a preemptive treatment and, with this, diminish the possibility of lethal infections<sup>36</sup>.

For this preemptive treatment, drugs with significant toxicities can be prescribed and require specific nursing care in the manipulation, administration and monitoring of the patients. According to the studies reviewed, for CMV, it were used ganciclovir, myelotoxic or *foscarnet*, nephrotoxic<sup>36,10</sup>. For BK and adenovirus, ciclofovir was administered and is also nephrotoxic<sup>21,27,30</sup>. For EBV, it was used rituximab, with known potential for hypersensitivity reactions<sup>10,19,29</sup>.

Viral hemorrhagic cystitis results in prolonged morbidity that increases the period of hospitalization, the consumption of hemocomponents and costs of transplantation. It also causes great suffering for the patients and relatives and requires many hours of nursing care.

It can manifest from days to months after haplo; for example, in the study of Bonfim et al.<sup>23</sup>, it presented between days +15 and +74. Its incidence in this review, varied from 7% to 50%<sup>7,30,23</sup>, while Rimondo et al.<sup>30</sup> referred a variation in the literature between 4% and 75%. The viruses BK were the main etiological agents, but it was also caused by the viruses John Cunningham (JC) and adenovirus<sup>10,27,29,30</sup>.

So far, the prophylactic aspect of the complication is still undefined. The use of quinolones in patients with positive BK was utilized because these drugs inhibit the viral replication<sup>21,27,30</sup>. However, there is not still a consensus about this intervention, since not all the positive patients will develop hemorrhagic cystitis and besides that, these antibiotic can induce the appearance of multiresistant bacteria<sup>32</sup>.

In what concerns the treatment, the recommendation with stronger interventions continue being the support measures as proper hydration and analgesia; transfusion of red cells and platelets to correct anemia and reduce the bleeding and continuous bladder irrigation with saline solution to avoid obstruction. If obstruction occurs, cystoscopies can be performed for clot removal<sup>32</sup>. The interventions with intravenous cidofovir<sup>21,27,30</sup>; hyperbaric oxygen therapy; formalin instillation of the bladder and vesical infusion of potassium alum-based solutions, silver nitrate, sodium hyaluronate, prostaglandins, granulocyte macrophage-colony stimulating factor (GM-CSF), cidofovir and fibrine glue have been reported as effective but evidences are still limited<sup>32</sup>.

A great challenge that the prolonged hemorrhagic cystitis presents for nursing is that bladder catheterization may have to be repeated several times because of blood clots that obstruct the catheters, which may require the use of catheters of inner greater caliber. This can cause irritations and lesions in the urinary tract, in addition of increasing the risk of associated bacterial infections. Therefore, the communication of the transplantation team with the urologist is essential.

Nursing actions must be directed for the proper control of the pain; maintenance of comfort and hygiene of the patient; monitoring of the hydric control; description of the aspect of bladder drainage and presence of clots; followed up of the daily levels of blood count; transfusion of platelets before and/or after the catheterizations; position and fixation of the catheter to avoid tractioning; control measures of infections in the manipulations of the system; emptying of the catheter and collecting duct in case of obstructions; education of the patient and its caretakers to avoid manipulating any part of the system asking for professional assistance whenever necessary and refer for psychological support. In order to avoid discomfort, it is advisable that the irrigation is made with saline solution in gravitational flow and ambient temperature<sup>32</sup>, except other specific recommendations of the urologist.

The studies that formed this review were in its majority, retrospective, observational and formed by small samples; this, without doubt, is a limitation when it is intended to evaluate the results of a certain intervention. However,

it was observed that in studies with small samples, the authors were more thorough in relation to the description of the process, the characteristics and complications and, for this, they were essential to reach the objectives planned.

The present study has its limitations as well. First, the fact that it was conducted by only one reviewer may have brought some flaw in the reliability and analysis of the data. But the second review with information extracted may have minimized this problem.

Second, the search strategies may not have been enough to identify nursing studies. However, former searches conducted by the author with other finalities and in other databases did not present nursing studies about the theme.

At last, the fact that the discussion was based, in part, in the personal experience of the author may have generated biases in relation to the themes discussed. However, they are frequent in the context of haplo with cyclophosphamide post-transplantation and require more attention from the teams who conduct it.

## CONCLUSION

It is believed that this review is one of the first to discuss the implication of haplo with cyclophosphamide post-transplantation for nursing care. Even with its limitations, the review might be a starting point in the continued education about the theme and a useful contribution in the construction of the knowledge of the professionals who work in HSCT.

The aspects that were discussed are caution about the necessity of improvement of the assistance. Important problems as the process of administration of cyclophosphamide post-transplantation and monitoring of the patients; support to the donors; management of the non-infectious fever after the infusion of the graft; early identification of viral infections and the control of symptoms and complications of hemorrhagic cystitis must be investigated completely through well designed nursing studies to improve the quality of life of the patients and reduction of morbidity and mortality related to haplo.

Because of the paucity of nursing specific studies about the theme, it is always important to remind that negative results can be as or more useful than positive results. Within a new therapeutic modality as haplo, if they occur, they should be disclosed.

## CONTRIBUTIONS

The author participated substantially in all the stages of the work and approved the final version to be published.

## DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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