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NURSING MANAGEMENT IN AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR MULTIPLE SCLEROSIS AND TYPE 1 DIABETES MELLITUS

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Abstract

Introduction

To identify clinical symptoms and nursing interventions during the conditioning period for autologous hematopoietic stem cell transplantation, while using antithymocyte globulin, in patients with multiple sclerosis who were receiving steroids and in patients with type 1 diabetes mellitus who were not receiving steroids. Patients with serious and progressive autoimmune diseases, such as multiple sclerosis and type 1 diabetes mellitus, that often develop resistance to conventional therapies with immunomodulatory and anti-inflammatory agents, which are rendered insufficient to impede irreversible damage to the affected systems. New therapeutic approaches, such as autologous hematopoietic stem cell transplantation, have been developed that offer promising global survival and progression-free levels.

Materials and methods

A cross-sectional study with retrospective data collection. Data were obtained from patient records with the aid of an instrument developed by the researcher.

Results

The number of patients with clinical symptoms in the type 1 diabetes mellitus group was substantially higher and more varied than the number in the multiple sclerosis group. During the conditioning period, the percentage of patients with complications increased progressively in the type 1 diabetes group, whereas the

multiple sclerosis group exhibited progressively lower levels of complications. The nature of these complications differed between the two groups.

Conclusion

Patients with multiple sclerosis and type 1 diabetes mellitus who undergo autologous hematopoietic stem cell transplantation demonstrate differences in their symptoms and implemented nursing practices.

Relevance to clinical practice

These results can help prevent the aggravation of complications by spreading awareness of the main clinical symptoms of conditioning when using antithymocyte globulin, reducing the therapy-related morbimortality, and predicting the need for nursing care.

Introduction

Autoimmune diseases are commonly associated with chronic morbidity, incapacity, as well as various, often fatal, physiological, motor, and cognitive damages [1]. Conventional therapies with immunomodulatory agents, immune suppressants, and anti-inflammatories are effective in controlling disease progression. However, people with serious and progressive conditions are often resistant to these therapies, which are rendered insufficient to avoid irreversible damage to the injured systems. Multiple sclerosis (MS) is a progressive demyelinating disease of the central nervous system, immune modulated by self-reactive T cells that induce inflammatory and immune events [2], resulting in the destruction of myelin and compromising the transmission of nerve impulses. It is more common in young adults, aged 20 to 40, who live in areas of the northern hemisphere with a temperate climate and affects two times as many women as men, and it is the main cause of incapacity in young adults [3,4]. In the case of type 1 diabetes mellitus (T1D), a chronic disease more common in childhood

and associated with hypoglycaemia, hyperglycaemia, and diabetic ketoacidosis, as well as long-term vascular sequelae [5], dependence on insulin therapy is life-long.

New therapeutic approaches for autoimmune diseases have been under development [6]. Among them, autologous hematopoietic stem cell transplantation (AH SCT) is a therapeutic alternative with promising global survival and disease progression-free rates, although still under evaluation [7].

With multiple sclerosis (MS), the hope is that a transplant will stabilize the progression of the disease [8-10]. In review about expanding indications for stem cell transplantation, patients with severe progressive MS disease were followed a median of 36 months (12-72 months), and all patients demonstrated clinical stabilization or improvement post AH SCT with a sustained clinical stabilization, free of treatments [11].

In the case of T1D, AH SCT offers the possibility of preserving residual β cells, and therefore facilitating endogenous mechanisms for these cells to regenerate, as long as treatment begins soon after diagnosis reconstituted to baseline levels approximately 2-3 months post AH SCT [12,13]. For both T1D and MS, the AH SCT procedure is similar, comprising: 1) mobilization of autologous hematopoietic stem cells (AHSCs), 2) high dose immunosuppressive conditioning regimen, followed by 3) infusion of AHSC [14]. Then the goal of conditioning regimen is to eliminate inappropriate immune responses. Available agents used in conditioning are nonselective, eliminating dysfunctional autoreactive immune responses and destroying adaptive immune responses. These agents have effects beyond cytoreduction of the immune system causing marrow aplasia, and gastrointestinal toxicity [15].

Although AH SCT is less aggressive than allogeneic transplantation, it still involves risks. Moreover, clinical symptoms may aggravate and negatively impact

success of treatment [16]. An important determinant of transplant success is the ability of patients to tolerate the conditioning regimen [17]. For example, the antithymocyte globulin (ATG) used in conditioning can cause various clinical symptoms, such as urticarial skin lesions, cutaneous rashes, headache, tremors, fever, and anaphylactic reactions, which can be usually suppressed or relieved with corticotherapy [18]. However, to date, no study has characterized clinical symptoms or nursing interventions required during AHSCT for autoimmune diseases. It is expected that diabetes patients present more exacerbated symptoms, once steroids are contraindicated due to pancreatic β -cell toxicity [19], and the induction of hyperglycaemia. Thus, we need to understand the clinical symptoms of this procedure, in order to plan and implement rapid and effective nursing interventions, thereby maximizing the probability of a successful therapy.

There are countless autoimmune diseases, which makes it difficult to obtain the global prevalence. Hence, existing data refer to each disease according to its region.

In Brazil, the mean prevalence of MS corresponds to 18/100,000 inhabitants, against 135/100,000 in Canada [20]. It represents the main cause of disability in young adults, with high levels of cognitive damage and mobility limitations [3].

Type 1 diabetes mellitus, on the other hand, is the most frequent chronic illness in childhood, with a prevalence of 2/1,000 inhabitants in the United States of America (USA) among white and non-Hispanic individuals, younger than 19 years of age [21]. In the long term, it can entail vascular sequelae, psychiatric disorders, hypoglycaemia, hyperglycaemia and diabetic ketoacidosis, common in childhood [22].

In view of the morbidity and refractoriness of autoimmune diseases to conventional treatments, new therapeutic approaches have been studied and employed [6], among

which AHSCT is an alternative that has been used since 1997 [23].

It is estimated that 3000 patients with autoimmune diseases have been submitted to AHSCT around the world [24]. The databases European Bone Marrow Transplantation (EBMT) and European League against Rheumatism (EULAR) contain treatment records involving AHSCT of patients from 172 institutions in 27 countries [16]. The authors considered the data extracted from the EBMT database as positive, concerning 900 patients submitted to autologous transplantation for autoimmune diseases, and demonstrated a disease-free global survival of 85%, survival free from disease progression corresponding to 43% and transplant-related mortality during the first 100 days corresponding to 5% in these patients [7]. Despite the benefits, however, this treatment entails risks and possibilities of clinical manifestations that aggravate and compromise the treatment success [16].

Translating this data to the autoimmune diseases evaluated in this study, the authors reviewed the literature to answer the question about how and why AHSCT is used to treat MS. They identified that the transplant was able to stop progression of the incapacities caused by the disease and that the EDSS score remained stable for 5 to 7 years after the transplant in 45% of the patients treated [8].

The authors reported AHSCT in 65 patients with T1D from three independent clinical trials, one based in Poland and two in China. They observed that six months after the transplant, 36 of the 61 patients did not need to use insulin any more. The authors concluded that the study suggested that remission of T1D is possible. However, complications associated with the transplant procedure were detected in about half of the study population, indicating that further knowledge about these complications with a view to nursing action planning is still warranted [25].

In recent cohort associated clinical outcome after AHSCT in T1D observed the insulin doses were progressively reduced post AHSCT, based on glycaemia levels, until complete suspension. Twenty-one patients became insulin free for median of 43 months (6-100 months) and three these patients are completely still free from insulin [13].

The place of study has pioneered AHSCT for T1D [26]. At the beginning of the study, nursing professionals, responsible for patient care, sought studies published in the literature to support their practice. The global scientific production in nursing about AHSCT for autoimmune diseases is scarce though, and no recommendations have been published about the nursing care that should be delivered to patients during this treatment. Therefore, we decided to contribute to the field, by describing the particularities in the treatment of each autoimmune disease, the main signs and symptoms identified in each group and the nursing care related to these manifestations, registered in the course of the transplantation period. This study can help to organize future transplantation centers for treatment of autoimmune diseases, enhancing the scientific and technological development for nurses' professional practice.

In this context, to the best of our knowledge, there are no earlier studies that describe nursing management of transplant conditioning-associated complications in autoimmune diseases. The available literature on the theme comprises mostly medical publications discussing the rationale of AHSCT in the treatment of autoimmune diseases and patient outcomes [2, 6,7,19].

This study aimed to identify clinical symptoms and nursing interventions during the period of AHSCT conditioning, including ATG, in MS patients who were receiving steroids and in T1D patients who were not receiving steroids. Our results will enable nurses to make plans and interventions, so as to optimize the success of the therapy in these populations.

Materials and Methods

Location, date and study design

This is a cross-sectional study, with retrospective data collection, from the records of patients with a diagnosis of T1D or MS undergoing their first AHSCT. The transplant procedures were performed in an immunological therapy inpatient unit at a university hospital in Ribeirão Preto, São Paulo State, Brazil, from January 2004 to December 2010.

Participants

We reviewed the records of patients with MS and T1D who had undergone AHSCT. According to eligibility criteria for AHSCT, MS patients aged 18 years or older, the therapeutic protocol for AHSCT eligibility in patients with MS is being over 18 years of age, having Expanded Disability Status Scale (EDSS) [27], scores up to 6.5, and being refractory or intolerant to first-line conventional therapies. Patients with T1D aged from 12 to 35 years and had less than 6 weeks of clinically diagnosed T1D, presenting positive anti-glutamic acid decarboxylase (GAD) antibody levels [19]. Both groups received conditioning regimen with cyclophosphamide and rabbit ATG (Figure 1). Twenty-one patients who had incomplete medical records were excluded from the analyses, resulting in a final sample size of 72 patients, divided in 23 with T1D and 49 with MS.

Procedure

One instrument was developed for registration of sociodemographic characteristics, clinical symptoms, and possible nursing interventions. A committee of specialists composed of three judges, were instructed by the researcher about the questionnaire, and validated the instrument regarding form and content. All suggestions were incorporated, and the following items were added: date of birth, type of central venous catheter, service of origin, duration of aplasia, and length of hospital stay. Next, patient data were collected from the medical records

archived at the documentation section of the university hospital, and the instrument was completed.

Data analysis

A database was created for each disease using Microsoft® Excel 2010, which was validated for double entry, independently. Contents were then transferred to SPSS®, version 16.0 for Windows® and data were analysed using descriptive statistics, presented as a percentage for nominal variables and as the minimum, maximum, average, and standard deviation (SD) for numerical variables.

Ethics

The Research Ethics Committee at the University Hospital of the Ribeirão Preto Medical School at the University of São Paulo, Brazil, approved the study, registered under protocol number 12008/2010 following resolution number 196/96 CNS/MS. Data were obtained by consulting patient records. Therefore, we asked the Research Ethics Committee to excuse the application of informed consent forms, under assurance of keeping patient identification confidential. The study was conducted following all ethical procedures, according to the resolutions in force in the country of origin.

Results

Demographic clinical profile

Files from 72 patients who underwent AHSCT were reviewed. Serum glycaemic values at time of diagnosis were available for 18 of the 23 T1D patients, and ranged from 120 to 600 mg/dl (391.1 ± 128.2 mg/dl). For the 49 MS patients, the EDSS ranged from 3.0 to 6.5 (5.3 ± 1.16). As shown in (Table 1), two patients with T1D were treated with steroids during conditioning, due to severe ATG-related complications. Conversely, two patients with MS had previous type 2 diabetes mellitus, and therefore were not treated with steroids before ATG infusion.

Table 1: Characteristics of patients with type 1 diabetes mellitus (n = 23) or multiple sclerosis (n = 49) undergoing autologous hematopoietic stem cell transplantation at a university hospital (Ribeirão Preto, Brazil, 2004–2010)

Variables	Type 1 diabetes mellitus	Multiple sclerosis
	n (%)	n (%)
Sex		
Female	7 (30%)	33 (67%)
Male	16 (70%)	16 (33%)
Age		
Range	Dec-35	19-60
Average (SD)	18.6 (± 4.4)	37.2 (± 10.38)
Median	16	38
Use of steroids in the transplant	2 (9%)	47 (96%)

Clinical symptoms of AHSCT

(Table 2) shows clinical symptoms observed during conditioning regimen with ATG in patients with MS, most of whom used corticosteroids, and in patients with T1D, most of whom did not receive corticosteroids. Compared to the MS group, patients with T1D had higher frequency and variety of symptoms.

The percentage of T1D patients with complications increased progressively during the conditioning period. More than 50% of T1D patients had nausea on every day of conditioning. Fever and vomiting were frequent in most of these patients during the first 4 days, and water retention occurred in 60% of T1D patients only during the first 2 days of conditioning. Among patients with T1D, 65% had shivering on the first day of conditioning, a symptom that grew less frequent over the following 4 days. Cutaneous rash was present from the first day and increased in prevalence over time, reaching 70% on last day of conditioning (Day -1).

Conversely, the percentage of MS patients with complications progressively decreased over the conditioning period, and the nature of complications differed from those in the T1D group. Water retention was detected in more than 70% of MS patients during the first 4 days of conditioning and still affected 51% on the

Table 2: Percentage of clinical symptoms presented during conditioning by patients with type 1 diabetes mellitus (n = 23) or multiple sclerosis (n = 49) treated with autologous hematopoietic stem cell transplants (Ribeirão Preto, Brazil, 2004–2010)

Clinical symptoms	Day of conditioning % of occurrence/disease									
	-5		-4		-3		-2		-1	
	MS	T1D	MS	T1D	MS	T1D	MS	T1D	MS	T1D
Fever (Tax ≥ 37.8°C)	8	83	4	83	4	65	4	35	2	78
Water retention	71	61	96	70	84	26	75	26	51	26
Shivering/ Tremors	6	65	2	52	2	22	0	9	0	13
Nausea	4	65	22	96	39	91	49	87	33	78
Headache	33	48	22	35	26	22	12	17	6	13
Vomiting	6	48	8	78	14	83	24	74	16	65
Lack of appetite/Anorexia	2	26	4	43	4	48	8	48	6	35
Cutaneous rash	6	22	31	22	35	35	29	61	18	70
Hiccups	6	4	22	4	20	9	4	4	4	4
Itchy skin	2	0	2	0	6	4	2	17	2	35
Diarrhoea	2	0	2	0	0	9	16	9	20	13

MS, multiple sclerosis; T1D, type 1 diabetes mellitus; Tax, axillary temperature.

Table 3: Percentage of records of nursing interventions in patients with type 1 diabetes mellitus (n = 23) or multiple sclerosis (n = 49) undergoing autologous hematopoietic stem cell transplants during conditioning with ATG (Ribeirão Preto, Brazil, 2004–2010)

Nursing interventions	Day of conditioning % of occurrence/disease									
	-5		-4		-3		-2		-1	
	MS	T1D	MS	T1D	MS	T1D	MS	T1D	MS	T1D
Water balance	100	100	100	100	100	100	100	100	100	100
Monitoring of vital signs	100	100	100	100	100	100	100	100	100	100
Use of a diuretic	73	70	92	65	86	30	78	30	51	30
Use of a 1 st choice antipyretics	20	87	14	87	20	74	10	74	6	78
Use of a 2 nd choice antipyretics	8	13	0	4	2	4	0	9	0	4
Blood sample	4	70	2	48	4	26	2	35	2	39
Interruption of ATG infusion	4	39	0	13	0	0	0	4	0	0
Reduction of the ATG speed	4	30	4	4	4	9	2	9	2	9
Use of an antihistamine	2	13	4	30	4	39	4	56	4	65
Use of hydrocortisone	2	9	0	0	2	0	0	0	2	0
ATG fractioning	2	0	6	22	4	13	4	22	4	22
Use of synthetic opioids	0	35	0	17	0	22	0	26	2	13
Optimization of anti-emetics	0	26	6	56	12	52	26	39	8	4
Taking the patient for a bath	0	0	0	0	0	0	0	0	0	4
Application of a cold compress	0	0	0	0	2	0	2,0	9	4	9

MS, multiple sclerosis; T1D, type 1 diabetes mellitus; ATG, antithymocyte globulin.

last day. Nausea worsened during conditioning for these patients, affecting 39%, 49%, and 33% of patients on days -3, -2, and -1, respectively.

Other clinical symptoms, such as edema, nasal obstruction, runny nose, seborrhoea, arthralgia, and intestinal constipation, were recorded at some point during the conditioning period in both groups, but at a percentage below 20%. Additional clinical symptoms were indicated with less frequency.

Need for assistance: nursing interventions

To determine need of nursing care arising from clinical symptoms during AHSCT in the two groups of patients, we reviewed the interventions performed in each case (Table 3). In 100% of cases, water balance and vital signs were verified and described on the vital sign charts or in the nurse medical records. Diuretics were administered in over 50% of MS cases on all days of conditioning. The speed of ATG infusion was reduced in at least one T1D patient, on every day of the entire conditioning period. In general, administration of the prescribed medications to reduce patient discomfort was an important practice

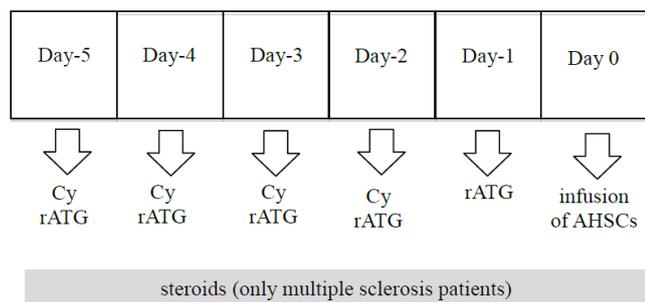


Figure 1: Scheme for AHSCT conditioning

Caption: Multiple sclerosis and type 1 diabetes patients receive cyclophosphamide (Cy) and rabbit anti-thymocyte globulin (rATG) in four consecutive days plus an additional dose of rATG on the day before autologous hematopoietic stem cell (AHSC) infusion. According to protocol, only multiple sclerosis patients receive prophylactic steroids to avoid conditioning-related adverse events.

performed by the nurses for both populations studied.

Discussion

We identify the most common clinical symptoms during conditioning of patients with MS and T1D undergoing AHSCT, as well as the care needs and nursing interventions arising from these symptoms. The nature, frequency, and intensity of the symptoms were distinct for the two groups of patients. The T1D group exhibited a large incidence and variety of symptoms, which increased progressively during the conditioning period. The percentage of MS patients with clinical symptoms decreased during the conditioning period. The main nursing interventions were reduction in the speed of ATG infusion and the administration of medicines to reduce discomfort.

Fever, shivering, and skin rash events were more common in patients with T1D during the conditioning period, compared to patients with MS. These observations are consistent with the fact that most MS patients used steroids, while the majority of T1D patients did not, since corticotherapy considerably reduces the toxicity related to the administration of ATG [16]. Fever events were quite frequent at the start of conditioning in patients with T1D. These events were associated with ATG infusions. Their frequency declined, again increasing on the last day. The

initial decline may be related to the optimization of ATG prophylactic medications and, when necessary, to the interruption or gradual reduction of the speed of ATG infusion. We believe that the increase in fever episodes observed on the last day of conditioning may be related to the start of the neutropenia phase and to the incidence of infections, because the immunoablative conditioning promotes immunosuppression [28].

It is important to remember that despite initial enthusiasm in using AHSCT in individual with severe autoimmune diseases, significant barriers still exist due to the toxic side effects of associated immunosuppression, that may promote opportunistic infections, thus limiting the potential curative benefits [29]

Skin rash, nausea, and vomiting episodes among T1D patients progressively increased during conditioning, which may be related to the total dose of ATG administered, and to the fact that the dose was distributed at increasing levels during conditioning [19]. Thus, the increase in reactions on the last day may have been a cumulative reaction to the various days of conditioning, which was not suppressed by the use of corticotherapy in T1D patients.

Noteworthy, the protocol for the conditioning regimen contained cyclophosphamide, an antineoplastic immunosuppressant with important emetic effect [30], which may explain the increased rates of vomiting during conditioning. A system that combines anti-emetics and nursing interventions is needed to alleviate such discomforts.

In patients with MS, we observed a higher frequency of water retention compared to patients with T1D. The water retention, which was treated with diuretics, may have been related to the impaired physical mobility presented by these patients, i.e., the limitation of independent and voluntary physical movement of one or more body parts, which can contribute to a reduction in venous return [31].

In addition, the use of steroids by this group may have been associated with greater retention of sodium and water [32], which can lead to pulmonary congestion, a serious situation that may be associated with risk of death.

Both groups exhibited high frequency of headache episodes on the first day of conditioning. The frequency of headache events decreased over the course of conditioning, perhaps due to fractioning of the ATG dose, to the association of the first- and second-choice synthetic Opioids and antipyretic medications with the antihistamine administered before drug infusions [16], and to development of tolerance to ATG. In general, the other clinical symptoms presented in this study affected patients less frequently. However, all of the observed clinical symptoms may precede complications that worsen with time and increase transplant-related mortality [7,16]. Therefore, it is important to anticipate these manifestations and plan interventions that allow for adequate control of the clinical picture, including the administration of conditionally prescribed medications based on the symptoms observed.

Considering the complications and nursing interventions identified in the populations studied, we observed that diuretics were administered when water retention occurred, with similar frequency for DM1 and MS patients.

Episodes of nausea and vomiting observed in MS patients occurred in proportion to the optimization of antiemetics administered. In this MS population, these events may have occurred less often and been more easily controlled because of other interventions, such as the use of corticosteroids, which potentialise the effect of the antiemetics and reduce the side effects of the conditioning. However, in DM1 patients, the frequency

of nausea and vomiting increased during conditioning; the optimization of antiemetics, although frequent, did not follow the same proportion as the occurrence of side effects. Perhaps because they had exhausted the available therapeutic arsenal or because it was not possible to aggregate other intensifying measures of the antiemetic power, such as the use of steroids.

ATG, as previously mentioned, can cause rash, fever and tremors as side effects. These events were recorded in at least one patient from the two study groups during every day of the conditioning, exception to the final days of treatment, during which no patient with MS had tremors or shivering. We identified various nursing interventions to manage these reactions, all of which were more common in DM1 patients, who also had a higher frequency of these reactions. Antihistamines were increasingly administered over the course of the conditioning in DM1 patients proportional to the occurrence of Cutaneous rash and might have reduced the occurrence of shivering and tremors. Other interventions, such as interrupting the ATG infusion or reducing the speed of the infusion or fractionating, were also identified, although at a lower frequency. The use of synthetic opiates was also identified in DM1 patients to manage regularly occurring reactions over the course of the treatment.

A critical prognostic factor for transplant-related mortality is the center's clinical experience, based on the number of patients receiving AHSTC for autoimmune diseases [7]. The so-called learning curve, in which experience in managing patients improves as the number of transplants increases, involves the entire transplant team. Thus, these findings should be helpful for transplant centers that have recently incorporated AHSTC therapy for autoimmune diseases, by providing knowledge of the probable signs and symptoms associated with the therapy and helping to plan interventions that have not yet been incorporated through practice.

Importantly, this is an observational study that aimed

to identify and describe the distribution of the studied events.

Study Limitations

It is not possible to overlook the possibility that other clinical symptoms and needs for nursing interventions were also present, but did not appear in this study because of possible underreporting. Another of the study's limitations is that it only characterised patients with multiple sclerosis or type 1 diabetes mellitus who had undergone AHSCT, as these were the pathologies most commonly treated at that particular immunology center, so the results cannot be generalized for all autoimmune diseases.

Conclusions

This study is the first report of a systematic investigation of the clinical symptoms and the need for nursing interventions in AHSCT for autoimmune diseases. We observed differences between MS and T1D patients regarding symptoms and implemented nursing interventions, indicating that approaches should be disease-specific. Our results can be used to help prevent the aggravation of complications by spreading knowledge about the main clinical symptoms arising during conditioning with ATG. Moreover, our study will help new transplant centers to manage possible complications and develop protocols for giving patients individualised attention, based on the disease to be treated. Thus, we hope to reduce nursing needs, to systematise the care given to patients and, as a result, to contribute to reduce transplant-related morbimortality.

Relevance to Clinical Practice

These results can help prevent the aggravation of complications by spreading awareness of the main clinical symptoms of conditioning when using antithymocyte globulin, reducing the therapy-related morbimortality, and

predicting the need for nursing care.

Contributions

Study design: LN, MCO, RCCPS; data collection and analysis: LN, MCO, RCCPS, and manuscript preparation: LN, LCC, PSF, MCO, CMG, RCCPS.

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