Evidence for Dry Eye Treatment in Hematopoietic Stem Cells Post-Transplantation

REVIEW

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Abstract

Introduction: Hematopoietic Stem Cell Transplantation (HSCT) is a treatment modality for oncology and hematological diseases genetically inherited or acquired. The morbidities and mortalities related to HSCT are evident in its different phases, such as the Graft Versus Host Disease especially on dry eye syndrome, one of the most complication of chronic phase, characterized as a multifactorial disease of the ocular surface. Several treatments may be directed to the dry eye and the consequences caused by it during the HSCT post-period.

Objective: To reveal the treatments for dry eye in patients after HSCT period.

Method: This is a literature integrative review performed by the SCOPUS databases, National Library of Medicine (PubMed); Web of Science and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Results: Of the 1,551 articles identified, there were 21 in the final sample. Regarding the treatments addressed, the most often used was found the cyclosporine 0.05%, followed by allogeneic and autologous drops.

Conclusion: There was no consensus identified as the best type of treatment for these patients. However, it is known that depend mainly on clinical features of chronic graft-versus-host eye on the post-transplantation situation.

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Keywords

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Sicca; Dry Eye Syndromes.

Introduction

The Hematopoietic Stem Cell Transplantation (HSCT) is a treatment modality used more frequently for oncology and hematological diseases genetically inherited or acquired [1-2]. The HSCT may occur by autologous transplantation, when Hematopoietic Progenitor Cells (HPC) are from the patient; allogeneic when HPC come from donors with compatible Human Leukocyte Antigen (HLA), related when they are of the same family and not related if it is not from an inbred donor; or syngeneic transplantation, when HPC are from identical twins [3].

The morbidities and mortalities related to HSCT are expressive in its different phases, from pre-transplantation and conditioning until the stage of post-transplantation recovery, in which these risks are magnified [2]. The graft-versus-host disease (GVHD) is presented as the main complication after HSCT, more frequently in allogeneic transplantations [1-3]. This can affect many organ systems and cause consequences to transplant patients, both in an acute form, in the first 100 days after HSCT as in the chronic form after this period [4].

One of the main complications of GVHD chronic phase is the dry eye syndrome, characterized by a multifactorial disease of the ocular surface that results in discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface resulting mucin dysfunction [5] of immune-mediated inflammation and fibrosis [6].

Dry eye syndrome is divided into two phases, which mechanisms include irritating environmental stimuli to ocular tissues during the first phase; and developments neuropathic, metabolic or inflammatory in the second phase with the consequent instability of the tear film, decreased tear secretion and increased evaporation or change in the composition of the tear [7-8].

Several treatments may be directed to the dry eye, to problems and complications caused by it during the HSCT post-period. Thus, it was decided to carry out an integrative literature review to highlight

the treatments for dry eye in patients after HSCT period to support discussions on the subject.

Method

It is an integrative literature review defined as a specific method to synthesize and evaluate evidence available in the literature to provide a greater understanding of specific research problem [9-10].

The following steps were created to check the critical scientific review: identification of the problem or research question; literature search, with inclusion of the definition of inclusion and exclusion criteria of the articles; evaluation of data for defining the information to be extracted from selected articles; critical analysis of selected studies and the presentation of the review [10].

In the origin of the study there was the following question: What are the treatments for dry eye in patients in transplantation of hematopoietic stem cells post-period?

The search in the databases occurred in June 2015, conducted by peers using proxy licensed by the Federal University of Rio Grande do Norte/Brazil (www.capes.ufrn.br/porta 3128) on different machines, at the same time and same network internet through the access to the following databases: SCOPUS, National Library of Medicine (PubMed); Web of Science and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

To search databases, the following keywords and their synonyms were used, identified in the Medical Subject Headings (MeSH): 1# (Hematopoietic Stem Cell Transplantation OR Transplantation, Hematopoietic Stem Cell OR Stem Cell Transplantation, Hematopoietic); 2# (Bone Marrow Transplantation OR Transplantation, Bone Marrow OR Grafting, Bone Marrow OR Bone Marrow Grafting OR Bone Marrow Cell Transplantation OR Transplantation, Bone Marrow Cell); 3# (Dry Eye Syndromes OR Dry Eye Syndrome OR Syndrome, Dry Eye OR Syndromes, Dry Eye); 4# (Therapeutics OR Therapeutic OR

Treatment OR Treatments OR Therapy OR Therapies). The crosses were performed with the use of Boolean operator as 1# AND 3# AND 4# and 2# AND 3# AND 4#.

Each database carried out a not controlled search to identify studies that by indexing differences would not be located using the controlled descriptor.

For a selection of the studies, the following inclusion criteria were used: full articles available on selected databases and articles addressing treatments for dry eye in patients of post-transplantation hematopoietic stem cells/bone marrow transplantation. Editorials, letters to the editor, abstracts, expert opinion, reviews, books, book chapters, theses, and dissertations were excluded.

After the search, studies were pre-selected with a careful reading of the titles and abstracts to identify the relationship with the guiding question of

the review and the adopted inclusion and exclusion criteria. Then, the reading of the pre-selected items was held in full by a pair of independent reviewers. Disagreements between reviewers were resolved by consensus or by the opinion of a third reviewer [11-12].

For the analysis and data extraction, a script that contains the following information was developed and used: a publication of the identification, location of the study, methodological aspects, adopted treatment, conclusions/limitations of the research [13]. The strategy used for critical evaluation of the studies was to identify the level of evidence and grade of recommendation. Articles were classified according to the level of evidence, to consider the research design of each study [14].

The electronic search process of studies in the databases resulted in 1,551 articles, of which 21

Figure 1: Synthesis of the studies selection process.

were selected to compose the review sample. The articles repeated in the database were excluded, as shown in **Figure 1**.

After reading the articles in full, the data have been described and presented in a **table 1** and **figure 2**.

Figure 2: The frequency of the types of treatment used in the studies. *Punctual cauterization, anakinra 2.5% autologous serum, Boston contact lenses.

Table 1. Characterization of the articles according to year, reference/database, place/language and method/level of evidence/grade of recommendation. Natal, 2016 (n = 21).

Year	Author/Database	Country/ Language	Méthod/Evidéce Level/Degree of Recommendation
2003	- Ogawa Y, Okamoto S, Mori T, Yamada M, Mashima Y, Watanabe R. et al. [15] - Scopus	- Japan - English	- Clinical essay study - Evidence II - Moderate degree
2012	- Pezzotta S, Fante CD, Scudeller L, Cervio M, Antoniazzi ER, Perotti C. [16] - Scopus/Web of Science	- Italy - English	- Clinical essay study - Evidence III - Moderate degree
2012	- Weng J, He C, Lai P, Luo C, Guo R, Wu S. et al. [17] - Scopus/Pubmed	- China - English	- Clinical essay study - Evidence III - Moderate degree
2010	- Ogawa Y, Dogru M, Uchino M, Tatematsu Y, Kamoï m, Yamamoto Y. et al. [6] - Scopus	- Japan - English	- Clinical essay study - Evidence III - Moderate degree
2008	- Wang Y, Ogawa Y, Dogru M, Kawai M, Tatematsu Y, Uchino M. et al. [18] - Scopus/Web of Science	- Japan - English	- Clinical essay study - Evidence III - Moderate degree

Year	Author/Database	Country/ Language	Méthod/Evidénc Level/Degree of Recommendation
2007	- Yoon KC, Jeong IY, Im SK, Park YG, Kim HJ, Choi J. [19] - Scopus	- South Korea - English	- Clinical essay study - Evidence III - Moderate degree
2013	- Sanz-Marco E, Udaondo P, García-Delpech S, Vazquez A, Diaz-Llopis M. [20] - Pubmed	- Spain - English	- Cohort study - Evidence IV - Moderate degree
2012	- Sabti S, Halter JP, Fränkl BCB, Goldblum D. [21] - Scopus/Web of Science	- Switzerland - English	- Cohort study - Evidence IV - Moderate degree
2012	- Na KS, Kim MS. [22] - Scopus/Web of Science/PUBMED/CINAHL	- South Korea - English	- Case-control study - Evidence IV - Moderate degree
2010	- Malta JB, Soong HK, Shtein RM, Musch DC, Rhoades W, Sugar A. et al. [23] - Scopus/Web of Science	- USA - English	- Case-control study - Evidence IV - Moderate degree
2009	- Dastjerdi MH, Hamrah M, Dana R. [24] - Pubmed	- USA - English	- Cohort study - Evidence IV - Moderate degree
2007	- Takahide K, Parker PM, Wu M, Hwang WYK, Carpenter PA, Moravec C. et al. [25] - Scopus	- USA - English	- Cohort study - Evidence IV - Moderate degree
2006	- Leite SC, Castro RS, Alves M, Cunha DA, Correa MEP, Silveira LA, et al. [26] - Scopus/Web of Science	- Brazil - English	- Case-control study - Evidence IV - Moderate degree
2006	- Lelli Júnior GJ, Musch DC, Gupta A, Farjo QA, Nairus TM, Mian SI. [27] - Scopus	- USA - English	- Cohort study - Evidence IV - Moderate degree
2006	- Rao SN, Rao RD. [28] - Scopus	- USA - English	- Cohort study - Evidence IV - Moderate degree
2015	- Yamane M, Ogawa Y, Fukui M, Kamoi M, Saijo-Ban Y, Yaguchi S. et al. [5] - Pubmed	- Japan - English	- Case study - Evidence VI - Weak degree
2014	- Grob S, Dana R. [29] - Cinahl	- USA - English	- Case study - Evidence VI - Weak degree
2012	- Yaguchi S, Ogawa Y, Kamoi1 M, Uchino M, Tatematsu Y, Ban Y. et al. [30] - Scopus	- Japan - English	- Case series study - Evidence VI - Weak degree
2007	- Jacobs DS, Rosenthal P. [31] - Scopus/Web of Science	- USA - English	- Case series study - Evidence VI - Weak degree
2007	- Chiang CC, Lin JM, Chen WL, Tsai YY. [32] - Scopus	- China - English	- Case study - Evidence VI - Weak degree
2001	- Ogawa Y, Okamoto S, Kuwana M, Mori T, Watanabe R, Nakajima T. et al. [33] - Scopus/Web of Science	- Japan - English	- Case study - Evidence VI - Weak degree

Results

Out of 1.551 articles identified, there were 57 included in the first selection (title and abstract reading). Of them, 33 were excluded because they were repeated in the bases. Thus, 24 were elected to reading the full text, however, three were excluded because they did not fit the inclusion criteria and answer the guiding question adopted. Thus, the final review sample was composed of 21 studies of selected for reading in its full.

Table 1 shows the consolidated of the studies included in the review. Regarding the country of such studies, it was found that seven (33.33%) were developed in Japan, followed by six (28.57%) in the United States of America (USA), two (9.52%) in China, two (9.52%) in South Korea, one (4.76%) in Brazil, one (4.76%) in Italy, one (4.76%) in Switzerland and one (4.76 %) in Spain. According to the language and year of publication, it was found that all articles (100%) were in English, and ten (47.61%) were published in the last five years.

As for the method used, six articles (28.57%) used the clinical essay, six (28.57%) were cohort studies, four (19.04%) were case studies, three were case-control (14.28%) and two were series of cases (9.52%). Concerning to the evidence level/degree of recommendation, fifteen articles (71.42%) showed evidence level III and IV and a moderate degree of recommendation and the rest had evidence level VI and low degree of recommendation. (**Table 1**)

Figure 2 represents the consolidation of the types of treatments used in the studies. It was shown more frequently to the use of Cyclosporin 0.05% in all four studies (19.04%), followed by allogeneic drops in two studies (9.52%) and two other autologous drops (9.52%). Other therapeutic appeared only in one study each (4.76%).

Discussions

The identification and analysis of the studies' components in this review identified the scientific evidence for the treatment of dry eye in patients after HSCT. Several dry eye treatment strategies were found, such as the use of topical cyclosporine, linoleic acid, omega-3 fatty acids, androgens, some types of tetracyclines and steroids [34]. However, a consensus to define the best treatment for dry eye in the reviewed studies has not identified. The choice of appropriate treatment will depend in particular clinical characteristics presented in the post-transplantation with chronic ocular graft-versus-host.

The use of cyclosporine 0.05% occurred more frequently among the studies (19.04%). On this treatment, other studies report that the drug acts as an immunomodulatory agent that blocks the proliferation of T cells and receptor signal transduction [35-36-37-38]. When T cells are activated on the ocular surface in dry eye syndrome, corneal sensitivity is decreased, which results in an exacerbation of dry eye caused by the decrease in reflex tearing, which can cause damage to the ocular surface [35-39- 40]. Thus, cyclosporine results in a reduction of inflammation and an increased tear production [41].

Other studies have demonstrated the efficacy of topical cyclosporine 0.05% in treating dry eye [35-42-43] and corroborated the findings of this review. On the other hand, a survey reveals that in Japan, the use of cyclosporin A is not an approved treatment for dry eye. [44]

Other therapeutic options used are the allogeneic and autologous drops. A cohort study of patients with severe ocular disorder demonstrated the safety of the use of allogeneic serum eye drops for dry eye treatment since there are no universal consensus criteria for selecting patients suitable for autologous blood donation. It is known that therapeutic option is contraindicated in elderly patients, children, and patients with certain disorders. It is noteworthy that the serum from a patient may contain potentially

harmful drug metabolites, as well as the presence of pro-inflammatory mediators [45].

The use of diquafosol ophthalmic solution 3% and rebamipide was reported in a study conducted in Japan as new pharmacological agents for the treatment of dry eye [44]. The solution diquafosol 3% ophthalmic stimulated tear and mucin secretion on the ocular surface directly and rebamipide favored mucin secretion by goblet cells attached directly to the conjunctiva of the eye surface. The eye drops treat selectively the layer of the tear film and increases their stability, making them effective for the treatment of dry eye [46].

The drops tacrolimus 0.03% were also shown as a form of treatment for dry eye. Research reported that tacrolimus, also known as FK506, is an immunosuppressive drug that inhibits the immune response mediated by T cells, about 10 to 100 times more potent than cyclosporine [47].

A retrospective study also described the effectiveness and safety of topical tacrolimus ointment 0.02% in patients with GVHD with chronic eye inflammation of the ocular surface but reported that the concentration of tacrolimus for the control of ocular diseases caused by immune system even has been established [47]. When investigated the efficacy of topical ophthalmic drops of 0.03% tacrolimus to the treatment of dry eye in GVHD in resistant or intolerant patients to topical cyclosporine 0.05%, there is evidence that these resistant or intolerant patients to Cyclosporin can be effectively treated by the use of tacrolimus 0.03% [20].

Regarding the use of rich autologous plasma drops in growth factors, its effect is similar to the use of allogeneic eye drops, as mentioned above. However, the growth factors present also contribute to the renewal of the corneal epithelial cells because they are involved in the proliferation, differentiation, migration, and apoptosis [16-48].

Another therapeutic measure identified was occlusion of lachrymal puncta. As shown by the study, caps are placed on the upper or lower points to

occlude the opening to decrease the output of the few tears produced, increasing the retention time, and thus moisture outside the eye [49].

Mesenchymal stromal cells act as sulfasalazine, making them remedial once limited to tissue destruction and enhance the repair in various diseases [50]. Thus, these cells protect the ocular surface inflammation by suppressing the dry eye disease [51].

The use of Tranilast® inhibits the production and release of inflammatory mediators, eye cytokines and inhibits collagen synthesis. Although not widely studied, a study has shown that its use improved tearing reflection. Moreover, the topic Tranilast® can act in preventing fibrosis of the surface around the holes of the tear ducts near the exterior ocular surface, where the intact acini of the lacrimal gland are present in the light phase of dry eye. Therefore, this therapy is effective in the initial stage of the dry eye [6].

Treatment with a gas-permeable scleral lens allows control of evaporation, acting as a permeable protective covering gas to the cornea and conjunctiva. The protection against evaporation and mechanical trauma to the eyelid blinking allows the regeneration of corneal defects in the presence of appropriate gas infusion [25]. Another study that evaluated the use of this lens for the severe dry eye by aqueous deficiency reported benefits for rehabilitation of dry eye [52].

The umbilical cord serum eye drops also recommended as a treatment for dry eye is targeted with many advantages over the peripheral blood serum. It contains higher concentrations of neurotrophic growth factors and promotes proliferation and differentiation of corneal epithelium [53-54].

Another form of treatment used was the association between FK506 and corticosteroids, which has proven effective in the treatment of severe dry eye in patients with chronic GVHD. The beneficial effect of corticosteroids reported on the findings [33] corroborates those described in other studies,

the use of which is recommended especially when there is a proliferation of signs of inflammation [55].

Another review article reported that corticosteroids continue to be essential for the control of chronic GVHD. Systemic use is the base of treatment of acute exacerbations of chronic GVHD. However, there is insufficient data to demonstrate the efficacy of topical steroids in chronic GVHD eye [56].

Conclusion

In this review, various types of treatments used for dry eye in patients after HSCT became clear. However, there is no consensus as to the best type of treatment for these patients. It is known that the appropriate therapy will depend primarily on the clinical characteristics presented when in a post-operative situation with chronic graft-versus-host eye.

Evidence identified demonstrated a degree of recommendation from moderate to weak, which suggests the urgent need for studies with designs that have a high level of evidence and the degree of strong recommendation to be stronger evidence established for the treatment of dry eye in the types of patients covered in this review, considering the high frequency of this syndrome.

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