Acute and chronic Graft-versus-host disease after hematopoietic stem cell transplantation

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Abstract

graft-versus-host disease (GVHD) is one of the main complications of hematopoietic stem cell transplantation, affecting about 50% to 80% of the patients. Acute GVHD and its clinical manifestations are discussed in this article, as well as the new NIH criteria for the diagnosis and classification of chronic GVHD. Therapy for both chronic and acute GVHD is an important field of discussion, as there is no proven superiority for the majority of therapies used after primary treatment has failed. Hence, this review is meant to be a useful consultation tool for hematologists dealing with this complex transplantation procedure complication.

Keywords: Graft versus host disease, hematopoietic stem cell transplantation.

Introduction

Approximately 50% of the hematopoietic stem cell transplant (HSCT) recipients develop Graft-versus-host disease (GVHD) with varying degrees of severity and mortality, which can affect 20% of transplanted patients[2]. The published data on the incidence and severity of chronic GVHD are heterogeneous, but it is estimated that 60-80% of long-term HSCT survivors have some degree of disease activity with immunosuppressive therapy indication for long periods after transplantation[3].

Acute graft versus host disease (aGVHD)
Diagnosis

In 2005, the National Institutes of Health (NIH) published a consensus document aimed to address several aspects of the diagnosis, classification and treatment of chronic GVHD (cGVHD)[4]. Therefore, it was possible to establish clear distinctions differentiating these two entities through a better characterization of cGVHD. After 2005, patients with the clinical syndrome before the D+100 were considered as having the "classic acute GVHD" and when it appeared after D+100, it was classified as "late, persistent or recurrent GVHD"[4].

Epidemiology and risk factors

Several studies have identified the following risk factors for increased incidence of GVHD: HLA disparity between donor and patient (HLA mismatch, or unrelated donor, donor and patient of different sexes (especially female donor for male recipient); intensity of conditioning regimen; prophylactic regimen used, source of progenitor cells (peripheral blood or bone marrow > cord)[5].

aGVHD: clinical presentation

The skin, gastrointestinal tract and liver are the main target organs affected in aGVHD. The first organ usually affected is the skin, in the form of a maculopapular rash in areas of the neck, ears, shoulders (cephalic end), palms and soles. It can disseminate throughout the body surface (BS) becoming confluent and causing pruritus, sometimes painful. In the severe form, it resembles Stevens-Johnson syndrome with bullous lesions secondary to epidermal necrosis. Regarding the gastrointestinal tract (GIT), the involvement of the upper and lower portions is often observed. The clinical presentation ranges from nausea, vomiting and anorexia to diarrhea and abdominal pain[6]. The involvement of the lower GIT is usually severe, with diarrhea accompanied or not by hematochezia and abdominal cramps. The diarrheal volume may be greater than 10 liters/24h, with an aqueous pattern and frequently progresses to bloody stools[7]. Liver damage caused by aGVHD usually occurs in patients with signs of skin and/or GIT aGVHD. The liver is rarely moderately or severely

affected without involvement of other organs. Liver function tests (LFTs) show alterations, with elevated total bilirubin (predominantly the conjugated form) and alkaline phosphatase levels[8].

aGVHD STAGING AND CLASSIFICATION

The first aGVHD staging system was published in 1974 by Glucksberg et al.[6]. Each organ was evaluated separately according to the clinical/laboratory involvement stage and the resulting data provided an overall grading of GVHD (Tables 1 and 2)[6,9].

The initial grading of aGVHD is important to assess response to treatment or prophylaxis, in addition to correlating it to overall survival after hematopoietic stem cell transplantation (HSCT)[10]. Patients who develop the moderate or severe forms of the disease (overall stages II-IV) have a significantly higher mortality rate than those with the mild form. The moderate and severe forms occur in approximately 40% of all allogeneic HSCTs and without effective prophylaxis, it becomes a severe complication[11,12].

aGVHD TREATMENT

The choice of the initial therapy for aGVHD depends on the organs involved, symptom severity, the prophylactic regimen used and, to some extent, the importance of the GVT effect in that particular clinical setting.

aGVHD grade I

The treatment of aGVHD grade I (mild) should comprise the optimization of the prophylactic regimens, for instance, adjusting cyclosporine or tacrolimus levels to therapeutic serum levels, use of topical agents (corticosteroids or tacrolimus) and adjuvant therapy, such as antihistamines to control pruritus. There is no indication for systemic immunosuppression[13].

aGVHD grade II-IV

aGVHD patients with grade II to IV should start treatment with methylprednisolone (MP) at a dose of 2 mg/kg/day of prednisone or equivalent. Its effect is related to lympholytic and anti-inflammatory properties and has been used as standard therapy for several decades[14]. At the same time, the drug used in the prophylaxis (CSA or FK) must not be interrupted. In a retrospective study of 733 patients, the use of MP at a dose of 1 mg/kg/day for the less severe forms of the disease (aGVHD grade II) increasing it to 2 mg/kg if there is symptom worsening after 72 hours, did not bring an adverse impact on survival rate and allowed the use of MP doses that were 50% lower than the standard ones[15].

"Nonabsorbable" glucocorticoids (beclomethasone and budesonide) have been used in the treatment of mild GVHD in the upper or lower GIT (500-1000 mL/24 h) as adjunctive therapy to systemic corticosteroid therapy[16,17]. Only approximately 60% of patients respond to the initial treatment with systemic corticosteroids and many of these responses are not long-lasting[18].

SECOND-LINE TREATMENT FOR GRADE II-IV aGVHD

If aGVHD progresses within the first 3 days (72h) or if there is no improvement after 5-7 days of the onset of initial therapy with MP 2 mg/kg/day plus calcineurin inhibitor, the disease is considered cortico-refractory and a second-line treatment is indicated. Cortico-refractory aGVHD has a poor prognosis and the second-line therapies have high failure rates. The overall survival of this population at one year is about 20-30%[19].

TABLE 1. aGVHD staging per organ			
Staging	Skin findings	Liver findings	Intestinal findings
+	Maculopapular exanthema in <25% of body surface	Bilirubin: 2-3 mg/dL	Persistent diarrhea (500-1000 mL) and nausea
++	Maculopapular exanthema in 25-50% of body surface	Bilirrubina: 3-6 mg/dL	Diarreia (1000-1500 mL)
+++	Generalized erythroderma	Bilirrubina: 6-15 mg/dL	Diarreia > 1500 mL)
++++	Desquamation and blisters	Bilirrubina > 15 mg/dL	Pain with or without obstruction

TABLE 2. Overall graduation of aGVHD				
Degree/stage	Skin	Liver	Intestine	Functional disorder
0 (None)	0	0	0	0
I (Mild)	+a++	0	0	0
II (Moderate)	+a+++	+	+	+
III (Severe)	++a+++	++a+++	++a+++	++
IV (Life-threatening)	++a++++	++a++++	++a++++	+++

Few prospective studies have been published with 2nd-line agents and due to their heterogeneity, the results are difficult to compare. As the superiority of one agent over the others has not been demonstrated, the choice should be directed by factors such as the effects of any prior therapy, interaction with other drugs (including those used for prophylaxis) availability, cost and the health team's familiarity with its use. In general, the mean rate of response of these agents is 50% with a median survival of at least 60% at six months after treatment, many without evidence of active aGVHD [19,20]. The results obtained with the most commonly used agents are summarized below.

Mycophenolate mofetil (MMF)

MMF acts by inhibiting the synthesis of guanosine triphosphate, of which lymphocytes depend for proliferation, therefore being preferentially affected. It was one of four drugs used in the phase-II, randomized BMT CTN 0302[21] as the initial therapy together with MP. However, the addition of MMF to the MP in a subsequent, phase III, randomized, double-blind study, with a similar endpoint to the previous study (BMT CTN 0802) did not significantly alter aGVHD-free survival or the cumulative incidence of chronic GVHD at 12 months[22]. Retrospective studies show RC/RP ratios of up to 77% at 6 months, thus being an option to be considered in these cases[23-24].

Extracorporeal photopheresis (ECP)

The ECP consists of the irradiation of circulating lymphocytes in peripheral blood collected by apheresis and incubated with 8-methoxypsoraleno with phototherapy (UV-A). The ECP induces apoptosis in all lymphocytes (including activated T-cells) within 24 hours after the treated blood is returned. The reinfusion of these cells and subsequent phagocytosis by antigen-presenting cells (APCs) can regulate immune homeostasis by modulating cytokine production and tolerance induction by expanding the regulatory component of T lymphocytes (Treg) observed in murine models[25]. A prospective, phase II study was published in 2006, which included 59 patients with cortico-refractory or cortico-dependent aGVHD. Complete responses (CR) were observed in 82% of patients with skin involvement, 61% with hepatic GVHD and in 61% of cases with gastrointestinal disease [26]. Associated opportunistic infections were not reported, or loss of the GVT effect with higher relapse rate of malignancy, as it is an immunomodulatory therapy, not an immunosuppressive one[26].

Antithymocyte globulin (ATG)

Polyclonal or monoclonal antibodies are the worldwide most often used second-line agents. There is considerable experience with ATG, which has been used for more than three decades. However, the literature describes responses in 20 to 50% of cases, especially in skin GVHD[27,28].

Antibodies against IL-2 receptor

The α subunit (CD25) of interleukin-2 (IL-2) receptor is expressed predominantly in activated T lymphocytes. Basiliximab is a chimeric antagonist of IL-2 receptor and has shown promising results by achieving 71% of CR in a phase I study published in 2002 with 17 patients[29]. Funke et al. published in 2005 their experience in 34 patients with refractory aGVHD grade III-IV, with approximately 80% of response and 30% overall five-year survival[30].

Tumor necrosis factor antagonists (Infliximab, Enbrel)

Mainly used in situations of refractory aGVHD involving the gastrointestinal tract, several series have been published, most of them by Couriel et al.[31], who found an overall response of 70% in 37 patients with aGVHD. A complete response in 62% of patients was seen with the use of this agent associated with corticosteroids and tacrolimus as the first line[31].

Chronic graft versus host disease (cGVHD)

cGVHD is a major cause of morbidity and late mortality of allogeneic HSCT occurring in 30-70% of patients[32-34]. The cumulative incidence at 2 years of chronic GVHD, defined according to the National Institute of Health (NIH) after allogeneic HSCT with bone marrow or peripheral blood from related or unrelated donors, in a study that evaluated the risk factors for aGVHD and cGVHD was 34% (32%-35% range)[35]. The clinical manifestations of cGVHD may be restricted to a single organ or can be disseminated, with profound impact on quality of life[36]. The pathophysiology of cGVHD involves inflammation, cell and humoral immunity and fibrosis[36].

This immunological complication resembles autoimmune diseases with clinical manifestations of collagen vascular diseases, such as oral lichen planus, keratoconjunctivitis sicca, xerostomia, polyserositis, esophagitis and esophageal stricture, vaginal ulceration and stenosis, intrahepatic obstructive liver disease, obstructive pulmonary disease, scleroderma, fasciitis and myositis. Clinical manifestations usually appear in the first two years after transplantation[36].

Diagnosis of cGVHD and differentiation from aGVHD

As the 2005[4] consensus criterion, the consensus of 2014[36] recognizes two main categories of GVHD (acute

and chronic). aGVHD includes (1) classical aGVHD that occurs before 100 days after HSCT, without diagnostic or distinct signs of cGVHD; (2) late aGVHD, persistent or recurrent: shows changes of the classical aGVHD, but no diagnostic or distinct signs of cGVHD and occurs after 100 days of HSCT. In the 20054 criterion, the cGVHD included (1) classic cGVHD without characteristics of aGVHD; (2) overlap syndrome, in which the characteristics of aGVHD and cGVHD appear concomitantly.

Better clarification of the overlapping cGVHD subcategory definition has been provided in the 201436 criterion. It is the clinical manifestations, and not the time of symptom onset after HSCT, which determine if the GVHD is acute or chronic. Diagnostic signs and symptoms are manifestations establishing the presence of cGVHD without the need for further tests or evidence of other affected organs, generally represented by lichenoid lesions or sclerosis. Distinct signs and symptoms are not commonly found in aGVHD, but are not considered sufficient to establish an accurate diagnosis of cGVHD (e.g., vitiligo, ocular sicca)[36].

Common signs and symptoms are observed in both aGVHD and cGVHD[36]. For the diagnosis of cGVHD, it is necessary to have at least one diagnostic manifestation of cGVHD or at least a distinct manifestation confirmed by appropriate biopsy or laboratory testing, or evaluation by a specialist (ophthalmologist gynecologist) or radiological images, in the same or another organ, unless otherwise stated[36].

Clinical organ scoring system

the organ scoring system of the 20054 consensus has been modified based on the available evidence, or lack thereof, as well as by the questions raised by researchers and clinical practice[37]. The local organs most often considered for the scoring system include the skin, mouth, eyes, GIT, liver, lungs, joints, fascia and genital tract. Each organ or site is scored on a 4-point scale (0-3) with 0 representing no involvement and 3 representing severe impairment. Several studies have shown that the overall severity at diagnosis, according to the NIH 2005 criteria is associated with the overall survival and TRM and some scoring elements have been validated with quality of life measures[37]. The light, moderate and severe classification reflects the degree of impact and functional impairment in each organ or site, due to cGVHD.

Treatment of chronic GVHD (cGVHD)

Mild asymptomatic cGVHD can be often treated with local therapy (e.g., topical corticosteroids for skin involvement). In patients with three or more affected organs or a score of 2 or greater in any organ, systemic treatment should be considered. Although associated with lower recurrence rate, cGVHD remains a major cause of late morbidity and mortality in HSCT recipients[38]. The frequent involvement of several organs and pleomorphic clinical picture of this complication require multidisciplinary management, which includes, in addition to several medical specialties, nutritional counseling, physical and psychological therapy, dental, social and occupational therapy[39]. Sporadic quality of life assessment is recommended in patients with cGVHD, representing an effective treatment response tool[40].

Treatment of mild cGVHD

The symptomatic mild form should generally be treated with topical agents only, but some data should be considered, such as the underlying disease (malignant or non-malignant) and its status at transplantation, presence of high-risk factors for mortality associated with cGVHD (thrombocytopenia, progressive disease onset)[39]. Moreover, mild cGVHD manifestations that do not respond satisfactorily to topical treatment, such as hepatic cGVHD or fasciitis can be treated with corticosteroids alone[39].

Treatment of moderate to severe cGVHD

First-line systemic treatment

The criteria defined in the NIH Consensus for systemic treatment include: score >2 in an organ, involvement of three or more organs and mild cGVHD with high-risk characteristics (platelet count <100,000/mm^3 and use of immunosuppressants at the diagnosis of cGVHD)[4].

The initial standard systemic therapy consists of prednisone 1 mg/kg/day and cyclosporine (CSA) at a dose de10 mg/kg/day in 2 divided doses, administered orally, with CSA dose adjusted by the plasma level[39]. Tacrolimus has also been used to replace cyclosporine, with similar responses. The withdrawal should be initiated, if there is a stable response or manifestations after two weeks of treatment, reducing the dose of prednisone by 25% per week until, at 6 to 8 weeks, the target dose of 1 mg/kg on alternate days is reached, which must be maintained for 2 to 3 months in cases of incomplete response, severe forms or presence of risk factors. Subsequently, it must be reduced by 10 to 20% per month until the total withdrawal at 9 to 12 months according to patient tolerance[39]. The main drugs used in the first-line treatment are listed in Table 2.

Cortico-refractory cGVHD is defined by progression of the disease after 2 weeks of therapy (prednisone at a dose of 1 mg/kg/day); stable disease with prednisone use

(>0.5 mg/kg/day) for 4-8 weeks or inability to reduce the prednisone dose to below 0.5 mg/kg/day[49]. Indication for second-line treatment include worsening of cGVHD manifestations in a primarily involved organ, the absence of any response after one month of treatment, or inability to reduce the prednisone dose to below 1 mg/kg/day within 2 months[39].

Second-line systemic treatment

Several therapeutic options have been tested in patients with cGVHD refractory to first-line treatment. The choice of treatment, therefore, depends on the chosen medication toxicity pattern, the organs involved, the patient's preference and the availability of the transplant center[39].

The main agents used in the treatment of refractory cGVHD are summarized below.

EXTRACORPOREAL PHOTOPHERESIS (ECP)

Extracorporeal photopheresis (ECP) is an immuno-modulatory cell therapy, in which mononuclear cells are collected and irradiated with UV in the presence of a photo-sensitizer, 8-methoxypsoralen. It is postulated that during the ECP, in addition to lymphocyte apoptosis, inhibition of pro-inflammatory cytokine production occurs, with increased production of inflammatory cytokines, reduction of stimulation of effector T cells, changes in dendritic cell function and activation of regulatory T cells, favoring the energy of T41 cells. ECP has been widely used as second-line therapy for mucocutaneous cGVHD, with complete response rates above 80% and significant improvement in cGVHD with sclerosis. Recently, Flowers et al.[41] reported results of a prospective, randomized, double-blind phase II trial in 95 refractory patients, dependent or intolerant cGVHD, treated with FEC in combination with conventional immunosuppressive agents. There was no significant difference in the total skin score (TSS) improvement at week 12; however, there was a higher rate of complete and partial responses of cGVHD in the skin at the ECP arm in comparison to the control arm; more patients in the ECP arm had at least a 50% reduction in the steroid dose and at least a 25% reduction in total skin score (TSS) at week 12[41]. In the extension study, the group submitted to ECP had a significant improvement in the skin score at week 24, when compared to the group without ECP[42]. ECP has the advantage of not increasing the risk of infection and having few adverse effects.

MYCOPHENOLATE MOFETIL

this immunosuppressant, of which prodrug, mycophenolic acid, interferes with purine synthesis and produces a cytostatic effect on T and B lymphocytes, is often used in rescue therapy for refractory cGVHD. The overall response rates vary between 23 and 79% of patients in several case series[43]. Lopez et al.[44] reported in 2005 on the largest series of cases with 35 patients with cortico-refractory cGVHD. There was 79% overall response and 35% complete responses. Seventy-three percent of patients were able to discontinue immunosuppression after the addition of this drug and only 3% of treated patients discontinued it due to toxicity.

MAMMALIAN TARGET OF RAPAMYCIN (mTOR) INHIBITORS: SIROLIMUS

These drugs combine immunosuppressive effects and antiproliferative properties in fibroblasts and smooth muscle cells. There are reports of antineoplastic effects. Sirolimus and everolimus bind to mTOR to form a complex that induces cell cycle arrest in G1 by inhibiting DNA transcription and translation and protein synthesis. In contrast to calcineurin inhibitors, these drugs promote the generation of regulatory T cells[45].

Jurado et al.[46] published a series of cases in 2007 of 47 patients using sirolimus as secondary treatment in combination with other drugs. The overall response rate was 81%, with 38% complete responses; 47% of these patients discontinued immunosuppression and the overall survival was 57% in three years. Couriel et al.[47] also reported their experience with sirolimus as rescue therapy in 35 patients with skin and visceral cGVHD. There was an overall response of 63%, being 17% complete and 34% of patients discontinued immunosuppression. The overall survival at 2 years was 41%.

RITUXIMAB

Rituximab binds to the extracellular portion of the CD20 surface molecule and induces apoptosis and cell death mediated by complement or direct of neoplastic B or normal cells[48]. Cutler et al.[49] carried out the first phase I-II prospective study reporting the efficacy of rituximab (375 mg/m^2) in 21 patients receiving a total of 38 cycles. Objective responses were observed in 70% of patients, allowing a significant reduction in the steroid dose. Patients with skin or musculoskeletal manifestations of cGVHD showed better responses. VonBonin et al.[50] used lower doses of 50 mg/m^2/week for 4 weeks in 11 patients with refractory cGVHD and 2 with post-transplantation autoimmune disorders (immune-thrombocytopenia and glomerulonephritis) observing an overall response rate of 69%, including 3 patients (23%) with complete remission (CR). Recently, Arai et al.[51] published a prospective randomized study comparing imatinib and rituximab.

Significant clinical response was observed in 9 of 35 (26%, 95%CI: 13-43%) participants randomized to imatinib and 10 of 37 (27%, 95% CI: 14-44%) randomized to rituximab.

IMATINIB

Imatinib, an inhibitor of several kinases and successfully used in positive BCR-ABL malignancies, has recently been used for the treatment of cGVHD based on its antifibrotic activity by blocking platelet-derived growth factor receptor (PDGFR) and Transforming Growth Factor beta (TGFß)[51]. The main adverse events with the drug include hematologic toxicity, fluid retention and dyspnea, which lead to drug discontinuation in 15 to 25% of patients. Responses between 50% and 80% were observed in patients with skin, ocular and bowel involvement in cGVHD for a period of six months. In cases of pulmonary involvement, the best responses were observed in mild bronchiolitis[51,52].

LOW-DOSE METHOTREXATE (MTX)

Methotrexate is an antimetabolite, which at low doses has immunomodulatory and anti-inflammatory properties. Giaccone et al.[53] reported 71% (10/14) of control of refractory cGVHD, with a decrease in prednisone dose to <1 mg/kg/every other day, with a long-term regimen of 7.5 mg/m²/week of MTX in patients with refractory cGVHD, with five affected sites, on average, survival of 92.8%, median follow-up of 25 weeks and no toxicity grades III/IV. A more recent series of 27 children with refractory GVHD (17 with the chronic form), treated with MTX doses of 3-10 mg/m²/week showed 58.8% overall response for cGVHD with prednisone withdrawal in 7/17 and decrease (dose <0.4 mg/kg) in 9/17 patients[54].

RESUMO

Doença do enxerto contra o hospedeiro aguda e crônica após transplante de células-tronco hematopoiéticas

A doença do enxerto contra hospedeiro (DECH) é uma das principais complicações do transplante de células-tronco Hematopoéticas, acometendo cerca de 50% a 80% dos pacientes. A DECH aguda e suas manifestações clínicas são discutidas neste artigo, bem como a classificação revisada do NIH para diagnóstico e classificação da DECH crônica. A terapêutica para DECH aguda e crônica é um importante campo de discussão uma vez que não há superioridade comprovada para a maioria das terapêuticas utilizadas após o tratamento primário. Assim, esta revisão pretende ser instrumento de consulta para hematologistas transplantadores que lidam com esta complexa complicação do procedimento.

Palavras-chave: Doença do enxerto contra hospedeiro, Transplante de células-tronco hematopoéticas.

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ANAIS DO XX CONGRESSO BRASILEIRO DA SOCIEDADE BRASILEIRA DE TRANSPLANTE DE MEDULA ÓSSEA | REV. ASSOC. MED. BRA. 2016; 62 (SUPPL. 1):44-50

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