

ACUTE AND CHRONIC GRAFT VERSUS HOST DISEASE AFTER HEMATOPOIETIC STEM CELL TRANSPLANT

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ABSTRACT

Graft versus host disease is one of the main complications of Hematopoietic stem cell, involving about 50% to 80% of the patients. Acute GVHD clinical manifestations and therapy is discussed, as well as new NIH criteria for the diagnosis and classification of chronic GVHD. Therapy for both refractory chronic and acute GVHD is an important field of discussion once there is no superiority for the majority of the agents after primary therapy has failed. Hence, this review is meant to be a useful tool of consultation for clinicians who are dealing with this complex complication.

Key words: graft versus host disease, hematopoietic stem cell transplant

INTRODUCTION

Nearly 50% of Hematopoietic Stem Cell Transplant (HSCT) patients develop graft versus host disease (GVHD), some of them severe, leading to mortality of up to 20% [1]. Published data on incidence and severity of GVHD are heterogeneous. However, there are estimates that 60-80% of long-term survivors have some GVHD activity and need long time immunosuppressive therapy after HSCT [2].

ACUTE GRAFT VERSUS HOST DISEASE (AGVHD):

Diagnosis

In 2005, National Institute of Health (NIH) Consensus document on cGVHD was published with the objective of standardize diagnosis and classification of this disease. [3] The new classification proposed the categories of classic acute GVHD for those patients who developed the characteristic inflammatory syndrome generally before day +100 after HSCT, and the category of late, persistent or recurrent acute GVHD for those patients with no clinical signs of chronic GVHD who developed acute GVHD symptoms after day +100 [3].

Epidemiology and risk factors

Risk factors for aGVHD were identified by several studies as follows: HLA mismatch, alternative donors (unrelated or haploidentical donors), sex disparity (especially female donor to male patient), myeloablative conditioning regimen, immunophrophylaxis, stem cell source (peripheral blood) [4].

Acute GCHD Clinical Picture

Skin, gastrointestinal tract (GI) and liver are the main involved sites affected by aGVHD. Skin is usually the first organ noticed, presenting as a maculopapular erythema frequently involving palms, soles and ear pavilions as well as nape and shoulders. It can disseminate by all over the body surface becoming confluent and pruriginous, sometimes even painful. On severe forms it looks like Stevens-Johnson syndrome, with epidermal necrosis and bullae formation. Superior (esophageal and gastric mucosa) or lower GI tract (bowel) can be involved. Clinical presentation varies from anorexia, nausea and vomiting to severe diarrhea usually accompanied by abdominal pain, and sometimes bleeding. [5] Severe lower GI tract is

associated to mortality and lower overall survival in those patients. Stool volume can be higher than 10 liters in 24 hours. 6 Hepatic aGVHD occurs generally in patients with skin or GI involvement, but it can be rarely isolated. Hepatic and canalicular enzymes (AST, ALT, predominantly conjugated bilirubin, alkaline phosphatase and gamma glutamyl transferase) are elevated. [7]

Acute GVHD staging and classification

The first staging system for acute GVHD was published in 1974 by Glucksberg *et al.* [5] Each organ was evaluated according to the severity of involvement and resultant data were globally graded. [5,7] After two decades this classification was reviewed by Keystone aGVHD Consensus, which confirmed the predictive value of severe acute GVHD (II to IV) for mortality rate at day 100. Furthermore, upper GI acute GVHD was recognized and for lower GI involvement, bleeding and severe pain were included as grade IV aGVHD together with stool volume (table 1). [8]

AGVHD staging is important for evaluating therapy response and correlates to overall survival after HSCT as mentioned before. [9] Patients who develop grade II-IV aGVHD have lower overall survival compared to mild ones (grade I). Upper GI involvement has better prognosis and better response to low dose steroids than lower GI acute GVHD. Moderate and severe GVHD are seen in up to 40% of allogeneic HSCT. [10] Recently an international Consortium for diagnosis and staging of acute GVHD, Mount Sinai Acute GvHD International Consortium (MAGIC), revised those criteria based on a very robust database. Main changes were definition of GI Grade IV acute GVHD and upper GI acute GVHD. This turned out to be a very important instrument for multicentric transversal and prospective studies and is now recommended by CIBMTR, EBMT and NIH for the classification of acute GVHD. Correlative studies with biomarkers were also possible using this platform. [11,12]

ACUTE GVHD THERAPY

The choice of initial therapy for acute GVHD depends on organs involved, severity of symptoms, and weight of graft versus leukemia effect on the individual clinical context.

Grade I acute GVHD

Mild acute GVHD (grade I) therapy consists mainly of using topical agents along with optimization of prophylaxis (serum level of calcineurin inhibitor adjustment). Adjuvant therapy as antihistaminic med-

ications can also be used for pruritus control. The is no indication for systemic therapy. [13]

Grade II-IV acute GVHD

Patients with moderate acute GVHD (grade II-IV) should receive methylprednisolone (MP) or prednisone at a dose of 2mg/kg/day. This has been the standard therapy for decades and its effect is related to both lymphocytic and anti-inflammatory effect. [13] At the same time, drugs used as immunophrophylaxis as cyclosporine or tacrolimus should not be discontinued. In a retrospective study of 733 patients, use of MP at lower doses as 1mg/kg/day was effective and not harmful for those patients with acute GVHD grade I-IIa. Dose could be escalated to 2mg/kg/day when necessary, if symptoms worse within 72 hours. For this subgroup survival was comparable and this approach allowed the use of 50% steroid doses. [14] Use of non-absorbent steroids (beclomethasone e budesonide) has also been used as adjuvant therapy together with systemic steroids for upper or lower acute GVHD. [15,16] About 60% of patients respond to initial therapy but some of these responses are not durable. [17]

Secondary therapy for acute GVHD grade II-IV

Progression after three days, no improvement after seven days or no resolution after 14 days of therapy with MP 2mg/kg/day associated to calcineurin inhibitor defines steroid refractory acute GVHD and a second line therapy is indicated. Refractory acute GVHD has poor prognosis as secondary therapy is unsuccessful. One year overall survival for this population was only 20-30%. [18]

Few prospective studies have been published with second line agents, but results are hardly comparable due to high heterogeneity among drugs, centers and approaches. Bad quality historical controls are additional obstacles, partially due to low accuracy on grading initial acute GVHD. As there is no superiority of any agent, choice should be guided by factors as previous therapy effects, drug interaction, availability, costs and team experience. Generally, mean response rate is about 50%, and median survival of about 60% at six months after therapy. [18] Main results published with these agents are summarized below.

Mycophenolate Mofetil (MMF)

MMF acts through inhibition of guanosine triphosphate synthesis, which is important for lymphocyte proliferation. MMF was one of four drugs tested as initial therapy added to MP at BMT CTN 0302, a ran-

domized phase II trial. [19] However this association was not superior and had more adverse events when compared to standard therapy at a blinded phase III randomized trial (BMT CTN 0802). There was no difference in GVHD free survival or cumulative incidence of chronic GVHD in 12 months. [20] Retrospective studies using MMF as second line therapy show rates of complete and partial remission of about 77% in six months and is a clinical option in this scenario. [21, 22]

Extracorporeal Photopheresis (ECP)

ECP consists of irradiation of circulating lymphocytes collected by apheresis, incubated with the sensitizing agent 8-methoxypsoralen, and exposed to UVA phototherapy. It induces apoptosis of all cells, including activated T-cells after 24 hours. Reinfusion of these apoptotic cells stimulates antigen presenting cells (APCs), which regulate immune homeostasis through production of anti-inflammatory cytokines and regulatory T cell recruitment and expansion, inducing immune tolerance. [23]

In 2006 a prospective phase II study was published evaluating ECP and included 59 patients with severe steroid refractory or steroid dependent acute GVHD. Complete responses were seen in 82% of patients with cutaneous involvement, 61% of those with liver GVHD and 61% of patients with GI GVHD. [24] No opportunistic infections were observed and there was no increment of relapse rate. [24]

Antithymocyte globulin (ATG)

These polyclonal antibodies are the most frequently used all over the world for acute GVHD second line therapy. Although there is large experience with this agent for more than three decades, response rates are achieved in only 20 to 30% of the patients, with poor overall survival of less than 10%. Better responses are seen in cutaneous acute GVHD. [25,26]

Anti IL-2 receptor monoclonal antibodies (basiliximab, daclizumab)

These drugs bind to alpha subunit of interleukin 2 receptor (CD25) at activated T lymphocytes. Basiliximab is a chimeric antagonist of IL-2 receptor and has been successfully used as secondary therapy for acute GVHD, achieving up to 71% of overall response rate in a phase I trial published in 2002 with 17 patients [27]. Funke et al published in 2005 a single center experience in 34 patients with severe acute GVHD (grade III-IV) refractory to steroids. Overall response rate was 80%, and five years overall survival was 30%. [28]

Tumoral Necrosis Factor Antagonists (Infliximab, Embrel)

These drugs are frequently used as therapy for severe acute GVHD refractory to steroids and involving lower GI tract [18]. The biggest experience was published by Couriel and cols [29], who studied 37 patients diagnosed with refractory acute GVHD and achieved an overall response rate of 70%.

Ruxolitinib

Formerly used as therapy for chronic myeloproliferative disorders (primary myelofibrosis and Polycythemia Vera), ruxolitinib inhibits γ -interferon receptor signaling. With this rationale, it started also to be tested in GVHD patients. Janus kinases (JAKs) are important effectors in all three recognized acute GVHD pathogenetic phases. Ruxolitinib blocks cytokine production and signaling and regulate development and function of T cells and APCs. Furthermore, Jak-STAT inhibition in pre-clinical models reduced GVHD without compromising GVL. [30, 31]

Two studies were performed sequentially using ruxolitinib as a 2-line therapy for refractory GVHD (grade II-IV). The first called REACH1 (phase II, prospective, single arm) reported a global response (RC + RP) of 54.9% at D28 in a cohort of 49 patients. The dose ranged from 10 to 20mg / day, with cytopenias and viral reactivation being the main toxicities to the drug. Still in need of treatment 31. This study also evaluated overall survival at D180 and reached the percentage of 73% with only 11 patients (15%) still in need of treatment after six months. [32]

In 2019, ruxolitinib became the first (and only to date) treatment approved by the FDA (Food and Drug Administration) for corticosteroid refractory aGVHD.

The second study, called REACH 2, was published in April 2020 and was the third phase 3 study described in the literature. It consisted of a multicenter, randomized trial comparing the efficacy and safety of the use of ruxolitinib in the oral dose of 20mg with a control arm that consisted of one of nine therapies frequently used to rescue corticosteroid disease (this treatment was of the investigator's choice). A total of 309 patients were randomized and the overall response rate at D28 was significantly higher in the ruxolitinib group compared to the control group (62% vs 39%, odds ratio, 2.64, 95% CI 1.65 to 4.22, $P < 0.0001$). The lasting global response in D56 was also significantly higher in the inhibitor group (40% X 22%). When extending the follow-up period to 6 months (180 days), a 10% loss of therapeutic response can be observed in the ruxolitinib group compared to 39% in the control. [33]

4. CHRONIC GRAFT VERSUS HOST DISEASE (CGVHD):

GVHD is the major cause of late allogeneic HSCT morbidity and mortality, occurring in 30-70% of patients. [34] The 2-year cumulative incidence of cGVHD, as defined by the National Institute of Health (NIH) criteria, after allogeneic HSCT with bone marrow or peripheral blood from related or unrelated donors, in a study that assessed risk factors for aGVHD and cGVHD was 34% (range 32% -35%). [35] The clinical manifestations of cGVHD can be restricted to a single organ or can be disseminated, with a profound impact on quality of life. The pathophysiology of cGVHD involves inflammation, cellular and humoral immunity and fibrosis. [36] This immunological complication resembles autoimmune diseases with clinical manifestations of collagen vascular diseases, such as oral lichen planus, sicca keratoconjunctivitis, xerostomia, polyserositis, esophagitis and esophageal stenosis, ulceration and vaginal stenosis, intrahepatic obstructive liver disease, obstructive lung disease, scleroderma, fasciitis and myositis. Clinical manifestations almost always appear in the first two years after transplantation. [36]

Chronic GVHD diagnosis and differentiation from acute GVHD

There were few changes from 2005 NIH consensus to 2014 NIH Consensus on chronic GVHD. [4,37] Acute GVHD includes two categories : (1) Classic acute GVHD, usually within 100 days of HSCT and with no diagnostic or distinctive signs of chronic GVHD; (2) Late, persistent or recurrent acute GVHD, also without signs of chronic GVHD (cGVHD) but occurring later than 100 days of HSCT. For both 2005 and 2014 Consensus documents, chronic GVHD consisted of one of two categories: (1) classic cGVHD, with no signs of acute GVHD; (2) Overlap syndrome, where the patient has concomitant diagnostic or distinctive signs of cGVHD and inflammatory manifestations (liver or GI activity, skin erythema). This entity was better defined at 2014 consensus. [37] Clinical manifestations, either than timing, will determine the diagnosis of acute or chronic GVHD. Diagnostic symptoms or signs of chronic GCHD are enough for diagnosis, without the need for biopsy or other tests from other organs involved. Lichenoid changes and sclerosis are diagnostic for chronic GVHD. Distinctive signs are defined as those commonly found in chronic GVHD but there is the requirement of a biopsy for confirmation (e.g ocular sicca, vitiligo). [37] For cGVHD diagnosis is necessary at least one diagnostic manifestation or at least one distinctive manifestation confirmed by biopsy or lab tests, spe-

cialist evaluation (ophthalmologist, gynecologist) or radiology images, at the same or in another organ, except when contra-indicated. [37]

Clinical organ scoring system

The scoring system of the 2005 consensus 4 was modified based on the available evidence, or lack of it, and the doubts generated by the researchers and the clinical practice. [37] The organs considered for scoring include skin, mouth, eyes, GI tract, liver, lungs, joints, fascia and genital tract. Each organ or location is scored on a 4-point scale (0-3) with 0 representing non-involvement and 3 reflecting serious impairment. Several studies have shown that the global severity, by 2005 NHI criteria, at diagnosis, is associated with overall survival and TRM. Some elements of the score were validated as measures of quality of life. [37] The mild, moderate, and severe description of reflects the degree of impact and functional impairment, in each organ or location, due to cGVHD. Tables 2 and 3 summarize NIH consensus clinical score system and global scoring for GVHD.

Chronic GVHD therapy

Mild asymptomatic GVHD can often be managed with local treatment (eg, topical corticosteroids for skin involvement). In patients with three or more organs, or with a score of 2 or higher, in any organ, systemic treatment should be considered. Although it is associated with a lower relapse rate, cGVHD remains the main cause of late morbidity and mortality in HSCT recipients. [38] The frequent involvement of several organs and the pleomorphic clinical picture of this complication require multidisciplinary management, which includes, in addition to several medical specialties, nutrition, physiotherapy, psychological, dental, social and occupational therapy. [39] Periodic assessment of quality of life is recommended in patients with cGVHD, representing an efficient instrument for response to treatment. [40]

Mild chronic GVHD therapy

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

MODERATE AND SEVERE CHRONIC GVHD THERAPY

First line therapy

The criteria defined by NIH Consensus for systemic treatment include: scores >2 in one organ, involvement of three or more organs and mild GVHD with high risk characteristics (platelet counts <100,000 / mm³ and use of immunosuppressants for the diagnosis of GVHD). [37]

The standard initial systemic treatment consists of prednisone 1 mg / kg / day and cyclosporine (CSA) 10 mg / kg / day divided into 2 doses, administered orally, with a dose of CSA adjusted by the plasma level. [41] Tacrolimus has also been used to replace cyclosporine with similar responses. Withdrawal should be initiated, if there is a response or stable manifestations, after two weeks of treatment, reducing the dose of prednisone by 25% each week until reaching, in 6 to 8 weeks, the target dose of 1 mg / kg every other day, which should be maintained for 2 to 3 months in cases of non-complete response, severe forms or the presence of risk factors. Then, reduce 10 to 20% per month until total suspension in 9 to 12 months according to tolerance. [41]

Steroid refractory GVHD is defined by disease progression after 2 weeks of therapy (prednisone at a dose of 1 mg / kg / day); stable disease using prednisone (> 0.5 mg / kg / day) for 4-8 weeks or inability to reduce the prednisone dose below 0.5 mg / kg / day. [49] Indications for second-line treatment include worsening manifestations of GVHD in an organ primarily involved, absence of any response after one month of treatment, or inability to reduce the dose of prednisone below 1 mg / kg / day within 2 months. [41]

Second line therapy

Several therapeutic options have been tested in patients with GVHD refractory to first-line treatment. The choice of treatment, therefore, will depend on the toxicity pattern of the medication chosen, the organs involved, the patient's preference and the availability of the transplant center. [41]

The main agents used in the treatment of refractory GVHD are selected in table 4 and summarized below.

Extracorporeal Photopheresis (ECP)

ECP has been widely used as a second-line therapy for muco-cutaneous cGVHD, with complete response rates above 80% and significant improvement in cGVHD with sclerosis. Recently, Flowers et. Al42 reported results of a prospective randomized double-blind

phase II study in 95 patients with steroid refractory, dependent, or intolerant cGVHD treated with FEC in combination with conventional immunosuppressants. There was no significant difference in the improvement of the total skin score (TSS) at week 12, however, a higher rate of complete and partial responses of GVHD in the skin was observed in the ECP arm compared to the control arm; more patients in the ECP arm had at least a 50% reduction in the dose of steroids and at least a 25% reduction in total skin score (TSS) in week 12. [42] In the extension study, the group undergoing FEC had a significant improvement in skin score at week 24 when compared to the group without intervention. [43] FEC has the advantage of not increasing the risk of infections and having few adverse effects.

Mycophenolate Mofetil (MMF)

This immunosuppressant, whose prodrug, mycophenolic acid, interferes with purine synthesis and produces cytostatic effect on T and B lymphocytes, is frequently used in rescue therapy for refractory cGVHD. Global response rates vary between 23 and 79% of patients in several case series. [44] Lopez et. Al45 reported in 2005 the largest series of cases with 35 patients with steroid refractory cGVHD. There was 79% overall response and 35% complete responses. Seventy-three percent of patients were able to discontinue immunosuppression after adding this drug and only 3% of treated patients discontinued due to toxicity.

Rapamicin (mTOR) mammalian receptor inhibitors: sirolimus

These drugs combine immunosuppressive effects and antiproliferative properties in fibroblasts and smooth muscle fibers. There are reports of antineoplastic effects. Sirolimus and everolimus, bind to mTOR forming a complex that induces the cell cycle to stop in G1 by inhibiting transcription, DNA translation and protein synthesis. In contrast to calcineurin inhibitors, these drugs promote the generation of regulatory T cells. [46]

Jurado et. Al47 published a case series in 2007 of 47 patients who used sirolimus as a 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. Al48 also reported their experience with sirolimus as rescue therapy in 35 patients with cutaneous and visceral GVHD. There was a 63% global response, 17% of which were complete and 34% of patients discontinued immunosuppression. The overall 2-year survival was 41%.

Rituximab

Rituximab binds to the extracellular portion of the CD 20 surface molecule and induces complement-mediated apoptosis and cell death, either directly or through normal or neoplastic B cells. [49] Cutler et. Al50 carried out the first prospective phase I-II study reporting the efficacy of rituximab (375 mg / m²) in 21 patients receiving a total of 38 cycles. Objective responses were observed in 70% of patients allowing for a significant reduction in the steroid dose. Patients with cutaneous or musculoskeletal manifestations of cGVHD showed a better response. VonBonnin et. Al51 used lower doses of 50 mg / m² / week for 4 weeks in 11 patients with refractory GVHD and 2 with post-transplant autoimmune disorders (immune glomerulonephritis and thrombocytopenia), observing an overall response rate of 69%, including 3 patients (23 %) with complete remission (CR). Recently, Arai et. Al52 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 used successfully in BCR-ABL positive malignancies, has recently been used to treat cGVHD based on its antifibrotic activity by blocking the platelet-derived growth factor (PDGFR) receptor and growth factor beta transformation (TGFβ). [53] The main adverse events with this drug include hematological toxicity, water retention, dyspnea, leading to discontinuation of the drug in 15 to 25% of patients. Responses were observed in 50% to 80% of patients with cutaneous, ocular and intestinal involvement by cGVHD over a six-month period. In cases of pulmonary involvement, the best responses were seen in mild bronchiolitis. [53]

Low dose Methotrexate

MTX is an antimetabolite that in low doses has immunomodulatory and anti-inflammatory properties. Giaccone et al54 reported 71% (10/14) of refractory GVHD control, with a prednisone reduction to dose <1 mg / kg / alternate days, with a 7.5 mg / m² / week MTX regimen in patients with refractory, long-term GVHD with 5 sites affected on average. At a median follow-up 25 weeks, overall survival rate was 92.8%, and no grade III / IV toxicity was observed. A more recent series of 27 children with refractory GVHD (17 with chronic form) treated with MTX doses of 3-10

mg / m² / week showed 58.8% overall response, with prednisone suspension on 7/17 and reduction (dose <0.4 mg / kg) in 9/17 patients. [55]

Ibrutinib

Ibrutinib is a drug of the tyrosine kinase enzyme inhibitor class, with recognized activity in the Bruton's tyrosine kinase (BTK) pathway which is predominantly expressed in the B lymphocytes. It inhibits signal transduction from the B cell receptor leading to blockade of the B cell receptor activation, interruption of the cell cycle and apoptosis. Its role in the treatment of lymphoproliferative malignancies of lineage B had already been recognized through several clinical studies and its use had been approved since 2017 by the FDA.

In addition to the BTK inhibition described above, ibrutinib is also able to alter the function of T lymphocyte through the inhibition of tyrosine kinase stimulated by IL-2 (ITK) which comes to reach T lymphopoiesis. Thus, it leads to decreased cell activation and proliferation of T lymphocytes, in addition to a decrease in the release of inflammatory cytokines. [56]

The rationale for the use of ibrutinib has led to its applicability as rescue therapy in refractory GVHD. To date, the only therapy approved for GVHD as 2-line by the FDA and recently also approved by ANVISA. A phase 1b / 2 study published by Miklos *et al* in 2017 used the daily dose of 420mg in a cohort of 42 patients with a median time to initial response of 87 days. The overall response rate was 67% and 21% had CR therapy. About 70% of patients showed sustained clinical response for > 5 months after starting the drug. In general, 26 patients in the cohort (62%) achieved a reduction of corticosteroids dose to <0.15mg/kg per day during the study. [56]

Ruxolitinib

The good results observed in GVHD with this agent has stimulated the industry and the results of a prospective phase III trial currently being recruited are awaited. The Spanish Group of Hematopoietic Transplantation and Cell Therapy (GETH) published in 2020 the results of a retrospective study with 56 heavily treated patients, with median of three previous therapies (1-10). The overall response rate was 57.1% in this adverse clinical group. There was gradual steroid taper and OS was 81% after 1 year of follow-up. [57]

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Table 1 - Comparison of the different guidelines available for acute GvHD assessment: individual organ severity staging¹²

Organ Severity Stage	Original Glucksberg criteria	“Modified Glucksberg” or “Keystone” criteria and IBMTR criteria	MAGIC criteria
Skin 0 1 2 3 4	No rash Rash < 25% of BSA Rash 25% to 50% of BSA Rash > 50% of BSA Generalized erythroderma with bullous formation	No rash Rash < 25% of BSA Rash 25% to 50% of BSA Rash > 50% of BSA Generalized erythroderma with bullous formation	No rash Rash < 25% of BSA Rash 25% to 50% of BSA Rash > 50% of BSA Generalized erythroderma with bullous formation
Liver 0 1 2 3 4	Total serum bilirubin < 34 µmol/L (< 2 mg/dL) or AST/SGOT 150-750 IU Total serum bilirubin 34-50 µmol/L (2 to 3 mg/dL) Total serum bilirubin 51-102 µmol/L (3.1 to 6 mg/dL) Total serum bilirubin 103-255 µmol/L (6.1 to 15 mg/dL) Total serum bilirubin > 255 µmol/L (> 15 mg/dL)	Total serum bilirubin < 34 µmol/L (< 2 mg/dL) Total serum bilirubin 34-50 µmol/L (2 to 3 mg/dL) Total serum bilirubin 51-102 µmol/L (3.1 to 6 mg/dL) Total serum bilirubin 103-255 µmol/L (6.1 to 15 mg/dL) Total serum bilirubin > 255 µmol/L (> 15 mg/dL)	Total serum bilirubin < 34 µmol/L (< 2 mg/dL) Total serum bilirubin 34-50 µmol/L (2 to 3 mg/dL) Total serum bilirubin 51-102 µmol/L (3.1 to 6 mg/dL) Total serum bilirubin 103-255 µmol/L (6.1 to 15 mg/dL) Total serum bilirubin > 255 µmol/L (> 15 mg/dL)
Upper GI 0 1	NA NA	No persistent nausea and no histologic evidence of GvHD in the stomach or duodenum Persistent nausea with histologic evidence of GvHD in the stomach or duodenum	No or intermittent anorexia or nausea or vomiting Persistent anorexia or nausea or vomiting
Lower GI 0 1 2 3 4	Diarrhea < 500 mL/day Diarrhea > 500 mL/day Diarrhea > 1000 mL/day Diarrhea > 1500 mL/day Diarrhea >2000 mL/day	Diarrhea < 500 mL/day Diarrhea > 500 mL/day Diarrhea > 1000 mL/day Diarrhea > 1500 mL/day Severe abdominal pain with or without ileus	Diarrhea < 500 mL/day or < 3 episodes/day for adults ^{b,c} Diarrhea 500-999 mL/day or 3-4 episodes/day for adults ^{b,d} Diarrhea 1000-1500 mL/day or 5-7 episodes/day for adults ^{b,e} Diarrhea >1500 mL/day or >7 episodes/day for adults ^{b,f} Severe abdominal pain with or without ileus or grossly bloody stools (regardless of stool volume)
Karnofsky Index	>30% <30%		

AST (Aspartate transaminase); BSA (Body surface area); GI (Gastro-intestinal tract); GvHD (Graft versus Host Disease); IBMTR (International Bone Marrow Transplantation Registry); IU (International units); MAGIC (Mount Sinai Acute GvHD International Consortium); NA (Not applicable); SGOT (Serum glutamic oxaloacetic acid transaminase)

^aTo be suggestive for GvHD: anorexia should be accompanied by weight loss, nausea should last at least 3 days, or be accompanied by at least 2 vomiting episodes per day for at least 2 days [16]

^bOne episode of diarrhea is considered to be about 200 ml for an adult and 3 ml/kg for a child (< 50 kg) [16]

^cDiarrhea <10 mL/kg/day or <4 episodes/day for children

^dDiarrhea 10-19.9 mL/kg/day or 4-6 episodes/day for children

^eDiarrhea 20-30 mL/kg/day or 7-10 episodes/day for children

^fDiarrhea > 30 mL/kg/day or >10 episodes/day for children

Table2 - Scoring system for chronic GVHD37

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: <input type="text"/> KPS ECOG LPS	Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	Symptomatic, ambulatory, capable of self-care, >50% of waking hours out of bed (ECOG 2, KPS or LPS 60-70%)	Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† <input type="text"/> SCORE % BSA <i>GVHD features to be scored by BSA:</i> Check all that apply: Maculopapular rash/erythema Lichen planus-like features Sclerotic features Papulosquamous lesions or ichthyosis Keratosis pilaris-like GVHD	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
SKIN FEATURES SCORE:	No sclerotic features		Superficial sclerotic features "not hidebound" (able to pinch)	Check all that apply: Deep sclerotic features "Hidebound" (unable to pinch) Impaired mobility Ulceration
<i>Other skin GVHD features (NOT scored by BSA)</i> Check all that apply: Hyperpigmentation Hypopigmentation Poikiloderma Severe or generalized pruritus Hair involvement Nail involvement Abnormality present but explained entirely by non-GVHD documented cause (specify): _____				
MOUTH <i>Lichen planus-like features present:</i> Yes No Abnormality present but explained entirely by non-GVHD documented cause (specify): _____	No symptoms	Mild symptoms with disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs with partial limitation of oral intake	Severe symptoms with disease signs on examination with major limitation of oral intake

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), WITHOUT new vision impairment due to KCS	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to KCS

Abnormality present but explained entirely by non-GVHD documented cause (specify):

GI Tract <i>Check all that apply:</i> Esophageal web/proximal stricture or ring Dysphagia Anorexia Nausea Vomiting Diarrhea Weight loss $\geq 5\%$ * Failure to thrive	No symptoms	Symptoms without significant weight loss* ($< 5\%$)	Symptoms associated with mild to moderate weight loss* (5-15%) OR moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss* $> 15\%$, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference with daily living
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Abnormality present but explained entirely by non-GVHD documented cause (specify):

LIVER	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤ 3 mg/dL or ALT > 5 ULN	Elevated total bilirubin > 3 mg/dL
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Abnormality present but explained entirely by non-GVHD documented cause (specify):

LUNGS** Symptom score:	No symptoms	Mild symptoms (shortness of breath after climbing one flight of steps)	Moderate symptoms (shortness of breath after walking on flat ground)	Severe symptoms (shortness of breath at rest; requiring O ₂)
Lung score: % FEV1 <input type="text"/>	FEV1 $\geq 80\%$	FEV1 60-79%	FEV1 40-59%	FEV1 $\leq 39\%$

Pulmonary function tests

Not performed

Abnormality present but explained entirely by non-GVHD documented cause (specify):

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought due to fasciitis, moderate decrease ROM AND mild to moderate limitation of ADL	Contractures WITH significant decrease of ROM AND significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
P-ROM score <i>(see below)</i>				
Shoulder (1-7):	___			
Elbow (1-7):	___			
Wrist/finger (1-7):	___			
Ankle (1-4):	___			

Abnormality present but explained entirely by non-GVHD documented cause (specify):

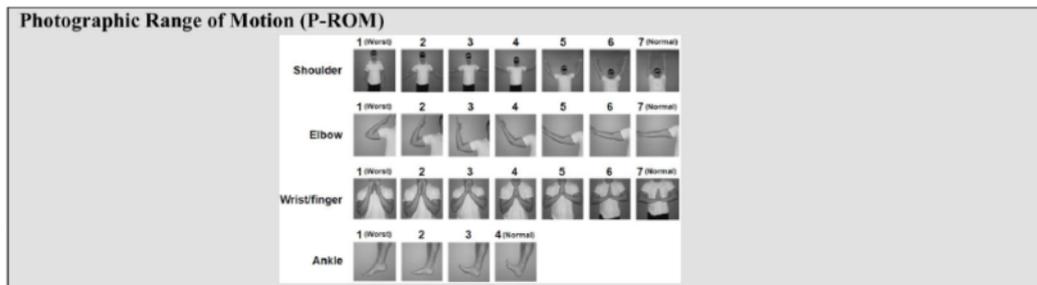
GENITAL TRACT <i>(See Supplemental figure[†])</i>	No signs	Mild signs [‡] and females with or without discomfort on exam	Moderate signs [‡] and may have symptoms with discomfort on exam	Severe signs [‡] with or without symptoms
Not examined				
Currently sexually active				
Yes				
No				

Abnormality present but explained entirely by non-GVHD documented cause (specify):

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0, mild -1, moderate -2, severe – 3)			
Ascites (serositis) ___	Myasthenia Gravis ___		
Pericardial Effusion ___	Peripheral Neuropathy ___	Eosinophilia > 500/µl ___	
Pleural Effusion(s) ___	Polymyositis ___	Platelets <100,000/µl ___	
Nephrotic syndrome ___	Weight loss >5%* without GI symptoms ___	Others (specify): ___	

Overall GVHD Severity
(Opinion of the evaluator)

No GVHD
 Mild
 Moderate
 Severe



[†] Skin scoring should use both percentage of BSA involved by disease signs and the cutaneous features scales. When a discrepancy exists between the percentage of total body surface (BSA) score and the skin feature score, OR if superficial sclerotic features are present (Score 2), but there is impaired mobility or ulceration (Score 3), the higher level should be used for the final skin scoring.

* Weight loss within 3 months.

**Lung scoring should be performed using both the symptoms and FEV1 scores whenever possible. FEV1 should be used in the final lung scoring where there is discrepancy between symptoms and FEV1 scores.

Abbreviations: ECOG (Eastern Cooperative Oncology Group), KPS (Karnofsky Performance Status), LPS (Lansky Performance Status); BSA (body surface area); ADL (activities of daily living); LFTs (liver function tests); AP (alkaline phosphatase); ALT (alanine aminotransferase); ULN (normal upper limit).

[‡] To be completed by specialist or trained medical providers (see Supplemental Figure).

Table 3 - GVHD severity

<p>Mild chronic GVHD 1 or 2 organs involved plus Score 1 of involved sites plus Lung score 0 Severe chronic GVHD At least one organ with score 3 or Lung score 2 or 3</p>	<p>DECH crônica moderada 3 or more site plus score 1 of involved sites or At least one site (except lung) with score 2 or Lung score 1</p>
<p>Key Points:</p> <p>1. On the skin: The highest score will be used to calculate the overall severity. 2. In the lung: FEV1 is used in place of the clinical score for the calculation of overall severity. 3. If an organ abnormality is unequivocally explained by a cause not associated with GVHD, the score of this organ will be zero for the calculation of global severity. 4. If an organ abnormality is attributed to multifactorial causes (GVHD plus other causes) the organ's score will be used to calculate the overall severity regardless of the contributing causes (the organ's score will not be disregarded).</p>	

Table 4 - Secondary therapy for chronic GVHD

TREATMENT	% OVERALL RESPONSE	SURVIVAL
ECP	65-70	70%-78% at 1 y
Rituximab	66-86	72% at 1 y
Imatinib	22-79	75%-84% at 1.5 y
Mycophenolate mofetil	26-64	67%-96% at 1 y
MTOR inhibitor	76	72% at 3 y
Low dose methotrexate	71%	92,8% in 25 weeks
Ruxolitinib	57%	81% at 1 y
Ibrutinib	67%	Not reported