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CONSENSUS UPDATE

VI CONSENSUS OF THE BRAZILIAN SOCIETY OF BONE MARROW TRANSPLANTATION (SBTMO) CONSENSUS ON GRAFT-VERSUS-HOST DISEASE (GVHD)

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Version 2022 updates of Version 2020 of the VI Consensus of the Brazilian Society of Bone Marrow Transplantation for Graft-versus-Host-Disease (GVHD) include:

Table 1: GVHD prophylaxis regimens used, with levels of evidence and grades of recommendation:

New evidence of GVHD prophylaxis with post-transplantation cyclophosphamide (PTCy) in myeloablative (MA) allogeneic hematopoietic stem cell transplantation (allo-HSCT) from matched related and matched and mismatched unrelated donors;

New evidence of GVHD prophylaxis with PTCy in reduced intensive conditioning (RIC) and non-myeloablative (NMA) allo-HSCT.

Table 2: First-line therapy for grade I-IV acute GVHD (aGVHD), with levels of evidence and grades of recommendation:

Included treatment for Grade I and IIa aGVHD;

Included definition of Grade IIa aGVHD and options of topical therapies.

Included Table 3: chronic GVHD (cGVHD) indication for systemic treatment.

Included Table 4 with first-line therapy of cGVHD, with criteria for initiating systemic treatment, and with levels of evidence and grades of recommendation.

Included Table 5: Definition of steroid refractoriness or resistance, steroid dependence, and steroid intolerance for aGVHD and cGVHD.

Table 7: Second-line therapy of cGVHD, with levels of evidence and grades of recommendation:

New level of evidence for ruxolitinib, Level 1b, Grade of recommendation A;

Included belumosudil.

INTRODUCTION

Graft-versus-host disease (GVHD) can develop after allogeneic hematopoietic cell transplantation (allo-HSCT) when immune cells from a non-identical donor (the graft) initiate an immune reaction against a transplant recipient (the host). Acute GVHD (aGVHD) and chronic GVHD (cGVHD) are multisystem disorders that are distinguished by their clinical findings, according to National Institutes of Health (NIH) consensus criteria[1].

Despite prophylactic treatment with immunosuppressive agents, 20-80% of recipients develop aGVHD after allo-HSCT[2]. The main risk factors for aGVHD are HLA-mismatch between donor and recipient; gender disparity between donor and patient; conditioning regimen intensity; prophylaxis regimen used; progenitor stem cell source (peripheral blood > bone marrow > umbilical blood cord)[3].

The *Mount Sinai Acute GVHD International Consortium (*MAGIC) has recently allowed for a better standardization of the criteria for classification and data collection related to aGVHD[4]. It is currently regarded as the most appropriate method for the diagnosis, staging, and grading of aGVHD[4,5]. The app for grading can be accessed at https://www.uzleuven.be/egvhd.

With a prevalence of 30-70% among allo-HSCT recipients, cGVHD remains the main cause of long-term post-transplant morbidity and mortality in this population[6–8]. The cumulative incidence of cGVHD at 2 years in patients undergoing related or unrelated, bone marrow or peripheral blood stem cell allo-HSCT, as defined by the NIH criteria, was 34%[3]. Risk factors associated with cGVHD were HSCT with HLA-matched unrelated donors, HLA mismatched related donors, or HLA-mismatched unrelated donors, use of a female donor for a male recipient, grafting with mobilized blood, and older donor and recipient age[3]. cGVHD is classified and severity is graded according to the widely-accepted NNIH consensus criteria[1].The app for the assessment of cGVHD can be accessed at https://www.uzlHYPERLINK "https://www.uzleuven.be/egvhd"euven.be/egvhd.

TABLE 1: GVHD prophylaxis regimens, with levels of evidence and grades of recommendation

TYPE OF ALLO-HSCT	PROPHYLAXIS REGIMEN	LEVEL OF EVIDENCE
MA allo-HSCT from matched related and matched and mismatched unrelated donors	Calcineurin inhibitor and Methotrexate (MTX)9–15	Level 1a, grade of recommendation A
	Calcineurin inhibitor and Mycophenolate Mofetil (MMF)14–19	Level 1a, grade of recommendation B
	High-Dose PTCy (50 mg/kg on D+3 and D+4) 20–29 (for adults)	Level 2b, grade of recommendation C Level 3b, grade of recommendation B Level 2b, grade of recommendation B
RIC and NMA allo-HSCT	Calcineurin inhibitor and MMF30 PTCy (50 mg/kg on D+3 and D+431,32 (for adults)	Level 4, grade of recommendation C Level 2b, grade of recommendation B Level 1b, grade of recommendation A
HLA-identical allo-HSCT from related and unrelated donors using PBSC as stem cell source	Rabbit Antithymocyte Globulin (rATG) < 6 mg/kg33–40	Level 1a, grade of recommendation A
Haploidentical allo-HSCT – Baltimore protocol	High-Dose PTCy (50 mg/kg on D+3 and D+4) plus a calcineurin inhibitor and MMF41–43	Level 2b, grade of recommendation B
Haploidentical allo-HSCT – Beijing protocol	High-Dose rATG (10 mg/kg), MMF, calcineurin inhibitor, and MTX44	Level 2b, grade of recommendation B

Legend: GVHD: graft-versus-host disease; allo-HSCT: allogeneic hematopoietic stem cell transplant; MA: myeloablative; PTCy: post-transplant cyclophosphamide; NMA: non-myeloablative; RIC: reduced-intensity conditioning; HLA: human leukocyte antigen; PBSC: peripheral blood stem cells.

TABLE 2: First-line therapy for grade I-IV aGVHD, with levels of evidence and grades of recommendation

GRADE	TREATMENT	LEVEL OF EVIDENCE
I	Optimize prophylaxis regimen, adjust calcineurin inhibitor trough levels, add topical agents (corticosteroids or tacrolimus). No systemic immunosuppression is recommended45	Level of evidence 1b, grade of recommendation A
IIa (less severe forms)	Start MP 0.5-1mg/kg/day, escalating up to 2 mg/kg if worsening occurs after 72h46. Concomitant calcineurin inhibitor (cyclosporine or tacrolimus) prophylaxis should not be withdrawn Non-absorbable glucocorticoids (beclomethasone and budesonide) for mild upper or lower GI aGVHD (500-1000 ml/stool output/day) as an adjuvant to systemic corticosteroids47,48	Level of evidence 1b, Grade of recommendation A Level of evidence 1b, Grade of recommendation A
II-IV	Start MP 2mg/kg/day or its prednisone equivalent49. Concomitant calcineurin inhibitor (cyclosporine or tacrolimus) prophylaxis should not be withdrawn	Level of evidence 1a, Grade of recommendation A

Grade IIa: any combination that includes rash covering < 50% of the body surface area (BSA) and not progressing rapidly within the first 6-24 hours, anorexia, nausea, emesis or diarrhea < 1 L day (children < 20 mL/kg/day), and absence of liver involvement (bilirubin < 2 mg/dL in the absence of either hepatic complications or < 3 mg/dL if hepatic complications other than GVHD are present); mild GVHD confined to the skin which involves < 50% of the total BSA not rapidly progressing does not usually require treatment with prednisone50.

Legend: aGVHD: acute graft versus host disease; MP: methylprednisolone; GI: gastrointestinal.

TABLE 3: cGVHD indication for Systemic Treatment1 - Level of evidence 2b, Grade of recommendation B

GLOBAL SEVERITY	HIGH RISK FOR MORTALITY*	SYSTEMIC TREATMENT
Mild	No	No
Mild	Yes	Yes#
Moderate	No/Yes	Yes
Severe	No/Yes	Yes

* Platelets <100,000/mm3 or receiving steroids at time of diagnosis of cGVHD

The benefits of graft-vs.-tumor effect and the risk of cGVHD need to be weighed

TABLE 4: First-line therapy of cGVHD, with levels of evidence and grades of recommendation

Treatment	Level of evidence
Standard treatment consists of prednisone at a dose of 1mg/kg/day and cyclosporine2,51	Level of evidence 1c, Grade of recommendation A

Legend: cGVHD: chronic graft-versus-host disease.

Criteria for initiating systemic treatment for cGVHD: score >2 in at least one organ, involvement of three or more organs with score 1, lung score 1 or 2, and mild cGVHD with high-risk features (thrombocytopenia <100.000/mm3 and use of immunosuppressants at cGVHD diagnosis)52

TABLE 5: Definition of steroid refractoriness or resistance, steroid dependence, and steroid intolerance for aGVHD and cGVHD5 - Level of evidence 5, Grade of recommendation D

	AGVHD	CGVHD
Refractoriness or resistance	Progression of aGVHD within 3–5 days of therapy onset with ≥2 mg/kg/day of prednisone OR failure to improve within 5–7 days of treatment initiation OR incomplete response after >28 days of immunosuppressive treatment including steroids	cGVHD progression while on prednisone at ≥1 mg/kg/day for 1–2 weeks OR stable GVHD while on ≥0.5 mg/kg/day of prednisone for 1–2 months
Dependence	Inability to taper prednisone below 2 mg/kg/day OR recurrence of aGVHD activity during steroid tapering	Inability to taper prednisone below 0.25 mg/kg/day in at least two unsuccessful attempts separated by at least 8 weeks
Intolerance	Emergence of unacceptable toxicity due to the use of corticosteroids	

Legend: aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host disease.

TABLE 6: Second-line therapy for grade II-IV aGVHD, with levels of evidence and grades of recommendation

MMF	Level of evidence 2b, Grade of recommendation C53–56	Complete Response (CR) and Partial Response (PR) rates of up to 77% in 6 months.
Extracorporeal Photopheresis	Level of evidence 2a, Grade of recommendation B57–68	Overall response rates (ORR) of 84% in aGVHD of the skin and 65% in that of the gut
ATG	Level of evidence 2b, Grade of recommendation C69,70	ORR between 20% and 50%, particularly in aGVHD of the skin
Basiliximab	Level of evidence 2b, Grade of recommendation B71,72 Response rates of approximately 80%, with an overall survival of 30% at 5 years	
Infliximab and Etarnecept	Level of evidence 2b, Grade of recommendation C73	ORR of approximately 70%, particularly in aGVHD of the gut
Ruxolitinib	Level of evidence 1b, Grade of recommendation A74–79	REACH2* phase III study showed an ORR of 62% at 28 days, compared to a 39% ORR in the control group
Mesenchymal Stromal Cell infusion	Level of evidence 2c, Grade of recommendation B80	ORR 50%; the estimated probability of survival at 2 years was 17.4%.

Legend: MMF: mycophenolate mofetil; ATG: antithymocyte globulin; aGVHD: acute graft-versus-host disease.

TABLE 7: Second-line therapy of cGVHD, with levels of evidence and grades of recommendation

Extracorporeal Photopheresis	Level of evidence 1b, Grade of recommendation A67,81–85	Mucocutaneous manifestations, with complete response (CR) rates of > 80% and significant improvement of sclerotic cGVHD.
MMF	Level of evidence 4, Grade of recommendation B86,87	Overall response rates (ORR) vary between 23% and 79% in several case series
Sirolimus	Level of evidence 4, Grade of recommendation B88–90	ORR varying between 63% and 81% in several case series
Rituximab	Level of evidence 2b, Grade of recommendation B91– 93	Mucocutaneous and musculoskeletal manifestations, with an ORR of approximately 70%
Imatinib	Level of evidence 2b, Grade of recommendation B93, 94	Cutaneous, ocular, and gut manifestations, with an ORR between 50% and 80%
Methotrexate	Level of evidence 4, Grade of recommendation B95, 96	ORR varying between 58.8% and 71% in most case series
Ibrutinib	Level of evidence 2b, Grade of recommendation B97, 98	ORR of 67%, with a 21% CR rate
Ruxolitinib	Level of evidence 1b, Grade of recommendation A99	ORR of 49.7% vs 25.6% for ruxolitinib and controls, respectively (odds ratio, 2.99; P<0.001); longer median failure-free survival for ruxolitinib than control, >18.6 months vs. 5.7 months (hazard ratio, 0.37; P<0.001), and higher symptom response, 24.2% vs. 11.0% (odds ratio, 2.62; P = 0.001).
Belumosudil	Level of evidence 2b, Grade of recommendation B100	ORR for belumosudil 200 mg daily x 200 mg twice daily was 74% (95% CI, 62-84%) and 77% (95% CI, 65-87%); symptom reduction with belumosudil 200 mg daily and 200 mg twice daily was 59% and 62%, respectively.

Legend: cGVHD: chronic graft-versus-host disease; MMF: mycophenolate mofetil.

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