'Real-life' report on the management of chronic GvHD in the Gruppo Italiano Trapianto Midollo Osseo (GITMO)

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Several guidelines have been published about management of chronic GvHD (cGvHD), but the clinical practice still remains demanding. The Gruppo Italiano Trapianto di Midollo Osseo (GITMO) has planned a prospective observational study on cGvHD, supported by a dedicated software, including the updated recommendations. In view of this study, two surveys have been conducted, focusing the management of cGvHD and ancillary therapy in cGvHD, to address the current '*real life*' situation. The two surveys were sent to all 57 GITMO centers, performing allografting in Italy; the response rate was 57% and 66% of the interviewed centers, respectively. The first survey showed a great disparity especially regarding steroid-refractory cGvHD, although extracorporeal photo-apheresis resulted as the most indicated treatment in this setting. Another challenging issue was the strategy for tapering steroid: our survey showed a great variance, and this disagreement could be a real bias in evaluating outcomes in prospective studies. As for the second survey, the results suggest that the ancillary treatments are not standardized in many centers. All responding centers reported a strong need to standardize management of cGvHD and to participate in prospective trials. Before starting observational and/or interventional studies, a detailed knowledge of current practice should be encouraged.

INTRODUCTION

The prevalence and severity of chronic GvHD (cGvHD) have increased during the past 2 decades,[1,2] likely because of (1) increasing use of allogeneic hematopoietic stem cell transplantation (HCT) in older patients, (2) the widespread use of mobilized blood cells instead of marrow for grafting and (3) improvements in day-100 mortality.[1,3,4] Up to date, cGvHD still remains the leading cause of long-term nonrelapse morbidity and mortality following HCT.

Management of cGvHD is challenging because of polymorphic manifestations and lack of biomarkers for the diagnosis and assessment of disease activity. Although the National Institute of Health (NIH) consortium have made a considerable effort for sharing standardized guidelines published in 2005,[5] and more recently further updated,[2] a recent meta-analysis showed little progress in this field.[6]

On behalf of the Gruppo Italiano Trapianto di Midollo Osseo (GITMO), two questionnaires were proposed to Italian Centers performing allogeneic HCT, intended to address the 'real-life' management of cGvHD. Although heterogeneity of physician practice in allogeneic HCT has been demonstrated by many studies,[7–9] these surveys were focused on the practice of the centers (not single physician) and potential difficulties in following guidelines, with the aim to better design feasible prospective trials.

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Table 1. Cited guidelines

Diagnosis	N[a]	*First-line treatment*	N	*Second-line treatment*	N
Dignan *et al.*[12]	9	Dignan *et al.*[12]	9	Dignan *et al.*[12]	9
Filipovich *et al.*[5]	6	Wolff *et al.*[22]	9	Flowers *et al.*[10]	5
Flowers *et al.*[10]	5	Flowers *et al.*[10]	5	Wolff *et al.*[15]	2
Jagasia *et al.*[2]	2	Ruutu *et al.*[14]	5	Hildebrant *et al.*[30]	1
Carpenter[11]	2	Hildebrant *et al.*[30]	1		
Hildebrant *et al.*[30]	1	Dignan *et al.*[13]	1		
Dignan *et al.*[13]	1				

[a]Number of centers referring to the guideline.

MATERIALS AND METHODS

Invitations to participate in the surveys were emailed to the transplant program directors of all 57 centers that are part of the GITMO and that are performing allografting. As the aim was investigating the policies of the centers and not the single-physician approach, it was asked specifically to respond according to the common procedures of the center and not the individual one; the respondent was the director himself or his delegate. Two further reminders were sent to nonrespondents. Only one response per center was received, and surveys were collected using an online survey tool. The questions of both surveys have been preliminary discussed in a GITMO Meeting and reviewed by four experts in cGvHD, members of the GITMO GvHD Consortium and validated by the transplant team of the Hematology Department of Ancona.

The first survey was sent in 2015 and included 41 multiple-choice questions, with a few more in-depth open-ended questions, focused on management of cGvHD: use of published guidelines, choice of first line of treatment and handling of steroid-refractory cGvHD (see Supplementary Files 1a and b).

A second survey was sent in 2016 to investigate the use and diffusion of ancillary therapy and supportive care in patients affected by cGvHD: it consisted of 30 multiple-choice questions investigating business organization, medical needs, nursing, counseling and consultative medicine (see Supplementary Files 2a and b).

As applicable, participant and transplant center demographics and responses are summarized using descriptive statistics.

RESULTS

General issues

In the 6-month time frame, the survey on cGvHD management was accomplished by 32 respondents (28 adult transplant centers and 4 pediatric centers) for a response rate of 56%, similar to other reports.[7–9] In 2015, the median number of allogeneic transplants in the responding centers was 22 (range 2–78); 17/32 respondents belonged to academic hospital and 15 to community hospital. Answers from pediatric and adult centers did not differ, but only four pediatric centers completed the survey.

Twenty-nine centers referred to published guidelines for cGvHD management (Table 1). For diagnosis, most of them (N = 14) referred to guidelines proposed by the NIH or similar,[2,5,10,11] whereas the most cited guidelines for treatment were those of British and EBMT (European Society for Blood and Marrow Transplantation),[12–14] and those proposed by Wolff *et al.*[15] (Table 1). The NIH, British and European guidelines differ only for small details, but only 13/33 centers found them fully satisfactory. The main reasons for lack of satisfaction concerned the second-line approach (when to start treatment, treatment choice and/or absence of clear evidence in this setting) (Figure 1). At the time of survey, only three centers had a cGvHD trial open, all for steroid-refractory cGvHD.

First-line treatment

The criterion to start systemic treatment was the occurrence of moderate or severe cGvHD defined as per NIH indications[5,16] in 25 centers, and as per Shulman *et al.*[17] in 1 center, whereas 4 centers also considered the presentation with bad prognostic features, regardless the grading, and 2 centers treated all patients diagnosed with cGvHD.

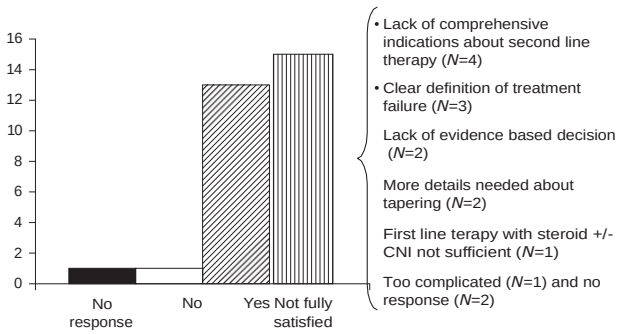

Figure 1. Are you satisfied by the current guidelines about chronic GvHD?

All centers indicated prednisone as first-line treatment that was started at the dose of 1 mg/kg in 27/32 centers, at 0.5 mg/kg in 4 centers and at 2 mg/kg in 1 center. Four centers used prednisone as single agent, whereas 28 preferred an association with other treatments: extracorporeal photo-apheresis (ECP, N = 25), calcineurine inhibitors (N = 17) and mycophenolate mofetil (MMF, N = 11), sirolimus (N = 2), imatinib (N = 2), pentostatin (N = 1) and rituximab (N = 1).

A broad inter-center variety has been reported regarding the duration of treatment, as well as the indication to and the choice of steroid-sparing agents. All but 6 centers used the updated NIH criteria to define response. Objective measurements (that is, pulmonary function and lab tests), patient reports and ability to treatment discontinuation were scored as very relevant for response judgment, whereas physician opinion was scored as medium. To evaluate response to treatment, 12 centers considered a fixed timepoint (such as 3 months), whereas 18 believed that response should be assessed at multiple timepoints to determine whether the benefit is sustained (2 not answered). In case of complete response, 30/32 centers tapered steroid slowly, but there was no uniformity on the definition of slow taper (Figure 2). In case of partial response, 18/33 centers tapered steroid as slowly as in complete response, 11/33 tapered steroid more rapidly and added another agent (3 no response).

Refractory cGvHD

Treatment failure, steroid refractoriness, dependency or intolerance were the main reasons for second-line therapy. Treatment failure was defined as follows: (1) progression or lack of response; and (2) clinically relevant flares of cGvHD within the first 3 months: 2 flares in 3 months according to 15 centers, 1 flare in 7 centers, 3 flares in 7 centers and 2 centers waited for more than 3 flares (1 did not answer). Twenty-two centers adopted the definition of

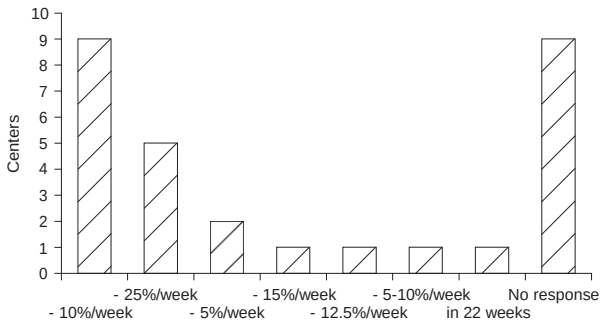

Figure 2. How did you manage steroid taper?

steroid dependency proposed by NIH: ≤0.25 mg/kg/day needed to prevent recurrence or progression of manifestations as demonstrated by unsuccessful attempts to taper the dose to lower levels on at least 2 challenges, separated by at least 8 weeks.[18] Six centers did not agree to wait 8 weeks and used a 3–5-week time frame instead, 3 centers disagreed with NIH criteria[18] without specifying their policy and 2 centers did not answer. Uncontrolled diabetes, hypertension, osteoporosis and psychosis were scored by at least 15 centers as main reasons for steroid intolerance.

Of the 32 centers, 26 usually considered second-line therapy between 4 and 8 weeks after initial approach. After the initial failure, 24 centers would use a different drug, whereas 7 would not (2 not answered). Sixteen centers had a policy for the choice of second-line treatment, and the choice was customized according to organ involvement and patient conditions in 24/32 centers (Table 2). Seven centers declared a policy for third line of treatment (Table 2). Overall, calcineurine inhibitors, ECP and MMF were the most used treatments for refractory cGvHD: calcineurine inhibitors regardless of the involved organ, ECP and sirolimus for skin, lung and gastrointestinal involvement, imatinib for skin and lung, infliximab and MMF for liver and gastrointestinal and rituximab for skin.

ECP was available in 25/32 centers (78%): ECP is delivered via 'closed' in 7 and via 'open' system in 16 centers. Patients were treated with ECP on 2 consecutive days at weekly intervals for the first month, then waned according to different schedules in 10 of the 25 centers; the ECP program was not declared in 11 centers, whereas it was as follows in the others: 2 consecutive days every other week ($N = 2$), 2 consecutive days weekly for 2–3 months ($N = 1$) and once weekly ($N = 1$). As shown in Table 2, ECP is often used for refractory cGvHD with cutaneous and mucosal involvement.

At the time of survey, 14 and 5 centers had 10–20 and 420 patients on active treatment for cGvHD, respectively. Figure 3 shows patient distribution according to centers and ongoing treatments.

Table 2. Centers' choice for refractory cGvHD according to organ involvement

	Second-line treatments (10 centers)				*Third-line treatments (3 centers)*			
	Skin mucosa	*GI*	*Liver*	*Lung*	*Skin mucosa*	*GI*	*Liver*	*Lung*
CNI	2	2	3	2	0	0	0	0
PUVA	1	0	0	0	0	0	0	0
ECP	7	4	3	2	1	1	2	1
Imatinib	3	0	0	7	2	0	0	1
Rituximab	3	0	0	0	2	0	0	0
Sirolimus	1	1	0	2	0	1	0	1
Methotrexate	1	0	1	0	2	0	0	1
High-dose steroids	0	0	0	1	0	0	0	0
MMF	0	2	4	0	0	0	2	0
Anti-TNFα	0	3	1	0	0	1	0	0
Azathioprine	0	1	1	0	0	0	1	0
Pentostatin	0	2	0	0	0	1	0	0
Montelukast	0	0	0	1	0	0	0	0
Azitromycin	0	0	0	1	0	0	0	0

Abbreviations: cGvHD = chronic GvHD; CNI = calcineurin inhibitor; ECP = extracorporeal photo-apheresis; GI = gastrointestinal; MMF = mycophenolate mofetil; PUVA = photochemotherapy.

Ancillary therapies and supportive care interventions

The survey on ancillary therapy was completed by 38 centers (32 adults and 6 pediatric), for a response rate of 67%, without differences raised from pediatrician centers. In 2015, the median number of transplants in the responding centers was 26.

The first set of questions focused on business organization (guidelines, presence of medical and nurses standard operating procedures (SOPs)). All centers declared to be compliant with the first consensus including the NIH recommendations,[19] and 31 out 38 had active projects or dedicated personnel to at least one aspect of ancillary therapy in their transplant programs. However, comprehensive medical procedures focused on topical therapies and drug-free collateral interventions were declared by 7 centers only. Fourteen centers did not mention ancillary therapies in their SOPs. Only 10 out 38 centers had specific SOPs for nursing care, whereas 13/38 centers included nurse tasks into some medical SOPs.

Then, the survey inquired about the presence of specific SOPs for each organ potentially target of ancillary therapies. As expected, the most covered issue was prevention and management of infectious disease (31/38 centers had dedicated SOPs), followed by oral (25 centers), lung (21), gynecologic (20) and eye care (18); neurocognitive functioning, depression and anxiety together were mentioned by all pediatric centers and only 7 adult ones. The results indicated that most of the centers have SOPs including some aspects of ancillary therapies, but very few of them accomplished all organs possibly involved. Similarly, many centers referred to specialists for multidisciplinary approach of cGvHD complications; however, 23/38 complained of the lack of consultant experts on organ-specific manifestation of cGVHD. Consequently, very few consultants felt competent enough to build a network of GITMO panel of experts.

Further questions investigated the degree of counseling about cGvHD late complications and quality of life post HCT. The majority (31/38) of centers addressed these topics before HCT, although only 20 of them believed to be exhaustive.

Future developments

All responding centers reported a strong need for and willingness to standardize first-line approach to cGvHD as, despite the accordance in the use of prednisone, the practical aspects remained uncertain: dose, management of toxicity, duration, taper and definition of common response criteria. Furthermore, there was a strong interest in prospective trials for steroid-refractory cGvHD. Only 2 centers have already had a protocol open for refractory GvHD.

Furthermore, all centers agreed to an incoming GITMO clarifying note on allogeneic HCT complications (GvHD, late complications and quality of life), properly revised, that may be used by all Italian transplant centers. With this platform, the GITMO GvHD Consortium designed a prospective censoring of cGvHD onset supported by a specific software based on the NIH diagnostic and response criteria.

DISCUSSION

Despite the high level of knowledge of the published guidelines, this survey showed a great disparity in the management of cGvHD, especially for steroid-refractory disease. Similarly, an international survey to assess the uptake of NIH recommendations conducted by EBMT–National Cancer Institute Chronic GVHD Task Force identified the therapeutic management of steroid-refractory cGvHD as the highest priority for research.[20] In a group of 235 patients with NIH-defined cGvHD, the median duration of systemic treatment from time of original onset was 28.7 months (range, 0.9–115 months),[21] meaning that the impact of this rare

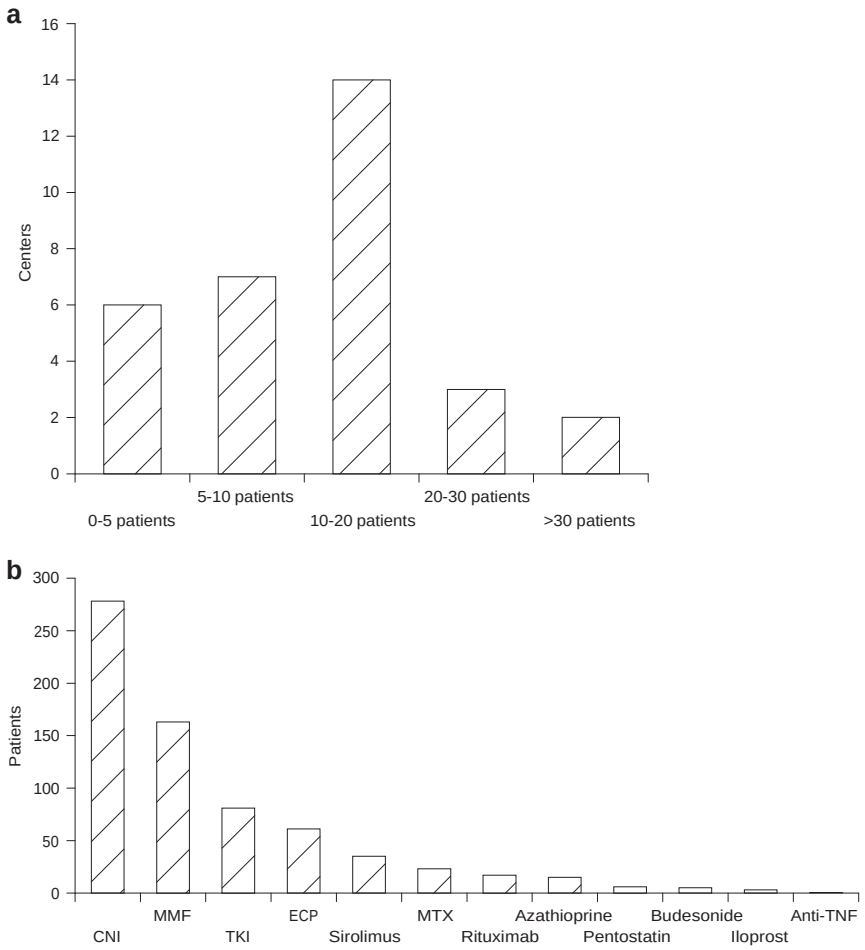

Figure 3. Patients on ongoing treatment for chronic GvHD. (a) Number of centers divided by the number of patients on current treatment. (b) Type of ongoing treatments. CNI, calcineurin inhibitor; MTX, methotrexate; TKI, tyrosine kinase inhibitor.

disease is still high, and further efforts should be done to improve treatment and quality of life.

This survey has been planned not only with the aim of collecting reliable information about the real-life practice in the Italian centers, but also because a new prospective observational study in newly diagnosed cGvHD was planned in the Italian GITMO centers. This noninterventional study will focus both on response evaluation (according to the updated NIH criteria) and long-term outcome with the support of a dedicated software that utilizes a complex algorithm to calculate both the single organ and the global response. In order to start this trial in all centers, based on a homogeneous platform, there was a general agreement about the need to define some basic standards about the major policies for the cGvHD management in the different Italian centers. These two surveys have been planned in order to have a common background and to speak the same language in this field; this aspect should be considered a true medical need, not only for some apparently shared definition of standard first-line treatment (including duration an tapering schedules), but also for the standardization of the ancillary treatments.

As expected, despite some inter-center disagreements, systemic corticosteroids were reported to be the first-line treatment for cGvHD in all GITMO centers; however, most of the centers associated steroids with ECP upfront, with the aim of increasing response rate and sparing steroids. The use of prednisone as first-line therapy is indeed widely supported by literature,[10,12,14,22] but randomized trials did not show any benefit from adding other drugs such as MMF,[23] azathioprine,[24] thalidomide[25] or hydroxychloroquine[26] to initial treatment of cGvHD. Furthermore, a trial comparing cyclosporine plus prednisone with prednisone alone showed no statistically significant differences in survival or the duration of treatment.[27] As for other alternative treatments (such as ECP) to be associated upfront with steroids, there are no clear evidences supporting its association, although this approach is theoretically attractive, given its tolerability and efficacy as second-line treatment.

Regarding first-line treatment, another challenging issue is the strategy for tapering steroid: our survey showed a great variance, mainly because of concern about side effects, although a rapid taper may cause cGvHD flares. A prototypic taper schedule proposed by the Seattle group[10] is designed to approximate a 20 to 30% dose reduction every 2 weeks, with smaller absolute decrements toward the end of the taper schedule, with adjustment according to disease response and toxicities.

General indications for secondary treatment include worsening manifestations in a previously affected organ, development of manifestations in a previously unaffected organ, absence of improvement after 1 month of treatment or inability to decrease the dose of prednisone below 1.0 mg/kg per day within 2 months.[10,15,18] In the GITMO survey, the general concepts appeared preserved, although there is some variability in the details mainly because of concerns about drug side effects as well as disease severity.

No consensus has been reached regarding the optimal choice of agents for secondary treatment of cGvHD. Treatment choices were based on physician experience, ease of use, need for

monitoring, kind of potential toxicity and risk of exacerbation of preexisting comorbidity.[10,15] Reports from the retrospective and prospective studies on this field indicated high response rates, but results remain difficult to interpret because of deficiencies in study design.[6,10] As consequence, in a recent consensus conference, steroids only achieved a strength of evidence level BIII-I, whereas all other options were graded less.[15] According to the cGvHD survey, ECP and MMF were the most widely used treatments, other than rechallenge with steroids and calcineurine inhibitors, and this is in line with most of the published indications.[15]

ECP was available in 25/33 centers and widely used, although with different schedules and not on many patients (Figure 3b). Recent recommendations from the Italian Society of Hemapheresis and Cell Manipulation and the GITMO included ECP in both adults and pediatric patients with cGvHD, either steroid resistant or steroid dependent.[28] ECP increases the costs for the management of GvHD, but the clinical improvement obtained through ECP makes the incremental costs economically 'acceptable'.[28]

Steroid-refractory cGvHD is an orphan disease without approved therapy, has low appeal for the companies, and this disease is very difficult to manage, with multiorgan involvement and unpredictable trajectory and response. The inter-center discrepancies in its management reflected more the complexity and polymorphism of the disease than the lack of clear and trusted guidelines. In 2011, Wolff *et al.*[15] published a consensus on the current evidence of treatment options for steroid-refractory cGvHD: ECP, thalidomide and methotrexate showed higher efficacy on mucocutaneus manifestations, rituximab on scleroderma and autoantibody-mediated cytopenia, etanercept and infliximab in gastrointestinal GvHD and imatinib, on the basis of its antifibrotic activity, on sclerodermic and mild lung manifestations. Although different treatment options are available, the sparse evidence for most treatment entities indicates the urgent need for specific trials.

The delayed immune reconstitution, caused by disease and treatment targeting the immune system, the refractory nature of cGvHD-related fibrosis and the limited success of systemic immunomodulatory treatments lead to significant persistence of morbidity for prolonged periods of time. Thus, ancillary therapies and supportive care became central components in the long-term management of cGvHD after HCT for most of the centers. For a comprehensive patient care, multidisciplinary approach involving different specialists is mandatory; however, lack of dedicated consultants and personnel emerged as the main pitfall in the survey, and more efforts are required in this field.

A particular scenario of jammed drug development happened; indeed, the overestimation of the response rate generated a plethora of promising drugs/interventions, making it difficult to select a shared investigational drug to compare with an undefined standard treatment. Today, after a long period of stagnation, new approaches for cGvHD treatment have been proposed thanks to the recent advances of our understanding of cGvHD pathophysiology[29] these new opportunities should start a new era of randomized clinical trials in this field after decades of small-size phase 2 trials or retrospective studies. However, a reliable tool for response evaluation is mandatory in order to avoid an overestimation of the response rate that is a common finding in most old-generation studies where the NIH response criteria have not been extensively used.

Overall, all involved GITMO centers professed a great interest and need for prospective trials investigating this setting. In this view and given the discrepancies enlightened by the surveys, a prospective observational study conducted by the GITMO is ongoing. This study will employ a software for cGvHD management that allows the automatic calculation of the global severity score of cGvHD, according to the recent NIH consensus and the standardized evaluation of the response in the different organs. Furthermore, these surveys raised the need of common GITMO SOPs that should include sharing consultants and specific centers' skills. These facilities should constitute a solid foundation for subsequent reliable interventional prospective studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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