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INVITED REVIEW

ADVANCES IN CELL AND GENE THERAPY WILEY

Advances in the treatment of chronic graft-versus-host disease

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Abstract

Chronic Graft Versus Host Disease (cGVHD) occurs in over 50-70% of patients undergoing hematopoietic stem-cell transplantation (HSCT) and is the leading cause of late non-relapse mortality. cGVHD typically has insidious multi-organ involvement and has been associated with a worse quality of life, functional status, and increased risk of subsequent comorbidities. The last several years have seen advances in the understanding of the disease, which provided a framework for the design of translational and clinical studies with newer agents currently at different phases which that may hopefully change the course of the disease. This review provides an overview of more commonly used and newer second line options for the management of cGVHD.

KEYWORDS

bone marrow transplantation, chronic graft versus host disease, graft-versus-host disease, survivorship

1 | BACKGROUND

Chronic Graft-Versus-Host Disease (cGVHD) occurs in over 30%-70% of patients undergoing hematopoietic stem-cell transplantation (HSCT)[1] and is the leading cause of late nonrelapse mortality.[2] Furthermore, cGVHD has been associated with a worse quality of life, functional status, and increased risk of subsequent comorbidities. Unfortunately, advances in the practice of HSCT over the last several years have not decreased the incidence or severity of this complication.[3] This is thought to be at least in part due to increased survival after HSCT and the use of pooled peripheral blood mononuclear cells. Thus, although many GVHD prevention regimens have reduced the incidence of acute graft-versus-host disease (aGVHD), cGVHD has been less affected.[4]

Chronic GVHD typically has insidious multi-organ involvement, predominantly of mucocutaneous tissues. This defines two different and typical clinical presentations: lichen planus-like or lichenoid and sclerodermatous. The lichenoid form resembles lichen planus, with a similar pattern of involvement of cutaneous and mucosal tissues. Sclerodermatous cGVHD is a fibroproliferative disease that when severe can involve the joints with potentially severe impact on mobility. Both of these clinical presentations can coexist, and include other organs like gastrointestinal, pulmonary, hepatic, and musculoskeletal tissues.[3]

Although some forms of transplant such as T-cell depleted,[5] cord blood[6] and haploidentical with posttransplant cyclophosphamide[7] have been associated with less cGVHD or duration of immunosuppression, the problem is far from eradicated. A substantial number of patients who are otherwise cured from their malignancies continue to suffer from the consequences of cGVHD, so the search of effective therapies beyond corticosteroids is critical.

1.1 | The treatment of chronic GVHD

The treatment of cGVHD has relied on corticosteroids for decades.[8] So far, no other single agent or combination has shown more efficacy than corticosteroids alone. Prednisone is usually given over prolonged periods of time with a relatively slow taper, which sometimes leads to severe long-term effects that add to the morbidity of cGVHD.[9] Unfortunately, the outcomes are less than optimal. The initial response to prednisone, usually started at a dose of 1 mg/kg, is about 50%, over a long period of time. Calcineurin inhibitors do not seem to enhance the efficacy of steroids, though they may spare long-term steroid-related toxicity such as avascular necrosis of the bone.[10]

TABLE 1 Phase one trials

ClinicalTrials.gov identifier	Experimental arm
NCT01954979	Abatacept
NCT00397332	Alefacept
NCT00529035	IL-2
NCT01522716	Mesenchymal Stromal Cells
NCT01672229	Bortezomib
NCT01680965	Ofatumumab
NCT01937468	Treg-enriched infusion + IL-2
NCT02195869	Ibrutinib
NCT03790332	Ibrutinib
NCT02250300	MLN9708
NCT02318082	IL-2
NCT02385019	Donor regulatory T cells
NCT02749084	Donor-derived purified T regulatory cells (T reg DLI)
NCT02759731	Baricitinib
NCT03225417	Ixazomib + Tacrolimus + Sirolimus
NCT03415867	Glasdegib
NCT03604692	SNDX-6352
NCT03683498	Donor regulatory T cells

Above is a list of ongoing Phase 1 clinical trials currently active or recently completed, which are listed at "https://clinicaltrials.gov."

The last several years have seen advances in the understanding of the disease,[11] which provided a framework for the design of translational and clinical studies with newer agents currently at different phases (Tables 1, 2, and 3) that may hopefully change the course of the disease. In this review, we provide an overview of more commonly used and newer second line options for the management of cGVHD. The studies listed on Tables 1, 2, and 3 are currently active or recently completed, and listed on Clinicaltrials.gov.

2 | IN VIVO T-CELL DEPLETION: ALEMTUZUMAB AND ANTI-THYMOCYTE GLOBULIN

2.1 | Alemtuzumab

Alemtuzumab (Campath) is a recombinant DNA-derived humanized monoclonal antibody (Campath-1H) directed against the 21-28 kD cell surface glycoprotein, CD52. CD52 is expressed on T and B lymphocytes, monocytes, monocyte-derived dendritic cells, macrophages, and eosinophils. Some studies suggest the potential role of alemtuzumab in minimizing aGVHD when used as part of the conditioning regimen for allogeneic HSCT.[12,13] Toxicities include: hematologic toxicities such as pancytopenia/marrow hypoplasia, autoimmune idiopathic thyrombocytopenia, autoimmune hemolytic anemia. Infusion-related reactions are also observed and infectious complications, particularly opportunistic infections have also been observed. There are limited data to support use in cGVHD. Clinical Trials: NCT01042509.

2.2 | Anti-thymocyte globulin

Anti-thymocyte globulins (ATG) are polyclonal immunoglobulins produced by immunizing rabbits with the T-lymphoblastic Jurkat cell line or immunizing horses with human thymus lymphocytes. These cytotoxic antibodies are directed against antigens expressed on human T lymphocytes resulting in T-cell depletion through cell lysis. Recent prospective randomized trials suggest benefit of ATG in the prevention of cGVHD,[15,16] although results have not been consistent across studies,[17] particularly on survival outcomes. This is likely to be at least partially related to study design, differences in target population, ATG preparation and dosage and schedules of administration. Further analysis of these data will help define the exact role of ATG in the prevention of cGVHD without jeopardizing the desirable graft-versus-tumor effect. Toxicities of ATG include a rare but severe, and sometimes life threatening, infusion transfusion reactions ranging anaphylaxis to a mild flu like symptoms which can occur weeks after infusion. Fever, chills, reversible oxygen desaturation, and nonischemic chest pain are also potential toxic side effects of treatment. Clinical Trials: NCT00678275 and NCT01295710.

3 | COSTIMULATORY BLOCKADE: ABATACEPT AND ALEFACEPT

3.1 | Abatacept

Abatacept is an immunomodulatory drug that acts as an inhibitor of T-cell activation via costimulatory blockade, specifically which links the extracellular domain of human cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) to the modified Fc portion of human immunoglobulin G1 (IgG1). This molecule has been found to downregulate activation in T cells in clinical responders. Several anti-CD28 antagonist monoclonal antibodies have been successfully utilized in animal models of renal allograft, heart allograft, and liver allografts. The most common adverse effects include headache, nausea, and increased risk for upper respiratory infections. Clinical trials ongoing are seeking for both a clinical response to treatment and a steroid-sparing effect.[18] Clinical Trials: NCT01954979.

3.2 | Alefacept

Alefacept, is an immunomodulatory drug that acts as an inhibitor of T-cell activation via costimulatory blockade, specifically it is a CD2-directed LFA-3/Fc fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc (hinge, CH2 and CH3 domains) portion of IgGl. Alefacept causes a selective reduction in circulating effector memory T cells and that there is a reduction in the total number of conventional memory T and natural killer (NK)-T cells. The most

TABLE 2 Phase two trials

ClinicalTrials.gov identifier	Experimental arm
NCT00003894	Thalidomide
NCT00054613	ECP
NCT00144430	Pentostatin
NCT00186667	Sirolimus
NCT01042509	Alemtuzumab and Rituximab
NCT01106833	Sirolimus + calcineurin inhibitor + prednisone
NCT01135641	Ciclosporine, Corticosteroids and Rituximab
NCT01161628	Rituximab
NCT01366092	IL-2
NCT01509560	Everolimus
NCT01862965	Prednisone and Everolimus
NCT02519816	Autologous peripheral blood mononuclear cells ex vivo depleted for reactive T cells
NCT02841995	KD025
NCT02997280	Ruxolitinib
NCT03007238	ECP plus IL-2
NCT03082677	Ixazomib
NCT03083574	Photopheresis Theraflex ECP
NCT03109353	ECP with 5-aminolevulinic acid
NCT01862965	Prednisone + Everolimus (PredEver)
NCT02340676	ECP plus IL-2
NCT02966301	Arsenic Trioxide
NCT02491359	Carfilzomib
NCT02513498	Ixazomib
NCT03640481	KD025
NCT03616184	Ruxolitinib
NCT03395340	Ruxolitinib
NCT00186628	Rituximab
NCT01688466	Pomalidomide

Above is a list of ongoing Phase 2 clinical trials currently active or recently completed, which are listed at "https://clinicaltrials.gov."

common adverse effects include headache, nausea, and increased risk for upper respiratory infections. Considering its relatively low rate of the toxicity, efficacy in psoriasis, and effect on T-cell subtypes, it may be a promising agent for the treatment of cGVHD, in particular with cutaneous manifestations.[19] Clinical Trials: NCT00397332.

4 | PROTEASOME INHIBITORS: BORTEZOMIB AND IXAZOMIB

Bortezomib a proteasome inhibitor, used in the treatment of multiple myeloma and mantle cell lymphoma, and also undergoing investigation for the treatment of steroid refractory cGVHD. Translational research has shown promise in bortezomib administrated at different stages of cGVHD. Bortezomib blocks NF-kappa β activation and augments the apoptotic response. This ultimately blocks T-cell activation, proliferation, and survival of alloreactive T cells. Bortezomib has shown activity in cutaneous cGVHD, including sclerodermatous forms.[20] Ixazomib is a reversible proteasome inhibitor, which targets the 20S proteasome. The most common toxicity of these therapies includes peripheral neuropathy, which represents the most common dose limiting toxicity as well as thrombocytopenia. There are ongoing trials evaluating its role in treatment of cGVHD. Clinical Trial: NCT02250300, NCT03225417, NCT03082677, NCT01672229, and NCT02513498.

5 | MTOR INHIBITORS: SIROLIMUS

Sirolimus is an mTOR inhibitor that has been used in the setting of both prevention of aGVHD and treatment of cGVHD. Sirolimus can promote the generation of regulatory T cells and has been shown benefit in cutaneous cGVHD, particularly sclerodermatous forms.[21,22] Common toxicities included infections, shortened prothrombin time, thrombotic microangiopathy, hyperlipidemia, and impaired wound healing.[21,22] Clinical Trial: NCT01862965, NCT01509560, NCT00186667, and NCT01106833.

6 | B-CELL MODULATION: RITUXIMAB, OFATUMUMAB, BTK/ITK, AND SYK INHIBITORS

6.1 | Rituximab

Rituximab, a chimeric monoclonal antibody, which targets CD20 + B Lymphocytes has been found to reduce the incidence of cGVHD through B-cell depletion. Cutler et al demonstrated overall response and complete response rates at 1 year of 70% and 10% respectively. More significant activity was shown for skin involvement (sclerodermatous and lichenoid), oropharyngeal and ocular GVHD.[23] Rituximab was also found to have an effect in reducing cGVHD requiring systemic therapy when used as part of the conditioning regimen in allogeneic transplantation.[24] Clinical Trials: NCT01161628, NCT01135641, and NCT00186628.

6.2 | Ofatumumab

Ofatumumab, a humanized IgG1 kappa monoclonal antibody (mAb), targets a unique epitope upon CD20 B cells. The mechanism of this monoclonal antibody is a potent complement-dependent cytotoxicity directed toward CD20 upon cellular surface. Like rituximab, it has a B-cell depleting effect, but with enhanced affinity of ofatumumab to CD20 and greater complement-dependent cytotoxicity. Additionally, ofatumumab has been shown in initial studies to elicit monocyte-derived macrophage mediated Ab-dependent cellular phagocytosis. Ofatumumab is approved for chronic lymphocytic

TABLE 3 Phase three trials

ClinicalTrials.gov identifier	Control arm	Experimental arm
NCT00031824	Conventional treatment	Conventional treatment + Hydroxychloroquine
NCT00678275	Conventional treatment	Conventional treatment + ATG FRESENIUS (Anti-Lymphocyte-Globulin)
NCT01295710	Placebo	US-ATG-F (Anti-Lymphocyte-Globulin)
NCT02291770	Placebo	Mesenchymal Stromal Cells
NCT02959944	Placebo + Prednisone	Ibrutinib + Prednisone
NCT03584516	Placebo + Prednisone	Itacitinib + Prednisone
NCT03474679	Ibrutinib (open label)	Ibrutinib
NCT03112603	Best Available Therapy	Ruxolitinib

Above is a list of ongoing Phase 3 clinical trials currently active or recently completed, which are listed at "https://clinicaltrials.gov."

leukemia therapy and has shown efficacy in other lymphoid malignancies as well as autoimmune conditions.[25] Given these experimental findings, clinical studies are under in the pretransplant as well as posttransplant settings. Clinical Trials: NCT01680965.

6.3 | Ibrutinib

Ibrutinib inhibits Bruton's tyrosine kinase (BTK) in B cells and interleukin-2–inducible T-cell kinase in T cells. This was the first drug which had received FDA approval for the treatment of CGHVD. It has shown some promise in one study where patients who have previously failed one or more line of therapy were trialed on Ibrutinib in addition to systemic corticosteroids. One clinical trial has shown that in 75% of those enrolled and responded to treatment with Ibrutinib, those subjects were able maintain a reduction in corticosteroid use for over 20 weeks following Ibrutinib therapy.[26] Most common side effects are gastrointestinal side effects, such as diarrhea, and hypertension has been associated with Ibrutinib (BTK inhibition). Cardiovascular side effects such as atrial fibrillation and other cardiac arrhythmias have consistently shown increased risk while on treatment with Ibrutinib. Increased bleeding risks while on treatment has also been observed so this medication should be held during significant bleeding events or for surgeries. Clinical Trials: NCT02959944, NCT02195869, NCT03790332, and NCT03474679.

7 | JANUS KINASE INHIBITORS: RUXOLITINIB, BARICITINIB, AND ITACITINIB

Janus kinase (JAK) is a family of intracellular, nonreceptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway. Various JAK inhibitors are approved or under investigation for treating various malignancies, autoimmune disorders, and inflammatory diseases. There are four members of the JAK family, of which JAK1, JAK2, and JAK3 seem to be most relevant for GVHD. JAKs broadly regulate immune processes that underlie autoimmunity and GVHD, including APCs, T cells, and B cells. Preclinical and clinical studies suggest that JAK inhibition may disrupt GVHD without negatively affecting GVL activity. After alloHCT, JAKs are important effectors of all three phases leading to GVHD, (ie tissue inflammation, T cell/ APC interaction and immune cell migration with tissue damage), transducing inflammatory signaling downstream of cytokines and regulating development and function of immune cells including APCs and T cells.[27] The most common side effects related to JAK inhibition include: significant cytopenias; in particular drug-induced anemia and thrombocytopenia.

JAK inhibition has shown promise on a variety of organ systems, there are ongoing studies investigating the efficacy of JAK inhibitors in the prevention and treatment of cGVHD.[27] Ruxolitinib is an oral selective Janus-associated kinase 1(JAK1) and JAK2 inhibitor that was approved by the FDA in 2011 for the treatment of patients with myelofibrosis. Ruxolitinib is a JAK1 and 2 inhibitor that has shown excellent activity in both aGVHD and cGVHD. In cGVHD, the overall response rate was over 80%, with 36% recurrence of cGVHD at 1 year and durable for 6 months. These responses were seen in both cutaneomucosal and visceral cGVHD.[28,29] Baricitinib (JAK1/2 inhibitor) and Itacitinib (JAK 1 inhibitor) are currently being studied in the treatment of cGVHD. Clinical Trials NCT02759731, NCT02997280, NCT03584516, NCT03616184, NCT03395340, and NCT03112603.

8 | INDUCTION OF IMMUNE TOLERANCE: EXTRACORPOREAL PHOTOPHERESIS AND INTERLEUKIN-2

8.1 | EXTRACORPOREAL PHOTOPHERESIS

Extracorporeal photopheresis (ECP) for the treatment of GVHD has been one of the most extensively evaluated therapies in the setting of cGVHD failing frontline corticosteroids. While these reports have all concluded ECP to be efficacious in the treatment of patients with cGVHD, almost all of these studies have design problems which are common in cGVHD clinical trials, including: small number of patients, heterogeneous forms of cGVHD (progressive, quiescent, de novo),

organ involvement, disease duration, specific report on concurrent and prior therapies, and inconsistent response assessment among the different studies. Most patients who included in ECP trials failed multiple prior lines of therapy and were on corticosteroids at the time of initiation of ECP. Couriel et al reported an overall response rate of 60%, and the majority of these persisted at 6 months of ECP initiation. The organs that showed the best responses were skin, particularly sclerodermatous type, oral mucosa, liver, and lung. The cumulative incidence of corticosteroid discontinuation at 1 year was 22%.[30] A randomized study that compared ECP with best available therapy in patients with cutaneous GVHD showed a higher efficacy and steroid-sparing effect in the ECP arm.[31] Trials are ongoing which are seeing the efficacy of ECP in addition to conventional therapies, specifically corticosteroids, IL-2, cyclosporine, and tacrolimus. One clinical trial is utilizing 5-aminolevulinic acid, which is a photosensitizing agent and may enhance responses to ECP. There are no medication toxicities associated with the use of ECP, given not a pharmacologic therapeutic, but there is an absolute contraindication to ECP use is in patient populations who cannot tolerate extracorporeal volume loss; such as in sepsis, shock physiology, or advanced heart failure. There are also procedural and logistical concerns with ECP use, given the costs and duration with performing ECP, potential for complications from long-term line placements such as central line infections or thrombosis. The logistical concerns for patients who require weeks of treatments, and risks for the development of iron deficiency during the course of treatment. Clinical Trials: NCT03007238, NCT03083574, NCT03109353, NCT00054613, and NCT02340676.

8.2 | Interleukin-2

Interleukin-2 (IL-2) is critical for Treg-cell development, expansion, activity, and survival. Koreth et al demonstrated responses to low dose IL-2 in patients with cGVHD who failed corticosteroids. Administration was associated with preferential, sustained Treg-cell expansion in vivo and amelioration of the manifestations of cGVHD in a substantial proportion of patients. [32,33] There are ongoing trials evaluating different treatment schedules of IL-2 and combination with other strategies like ECP and Treg-enriched infusions. Clinical Trials: NCT01937468, NCT00529035, NCT02318082, and NCT01366092.

9 | CELLULAR THERAPIES

9.1 | Mesenchymal stem cells

Mesenchymal stem cells (MSC) are a heterogeneous population of pluripotent mesenchymal stromal cells which exhibit fibroblast morphology. These cells have the ability to differentiate immunosuppressive function and immunomodulatory effects. Despite *in vitro* experiments confirming that MSC suppress mixed lymphocyte reactions and in vivo evidence from mouse models that show evidence that MSC can ameliorate GVHD, clinical trials to date using MSC to treat GVHD have shown mixed results in the setting of both aGVHD and cGVHD.[34] There are ongoing studies for further examination of the potential role of MSC in the treatment or prevention of cGVHD. Toxicities of this therapy are related to infusional toxicity storage of donor MSC's and potential infectious contamination. Clinical Trials: NCT02291770 and NCT01522716.

9.2 | Regulatory T (Treg) cells

Regulatory T cells are a subset of T cells that can originate in the thymus (natural Treg cell) or can be produced in peripheral lymphoid organs (induced Treg cell). Regulatory T cells can suppress effector T-cell response and the activity of additional immune cells, including dendritic and B cells. A balance among effector T cell and Treg cell populations is essential in achieving control of the quality and extent of adaptive immune responses, for establishing self-tolerance, and intolerance to nonself antigens. The ability of Treg cells to suppress aberrant immune responses, regulate T cell homeostasis, and to maintain tolerance, prompted interest in their impact in the treatment of cGVHD.[35,36] Toxicities of this therapy are related to infusion reactions and potential infectious contamination of cells. Clinical Trials: NCT02749084, NCT02385019, and NCT03683498.

9.3 | IMIDs: Thalidomide and pomalidomide

Thalidomide is active in cGVHD, through inhibiting the production of interleukin (IL)-6, which is a growth factor for the proliferation of myeloma cells. In addition, they activate apoptotic pathways through caspase 8-mediated cell death. Thalidomide has shown some activity but also significant toxicity in the treatment of cGVHD, including: neutropenia, neuropathy, and somnolence.[38] Pomalidomide is a member of the class, which is 100-fold more potent than thalidomide in inhibiting production of TNFα and increasing Th1-cells and has less associated toxicity. The efficacy and safety of pomalidomide in patients with corticosteroid-resistant cGVHD have not been extensively studies, but preliminary data suggest some clinical activity in cutaneomucosal cGVHD.[39] Clinical Trials: NCT00003894 and NCT01688466.

9.4 | Hedgehog inhibition: Vismodegib and glasdegib

Glasdegib and vismodegib, both hedgehog inhibitors, are under investigation for patients with sclerodermatous cGVHD. Currently, three different hedgehog proteins have been identified: Sonic hedgehog (Shh), Indian hedgehog (Ihh), and Desert hedgehog (Dhh). Although all hedgehog proteins share significant sequence homology, their distribution patterns differ, with Shh being the most abundant hedgehog protein in the skin. The hedgehog pathway is activated through the binding of hedgehog proteins to the membrane receptor Patched homolog 1 (Ptch-1), leading to fibrogenesis. Early murine and in vitro studies have shown promise in the treatment of sclerodermatous cGVHD through the inhibition of hedgehog.[40]

There are ongoing clinical trials with vismodegib and glasdegib for the treatment of cGVHD. Common toxicities include dysgeusia, muscle spasms, and alopecia. QT prolongation is also a concerning feature of this therapy. Clinical Trials: NCT03415867.

10 | HOW TO MANAGE CGVHD

The treatment of cGVHD has become more structured since the first meeting of the NIH Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease.[3] The development and validation of more specific and consistent metrics for the diagnosis and assessment of response to therapy, have provided a framework for the development of guidelines for better trial design in cGVHD. Furthermore, the advent of new and potentially more active therapies, and recent FDA approval of the first specific treatment for cGVHD, ibrutinb, are all rapidly changing the treatment landscape.

This said, cGVHD continues to be a very challenging disease when it requires systemic therapy. Corticosteroids remain the single most active agent, and they require long-term administration, resulting in severe long-term effects that blend into the syndrome of cGVHD.

There are general aspects in the management of cGVHD that are applicable to the vast majority of patients. On the other hand, there is also a more individualized side that involves the choice of the specific immunomodulatory approach. Although we tend to emphasize the latter, it is important to understand that both are just as important and interdependent.

Below is a structured approach to the treatment of cGVHD into these two categories.

As quality data supporting a substantial proportion of recommendations are based on common sense and experience, they are meant to be regarded a general practice guidelines.

1. General Guidelines
    1. Chronic GVHD is rare and it requires a multidisciplinary approach. Consequently, its subspecialized nature has led to the creation of "cGVHD Clinics" across the world. These clinics gather providers with an interest in the disease, with the intention of continuity of care and a high level of specific expertise. Although the advantage of chronic GVHD Clinics has not been formally compared to other models of care, they surely provide a better structure and access easier access to different subspecialties with experience in the timely management of organ-specific complications
    2. Ancillary and supportive care is a major part of the treatment of cGVHD, and it is frequently forgotten. These measures are intended toward: 1- Education about the disease and realistic expectations about therapy, 2- Prevention of factors that may reactivate or worsen the disease or steroid-related complications and 3- Alleviation of symptoms to improve quality of life. Some of these measures can result in a much higher subjective or even objective impact than immunomodulation.
    3. The development of formal institutional guidelines following NIH Consensus recommendations to consistently operationalize these general aspects of care is becoming more common and will surely have a positive impact at multiple levels.
2. Choice of Immunomodulatory Agent:
    1. The choice of the specific immunomodulatory agent should always take into consideration efficacy data, including steroid-sparing effect, and provider and/or institutional experience with that particular intervention. The cure of cGVHD is ultimately immune tolerance.
    2. Clinical trial is always the best choice for first or any line of treatment of cGVHD. All the recommendations that follow assume that the patient could not be accrued into a clinical trial. In the absence of a clinical trial, first-line therapy should be initiated with prednisone or prednisone dose-equivalent corticosteroid at 1 mg/kg/day. This should not be delayed in any patient with moderately severe or severe cGVHD, where the potential benefit of GVL effect may be outweighed by the negative impact of GVHD-related immunosuppression or symptoms.
    3. The timing and decision of second or subsequent treatment should take into account NIH Consensus guidelines, and, very importantly, prevention of irreversible sclerotic manifestations or severe long-term effects of prolonged corticosteroid therapy.
    4. Cutaneomucosal cGVHD: Sclerotic forms of cGVHD favorably respond to ECP, and this is a reasonable second line of choice after corticosteroid failure. Lichenoid cGVHD, which frequently includes involvement of skin, ocular, oral, and vaginal mucosae and the cutaneous form may not be as responsive to ECP. Oral and vaginal cGVHD have been reported to have a high-response rate to ECP and are also responsive to rituximab. Therefore, second-line therapy for lichenoid cGVHD is usually rituximab, before committing the patient to a prolonged course of ECP. The recent FDA approval of Ibrutinib for cGVHD failing corticosteroids opened up a new treatment option, and over time we will have more data regarding what clinical presentations are more responsive. JAK inhibition is another pathway that has shown high-response rates steroid refractory cGVHD, and clinical trials are currently ongoing.
    5. Chronic GVHD of the lung, or bronchiolitis obliterans, is particularly problematic, particularly in corticosteroid-dependent, advanced stages, when the disease is almost always unresponsive to any additional lines of therapy. Beyond steroid inhalers, azithromycin and monteleukast, there is no standard second-line therapy for this condition. Based on our own previously reported experience, our usual second line is ECP. Beyond ECP, we would resort to newer agents like ibrutinib or ruxolitinib.

11 | CONCLUSION

For the first time in years, the treatment of cGVHD is changing. The development of novel strategies targeting multiple different pathways is a reality, and the combination of more active agents could entirely spare long-term corticosteroid toxicity. Ancillary and supportive care has also experienced major advances, such as new antimicrobial modalities, the development of scleral lenses and others. Furthermore, a better understanding of the disease could lead to a more personalized, targeted approach, leading to better survival and quality of life outcomes. Overall, the landscape is probably more optimistic than it has ever been. The majority of ongoing clinical trials, currently at an early stage will hopefully provide more guidance on how to best care for these patients over the coming years.

12 | FUTURE PERSPECTIVE

There have been exciting advances in the treatment of cGVHD, which is changing how this condition is being managed. The development of novel strategies targeting multiple different pathways are being refined and validated. The combination of more active agents should improve symptoms of cGVHD as well as spare corticosteroid toxicity related to long-term steroid dependence.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

CONFLICTS OF INTERESTS

The authors have no conflicts of interest to disclose.

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