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REVIEW

Chronic GVHD: Where are we? Where do we want to be? Will immunomodulatory drugs help?

YPL Linhares[1], S Pavletic[2] and RP Gale[3]

Chronic GVHD (cGVHD) is an important problem after allotransplants. Some risk factors for cGVHD are similar to those of acute GVHD (aGVHD) but others are distinct indicating sometimes overlapping but unique pathogeneses. Precise incidence and prevalence data of cGVHD are lacking because of diverse diagnostic criteria but a 50% risk is a reasonable estimate. Incidence and prevalence of cGVHD are probably growing because of increased use of unrelated donors, blood rather than bone marrow (BM) grafts, decreased early transplant-related mortality (TRM) and increasing frequency of allotransplants. Pathophysiology of cGVHD is complex and poorly understood. Notably, no reliable surrogate end point to predict mechanism(s) of cGVHD has been identified. Therapy of cGVHD is unsatisfactory. Corticosteroids are effective but other drugs are controversial and few are rigorously tested in randomized trials. Highly variable response rates are reported because of small sample sizes and inconsistencies in eligibility, diagnostic and response criteria. We focus on the possible role of immunomodulatory drugs (IMiDs), thalidomide lenalidomide and pomalidomide, in preventing and treating cGVHD. The data suggest activity of thalidomide but at doses not clinically practical in many instances. There are few data with lenalidomide. Trials of pomalidomide, which has immune activities like thalidomide but with fewer adverse effects, are beginning. Because cGVHD is not recently reviewed in *Bone Marrow Transplantation*, we give a brief background and discuss challenges in diagnosing, understanding and treating cGVHD including the recently proposed National Institutes of Health consensus criteria for cGVHD.

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INTRODUCTION

Chronic GVHD (cGVHD) is an important complication of allogeneic hematopoietic cell transplantation.[1–3] It occurs in about 50% of persons surviving >1 year post transplant and causes substantial morbidity and mortality. There has been little progress over the past 30 years in preventing and/or treating cGVHD. Moreover, incidence and prevalence are increasing because of several factors including: (1) increased use of blood cell rather than BM grafts; (2) increasing use of incompletely HLA-matched related and unrelated donors; (3) increased use of donor-lymphocyte infusions, especially in the context of reduced-intensity allotransplants; (4) increased number of transplants done each year; and (5) increased proportion of transplants in older persons.[4–6] The focus of our review is on the use and potential of IMiD-class drugs to prevent and/or treat cGVHD. These drugs have unique, complex immune regulatory activities. As a prelude, we review some relevant definitional, laboratory and clinical features of cGVHD.

CHRONIC GVHD

Reported incidences of cGVHD vary dramatically: 6–80% but 50% is a reasonable estimate.[7–9] Several important subject-, disease- and transplant-related variables correlate with the risk of cGVHD including: (1) recipient and/or donor genetic disparity (like related or unrelated, degree of HLA matching); (2) graft type (blood, BM or umbilical cord blood): (3) graft manipulation (like T-cell depletion); and (4) whether donor-lymphocyte infusions are given post transplant, which are unadjusted for in these reports with diverse incidences.[10] Some data indicate that male recipients of grafts from female donors, especially those who are multiparous, have an increased risk of cGVHD. This increased risk from multiparity may also apply to female recipients. It is unknown whether progeny gender of multiparous donors correlates with risk of cGVHD.[11] Detection of antibodies to Y-chromosome encoded antigens in male recipients of grafts from female donors correlates with an increased risk of cGVHD.[12] Whether this is a cause: effect relationship is unknown.

Some studies report prior acute GVHD (aGVHD) strongly correlated with cGVHD.[13] A recent multivariate analysis by Flowers *et al.*[14] in which National Institutes of Health (NIH) definitions for aGVHD and cGVHD were used showed grade-3/-4 aGVHD was a risk factor for cGVHD. However, there were also some unique risk factors correlated solely with cGVHD including: (1) blood cell grafts and (2) older donor age. Also, use of female donors for male recipients had a greater effect on risk of cGVHD than on aGVHD. There was little change in hazard ratios with other variables after adjusting the hazard ratio of cGVHD for aGVHD. This suggests that the association of certain risk factors with cGVHD is independent of aGVHD. These data support the notion cGVHD is not merely a time-dependent expression of aGVHD.

aGVHD and cGVHD were previously considered to have distinct clinical and temporal features. By convention, the temporal cutoff for classifying a clinical syndrome as aGVHD or cGVHD was 100

[1]Department of Medicine, Division of Hematology/Medical Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]GVHD and Autoimmunity Unit, Experimental Transplantation and Immunology Branch, National Cancer Institute, Bethesda, MD, USA and [3]Department of Medicine, Section of Haematology, Division of Experimental Medicine, Imperial College, London, UK. Correspondence: Dr RP Gale, Department of Medicine, Section of Haematology, Division of Experimental Medicine, Imperial College, 11693 San Vicente Boulevard, Suite 335, Los Angeles, CA 90049-5105, USA.
E-mail: robertpetergale@aol.com
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days post transplant. However, this binary classification is obscured when aGVHD occurs after day 100, when there is delayed development of hematopoietic chimerism, when there are flares after tapering post transplant immune suppression or following post transplant infusions of donor lymphocytes. In 2005, the NIH consensus project proposed two main GVHD categories each with two subcategories.[10,15] For aGVHD there is (1) *classic* aGVHD occurring within 100 days post transplant and (2) *persistent, recurrent or late onset* aGVHD, a clinical syndrome resembling aGVHD but persisting beyond or developing after 100 days post transplant commonly referred to just as 'late' aGVHD. For cGVHD there is (1) *classic* cGVHD subtype (without features characteristic of aGVHD) and (2) *overlap syndrome* with synchronous clinical features of cGVHD and aGVHD. The old 'limited' and 'extensive' cGVHD staging nomenclature is replaced with the more informative individual organ severity scoring (grades 0–3) and global cGVHD (mild–moderate–severe) stage which in addition to cGVHD manifestations also account for subjects symptoms and quality of life.[10,16] Feasibility of use and clinical utility of the NIH consensus cGVHD classification and severity scoring is validated in several prospective studies.[8,16,17] Several retrospective and prospective analyses identified additional prognostic variables which complement the NIH consensus staging system including low platelet levels, poor performance score when cGVHD is diagnosed, and gastrointestinal tract involvement which significantly influence outcome and progressive onset type of cGVHD as adversely affecting survival.[18,19] These correlations need confirmation.

cGVHD is a multiorgan alloimmune and autoimmune disorder characterized by immune dysregulation, immune deficiency, impaired end-organ function and decreased survival.[20] Although these features of cGVHD were noted >30 years ago there has been little progress sorting out the precise mechanism(s). Therapy of cGVHD, whatever the cause(s), is typically prolonged immune suppression which may further aggravate the immune suppression intrinsic to cGVHD.[21]

PATHOPHYSIOLOGY

The pathophysiology of cGVHD is poorly understood (to say the least) despite several decades of research. T cells (Th_1 and Th_2) and B cells are important suggesting a global loss of immune tolerance including abnormalities in the function of regulatory T cells (T_{regs}; CD4+, CD25+, FoxP3+) which maintain self-tolerance.[22] Studies in mice indicate that normal T_{regs} can suppress aGVHD and cGVHD and that deficient and/or defective T_{regs} worsens aGVHD and cGVHD.[23] There are conflicting data in humans concerning the role of T_{regs} in the development of cGVHD.[24] A recent study suggests that therapy with low-dose IL-2 can increase T_{regs} and improve severe cGVHD.[25]

Several studies suggest that aGVHD is associated with predominant Th_1-type immune response and cGVHD with a predominant Th_2-type immune response.[26] Th_1 cells produce IFN-γ that mediates cell-mediated immunity whereas Th_2 cells produce IL-4, IL-5 and IL-13 that mediate humoral immunity. T-cell dysregulation results in cytokine abnormalities which may be important in cGVHD. High levels of TNF-α, IL-6, TGF-β and IL-1β and low levels of INF-γ and IL-10 are reported in persons with cGVHD.[27–31] A recent study by Imanguli *et al*.[31] challenges this paradigm of cGVHD as type-II cytokine-mediated disorder. Data from this study suggest that activation of the type-I IFN axis is important in oral cGVHD.

Autoimmunity and autoreactive T cells are important in cGVHD. Some studies report a functional host thymus is not required to induce cGVHD and that quiescent autoreactive T and B cells in transplants from non-autoimmune donors can be activated and expanded to induce cGVHD.[32] In contrast, involvement of thymus-dependent T-cell pathways in cGVHD development begins with injury to the thymus from chemotherapy and/or radiation and/or from aGVHD leading to loss of self-tolerance.[26,33,34] Some data in mice suggest that during aGVHD graft-donor CD4+ T cells that can recognize and react against host tissues develop in the thymus in and mediate cGVHD.[34]

Some data suggest an important role for B cells in cGVHD. Because B cells produce antibodies and can, in some instances, expose or present antigen to T cells, it may enhance development of cGVHD. Anti-nuclear, -mitochondrial, -parietal, -smooth muscle and -parotid autoantibodies are present in some persons with cGVHD.[35,36] Also, persons with autoantibodies have more cGVHD-associated symptoms than persons without autoantibodies.[35] Autoantibodies against platelet-derived growth factor receptor may have a role in cGVHD.[37] These platelet-derived growth factor receptor-α autoantibodies stimulate thyrosine phosphorylation, resulting in a cascade of events that may contribute to inflammation and fibrosis.

Some studies report elevated levels of BAFF (B-cell activating factor of the TNF family) in persons with cGVHD. BAFF is produced by T cells and granulocytes and supports differentiation and survival of normal B cells in persons with cGVHD and autoimmune diseases.[23,38] Fujii and coworkers reported persons with early onset cGVHD have elevated levels of sBAFF, sIL-2Rα, sCD13 and anti-dsDNA autoantibodies. sBAFF, anti-dsDNA and antinuclear antibody are elevated in late onset cGVHD, suggesting B-cell activation.[39–41] These observations may explain occasional reports of benefit of therapy of cGVHD with anti-B-cell antibodies like anti-CD20 (rituximab for instance).[40]

These T- and B-cell pathways and others are potential targets for treating cGVHD. However, it is important to note no immune parameter(s) is a reliable biomarker of diagnosis, severity, prognosis or therapy outcome of cGVHD.[42] Consequently, clinical trials, ideally randomized, blinded and placebo controlled, are the sole way to know whether a therapy intervention in cGVHD is safe and effective.

CLINICAL FEATURES

cGVHD usually targets the skin, eyes, mouth, gut, liver, lungs, joints and genitourinary system. Typical skin manifestations are sclerosis and poikiloderma and lichen-type lesions. There are often hyperkeratotic oral plaques. A lung biopsy may show bronchiolitis obliterans. These clinical features resemble autoimmune diseases like progressive systemic sclerosis, systemic lupus erythematosis and Sjögren's syndrome.[10]

cGVHD is categorized in the NIH global scoring system as mild, moderate or severe depending on the number of organs involved and the severity of the abnormality(ies).[10,15] Systemic immune suppression is usually advised for persons with moderate or severe cGVHD. Systemic therapy is also considered in persons with thrombocytopenia (platelets $<100\times10e9/L$) or progression while receiving prednisone.[43] cGVHD eventuates in impaired performance score, poor quality-of-life and death. [8-10,21,44-46]

TREATMENT

Pharmacological interventions that prevent aGVHD are not effective in preventing cGVHD. Strategies using anti-thymocyte globulins for *in-vivo* T-cell depletion show promise but no benefit on survival.[47] The standard initial therapy of cGVHD is prednisone with or without a calcineurin inhibitor. However, only about 50% of persons have a durable response.[22,43] There is no standard next therapy. Recommended interventions include about 40 drugs, all studied in poorly standardized, phase-2 trials or reported in retrospective case analyses, including sirolimus, tacrolimus, mycophenolate, MTX, MoAbs, pentostatin, imatinib, extracorporeal photopheresis, low-dose IL-2 and many others.[25,48-49] Choice

between drugs is based on logistics; cost, failed prior treatments, toxicity profile and subject or clinician preference.

Therapy of cGVHD is a difficult problem to address because of the logistical challenges in conducting such trials and the lack of standardized criteria for study design. To improve conduct and interpretation of clinical trials, the NIH-Sponsored Consensus Development Project published guidelines addressing diagnosis and staging, histopathology, biomarkers, assessment of therapy response, ancillary therapy and supportive care and the design of cGVHD clinical trials.[10,50–54]

cGVHD typically is diagnosed within 6 months post transplant and lasts 2–5 years. About 85% of survivors can discontinue systemic immune suppression by that time. Five-year survival of persons with cGVHD is 30–40% for those with high-risk disease and for persons failing corticosteroids. There is better 5-year survival, about 70–80%, in persons with lower risk cGVHD and those responding to corticosteroids.[9,55,56]

Treatment goals for cGVHD include reversing symptoms and signs, preventing recurrence, disability or death. A goal could be also correcting associated immune abnormalities. This is, of course, challenging, as therapy of cGVHD typically involves immune-suppressive drugs that have multiple acute and cumulative toxicities. The therapy of cGVHD is largely unsatisfactory and most persons, especially those who fail corticosteroids, should be treated on investigational protocols whenever possible.[45]

IMID-CLASS DRUGS

Thalidomide

Thalidomide is effective in modulating cGVHD in rodents and is studied as therapy and prevention of cGVHD in humans.[57] Vogelsang *et al*.[58] reported that thalidomide is a safe and effective treatment for severe cGVHD. Several other studies reproduced these findings. Thalidomide is the third most commonly used drug in phase-2 trials of therapy of cGVHD in persons failing corticosteroids.[59]

Thalidomide has diverse immune-modulating effects including: (1) reduced levels of TNF-α; (2) co-stimulation of T cells to produce IL-2 and IFN-γ; (3) inhibition of other cytokines like IL-1β, IL-6, IL-12; (4) downregulation of cell surface adhesion molecules involved in leukocyte migration; and (5) anti-angiogenesis.[48,57,60] Its biological activities are contrasted with other IMiDs in Figure 1. There are seven phase-2 and three phase-3 trials of thalidomide in cGVHD. Analysis of the trials is complex for several reasons: (1) different definitions of cGVHD; (2) different response criteria; (3) inclusion of children in some studies; (4) different doses of thalidomide; (5) different prior therapy (ies); (6) different objectives (for example, therapy vs prevention and initial therapy vs second-line therapy after corticosteroid failure); and (7) thalidomide alone vs combinations and other variables. This heterogeneity, not uncommon in cGVHD trials, makes it difficult/impossible to draw precise conclusions regarding safety and efficacy of thalidomide in cGVHD.

Table 1 summarizes data from 7 trials in 245 subjects with cGVHD receiving thalidomide after failing initial therapy at dosesof 100–1600 mg/day. These data include children and adults in diverse therapy settings and using diverse response criteria. In all, 46 subjects are reported to have had a complete (19%) and 51 a partial response (21%) for an overall response in 97 subjects (40%). This result is encouraging but there is the undoubtedly important issue like possible of selective reporting of favorable outcomes. These trials are reviewed in below.

Vogelsang *et al*.[58] used thalidomide, 800–1600 mg/day, as initial therapy of 21 subjects with high-risk cGVHD and as salvage therapy for 23 subjects with cGVHD failing initial therapy. Initial dose in children was 3 mg/kg given four times daily. Complete response was reported in 14 subjects and partial response in 12.

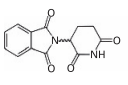
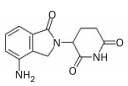
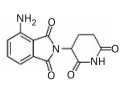
	Thalidomide	Lenalidomide	Pomalidomide
			
Anti-inflammation	+	++++	+++++
T-cell stimulation	+	++++	+++++
Anti-angiogenesis	++++	+++	++++
Anti-proliferation	+	+++	++++
Pro-erythroid	+	+++	++++

Figure 1. Biological activities of IMiDs.

Survival was 64% with 55 months follow-up and 76% in persons failing prior therapy and 48% in those with previously untreated high-risk cGVHD. Confidence intervals were not reported and there was no comparator cohort. Main adverse effects were sedation, neuropathy and constipation.[58] Heney *et al*.[61] reported responses in five of six persons receiving thalidomide, 100–200 mg/day. Response was best in skin cGVHD. Two subjects developed neuropathy. Cole *et al*.[62] reported five children with advanced cGVHD treated with thalidomide, 12–25 mg/kg/day. There was one complete response and four partial responses. Adverse effects were minimal and there was no neuropathy. Parker *et al*.[63] treated 80 subjects with advanced cGVHD with thalidomide, 400–1200 mg/day. There were nine complete and seven partial responses. Twenty-nine subjects discontinued because of adverse effects, including sedation, constipation, neuritis, neutropenia and rash. Rovelli *et al*.[64] used thalidomide, 3–12 mg/kg/day in 14 children with cGVHD. Six complete responses and four partial responses were reported. Browne *et al*.[65] treated 37 subjects with advanced cGVHD with thalidomide, 200–800 mg/day. In all, 1 subject had a complete and 13, partial responses. Responses were more common in children than in adults. Kulkarni *et al*.[66] reported data on 59 subjects with advanced cGVHD using thalidomide, 600–1200 mg/day. Thirteen subjects had a complete and eight, a partial response. Two subjects developed poly-neuropathy, two, deep vein thromboses and one, thrombocytopenia. There are a case series and two case reports not included in Table 1. Mehta treated two children with cGVHD. One had a complete and the other a PR. Adverse effects were sedation and constipation.[67] Forsyth reported a response to thalidomide, 400 mg/day, in a case of bronchiolitis obliterans from cGVHD.[68] Staumont-Salle reported a response to thalidomide, 100 mg/day, in a subject with lichenoid vulvar lesions from cGVHD.[69]

Table 2 summarizes data from three randomized trials. Two were attempts to treat cGVHD and one, to prevent it.[70–72] Koc *et al*.[70] reported a placebo-controlled trial of thalidomide, 200–800 mg/day, in adults and 3–12 mg/kg/day in children. Thalidomide was discontinued in 23 of 25 subjects in the thalidomide cohort and 17 of 26 subjects in the placebo cohort because of intolerance, mostly neutropenia, sedation and neuropathy. This high discontinuation rate in the placebo cohort underscores the variable natural course of cGVHD and subsequent difficulty of performing clinical trials in persons with advanced cGVHD. It also underscores the need for placebo-controlled double-bind studies. It is also possible that thalidomide was ineffective in this population. Arora *et al*.[71] reported a randomized, placebo-controlled trial of initial treatment of cGVHD with thalidomide. There was no benefit of adding thalidomide, 200–800 mg/day, vs placebo to cyclosporine and prednisone. Chao *et al*.[72] reported thalidomide increased the incidence and severity of cGVHD when given in a prevention study.

Table 1. Phase-2 trials of thalidomide in advanced cGVHD

	Dose	N	*Response*
Vogelsang *et al.*[59]	800–1600 mg/day (⩾3 mg/kg/day children)	44	CR-14; PR-12
Heney *et al.*[62]	100–200 mg/day	6	CR-2; PR-3
Cole *et al.*[63]	12–25 mg/kg/day	5	1 CR; PR-4
Parker *et al.*[64]	400–1200 mg/day	80	CR-9; PR-7
Rovelli *et al.*[65]	3–12 mg/kg/day	14	CR-6; PR-4
Browne *et al.*[66]	200–800 mg/day	37	CR-1; PR-13
Kulkarni *et al.*[67]	600–1200 mg/day	59	CR-13; PR-8

Abbreviation: cGVHD = chronic GVHD.

Table 2. Phase-3 trials of thalidomide in initial therapy or prevention of cGVHD

	Dose	N	*Response*
First therapy			
Koc *et al.*[71]	200–800 mg/day	51	Early discontinuation due to toxicity
Arora *et al.*[72]	200–800 mg/day	54	No difference
Prevention			
Chao *et al.*[73]	400 mg/day	59	Increased cGVHD

Abbreviation: cGVHD = chronic GVHD.

In summary, several phase-2 trials report about 50% responses to thalidomide doses of 100–1600 mg/day. Much of the variability between trials reflects small sample sizes, heterogeneous subjects and diverse, poorly defined response criteria among other complexities discussed above. Thalidomide doses of >200 mg/day were poorly tolerated. Phase-3 trials show no convincing benefit of thalidomide for prevention or initial therapy of cGVHD. Although thalidomide may be active against cGVHD at high doses in rodents, these doses cannot be reproducibly and safely achieved in humans in most instances. An alternative, not mutually exclusive problem is the variable course of cGVHD with exacerbations and improvements unrelated to therapy interventions, which may mimic drug adverse effects and/or therapy response.

Lenalidomide

Given the many reports and widespread use of thalidomide in corticosteroid-resistant cGVHD, there are remarkably few data on use of lenalidomide in this setting. A recent Boolean PUBMED search of the English-language literature 1966-present using the search terms *lenalidomide* AND *chronic graft-versus-host disease* identified fewer than 10 reports most of which were anecdotes. One phase-2 study of lenalidomide maintenance for myeloma after allogeneic transplantation was discontinued because of a claimed increased risk of aGVHD.[73] However, there was no concurrent control arm. Another report suggested that lenalidomide induced a syndrome resembling aGVHD in autotransplant recipients.[74] It is difficult to interpret these few data. One possibility is that concerns about BM toxicity of lenalidomide preclude widespread use. Another is publication bias: trials or treatments may have been done but were not reported because of unfavorable results. The bottom line is efficacy of lenalidomide in corticosteroid-resistant cGVHD is not known because it appears not extensively studied.

Pomalidomide

Pomalidomide is a novel immune-modulating drug with 4000-fold greater inhibition of TNF-α production compared with thalidomide.[75] A comparison of biological activities of pomalidomide with thalidomide and lenalidomide is included in Figure 1. Pomalidomide is extensively used in humans in the setting of clinical trials primarily for the treatment of multiple myeloma and myeloproliferative neoplasm-associated myelofibrosis.[76,77] It offers high potency without the dose-limiting toxicities of neuropathy and sedation. In persons with multiple myeloma, the dose-limiting toxicity is BM suppression with a maximum-tolerated dose of 2 mg/day.[78] Several features of pomalidomide suggest it may be useful in treating cGVHD including: (1) *in-vitro* suppression of TNF-α (human monocytes);[79] (2) increasing Th_1 (mouse cancer vaccine, human CD4+ T cells *in vitro*);[80,81] (3) suppression of Th_2 (mouse cancer vaccine);[80] and (4) stimulation of IL-12 and sIL-2Rα (humans).[78,80] However, other effects of pomalidomide have potential adverse effects in treating cGVHD including: (1) increased CD45RO+ (memory) CD4 and CD8 T cells (humans);[78] (2) decreased T_{regs};[82] (3) increased Th_2 (polarized human CD4+ T cells *in vitro*);[81] and (4) increased B cells (*in-vitro* human CD19+ cells).[83] Recently, cereblon was identified as an essential mediator of lenalidomide and pomalidomide anticancer activity in multiple myeloma. These drugs react with cereblon to mediate IFN-regulator factor downregulation. This may affect development of Th-17 cells sometimes implicated in the development of cGVHD.[84,85] Whether this is a possible target of activity of pomalidomide in cGVHD is unknown. Pomalidomide is effective in treating experimental scleroderma in mice and in a model of bleomycin-induced skin fibrosis (Celgene Corp; unpublished data). Because, as discussed, the precise pathogenesis of cGVHD is unknown (and may differ in different persons), it is impossible to predict the impact of therapy with pomalidomide outside the context of a controlled clinical trial.

There is one report of a small phase-2 study of pomalidomide in cGVHD. Pusic *et al.*[86] treated eight subjects failing corticosteroids. Subjects received 3 mg/day with dose reductions to 2 mg, 1 mg and 0.5 mg/day. Seven subjects had dose reductions because of muscle cramps, tremor and fatigue. Five subjects discontinued therapy for worsening cGVHD of the skin and mouth ($N=1$), pain ($N=1$) and no response ($N=3$). There was no BM suppression, somnolence, constipation or thromboembolic events. Three persons reached the primary evaluation end point at 6 months at the 2 mg ($N=2$) or 1 mg dose ($N=1$). These three had global PRs per NIH criteria (erythema and gastrointestinal) and <PR ongoing improvements (skin, mouth and eyes). This study shows

feasibility of giving pomalidomide to humans with cGVHD and absence of serious side effects at doses of $\leqslant 2$ mg/day. A randomized phase-2 trial of pomalidomide in persons with corticosteroid-resistant cGVHD is planned. There are also large, ongoing studies of pomalidomide in multiple myeloma and myeloproliferative neoplasm-associated myelofibrosis.

CONCLUSIONS

Considerable preclinical data support efficacy of thalidomide therapy for cGVHD. Data from uncontrolled clinical trials of therapy after failure of other drugs, mostly corticosteroids, support this notion. Randomized trials have not been performed for the second-line cGVHD treatment. Data from randomized trials of cGVHD prevention or initial therapy are less convincing. One randomized therapy trial could not be completed because few subjects could tolerate the prescribed dose (nor could subjects receiving placebo) whereas another study showed no benefit when thalidomide was added to standard post transplant immune suppression. The one prevention trial showed no benefit.

Disparate results of intervention to prevent and/or treat aGVHD or cGVHD are common. Examples include daclizumab that seems effective in corticosteroid-resistant aGVHD but detrimental when added to corticosteroids as initial therapy or mycophenolate that is ineffective when added to steroids for the initial treatment of cGVHD.[87,88] Reasons for this are complex and incompletely understood. Its possible corticoisteroid-resistant cases of GVHD are biologically different than untreated cases. We conclude thalidomide is likely to be effective as second-line therapy of cGVHD therapy but that it is difficult to give doses compatible with those effective in preclinical models.

There are few data regarding lenalidomide therapy or prevention of cGVHD. It is unclear whether this represent publication bias, limited use or other factors. Persons with cGVHD typically have various degrees of BM dysfunction and the BM toxicity of lenalidomide poses a substantial challenge. Although low-dose lenalidomide has not been extensively evaluated, it seems unlikely this will be a useful approach to therapy or prevention of cGVHD.

There are few data of pomalidomide in cGVHD. The single phase-1/-2 trial is difficult to interpret. A randomized phase-2 study will start soon. Lack of neurotoxicity and BM toxicity is attractive but additional clinical data are needed.

There are major challenges to developing therapy for corticosteroid-resistant cGVHD. Prominent among these are (1) cGVHD is complex and there are no convincing surrogate *in-vitro* or *in-vivo* parameters to predict benefit. We are left with clinical trials and ultimately, placebo-controlled randomized trials, which are difficult and costly to perform; (2) although there are considerable efforts to define cGVHD and therapy response, none is prospectively validated. This confounds design and execution of clinical trials using end points other than survival; (3) one of the major consequences of cGVHD is immune suppression. However, immune-suppressive drugs are our dominant therapy intervention. This may aggravate rather than help cGVHD outcomes; (4) cGVHD has multiple impacts confounding outcomes analyses. cGVHD is correlated with decreased survival and with disability, but preventing or decreasing cGVHD is correlated with increased graft failure, infections and cancer recurrence. Consequently, the most convincing outcome of a trial of cGVHD intervention is a survival benefit. This is difficult to show in a chronic disease and is confounded by competing, unrelated causes of therapy failure. Progress in treating and/or preventing cGVHD is a substantial challenge in improving survival of recipients of blood cell or BM allotransplants. Whether IMiD-class drugs will be useful in this setting remains to be determined. Current focus is on pomalidomide; trials are progressing.

FUTURE CONSIDERATIONS

Progress in diagnosing, staging and treating cGVHD is ideally based on an accurate and reliable understanding of pathogenesis. Unfortunately, this is unlikely and we remain with empirical clinical trials of drugs that seem promising. We can make progress in cGVHD by standardizing diagnosis, staging and evaluation of response using the proposed NIH consensus criteria, perhaps with some added variables. Use of validated biomarkers may also help but none are currently available. There is progress in developing collaborations and further testing the NIH criteria in large prospective observational and interventional trials.[89–91] The end point of any therapy intervention in cGVHD must be a clinically important improvement in transplant outcomes, especially survival and quality of life needs to be confirmed in a double-blind randomized clinical trial. Substantial progress in preventing and treating aGVHD was made 30 years ago without a precise understanding of etiology or pathogenesis. We hope similar progress may be made in preventing and treating cGVHD which is an even more complex and challenging problem because of multiple confounded outcomes of therapy interventions. The goal is to prevent cGVHD-associated morbidity and mortality without losing graft-vs-cancer effects in diseases where it exists. Lack of specificity of current cGVHD therapies makes achieving this goal challenging and difficult. Currently, we need to focus on developing better treatment strategies.

CONFLICT OF INTEREST

SZP is an employee of the Center for Cancer Research, National Cancer Institute and National Institutes of Health. RPG is a parttime employee of Celgene Corp.

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