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Corticosteroid-Free Primary Treatment of Chronic Extensive Graft-versus-Host Disease Incorporating Rituximab

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Chronic graft-versus-host disease (cGVHD) is a significant determinant of overall outcome and quality of life in survivors of allogeneic hematopoietic cell transplantation. Standard initial therapy of cGVHD is based on prolonged use of corticosteroids and a calcineurin inhibitor and has not changed for over 3 decades, despite limited efficacy and long-term toxicity. Rituximab is an attractive agent for the upfront treatment of cGVHD because of its favorable toxicity profile, efficacy in steroid-refractory cGVHD, and ability to serve as a steroid-sparing agent in autoimmune diseases. We hypothesized that a corticosteroid-free regimen incorporating rituximab would result in improved outcomes when used for the initial treatment of cGVHD. Twenty-five patients (median age, 56 years; range, 29 to 77) with extensive cGVHD were enrolled on a prospective phase II trial. Enrollment was limited to patients with first onset extensive cGVHD requiring systemic immunosuppression and without residual or concurrent acute graft-versus-host disease. cGVHD was classified as de novo, interrupted, and progressive in 12, 11, and 2 patients, respectively. cGVHD severity (National Institutes of Health grade) was mild, moderate, and severe in 3, 14, and 8 patients, respectively. All patients received rituximab 375 mg/m^2 $\times$ 4 weekly doses, then 1 dose every 3 months $\times$ 4 doses, in addition to mycophenolate mofetil and either tacrolimus or sirolimus. No other systemic immunosuppression was permitted, and only a short-course of steroids ($\leq$4 weeks) was allowed at physician discretion; otherwise, treatment was deemed a failure and patients were treated off study. Twenty-two of 25 patients (88%) responded to treatment. Of the 22 responding patients, the median time to maximum response was 161 days (range, 35 to 300 days) with maximum response being complete in 21 of 22 patients and partial in 1 patient. Excluding the 3 patients taken off study for treatment failure, corticosteroids were used sparingly, with only 2 patients receiving any steroids for a median of 15 days (range, 13 to 18 days). Immunosuppression was discontinued in 17 of 22 evaluable patients (77%) with a median time to discontinuation of 300 days (range, 138 to 488 days). After immunosuppression discontinuation, cGVHD did recur in 7 patients after a median of 166 days (range, 21 to 393 days), requiring reinstitution of systemic immunosuppression (estimated cGVHD recurrence rate of 37%). With a median follow-up of 27 months, estimated 2-year overall survival is 82%. This regimen utilizing rituximab in the initial therapy of cGVHD is effective and avoids the use of corticosteroids in the majority of patients. In permitting early discontinuation of immunosuppression while obviating the need for prolonged exposure to systemic corticosteroids, this regimen may result in reduced treatment-related morbidity and mortality associated with cGVHD and its treatment.

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is the most important cause of late morbidity and mortality after allogeneic stem cell transplantation, occurring in up to 60% to 70% of long-term survivors [1-4]. With the increasing number of allogeneic transplantations using peripheral blood stem cells and mismatched and unrelated donors, and with the increasing age of transplantation recipients, cGVHD will continue to be a serious challenge after allogeneic transplantation. cGVHD requires therapy for many months and often years [5,6], and it is the cause of death in up to one third of all long-term survivors after transplantation for leukemia [7]. Moderate-to-severe cGVHD markedly reduces quality of life, in addition to its effects on mortality [8-11]. Despite the

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prevalence of cGVHD and importance of prevention, an effective treatment strategy for cGVHD has been difficult to achieve because of the heterogeneous nature of the problem and the lack of clear evidence for the majority of treatment options.

Standard immunosuppressive therapy (IST) for cGVHD using glucocorticoids with a calcineurin inhibitor has not changed in several decades, despite the fact that most patients respond inadequately. If the total time to discontinue all systemic IST is measured as a surrogate for graft tolerance, it takes a median of 2 to 3 years from the onset of cGVHD therapy, depending on stem cell source and other factors [12]. Unfortunately, despite the relationship between cGVHD and reduced relapse risk, the prolonged duration of cGVHD makes it the leading cause of infection, morbidity, and late treatment-related deaths [8,13-17]. The widespread and sometimes irreversible manifestations of cGVHD may negatively impact quality of life, even after tolerance is achieved. New approaches to the treatment of cGVHD are needed to achieve early control of cGVHD manifestations and facilitate tolerance.

The morbidity and mortality associated with cGVHD are caused not only by cGVHD-associated immunodeficiency and organ dysfunction, but also by the immunosuppressive medications used treat it. Long-term glucocorticoid treatment impairs immune function and can, therefore, increase the risk of opportunistic infections. Other glucocorticoid therapy-related complications include avascular necrosis, glucose intolerance, hypertension, weight gain, changes in body habitus, cataracts, osteoporosis, myopathy, and disturbances of mood and sleep. Attempts to improve upon corticosteroids and a calcineurin inhibitor as initial therapy for cGVHD have been unsuccessful.

Failure to improve cGVHD therapy may be partly attributed to an incomplete understanding of the pathophysiology of cGVHD. cGVHD is traditionally thought to be mediated by donor-derived, alloreactive T cells, although studies have not consistently shown a favorable impact of T cell depletion on cGVHD [18,19]. There is now mounting evidence implicating B cells in the pathophysiology of cGVHD. Antibodies to Y chromosome–encoded minor histocompatibility antigens are generated after sex-mismatched allogeneic transplantation [20] and the presence of these antibodies has been correlated with the occurrence of cGVHD [21]. These findings led to the hypothesis that an anti–B cell monoclonal antibody may be an effective therapy for cGVHD. Clinical studies have subsequently confirmed the efficacy of rituximab in steroid-refractory cGVHD, with objective responses noted in 50% to 70% of patients, allowing tapering and, in some cases, withdrawal of IST [22-26]. Early evidence also suggests a role for rituximab during the early post-transplantation period for prevention of cGVHD [27,28].

In the current study, we hypothesized that rituximab would be efficacious in the upfront treatment of patients with extensive cGVHD. Incorporation of rituximab into the initial treatment of cGVHD may be advantageous because of its favorable toxicity profile, its proven efficacy in the treatment of steroid-refractory cGVHD, and its ability to serve as a steroid-sparing agent in other autoimmune diseases [29-34]. We hoped to demonstrate that rituximab would have significant activity in the initial therapy of cGVHD while eliminating the need for corticosteroids. In addition, we hypothesized that the early use of rituximab would allow for earlier discontinuation of IST, which should translate into reduced treatment-related morbidity and mortality.

PATIENTS AND METHODS

Eligibility and Enrollment

Eligible patients were those with a first episode of symptomatic extensive cGVHD, requiring systemic immunosuppression. The diagnosis of cGVHD was made by National Institutes of Health (NIH) consensus criteria [35], requiring, at a minimum, the presence of at least 1 diagnostic clinical sign of cGVHD or the presence of at least 1 distinctive clinical manifestation confirmed by biopsy or other relevant tests in the same or another organ. Patients were excluded from the study based on the following criteria: creatinine $>$ 2.0 mg/dL, uncontrolled infection, recurrent or progressive malignancy, residual or concurrent acute graft-versus-host disease (GVHD), systemic corticosteroid use $>$ 7 days before study initiation, or minimally symptomatic cGVHD requiring local therapy only.

Treatment Plan

Patients were initiated on a corticosteroid-free treatment regimen consisting of rituximab. A 375 mg/m^2 dose was administered for 4 weekly doses on day 1, 8, 15, and 22, then 1 dose every 3 months $\times$ 4 doses (3, 6, 9, and 12 months after study initiation). Tacrolimus was continued/resumed to maintain serum levels of 10 to 20 ng/mL (sirolimus could be substituted if there were a contraindication/intolerance to tacrolimus). Mycophenolate mofetil was started at a dose of 15 mg/kg twice daily. All other immunosuppressive agents, excluding locally acting corticosteroids or other topical agents, were not permitted. When cGVHD was inactive/quiescent for at least 4 weeks, immunosuppressive drugs were tapered at the discretion of the treating physician. Systemic corticosteroids could be added to the regimen, at the discretion of the treating physician, if cGVHD progressed after 2 weeks of therapy or showed no improvement after 4 weeks of therapy. If a patient then responded to systemic corticosteroids, they were subsequently tapered so as to be discontinued by 4 weeks. Patients requiring $>$4 weeks of systemic corticosteroids and/or additional immunosuppressive medications/interventions were considered to have treatment failures, and further treatment was performed off-study at the discretion of the treating physician.

Study Assessments

Formal study assessments were performed at 1, 2, 3, 6, 9, 12, 18, and 24 months, and included medical history, physical examination, laboratory evaluation, documentation of concomitant medications, completion of institutional GVHD assessment form, and completion of a GVHD patient self-report form. All patients, responders, and those with treatment failure had planned follow-up for a period of 2 years.

Study Endpoints

The primary objective of the study was to estimate the rate of complete and overall response of cGVHD to treatment. *Complete response* (CR) was defined as resolution of all reversible manifestations of cGVHD. *Partial response* was defined as improvement in global NIH severity grade (eg, from severe to moderate, from moderate to mild, etc). Secondary objectives were to estimate the requirement for and duration of systemic corticosteroids; time to immunosuppression withdrawal; and incidence of nonrelapse mortality (NRM), disease-free and overall survival, cGVHD recurrence after IST discontinuation, and need for second-line cGVHD therapy. *Second-line cGVHD therapy* was defined as requirement for corticosteroids $>$ 4 weeks, additional nonstudy therapeutic agents, or extracorporeal photopheresis. This was distinguished from the reinstitution of study drugs after IST withdrawal for cGVHD recurrence, which was not considered second-line cGVHD therapy.

Statistical Analysis

The study was powered to detect a statistically significant increase in cGVHD CR rate when compared with historical results in patients treated with systemic corticosteroids and a calcineurin inhibitor (approximately 50%) [36,37]. It was hypothesized that, under this protocol, the rate would be at least 80%. Thus, we statistically formalized this study by testing the null hypothesis that P, the CR rate, is .5 or less versus the alternative hypothesis that P is greater than .5. A sample size of 25 patients gives 90% power with an alpha $=$ .05, using the formula for a 1-sample binomial (2-sided) test of a proportion.

The Kaplan-Meier method was used to estimate the survival probabilities. The cumulative incidence was estimated for NRM, relapse, requirement of second-line treatment, and cGVHD recurrence to accommodate competing risk. NRM and relapse were competing risks for each other and were both competing risks for requirement of second-line treatment. The competing risk of cGVHD recurrence was non-cGVHD death. The start of the initial immunosuppression was considered as the time origin for all endpoints except for cGVHD recurrence, for which achievement of complete response was the time origin.