Randomized Trial of Hydroxychloroquine for Newly-diagnosed Chronic Graft-versus-Host Disease in Children: A Children’s Oncology Group Study

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Journal Title: Biology of Blood and Marrow Transplantation
Volume: Volume 18, Number 1
Publisher: Elsevier | 2012-01, Pages 84-91
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1016/j.bbmt.2011.05.016
Permanent URL: https://pid.emory.edu/ark:/25593/r839v

Final published version: http://dx.doi.org/10.1016/j.bbmt.2011.05.016

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Accessed August 16, 2019 3:41 AM EDT
Randomized Trial of Hydroxychloroquine for Newly Diagnosed Chronic Graft-versus-Host Disease in Children: A Children’s Oncology Group Study

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The Children’s Oncology Group conducted a multicenter Phase III trial for chronic graft-versus-host disease (cGVHD). The double-blind, placebo-controlled, randomized study evaluated hydroxychloroquine added to standard therapy for children with newly diagnosed cGVHD. The study also used a novel grading and response scoring system and evaluated clinical laboratory correlates of cGVHD. The primary endpoint was complete response (CR) after 9 months of therapy. Fifty-four patients (27 on each arm) were enrolled before closure because of slow accrual. The CR rate was 28% in the hydroxychloroquine arm versus 33% in the placebo arm (odds ratio [OR] = 0.77, 95% confidence interval [CI]: 0.20-2.93, \( P = .75 \)) for 42 evaluable patients. For 41 patients with severity assessment at enrollment, 20 (49%) were severe and 18 (44%) moderate according to the National Institutes of Health Consensus Conference global scoring system. The CR rate was 15% for severe cGVHD and 44% for moderate cGVHD (OR = 0.24, 95% CI: 0.05-1.06, \( P = .07 \)). Although the study could not resolve the primary question, it provided important information for future cGVHD study design in this population.


KEY WORDS: Chronic graft-versus-host disease, GVHD, Randomized, Hydroxychloroquine

INTRODUCTION

Chronic GVHD (cGVHD) is the major cause of morbidity and nonrelapse mortality (NRM) after hematopoietic stem cell transplantation (HSCT) [1]. Historically, complete response rates of cGVHD after 9 months of primary therapy are 33% to 37% [2], suggesting that better therapies are needed. Progress in treating cGVHD has been limited by the clinical complexity of the disease, lack of knowledge about the underlying pathophysiology, and paucity of Phase III clinical trials. A 2005 National Institutes of Health (NIH) Consensus Development Project on criteria for clinical trials of cGVHD provided guidelines for many of the diagnostic, response criteria, and supportive care issues [3-7]. Most Phase III studies of therapy for cGVHD have been conducted at single institutions. Landmark studies include randomized trials of prednisone versus prednisone and azathioprine [2], and prednisone versus prednisone and cyclosporine [8]. Two trials of thalidomide and 1 trial of mycophenolate mofetil (MMF) were closed before reaching their target accrual [9-11]. Despite these
trials, the outcomes for cGVHD have not improved over the last 20 years [12].

Hydroxychloroquine (HCQ) is a 4-aminoquinoline antimalarial drug that has activity as salvage therapy for steroid-resistant/dependent cGVHD [13]. A multi-institutional Phase II trial of HCQ in children and adults with steroid-resistant or steroid-dependent cGVHD utilizing HCQ dosing of 800 mg/day or 12 mg/kg/day (if weight <50 kg) demonstrated a response rate of 53% (3 complete response [CR] and 14 partial responses) in 32 evaluable patients. Responses were most notable in skin, oral, and liver cGVHD, and there was no significant toxicity associated with the HCQ.

HCQ interferes with antigen processing and presentation [14], decreases production of interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-\(\alpha\) [15,16], and decreases proliferation and cytotoxicity resulting from allore cognition [17]. HCQ also inhibits calcium signaling in T cells [18]. HCQ, and the closely related drug chloroquine is synergistic with cyclosporine and tacrolimus in vitro for suppressing alloreactive responses [17-21].

Based on the mechanisms of action of HCQ and the results of the Phase II study for cGVHD, we designed a randomized, double-blinded, placebo-controlled study of HCQ added to standard therapy for children with newly diagnosed extensive cGVHD. The study was designed as a multicenter study because of the low incidence of cGVHD in children [22] and to explore the feasibility of conducting multicenter studies of cGVHD. The study also used a novel scoring system for grading cGVHD manifestations and overall severity that is similar to that later proposed by the NIH Consensus Development Project [6]. Finally, there was a large research laboratory component to the study with the goal of advancing the understanding of cGVHD pathophysiology.

**METHODS**

**Patient Enrollment**

The study was conducted by the Children's Oncology Group from April 2002 to April 2005. Subjects were less than 30 years of age at time of study entry, had newly diagnosed extensive cGVHD, and had received a bone marrow, peripheral blood stem cell (PBSC), or cord blood (CB) transplantation from a family member or unrelated donor. Confirmation of cGVHD by biopsy was required. Patients could be taking steroids at a dose \(\leq 2\) mg/kg/day of prednisone or an equivalent dose of another steroid for the treatment or prophylaxis of acute GVHD (aGVHD), cyclosporine or tacrolimus, and other immunosuppressants for the treatment of aGVHD. Patients were required to have an absolute neutrophil count (ANC) \(\geq 1000/\text{mm}^3\) (unless because of cGVHD), adequate renal function, Lansky or Karnofsky performance score of \(\geq 50\), and a life expectancy of at least 2 months. Patients were not eligible if they had prior systemic treatment for extensive cGVHD, an uncontrolled infection, relapse of malignancy after transplantation, lysosomal storage disorder, glucose 6-phosphate dehydrogenase (G6PD) deficiency, psoriasis, or if they were pregnant. Informed consent was obtained from the patient or guardian in accordance with institutional policies and as approved by the U.S. Department of Health and Human Services. The trial was registered at ClinicalTrials.gov with identifier NCT00031824 on May 8, 2002.

**Study Design**

The study was a randomized, double-blinded, placebo-controlled trial. Sequential block randomized (block size of 2) assignment was performed electronically at the statistical coordinating center with the result of the randomization transmitted to the study pharmacist who then dispensed the study drug (HCQ or placebo in the same tablet form) in a blinded fashion to the treating physician. All patients received a standardized treatment of steroids and cyclosporine or tacrolimus, and were randomized to receive HCQ or matching placebo. Any systemic immunosuppressive therapy other than steroids, cyclosporine, or tacrolimus was discontinued at study entry. The use of topical steroids was permitted. Patients received prednisone 1 mg/kg/day for 2 weeks and then the dose was tapered to 1 mg/kg every other day over the next 6 weeks. Originally, the prednisone dose remained at 1 mg/kg every other day until 9 months after starting therapy. Patients receiving prednisone \(\geq 0.5\) mg/kg/day at study entry had a slower steroid taper and received methylprednisolone 15 mg/kg i.v. weekly \(\times 4\). Patients receiving prednisone 0.5-1 mg/kg/day, received 4 weeks of prednisone 1 mg/kg/day before the taper. Patients receiving prednisone >1-2 mg/kg/day remained on the same dose for 4 weeks followed by a taper of 10% weekly until a dose of 1 mg/kg/day was reached. The prednisone dose was then weaned to 1 mg/kg every other day over the next 6 weeks. Patients who had worsening of cGVHD during the steroid taper had the dose increased to the dose given 2 weeks earlier. This dose was continued for 2 weeks and then the taper was resumed. If the cGVHD progressed, the patient was taken off protocol therapy. An amendment in May 2003 incorporated a second steroid taper starting at 6 months after study entry that decreased the prednisone dose to 0.5 mg/kg every other day over 2.5 months.

Cyclosporine and tacrolimus were given at standard doses with target trough levels of 200-300 ng/mL and 5-15 ng/mL, respectively. The HCQ/placebo dose was 12 mg/kg/day (max 1000 mg), divided into
twice-daily dosing. The dose was adjusted for chole-
stasis (25% and 50% reductions for bilirubin > 6 and
>12 × the upper limit of normal, respectively). The
dose was also adjusted for decreased renal function
(25% and 50% reductions for creatinine ≥1.5 and
≥2 × the upper limit of normal, respectively). The
HCQ dosing was the same as that used for the Phase
II study [13]. HCQ and the matching placebo were
purchased from Sanofi Pharmaceuticals (New York,
NY). HCQ was provided under terms of a Food and
Drug Administration Investigational New Drug
(IND) application #44,717 issued to 1 of the authors
(A.L.G.).

Central Pathology Review

Biopsy specimens were reviewed by George Sale,
MD, a GVHD pathology expert, at Fred Hutchinson
Cancer Research Center, Seattle, WA. Biopsies were
reviewed centrally for retrospective analysis only.

Clinical GVHD Review

A panel of 5 members of the study committee
(A.L.G., D.A.W., K.R.S., F.D.G., D.A.J.) reviewed
the clinical findings at diagnosis. This included pho-
tographs of skin and oral involvement when available.

Required Observations

At study entry, patients had complete blood counts,
chemistries, liver function tests, quantitative immu-
noglobulins, direct and indirect Coombs, antinuclear
antibody (ANA), anti-double-stranded DNA (anti-
dsDNA), baseline ophthalmological exam, complete
evaluation for cGVHD, and a health-related quality
of life (QOL) assessment. Complete evaluations for
cGVHD and response were performed after 2, 6, and
9 months of therapy. ANA, anti-dsDNA, and Coombs
tests were only repeated if abnormal at entry. Ophthal-
mological exams with attention to possible HCQ-
related retinal toxicity were done at 6 and 12 months.

Response Criteria

Responses were evaluated after 2, 6, and 9 months
of therapy and categorized as complete response (com-
plete clinical resolution of all reversible GVHD mani-
festations), partial response (complete clinical
resolution in at least 1 involved site but persistent dis-
ease [not progression] in other sites), stable disease (no
clinical improvement in GVHD manifestations and
lack of clinical worsening), progressive disease (clinical
worsening of GVHD manifestations). Patients were
considered not evaluable for response at 9 months if
they terminated protocol therapy before this time for
reasons not related to progression of cGVHD, toxic-
ity, or relapse.

Improvement and worsening were assessed using
a grading system for each involved organ (Table S1,
online only). The grades included 0 (not involved), 1
(mild), 2 (moderate), and 3 (severe), and definitions
for the severity grading were provided for each organ.
Clinical response data were reviewed and adjudicated
centrally.

Off Protocol Therapy Criteria

Patients were removed from protocol therapy for
(1) progressive cGVHD after 2 months of therapy,
(2) life-threatening progression of cGVHD after ≥2
weeks, (3) inability to complete steroid taper because
of recurrent cGVHD flare, (4) no response (stable dis-
ease) after 6 months of protocol therapy (amended to 2
months in June 2004; only 2 patients affected by this
change), (5) lack of a complete response after 9 months
of therapy, (6) completion of treatment (9 months of
protocol therapy and completion of study drug taper-
ing without a flare, and completion of 9 months of
follow-up) for complete responders, (7) Grade III or
IV toxicity not resolving with dose modification or dis-
continuation of a protocol drug, or any visual impair-
ment attributable to HCQ, (8) intercurrent illness that
prevented further administration of treatment, (9) re-
lapse of malignancy, (10) withdrawal of consent, (11)
lost to follow-up, or (12) death.

Study Endpoints

The primary study endpoint was the complete re-
sponse rate after 9 months of therapy. Secondary end-
points included event-free survival (EFS), overall
survival (OS), and grade 3 and 4 toxicity.

Statistical Considerations

The primary question of treatment effect was as-
sessed by comparing the proportion of CR patients
in the HCQ arm to the proportion of CR patients in
the placebo arm. The target accrual was 232 patients
to have an 80% power at α = 0.05 (one-sided) to detect
an odds ratio (OR) of 2.0 comparing CR rates in the
HCQ arm to the placebo arm. The response OR was
estimated as the cross-product from the 2 × 2 table
of response (CR vs not CR) by treatment group with
95% Wald confidence intervals (95% CI) estimated
in the usual way. The Fisher exact test was used for
the response rate comparisons [23]. A post hoc analy-
was performed for CR + partial response (PR) for the
2 treatment arms in a similar fashion. Standard chi-
square tests were employed to identify significant
prognostic factors for response [24]. The probability
of survival as a function of time since enrollment was
calculated using the method of Kaplan and Meier
[25]. The survivor function was compared across treat-
ment regimens using the log-rank test [26]. A post hoc
analysis was performed to evaluate the relationship of
response rate and degree of severity based on the
global scoring system of cGVHD severity proposed
RESULTS

When the study was closed because of slow accrual, 54 patients had been enrolled with 27 assigned to each treatment arm. The participant flow diagram is shown in Figure S1 (online only). None of the patients were lost to follow-up.

Patient Characteristics

Among 54 enrolled patients, 37 (69%) were male and 17 (31%) were female. The median age was 12 years (range: 1-21). The stem cell source was bone marrow (BM) (n = 24), PBSCs (n = 20), or CB (n = 10). Donors were related in 43% of cases and unrelated in 57%. Forty-nine patients had received a transplant for malignant disease and 5 patients for nonmalignant disease. Thirty-four patients (63%) had a history of aGVHD, and 9 patients (17%) had progressive onset of cGVHD. The median time from transplantation to diagnosis of cGVHD was 6 months (range: 3-24). Twenty-one patients (39%) were receiving steroids at study entry. Thirty patients (56%) were receiving cyclosporine or tacrolimus, and 3 (6%) were receiving MMF at study entry.

P values for differences in characteristics scored 0-3 are from Fisher exact test of score 1-3 versus score 0. Percentages are from patients with nonmissing data.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>By Treatment Arm</th>
<th>Placebo (N = 27)</th>
<th>HCQ (N = 27)</th>
<th>P Value</th>
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<td>13 (3-20)</td>
<td>.21</td>
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<td><strong>Diagnosis</strong></td>
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<tr>
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<tr>
<td>Unrelated</td>
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<td>PBSC</td>
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<td>Cord blood</td>
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<td>11 (41)</td>
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<tr>
<td>Acute GVHD Grade (III-IV)</td>
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<td>5 (19)</td>
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<td><strong>Immunosuppression at study entry</strong></td>
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<td>Steroids</td>
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<td>Cyclosporine</td>
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<td>Tacrolimus</td>
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<td><strong>Gastrointestinal symptoms</strong></td>
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<td>5 (19)</td>
<td>7 (27)</td>
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(Continued)
were no significant differences for any of these parameters between the 2 arms.

**Clinical Manifestations of cGVHD**

Data regarding clinical manifestations at study entry were available for 52 patients. The proportion of patients with each manifestation is shown in Table 1. Several factors have been correlated with a worse prognosis for patients with cGVHD [27]. The proportion of patients with these adverse prognostic factors at study entry was: lichenoid rash involving >50% of the body surface area (9%), bilirubin >1.2 mg/dL (23%), progressive onset of cGVHD (17%), platelet count <100 K/mL (24%), presence of diarrhea/gastrointestinal (GI) involvement (27%/44%), and weight loss (35%).

Eosinophil counts, IgG levels, and ANA titers were available for most patients at the time of diagnosis of cGVHD. Eosinophils (absolute eosinophil count >500/μL) was present in 40% (18 of 45) of patients. Hypergammaglobulinemia (IgG level greater than the upper limit of normal) was present in 23% (11 of 48) of patients. None of these patients was receiving intravenous gammaglobulin. An ANA titer of ≥1:80 was present in 28% (12/43) of patients, and 9 of these patients had titers ≥1:160. At presentation, 62% (30/48) of patients had at least 1 of these 3 findings.

**Response Data**

Among 54 enrolled patients, 42 (18 in HCQ arm and 24 in placebo arm) were evaluable for response. Twelve patients were not evaluable for response: 7 patients had not been in the study for 9 months when the study was closed, and 5 patients were withdrawn at parental request. Out of the 42 evaluable patients, 13 (31%) had a CR at 9 months and 18 (43%) had a CR or a PR. The rate of CR at 9 months was 28% (5 of 18) in the HCQ arm and 33% (8 of 24) in the placebo arm (OR = 0.77, 95% CI: 0.20-2.93, P = .75). The rate of CR + PR at 9 months was 39% (7/18) in the HCQ arm and 46% (11/24) in the placebo arm (OR = 0.75, 95% CI: 0.22-2.60, P = .76).

**Toxicity Data**

All patients were evaluable for toxicity. Grade 3/4 toxicities, which occurred in more than 10% of patients, included hypertension (15%), elevated ALT (17%), and infection without neutropenia (18.5%). Grade 3/4 avascular necrosis and hyperglycemia each occurred in 4% of patients. There were no statistically significant differences between the 2 arms for grade 3/4 toxicities. Toxicities occurring in more than 10% of patients on either arm are shown in Table 2. There were no serious toxicities that were attributed to HCQ. Importantly, although retinal toxicity has been reported with HCQ, it was not seen in the 27 patients treated with HCQ.

**Infections**

There were 13 grade 3/4 infections in 12 (22%) patients (6 in each treatment arm). Three deaths that occurred during protocol therapy were associated with infection. Two of these were because of fungal infection and the organism was not known for the third.

**Central Pathological and Clinical Review**

Biopsy specimens were reviewed centrally. Specimens were reviewed for 37 of 54 (68%) patients enrolled on the study. Biopsies were from skin (n = 25), oral/lip (n = 9), liver (n = 7), GI tract (n = 5), lung (n = 1), and lacrimal gland (n = 1). Biopsies from more than 1 site were submitted for some patients. There was a high level of concordance between the central and institutional diagnosis of GVHD: 36 of 37 (97%) patients and 47 of 48 (98%) biopsies.

Clinical manifestations present at diagnosis and photographs when available were reviewed by a clinical review panel to evaluate the clinical diagnosis of cGVHD. Data were available for 46 of 54 (85%) patients at the time of the review. Photographs of skin and/or oral findings were available for 19 patients. A clinical diagnosis of cGVHD was confirmed for 45 of 46 (98%) patients for whom data were available.

**Survival Data**

Four of 54 (7%) patients died while on protocol therapy or within 1 month of discontinuation of therapy. The cause of death included progressive GVHD (n = 1), GVHD and infection (n = 1), and infection (n = 2). The cause of death for 8 patients who died at a later time was relapse of malignancy or complication of treatment of relapse (n = 5), GVHD (n = 1), GVHD and infection (n = 1), pulmonary fibrosis (n = 1), and lung disease not otherwise specified (n = 1). As seen in Figure 1, there is no evidence of
a difference in survival between placebo and HCQ patients \( (P = .41) \).

**Correlation of Response and cGVHD Severity**

Patients were retrospectively scored as having mild, moderate, or severe cGVHD based on the global scoring system recommended by the NIH Consensus Development Project on cGVHD [3]. There are small differences in some of the organ-specific grades between our grading table (Table S1, online only) and the one proposed by the Consensus. However, this did not affect the overall grading category for any patient.

For the 41 evaluable patients for whom grading data were available, 20 (49%) were graded as severe, 18 (44%) as moderate, and 3 (7%) as mild. The CR rate was 44% for patients with moderate cGVHD and 15% for patients with severe cGVHD (OR = 0.24, 95% CI: 0.05-1.06, \( P = .07 \)). The CR + PR response rate was 56% for patients with moderate cGVHD and 30% for patients with severe cGVHD (OR = 0.39, 95% CI: 0.11-1.41, \( P = .18 \)).

**DISCUSSION**

We report the first Phase III trial of cGVHD conducted solely in children. The study was designed to evaluate a therapeutic question, but also was the first study to explore the feasibility of conducting a multicenter Phase III trial for cGVHD. The study incorporated a grading system and central pathology and clinical review to address this issue. The study performed extensive immunological testing to evaluate the pathophysiology of cGVHD and these results have been published [28-30]. Despite not achieving the primary endpoint, the study provided data, including response rates with standard therapy and the correlation of local and central pathology, that will be useful for the design of future studies of cGVHD.

The primary aim of the study was to determine if the addition of HCQ to standard therapy, including prednisone and a calcineurin inhibitor, could improve the complete response rate of cGVHD after 9 months of therapy. This endpoint, which had been used for most Phase III studies before the initiation of our study, was chosen to allow sufficient time for maximal clinical response and for steroid tapering. The primary aim was not able to be addressed with adequate statistical power because of the limited patient accrual, but there was no suggestion of any significant difference between the 2 treatment arms. Several factors may have contributed to the suboptimal accrual. The eligibility criteria were complex and strict. In addition, the participating investigators struggled with differentiating the frequently insidious onset of cGVHD from persistence or exacerbation of aGVHD. This resulted in steroid pretreatment that made potential study subjects ineligible for the trial. In an attempt to isolate the specific impact of HCQ and to ensure that the arms were similar, the treatment plan rigidly controlled steroid dosing and tapering. The participating centers found this study requirement challenging because of competing reasons for which steroid dosing is adjusted (eg, toxicity, risk of relapse). Of note, subsequent multicenter trials for cGVHD have also struggled with accrual.

The study provided the only data available for response rates of children with newly diagnosed extensive cGVHD treated with standard therapy in a multicenter trial. The central clinical and pathology review to confirm the diagnosis of cGVHD showed excellent correlation between the local institution and central review. The results support multicenter studies of cGVHD and the use of institutional pathology for these trials.

The study used a unique scoring system for grading cGVHD manifestations similar to the one later proposed by the NIH Consensus Development Project [3]. There are small differences in some of the organ-specific grades between the scoring systems, but this did not affect the overall grading category for any patient. We were able to use the information gathered in our scoring system to analyze the patients according to the NIH Consensus global scoring system (mild, moderate, and severe) of cGVHD severity [3]. Our data suggest that the NIH Consensus global scoring system for cGVHD severity for patients with severe or moderate cGVHD correlates with the likelihood of response after 9 months of therapy. There were too few patients with mild disease to evaluate this group. Another study retrospectively evaluated the correlation between disease severity according to this scoring system and the ability to discontinue immunosuppression, which is an alternative endpoint to
response to therapy. Patients with more severe disease were significantly less likely to be able to discontinue immunosuppression [31]. Additional studies correlating response rates and cGVHD severity are warranted. The ability to identify patients unlikely to respond to standard therapy is important because it would support these patients being considered as candidates for studies of novel therapies at the time of diagnosis.

There is a paucity of Phase III studies of therapy for newly diagnosed cGVHD. A summary of these studies is shown in Table 3. Comparison between these studies is difficult because of differences in the proportion of patients with extensive cGVHD, sites of cGVHD involvement, severity, and type of onset of cGVHD, donor types, and other prognostic factors. There are also differences in response criteria and study endpoints, and most of the studies are single center studies. For example, a study reported by Sullivan et al. [2] in 1988 evaluated the addition of azathioprine to prednisone. Thirty-nine percent of the patients had subclinical cGVHD (GVHD on blind biopsy without clinical evidence of cGVHD) when therapy was started. The response definition was stricter than other studies, with a CR defined as clinically inactive cGVHD and a negative biopsy and a PR defined as clinically inactive cGVHD but biopsies showing active GVHD. The CR rate at 9 months was 33% for prednisone and 37% for prednisone/azathioprine. Some studies have used discontinuation of immunosuppression as an endpoint, so response data are not available [8,11].

For our study, the CR and CR + PR rates after 9 months of therapy for all patients (both treatment arms) were 31% and 43%, respectively, for 42 evaluable patients. The CR rate is comparable to a study by Sullivan et al. [7], but the CR + PR rate is lower. Both the CR and CR + PR rates are much lower than those in a study reported by Arora et al. [10]. This may be because of differences in study populations and the single versus multi-institutional setting.

Of note, 49% of the evaluable patients for whom data were evaluable in our study had severe disease according to the NIH Consensus criteria. Additional support for the fact that our patient population was skewed toward more severely affected patients is provided by a comparison to a report of a large cohort of children with cGVHD [22]. GI and lung involvement were seen in 44% and 20% of our patients and in 24% and 11% of that cohort, respectively.

Studying cGVHD at the time of initial diagnosis is a challenge. The initial presentation can be insidious and often develops at the time of taper of planned GVHD prophylaxis or aGVHD treatment. The early symptom complex at presentation can overlap with features of aGVHD and other posttransplantation complications (eg, infection, malabsorption). Subsequent trials might benefit greatly from the development of biomarkers specific to cGVHD that confirm the diagnosis at onset and possibly as surrogate indicators of response. A pretreatment window that allows a short course of steroids could make more patients eligible for future “front-line” studies and allow a less rushed study entry.

A less rigid and complex steroid taper would provide investigators with flexibility needed for individual patients, better reflecting current clinical practice.

The results of studies [2,10,11] in which a drug with activity in a Phase II salvage study fails to add benefit in a Phase III up-front treatment study suggest that a better approach may be needed. One approach is to perform a randomized Phase II study in the upfront setting before committing to a large Phase III trial. The caution is to avoid the assumption that agents active in the salvage setting will be beneficial at the time of initial diagnosis. Our study provides response rates for cGVHD in children in a multicenter trial setting, which can serve as a baseline for such trials. The results with the addition of a study drug would have to be substantially better than the baseline to warrant a Phase III trial. Finally, our data suggest that risk stratification based on the NIH consensus staging is likely to be useful for study design by identifying patients with severe cGVHD who have little chance of a complete response with standard therapy and for whom novel therapies need to be developed and tested.

### ACKNOWLEDGMENTS

We thank Stephanie Lee, MD, for her critical review of the manuscript.
Financial disclosure: The research was supported by the following grants from the National Cancer Institute, National Institutes of Health, Bethesda, MD: R01 CA 84137, U10 CA98543, and U10 CA98413.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2011.05.016.

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