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ORIGINAL ARTICLE

Reduced Intensity Bone Marrow Transplantation with Post-Transplant Cyclophosphamide for Pediatric Inherited Immune Deficiencies and Bone Marrow Failure Syndromes

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Abstract

Purpose Allogeneic bone marrow transplantation (alloBMT) is the only cure for many primary immune deficiency disorders (PIDD), primary immune regulatory disorders (PIRD), and inherited bone marrow failure syndromes (IBMFS).

Methods We report the results of 25 patients who underwent alloBMT using reduced intensity conditioning (RIC), alternative donors, and post-transplantation cyclophosphamide (PTCy). In an attempt to reduce regimen-related toxicities, we removed low-dose TBI from the prep and added mycophenolate mofetil and tacrolimus for graft-versus-host disease (GVHD) prophylaxis for all donor types in the latter 14 patients. Donors were haploidentical related ($n = 14$), matched unrelated ($n = 9$), or mismatched unrelated ($n = 2$). The median age was 9 years (range 5 months–21 years).

Results With a median follow-up of 26 months (range 7 months–9 years), the 2-year overall survival is 92%. There were two deaths, one from infection, and one from complications after a second myeloablative BMT. Three patients developed secondary graft failure, one at 2 years and two at >3 years, successfully treated with CD34 cell boost in one or second BMT in two. The remaining 20 patients have full or stable mixed donor chimerism and are disease-free. The incidence of mixed chimerism is increased since removing TBI from the prep. The 6-month cumulative incidence of grade II acute GVHD is 17%, with no grade III–IV. The 1-year cumulative incidence of chronic GVHD is 14%, with severe of 5%.

Conclusion This alloBMT platform using alternative donors, RIC, and PTCy is associated with excellent rates of engraftment and low rates of GVHD and non-relapse mortality, and offers a curative option for patients with PIDD, PIRD, and IBMFS.

Trial registration ClinicalTrials.gov Identifier: NCT04232085

Keywords Blood and marrow transplantation · primary immune deficiency disorders · primary immune regulatory disorders · inherited bone marrow failure disorders · alternative donor · post-transplant cyclophosphamide

Introduction

Allogeneic blood and marrow transplantation (alloBMT) is curative for many primary immune deficiency disorders (PIDD), primary immune regulatory disorders (PIRD), and inherited bone marrow failure syndromes (IBMFS). The best outcomes have used HLA-matched sibling donors and myeloablative conditioning (MAC); however, only 30% of children have an HLA-matched sibling [1]. The use of donors other than an HLA-matched sibling has historically been limited by high rates of transplant-related mortality (TRM) secondary to graft failure, infection, and acute and chronic graft-versus-host disease (GVHD) [2–7]. Reduced intensity conditioning (RIC) regimens are preferred in children with nonmalignant

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disorders as myeloablation offers no direct disease benefit, and RIC offers less short- and long-term morbidity. However, graft failure with RIC remains a critical obstacle, particularly with donors other than HLA-matched. A platform that expands the donor pool, optimizes engraftment, and minimizes toxicities for PIDD/PIRD/IBMFS patients would represent a significant advancement.

We have previously reported our promising single-institution pilot experience using RIC and alternative donors with post-transplant cyclophosphamide (PTCy) for a small cohort of PIDD/PIRD/IBMFS patients ($n = 11$) [8]. Successful engraftment and low rates of GVHD led us to offer this platform to additional patients with two major changes. First, in an attempt to reduce regimen-related toxicity, we removed the previously included low-dose total body irradiation (TBI) from the conditioning regimen. Second, in addition to PTCy, post-transplant mycophenolate mofetil (MMF) and tacrolimus were included for all donor types to minimize GVHD even further.

A uniform, "one size fits all" regimen for rare, heterogeneous diagnoses has precedence in the literature [4, 9, 10], and offers a safe and effective curative option for any PIDD/PIRD/IBMFS patient in need of a BMT, using a platform with a proven track record. We herein report our expanded institutional experience treating pediatric patients with life-threatening PIDD/PIRD/IBMFS with longer-term follow-up, including additional patients treated without TBI and with MMF and tacrolimus, where we observed a higher incidence of mixed chimerism in the PIDD/PIRD but not the IBMFS patients, and a lower cumulative incidence of GVHD in patient with 10/10 HLA-matched unrelated donors.

Materials and Methods

Patients

This retrospective study was approved by the institutional review board of The Johns Hopkins Hospital (JHH). All pediatric patients (age 1 month to 21 years) who underwent alloBMT at JHH from January 2009 to January 2019 for specified nonmalignant conditions (PIDD, PIRD, and IBMFS), and who did not have a matched sibling donor, were included. BMTs were performed as standard of care, and all patients/guardians provided informed consent for treatment.

Alternative donors included matched unrelated donors (MUD), mismatched unrelated donors (MMUD), or haploidentical related (haplo) donors. Inclusion criteria included adequate organ function testing and Karnofsky or Lansky performance status $\geq 60\%$. Exclusion criteria included positive leukocytotoxic crossmatch to mismatched donor HLA and uncontrolled infection. Data from the medical record including patient demographics, transplant and clinical data, complications, laboratory and radiologic studies, therapy received, overall outcomes, and transplant-related complications were abstracted and reviewed.

Regimen

In our previously reported patients ($n = 11$) [8], the preparative regimens varied. All of the newly reported patients received the same uniform regimen with alemtuzumab, fludarabine, and melphalan (Fig. 1), notably, without TBI and with post-transplant MMF and tacrolimus for all donor types. One newly reported patient did have TBI included on day − 1.

Alemtuzumab dosing was based on weight, with children > 10 kg receiving a total of 48 mg intravenously (IV) over 3 days, starting on day − 14, with an initial dose of 3 mg, followed by doses of 10 mg/15 mg/20 mg. Patients < 10 kg received a total of 33 mg, with a test dose of 3 mg followed by 10 mg/10 mg/10 mg. All patients received fludarabine 150 mg/m^2 divided over 5 days (or 1 mg/kg/day for 5 days for patients < 10 kg), starting on day − 8. The dosing for melphalan was 140 mg/m^2 (or 3.4 mg/kg for patients < 10 kg), either given as a single dose on day − 2 or equally divided over 2 days on days − 3 and − 2. In some patients, TBI of 200 cGy was given on day − 1.

GVHD prophylaxis consisted of PTCy, mycophenolate mofetil (MMF), and tacrolimus for all newly reported patients, regardless of donor type. In our previously reported patients [8], patients who received 10/10 HLA-matched unrelated donors (MUDs) ($n = 4$) received PTCy alone for GVHD prophylaxis, and patients who received haploidentical donors or mismatched unrelated donors received PTCy, MMF, and tacrolimus. Cyclophosphamide was given IV on days + 3 and + 4, at a dose of 50 mg/kg/day (excepting the two DKC patients, who received only one dose on day + 3), followed by MMF 15 mg/kg/dose IV or by mouth TID (maximum daily dose 3 g/day), and tacrolimus 0.015 mg/kg/dose IV every 12 h, both starting on day + 5. MMF was stopped on day + 35. Tacrolimus was switched to oral as tolerated, and dose adjusted to maintain a trough between 5 and 10 ng/mL. Tacrolimus was tapered starting on day + 150 and discontinued by day + 180 if there was stable donor chimerism and no active GVHD.

Donor Selection

Donors were molecularly typed at HLA-A, -B, -Cw, -DRB1, and -DQB1. Unrelated donors were matched at either 5/8 (DQB1 matching was not available) or 9 or 10/10. Haploidentical donors were 1st degree relatives or half-sibling who had one to five mismatches at the antigen or allele level. Donors were chosen based on age, gender, CMV status, medical comorbidities (for family members), and availability. Preference was given equally to 10/10

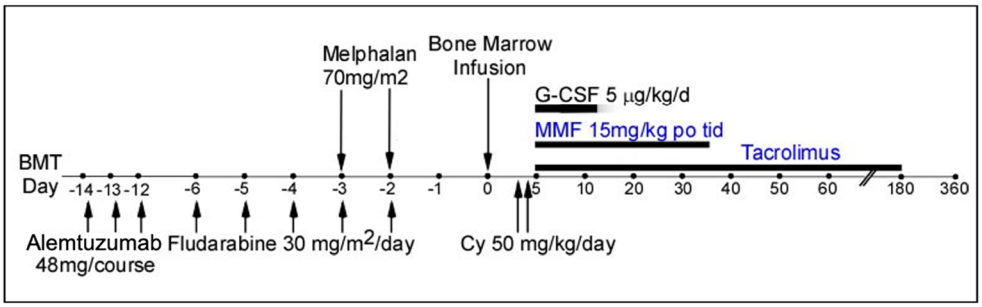

Fig. 1 Preparatory regimen and GVHD prophylaxis. Prep includes alemtuzumab, fludarabine, and melphalan. GVHD prophylaxis includes cyclophosphamide, tacrolimus, and mycophenolate mofetil. Cy, cyclophosphamide; GCSF, granulocyte colony stimulating factor; MMF, mycophenolate mofetil

MUDs and haploidentical donors. If neither a 10/10 MUD nor an unaffected, eligible haploidentical donor was available, then a mismatched unrelated donor was used.

Supportive Care

All patients received infectious prophylaxis for gram negative-bacteria through count recovery, for *Pneumocystis jirovecii* pneumonia (PJP) through 1-year post-BMT, and for fungal infections through day + 75. Patients at risk for CMV (defined as patient and/or donor seropositivity) or with a history of HSV infection received high- or low-dose acyclovir prophylaxis, respectively, through neutrophil recovery. Polymerase chain reaction (PCR) for CMV was monitored weekly in serum through day + 100 in all patients at risk for CMV. PCR for EBV and adenovirus were measured weekly in serum through day + 100 in all patients. GCSF 5 μg/kg/day IV was started on day + 5 and continued until the ANC was > 1×10^9/L for three consecutive days.

Definitions of Clinical Outcomes

Neutrophil recovery was defined as the number of days from BMT to the first of 3 consecutive days with an absolute neutrophil count above 0.5×10^9/L. Platelet recovery was defined as platelet count greater than 20×10^9/L for 3 consecutive days without transfusion in the preceding 7 days. Routine donor chimerism analysis was performed on days + 30, + 60, + 90, + 180, and 1 and 2 years after BMT. Chimerism was analyzed in whole blood (WB) and isolated CD3+ cells (TCs). Mixed chimerism was defined as ≥ 5% and < 95% donor cells, and full chimerism as ≥ 95% donor cells, in WB. Primary graft failure was defined as < 5% donor chimerism in WB by day + 60. Secondary graft failure was defined as loss of donor engraftment (< 5% donor chimerism in WB) after initially achieving neutrophil recovery and detection of donor chimerism. Secondary graft failure was further characterized as early (before day + 365) or late (at or after day + 365).

Acute GVHD (aGVHD) was graded per standard criteria [11], and chronic GVHD (cGVHD) was graded per NIH Working Group Reports [12, 13]. Invasive fungal infections were defined according to published guidelines [14]. Overall survival (OS) was defined as alive, and event-free survival (EFS) was defined as alive without graft failure. Disease-free survival (DFS) was defined as alive, with any detectable donor chimerism and without any symptoms of the underlying disease. Transplant-related mortality (TRM) was defined as death related to the transplant.

Statistical Analysis

Descriptive statistics were used to summarize baseline patient and transplant characteristics. The probability of OS was estimated using the Kaplan-Meier method with 95% confidence intervals (CIs) [15]. Cumulative incidences of relapse, TRM, and GVHD were estimated by competing-risk analysis using Gray's method [16]. Relapse and TRM were competing risks for each other. Death, relapse, and graft failure were competing risks for GVHD. Data were analyzed with the Prism version 8.2.0 (Graphpad Software, La Jolla, CA).

Results

Patient, Donor, and Graft Characteristics

Twenty-five patients were treated; donor and graft characteristics are summarized in Tables 1 and 2. The median follow-up of surviving patients is 26 months (ranging 7 months–9 years). None of the patients had detectable donor-specific anti-HLA antibodies at the time of BMT. Bone marrow was the preferred stem cell source for all patients; 24 patients (96%) received a bone marrow graft, and one patient received a PBSC graft because of donor preference.

Table 1 Patient, donor, and allograft characteristics

Characteristic	Number	Percent
Age at BMT, years		
Median	9	
Range	0.4–21	
Diagnosis		
CGD	11	44
Birc4/XIAP deficiency	2	8
DBA	2	8
DKC	2	8
Hyper-IgM	1	4
IPEX	1	4
HLH	1	4
GT	1	4
CVID	1	4
CTLA4 deficiency	1	4
STAT3 gain-of-function	1	4
ADA-deficient SCID	1	4
Male recipients	19	76
Graft source		
Bone marrow	24	96
Mobilized peripheral blood stem cells	1	4
Donor source		
HLA haploidentical related	14	56
10/10 HLA-matched unrelated	9	36
9/10 HLA-matched unrelated	1	4
5/8 HLA-matched unrelated	1	4
Relationship of haploidentical donors		
Parent	9	64
Father	7	50
Mother	2	14
Sibling	4	29
Uncle	1	7
Male donors	15	55
Female-into-male allografting	7	28
Preparative regimen		
Chemotherapy-only	17	68
Chemotherapy + TBI	8	32
GVHD prophylaxis		
PTCy + tacrolimus + MMF	21	84
PTCy	4	16
Donor age, years		
Median	30	
Range	10–49	
CMV at risk	9	36
Total nucleated cells/kg IBW infused		
Median	6.60×10^8	
Range	$2.06–22.8 \times 10^8$	
Target cell dose/kg IBW	4×10^8	
$CD34^+$ cells/kg		
Median	5.98×10^6	
Range	$2.45–16.2 \times 10^6$	
ABO mismatch		
Compatible	17	68
Major mismatch	4	16
Minor mismatch	4	16

ABO, blood group type; *ADA*, adenosine deaminase deficiency; *Birc4*, baculoviral IAP repeat-containing protein 4; *BMT*, bone marrow transplantation; *CGD*, chronic granulomatous disease; *CMV*, cytomegalovirus; *CTLA4*, cytotoxic T lymphocyte-associated protein 4; *CVID*, common variable immune deficiency; *DBA*, Diamond-Blackfan anemia; *DKC*, dyskeratosis congenita; *GT*, Glanzmann's thrombasthenia; *GVHD*, graft-versus-host disease; *HLA*, human leukocyte antigen; *HLH*, hemophagocytic lymphohistiocytosis; *IBW*, ideal body weight; *IPEX*, immune dysregulation polyendocrinopathy X-linked; *MMF*, mycophenolate mofetil; *PTCy*, post-transplant cyclophosphamide; *SCID*, severe combined immune deficiency; *STAT3*, signal transducer and activator of transcription 3, *XIAP*, X-linked inhibitor of apoptosis

Outcomes

Engraftment

All patients achieved prompt neutrophil and platelet recovery. Neutrophil recovery occurred at a median of 16 days (range 13–33). Platelet recovery occurred at a median of 21 days (range 15–55). The median absolute lymphocyte counts (ALC) are depicted in Fig. 2. The median ALC at days 30, 60, 180, and 1 year were 0.38×10^9/L (range 0.02–1.14×10^9/L), 0.60 (range 0.18–2.22×10^9/L), 0.95 (range 0.14–2.10) $\times 10^9$/L, and 1.76×10^9/L (range 0.37–4.35×10^9/L), respectively. Chimerism results are summarized in Tables 2 and 3 and depicted in Fig. 3. Notably, all 25 patients (100%) had detectable donor chimerism at day 30; and 23 of 24 (96%) evaluable patients had ≥ 95% donor chimerism in PB at day 30. In the patients with TBI-containing preps ($n = 8$), 6 of 7 evaluable patients (86%) had ≥ 95% donor chimerism in PB at 1 year, whereas in the patients with chemotherapy-only preps ($n = 17$), 7 of 14 evaluable patients (50%) had ≥ 95% donor chimerism in PB at 1 year ($p = 0.11$).

Of the 6 PIDD/PIRD patients treated with chemotherapy + TBI preps, there was one each of immune dysregulation polyendocrinopathy X-linked (IPEX), X-linked inhibitor of apoptosis (XIAP) deficiency, CGD, hyper-IgM syndrome, hemophagocytic lymphohistiocytosis (HLH), and common variable immune deficiency (CVID). Of these, four remain 100% donor, one had late secondary graft failure requiring a second BMT (Patient #1), and one died of transplant-related mortality (Patient #15). The two IBMFS patients treated with chemotherapy + TBI prep were both DKC patients, and both remain 100% donor at 4 and 7 years out from their BMTs.

Table 2 Patient characteristics and outcomes

Patient number	Diagnosis	Gender	Indication for BMT	Infections pre-BMT	Age at BMT	Donor	Prep regimen	Duration of follow-up	Whole blood chimerism (%)	T cell chimerism (%)	Chimerism time point	Outcome
1	IPEX	Male	PID with severe eczema/allergies, enteropathy with TPN dependence, and FTT		10 months	Haplo related	Chemo + TBI	9 years	100	100	2 years (after 2nd BMT)	Cured after 2nd MA BMT
2	Birc4/XIAP deficiency	Male	HLH		11 months	Haplo related	Chemo + TBI	7 years	100	100	2 years	Cured
3	DKC	Female	BMF		19 years	10/10 MUD	Chemo + TBI	7 years	100	89	2 years	Cured
4	CGD	Male	PID; brother with life-threatening infections		5 months	10/10 MUD	Chemo	7 years	100	100	2 years (after 2nd BMT)	Cured after 2nd RIC BMT
5	CGD	Male	PID with life-threatening infections, enteritis, FTT	*Klebsiella pneumonia*, Paecilomyces pneumonia	5 years	Haplo related	Chemo + TBI	5 years	100	100	2 years	Cured
6	DKC	Male	BMF		14 years	10/10 MUD	Chemo + TBI	4 years	100	100	2 years	Cured
7	CGD	Male	PID with life-threatening infections; enteritis, FTT	MRSA bacteremia, fungal pneumonia	8 years	10/10 MUD	Chemo	5 years	100	100	2 years	Cured
8	Hyper IgM	Male	LPD		12 years	10/10 MUD	Chemo + TBI	2 years	100	100	2 years	Cured
9	DBA	Male	Steroid refractory		3 years	10/10 MUD	Chemo	4 years	100	100	2 years	Cured
10	HLH	Female	Chemotherapy refractory		21 years	5/8 MMUD	Chemo + TBI	5 years	100	100	2 years	Cured
11	GT	Female	Platelet-refractory bleeding		8 years	Haplo related	Chemo	4 years	100	Not performed	2 years	Cured
12	CGD	Male	PID with life-threatening infections		9 years	9/10 MMUD	Chemo	12 months	94	86	1 year	Cured
13	CGD	Male	PID with life-threatening infections		12 years	Haplo related	Chemo	2 years	>95	>95	2 years	Cured
14	DBA	Male	Steroid refractory, neutropenia		4 years	Haplo related	Chemo	3 years	100	100	2 years	Cured
15	CVID	Female	Severe autoimmunity		7 years	Haplo related	Chemo + TBI	2 months				Deceased (disseminated ADV/CMV)
16	CGD	Male	PID with life-threatening infections		9 years	Haplo related	Chemo	2 years	42	63	2 years	Cured after CD34+ boost
17	CGD	Male	PID with life-threatening infections		10 years	Haplo related	Chemo	2 years	75	95	2 years	Cured
18	CGD	Male	PID with life-threatening infections		13 years	Haplo related	Chemo	2 years	>95	100	2 years	Cured
19	CTLA4 deficiency	Female	PID with life-threatening infections, autoimmune enteropathy	*Mycobacterium avium* pneumonia; *Klebsiella pneumonia*, *Enterococcus faecalis* bacteremia	19 years	Haplo related	Chemo	2 years	100	95	2 years	Cured
20	STAT3 GOF	Male	PID with life-threatening infections, autoimmune cytopenias		5 years	10/10 MUD	Chemo	7 months				Deceased after 2nd MA BMT (SOS)

Table 2 (continued)

Patient number	Diagnosis	Gender	Indication for BMT	Infections pre-BMT	Age at BMT	Donor	Prep regimen	Duration of follow-up	Whole blood chimerism (%)	T cell chimerism (%)	Chimerism time point	Outcome
21	CGD	Male	PID with life-threatening infections		9 years	Haplo related	Chemo	14 months	93	94	1 year	Cured
22	CGD	Male	PID with life-threatening infections		11 years	Haplo related	Chemo	13 months	86	20	1 year	Cured
23	CGD	Male	PID with life-threatening infections		3 years	10/10 MUD	Chemo	11 months	75	100	9 months	Cured
24	ADA SCID	Female	PID with life-threatening infections, failure to thrive	Frequent pneumonias, chronic diarrhea	15 years	Haplo related	Chemo	11 months	100	100	9 months	Cured
25	Birc4/XIAP deficiency	Male	PID with life-threatening infections, HLH, refractory Crohn's disease	Multi-organism intra-abdominal abscesses, CMV+ LRTI	20 years	10/10 MUD	Chemo	7 months	>95	84	6 months	Cured

ADV, adenovirus; *Alem*, alemtuzumab; *ADA*, adenosine deaminase deficiency; *Birc4*, baculoviral IAP repeat-containing protein 4; *BMF*, bone marrow failure; *BMT*, bone marrow transplantation; *Bu*, busulfan; *CGD*, chronic granulomatous disease; *CMV*, cytomegalovirus; *CTLA4*, cytotoxic T lymphocyte-associated protein 4; *CVID*, common variable immune deficiency; *Cy*, cyclophosphamide; *DBA*, Diamond-Blackfan anemia; *DKC*, dyskeratosis congenita; *Flu*, fludarabine; *FTT*, failure to thrive; *GT*, Glanzmann's thrombasthenia; *Haplo*, haploidentical; *HLH*, hemophagocytic lymphohistiocytosis; *IPEX*, immune dysregulation polyendocrinopathy X-linked; *LPD*, lymphoproliferative disease; *LRTI*, lower respiratory tract infection; *Mel*, melphalan; *MMUD*, mismatched unrelated donor; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *MUD*, matched unrelated donor; *PID*, primary immunodeficiency; *SCID*, severe combined immune deficiency; *SOS*, sinusoidal obstruction syndrome; *TBI*, total body irradiation; *TPN*, total parenteral nutrition; *XIAP*, X-linked inhibitor of apoptosis

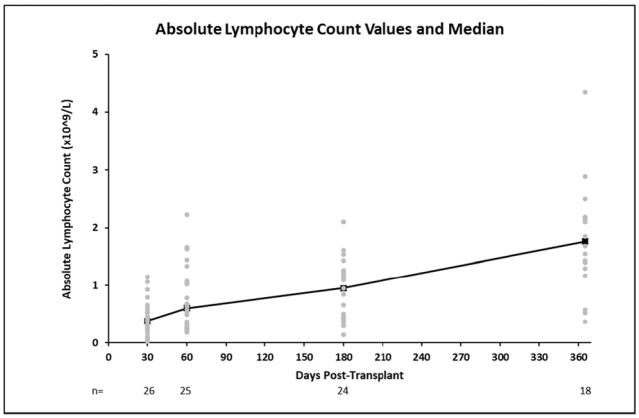

Fig. 2 Absolute lymphocyte count (ALC) values and median. The individual values for absolute lymphocyte count (ALC) are shown for days 30, 60, 180, and 365. The median ALC at each time point were 0.38×10^9/L (range 0.02–1.14×10^9/L), 0.60 (range 0.18–2.22×10^9/L), 0.95 (range 0.14–2.10) $\times 10^9$/L, and 1.76×10^9/L (range 0.37–4.35×10^9/L), respectively. The total number of patients at each time point is $n = 26$, $n = 25$, $n = 24$, and $n = 18$, respectively

Of the 14 PIDD/PIRD patients with chemo-only preps, 10 were patients with chronic granulomatous disease (CGD), and one each had signal transducer and activator of transcription 3 (STAT3) gain-of-function, adenosine deaminase deficiency (ADA) deficient severe combined immune deficiency (SCID), XIAP deficiency, and cytotoxic T lymphocyte-associated protein 4 (CTLA4) deficiency. Of the 10 CGD patients treated with chemotherapy-only, seven are mixed chimeras, one is 100% donor, one required CD34 boost (Patient #16), and one had late graft failure and was successfully re-transplanted (Patient #4). Of the non-CGD PIDD/PIRD patients treated with chemotherapy-only, two are 100% donor, one is a mixed chimera, and one had early mixed chimerism and died after a second myeloablative BMT attempt (Patient #20). Of the three IBMFS patients treated with chemo-only preps, two with Diamond-Blackfan anemia (DBA) and one with Glanzmann's thrombasthenia (GT), all are 100% donor at 2 years post-BMT.

In the CGD cohort ($n = 11$), all patients had nitro blue tetrazolium testing (NBT), testing at day 30 or 60 to confirm resolution of the underlying disease. All eleven patients' testing revealed normal oxidative bursts. One patient (patient #16), described below, did eventually develop CGD-related infections, requiring donor CD34 boost. Another CGD patient (patient #4), had stable mixed chimerism for over 3 years, without any evidence of infection. At 3.5 years after BMT, with donor chimerism around 8%, he did develop infections consistent with CGD, underwent a second RIC BMT from a different donor, and has been 100% donor #2, now more than 2 years out from his second BMT. The remaining nine CGD patients have not had any CGD-related infections.

Four patients (12%) ultimately required infusion of additional stem cell products. Two patients from our first cohort

Table 3 Comparing chimerism and GVHD in sub-groups

	Preparative regimen				GVHD prophylaxis for 10/10 MUD donors	
	TBI-containing		Chemotherapy-only		PTCy	PTCy + MMF + Tacro
Patients (*n*)	8		17		4	5
1-year full donor chimerism (*n*) (% of evaluable patients)	6 (86%) out of 7 evaluable		7 (50%) out of 14 evaluable			
	PIDD/PIRD Patients	IBMFS patients	PIDD/PIRD Patients	IBMFS patients		
Patients (*n*)	6	2	14	3		
1-year full donor chimerism (*n*) (% of evaluable patients)	4 (80%) out of 5 evaluable	2 (100%)	4 (36%) out of 11 evaluable	3 (100%)		
6-month acute GVHD all grades (*n*) (cum inc. %)					2 (50%)	0 (0%)
2-year chronic GVHD (*n*) (cum inc. %)					1 (50%)	0 (0%)

Cum inc., cumulative incidence; *GVHD*, graft-versus-host disease; *IBMFS*, inherited bone marrow failure syndromes; *MMF*, mycophenolate mofetil; *PIDD*, primary immune deficiency disorders; *PIRD*, primary immune regulatory disorders; *PTCy*, post-transplant cyclophosphamide; *SOS*, sinusoidal obstruction syndrome; *Tacro*, tacrolimus; *TBI*, total body irradiation

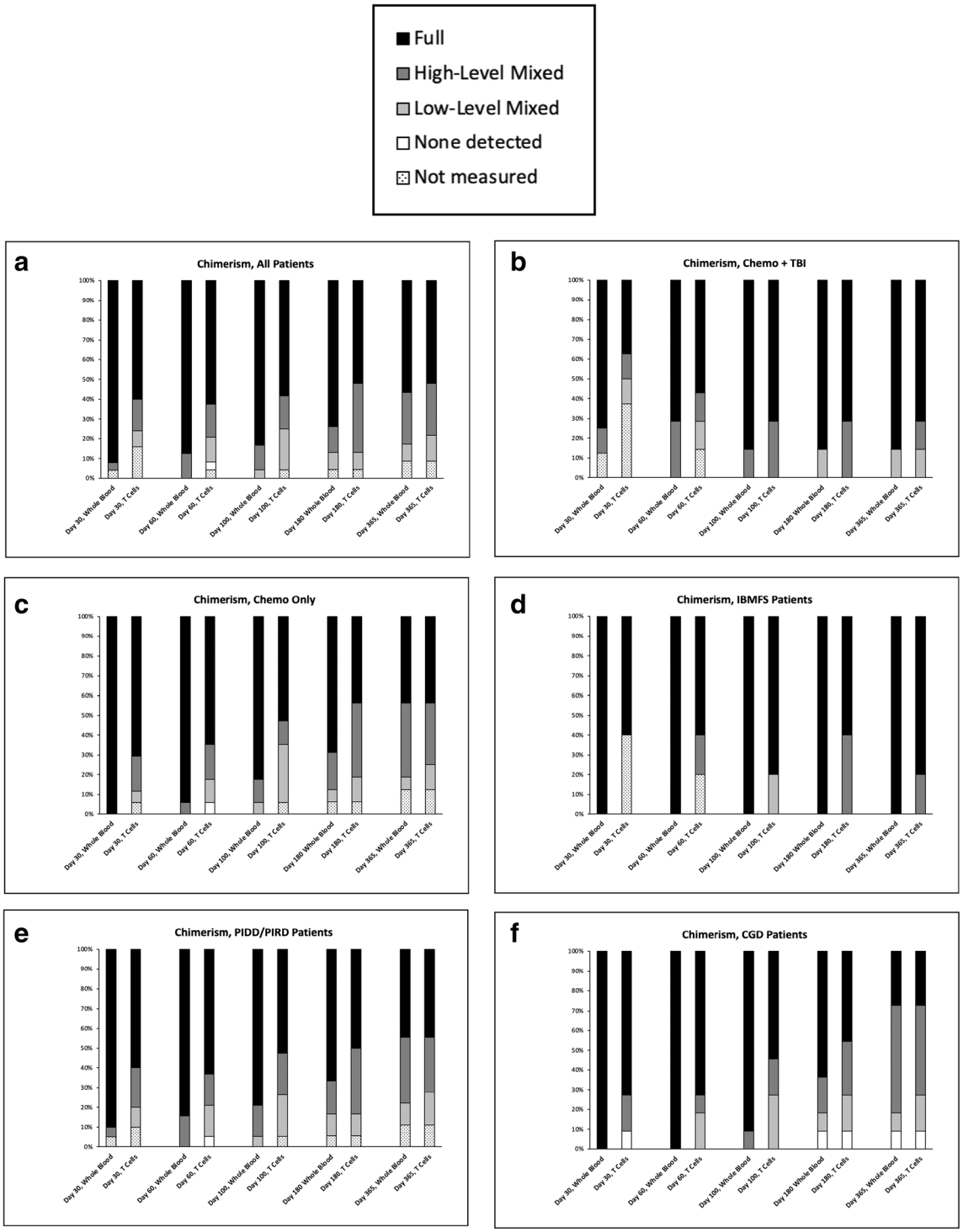

Fig. 3 Chimerism in whole blood and CD3+ compartment. Chimerism for all patients, $n = 25$ (A), chemotherapy + total body irradiation, $n = 8$ (B), Chemotherapy-only, $n = 18$ (C), IBMFS patients, $n = 5$ (D), PIDD/PIRD, $n = 20$ patients (E), and CGD patients, $n = 11$ (F). Graphs show percent of patients with full chimerism (defined as > 95%), high-level mixed (defined as 50–95%), low-level mixed (defined as < 50% but detectable), none detected, or not measured

[8] experienced late secondary graft failure, patient #1 with IPEX (TBI-containing prep) and patient #4 with GGD (chemotherapy-only prep), one patient with CGD (#16) (chemotherapy-only prep) was treated with a $CD34^+$ boost at 2 years post-BMT, and one patient with STAT3 GOF (#20) (chemotherapy-only prep) had early secondary graft failure, was treated with a myeloablative BMT, and ultimately died from transplant-related complications.

Patient #1 had detectable host as early as day 30 after BMT, with BM chimerism of 94%, and had a slow decline of donor chimerism over time. He had whole blood and CD3 chimerism of 5–8% donor at 1, 2, and 3 years after BMT, but no symptoms of his underlying disease. He developed an acute gastroenteritis and subsequently developed symptoms of IPEX. He was re-transplanted with the same haploidentical donor using a myeloablative regimen, and is alive, 100% donor, and free of IPEX-symptoms at 6 years since his second BMT. Patient #4 was 100% donor in whole blood at day 30, then had detectable host at day 60 with whole blood chimerism of 95%. He had a slow decline in donor chimerism, and had mixed chimerism in the 10–15% range in both whole blood and T cells at 1, 2, and 3 years after BMT, but no symptoms of CGD. At around 3.5 years after BMT, he developed retinitis, and repeat NBT testing showed no oxidative burst. He was re-transplanted using a busulfan-based RIC regimen using a haploidentical donor. He is alive, 100% donor, and has had no CGD-related infections at more than 2 years since his second BMT.

Patient #16 with CGD developed detectable host T cells at day +60 and remained a mixed chimera with declining donor for 2 years. Repeat NBT testing revealed defective oxidative burst of 6%, and he was treated with an unprepped $CD34^+$ selected stem cell boost from his haploidentical donor, with a cell dose of 31.2×10^6 TNC/kg and 30.5×10^6 $CD34^+$/kg. His subsequent percent donor chimerism rose, and repeat NBT testing revealed a normal oxidative burst of 63%. He has remained mixed chimerism, and free of CGD-related infections at 10 months since the CD34 boost. Patient #20, with STAT3 GOF mutation, had > 95% donor in WB and 20% in TCs at day 30. By day 60, the WB was 68% donor, with no detectable donor TCs. He developed symptoms of his underlying disease, and was re-transplanted 6 months later using a myeloablative regimen and the same donor. He achieved count recovery and donor chimerism of 100% in WB and > 95% in TCs by day 30, but unfortunately died from severe sinusoidal obstruction syndrome.

Graft-Versus-Host Disease

The 6-month cumulative incidence of grade II–IV aGVHD is 17%, with no cases of grades III or IV aGVHD. Six patients developed grades I ($n = 2$) or II ($n = 4$) aGVHD, and all responded to steroids and a calcineurin inhibitor. In patients who received MUD donors and PTCy alone ($n = 4$), two developed skin-only acute GVHD, one grade I and one grade II. In patients who received MUD donors and PTCy, MMF, and tacrolimus ($n = 5$), none developed acute GVHD. The 1-year cumulative incidence of any cGVHD is 14%, with severe cGVHD of 5%. Three patients developed cGVHD, two with mild limited, and one with severe extensive. In patients who received MUD donors and PTCy alone ($n = 4$), one developed mild limited chronic GVHD. In patients who received MUD donors and PTCy, MMF, and tacrolimus ($n = 5$), none developed chronic GVHD. Both patients with mild cGVHD were treated, and are off systemic immune suppression. One patient (#24) developed early, gut-only, grade II aGVHD, which responded to steroids and sirolimus. She later developed extensive cGVHD, including autoimmune cytopenias (see below), at 11 months post-transplant. As of this writing, she has responded to treatment with steroids and sirolimus with improvement of symptoms, and steroids are being weaned. Cumulative incidences of GVHD for different GVHD prophylaxis regimens with MUD donors are shown in Table 3.

Survival

The median follow-up of surviving patients is 26 months (ranging 7 months–9 years) (Table 2). Overall survival and disease-free survival at 2 years are both 92% (95% CI 72–98%). Event-free survival at 2 years is 87% (95% CI 64–96%) (Fig. 4). For the 17 surviving patients who have follow-up of or beyond 2 years, the OS is 90% (95% CI 64–97%) and the EFS is 68% (95% CI 38–86%). The 2-year OS and EFS in the TBI-containing versus chemotherapy-only preparative regimens are not statistically significantly different.

Transplant-Related Complications

Sinusoidal Obstruction Syndrome Three patients (12%) developed SOS, as defined by Baltimore criteria [17]. Two had severe sinusoidal obstruction syndrome (SOS) with multiorgan dysfunction (MOD) and were successfully treated with defibrotide (DF). One of these patients received TBI in the prep, and one had a chemotherapy-only prep. As described above, patient #20 developed fatal SOS with MOD following a second myeloablative BMT. Notably, patient #25 had a history of poorly controlled Crohn's and multiple intra-abdominal fistulae. He was treated with prophylactic DF from the start of his prep to day + 30, per a recently published phase

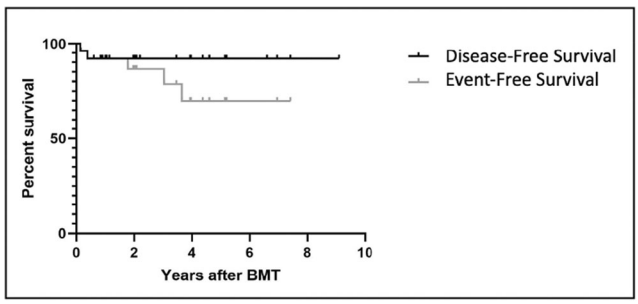

Fig. 4 Disease-free survival (DFS)/overall survival (OS) and event-free survival (EFS). Disease-free survival/overall survival and event-free survival for all patients. OS and DFS are the same at 2 years; three patients who developed secondary graft failure were successfully treated

3 trial [18], and did not develop any signs or symptoms of SOS.

Infections There was one mortality from infection. Patient #15 with common variable immune deficiency (CVID) developed concurrent adenovirus and CMV infections early after BMT following initial count recovery. This ultimately led to secondary graft failure, multi-organ failure, and death before day + 60 despite targeted anti-viral therapy and advanced supportive care.

There were two patients (8%) with CMV reactivation, two patients (8%) with BK hemorrhagic cystitis, two patients (8%) with lower respiratory tract influenza, three patients (12%) with EBV viremia, and one patient (4%) with HHV-6 viremia. All viral infections/reactivations occurred within the first 6 months after BMT. Four patients (16%) had *Clostridium difficile*-positive diarrhea, there were thirteen episodes of bacteremia in nine patients (36%), and one patient (4%) had a urinary tract infection. Patient #19 with CTLA deficiency had multiple episodes of bacteremia in the first year after BMT; the remaining bacterial infections in other patients occurred within the first 3 months after BMT. One patient (4%) had a fungal pneumonia, which occurred at day + 48 after BMT.

Autoimmune Cytopenias/Inflammation Three patients (12%) developed autoimmune cytopenias. All three had chemotherapy-only prep regimens, and all three received PTCy, MMF, and tacrolimus for GVHD prophylaxis. One patient (#21) developed direct antibody test (DAT)–positive hemolytic anemia at 10 months post-BMT. He was treated successfully with a high-dose steroid pulse followed by a taper. One patient (#22) developed unexplained neutropenia at 6 months post-BMT. He was treated with high-dose pooled intravenous immunoglobulin (IVIg), and his ANC rose to normal. Patient #24 had persistent unexplained thrombocytopenia accompanied by DAT-positive hemolytic anemia at 10 months post-BMT. She was treated with IVIg with a slight rise in her platelet count and hemoglobin. She subsequently developed fevers and dysregulated immunity—consisting of elevated ferritin, erythrocyte sedimentation rate, and triglycerides—and ultimately both skin and gastrointestinal biopsy-proven cGVHD. Her cytopenias and inflammatory markers improved after initiating cGVHD-directed therapy.

Cytokine Release Syndrome Cytokine release syndrome has been reported at high rates in recipients of haploidentical PBSC grafts, and at much lower rates with haploidentical T cell replete bone marrow [19, 20]. Based on standard cytokine release syndrome (CRS) grading criteria [21], none of the patients developed CRS. The patient who received a PBSC graft developed a fever after the infusion, but no other signs or symptoms of CRS.

Discussion

We provide an updated report of pediatric patients with PIDD, PIRD, and IBMFS treated with RIC alloBMT and PTCy for GVHD prophylaxis. We added 14 new patients who did not receive TBI and who received post-transplant MMF and tacrolimus, including 6 with rare diseases, and we report longer-term follow-up for the entire cohort. This study adds significant clinical equipoise, particularly for alloBMT using donors other than HLA-matched related donors. Our results using a uniform RIC preparative regimen demonstrate 2-year overall and event-free survivals of 92% and 87%, respectively, and for the patients who have follow-up of or beyond 2 years, we demonstrate overall and event-free survivals of 90% and 68%, respectively. We demonstrate cumulative incidences of aGVHD grade II to IV of 17%, with no grade III or IV aGVHD, cGVHD of 14%, severe cGVHD of 5%, and 1-year TRM of 4%. We also demonstrate robust median ALC recovery [22, 23], rapid neutrophil engraftment, and low rates of infectious complications, in the setting of limited rates of acute and chronic GVHD.

Based on our initial successful rates of early robust donor chimerism in our first eleven patients [8], we removed low-dose TBI from the preparative regimen for all but one of the additionally reported 14 patients. Since making this change, we have noted an increase in mixed chimerism in PIDD/PIRD patients, more predominantly in the CGD patients. By contrast, removal of TBI from the prep has not affected chimerism in the IBMFS patients, though it is unclear whether this is significant given the smaller number of IBMFS patients treated with chemotherapy-only ($n = 4$). The surviving PIDD/PIRD mixed chimera patients have no symptoms of their underlying diseases, with follow-up ranging 9 months–3.5 years, off immune suppression, and at varying percentages of donor chimerism. In many PIDD/PIRD patients, stable mixed chimerism may be sufficient for long-term cure, but these patients may be at risk for late graft failure. This is especially relevant for diseases where the defect does not impair T cell function, such as in CGD, wherein mixed chimerism in neutrophils, even with a low donor percentage, may be enough to cure the underlying disease. Based on the PIDD and PIRD patient outcomes, we believe that low-dose TBI in the conditioning regimen is more likely to result in full donor chimerism, thereby preventing late graft failure that may occur with mixed chimerism. We have therefore added TBI back into the regimen for all PIDD/PIRD patients only, but not for IBMFS patients, and are studying this in a prospective institutional trial (ClinicalTrials.gov Identifier: NCT04232085).

PTCy has been used successfully as sole GVHD prophylaxis in the matched donor setting for hematologic malignancies [24–26]. In our first publication [8], we used PTCy alone as GVHD prophylaxis in four patients with 10/10 MUDs. Two developed aGVHD, and one developed cGVHD. In an

attempt to further minimize GVHD and optimize engraftment in our additional patients, we added MMF and tacrolimus to PTCy for GVHD prophylaxis for all patients, regardless of degree of donor match, as was recently shown to be effective in a large study of patients with hematologic malignancies [27]. None of the five patients transplanted using MUDs and PTCy, MMF, and tacrolimus developed GVHD. Using PTCy, MMF, and tacrolimus for all donor types was successful in limiting acute and chronic GVHD.

Mallhi et al. recently published the outcomes of a similarly heterogeneous group of 23 patients with nonmalignant disorders, transplanted with a cyclophosphamide-based RIC regimen, and similar GVHD prophylaxis [9]. Four (17%) of their patients only received one dose of PTCy, and 26% received PBSC grafts. Their 2-year OS and EFS are excellent, 91% and 78%, but their rates of acute and chronic GVHD are much higher than other reported PTCy regimens [8, 28–31]. They observed acute GVHD grades II–IV and III–IV and chronic GVHD rates of 78%, 26%, and 42% [9], whereas in our cohort, those rates were 17%, 0%, and 14%. We have demonstrated similar OS and EFS with significantly lower GVHD rates.

Allen et al. recently published the outcomes from the BMT CTN 1204 study, wherein 46 patients with HLH or PIDD were transplanted using RIC and cyclosporine-based GVHD prophylaxis [7]. They reported 18-month OS 67%, grade II–IV aGVHD 26%, and cGVHD of 27% [7]. Unfortunately, mortality and graft failure remained problematic; two patients (4%) had primary graft failure, and the probability of being alive at 1 year, with donor chimerism significant to cure, and without any additional intervention, was 39% [7]. We recognize that this study had a much higher percentage of HLH patients than ours, which impedes any direct comparison.

In a more comparable patient population, Dimitrova et al. recently published the outcomes of twenty PIDD patients transplanted with serotherapy-free chemotherapy-only RIC and PTCy [32]. The outcomes for this study were 1-year OS 90%, grade II–IV aGVHD 20%, and no cGVHD; however, only 45% were alive and without additional infusion of stem cells at 1 year.

An additional notable comparison is provided by Gungor et al., who reported the outcomes of 56 CGD patients transplanted using busulfan-based RIC and CNI/MMF for GVHD prophylaxis [33]. The cumulative incidence of aGVHD grade II–IV was 11% and III–IV was 4%, and cGVHD of 0% with matched siblings and 11% with unrelated donors [33]. In this study, the probability of being alive and without infusion of additional stem cells at 1 year was 91%; later probabilities are not reported. In our CGD cohort (n = 11), two of our CGD patients did require infusion of additional stem cell products at later time points, resulting in the probability of being alive and without infusion of additional stem cells at 4 years of 82%. It is important to note that haploidentical donors were not studied in the Gungor report [33]; our successful use of PTCy in the RIC setting further expands the donor pool for those who do not have unrelated donors, while maintaining comparably high rates of engraftment at 1 year and low rates of GVHD.

An alternative approach to PTCy is ex vivo T cell receptor αβ+ and CD19+ cell depletion, which has been used in both the malignant and nonmalignant settings [34–37]. Shah et al. transplanted 25 children with PIDD using RIC and MMF/cyclosporine for GVHD prophylaxis [36]. OS and EFS at 3 years were 84% and 80%. Cumulative incidence of grade II–IV aGVHD was 22%, with no cGVHD, and TRM at 1 year was 16%. Ex vivo T cell depletion has many similar benefits to PTCy, in that it widely expands the donor pool and allows for decreased use of immune suppression after BMT. However, the cost of T cell depletion is high compared to unmanipulated strategies [38], and it is only available at centers with graft engineering expertise, thus making it less accessible.

We acknowledge the heterogeneity in our patient population, with an over-representation of CGD patients, an under-representation of HLH patients, and small numbers of IBMFS patients. Patients with PIDD/PIRD have a variety of underlying defects leading to chronic inflammation and chronic infection, leading to organ damage and reduced performance status, and ultimately to decreased life expectancy. Though varying in their defects, we believe there is benefit in treating all of these patients with a one-size-fits-all regimen, in order to simplify the regimen to make it accessible to patients with all diagnoses and with any donor type. Though eleven of our 25 patients (44%) have CGD, we believe the results herein are applicable to other PIDD/PIRD diagnoses. However, it is important to examine this in a prospective manner, as we are doing in our recently opened phase 2 ongoing institutional trial (ClinicalTrials.gov Identifier: NCT04232085), in order to more closely study engraftment and the kinetics of immune reconstitution for all PIDD, PIRD, and IBMFS patients.

Conclusions

Our results utilizing RIC with PTCy compare favorably to all of these studies, with low rates of GVHD and high rates of survival. All patients had prompt count recovery and no patients experienced primary graft failure. Though we have observed an increase in mixed chimerism since removing low-dose TBI from the preparative regimen, disease-free survival at 1 year, without infusion of additional stem cell products is 91% (21 of 23 evaluable patients). Three of the 21 patients did ultimately need additional stem cell products at time points later than 1 year. While this is a smaller, single-institution retrospective study with a skew towards CGD patients and

fewer HLH patients than some of the comparable data [4, 7, 39], our results are an important addition to the field, as more centers develop regimens with the goals of minimizing toxicity and improving engraftment. RIC with PTCy provides a platform for the safe and effective use of HLA-matched or mismatched unrelated donors and haploidentical related donors, and should be considered a curative therapeutic option for patients with IBMFS, PIDD, and PIRD.

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Compliance with Ethical Standards

Conflict of Interest K.R.C. serves on the Speaker Bureau and Advisory Board for Jazz pharmaceuticals and received a research grant from Jazz pharmaceuticals; he is on an investigator-initiated trial of post-transplant therapy for solid tumors that is supported in part by Bristol Meyers Squibb. H.J.S. is on the Speaker Bureau for Jazz pharmaceuticals and is on an investigator-initiated trial of post-transplant therapy for solid tumors that is supported in part by Bristol Meyers Squibb. None of these are in direct conflict with the manuscript.

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