Reduced Intensity Transplantation for Primary Immunodeficiency Disorders

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KEYWORDS

- Reduced intensity • Hematopoietic cell transplantation
- Primary immunodeficiency

It is more than 40 years since the first successful hematopoietic cell transplants (HCT) were reported in children with primary immunodeficiency disorders (PID).[1,2] Many advances have been made since that time such that most children with PID can now be cured from their otherwise lethal disorders through well-matched HCT procedures. Preexisting morbidity and infection remain the principal adverse factors for poor outcomes with HCT. To improve current results 3 aspects need to be considered: (1) earlier diagnosis; (2) well-tolerated pretransplant conditioning regimens; and (3) promotion of immune reconstitution.[3] This article addresses modifications in the conditioning regimen that might lead to further improvement in HCT outcomes.

Many children with PID have significant comorbidities at the time of HCT, and conventional myeloablative preparation may be associated with significant treatment-related toxicity. In the past decade reduced intensity transplantation (RIT) has become a well-established approach in adult patients with malignant disease, extending curative HCT to older individuals and patients with comorbidities otherwise ineligible for myeloablative procedures (reviewed in Refs.[4–6]). Because pediatric patients generally tolerate more intensive transplant approaches, myeloablative regimens are still preferred in childhood malignancies; this reluctance is compounded further by the fact that most RIT regimens use peripheral blood stem cells (PBSC) and pediatric centers have preferred bone marrow (BM) and cord blood (CB) because

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of a lack of a survival advantage with PBSC in pediatric recipients[7] and reluctance to collect PBSC from minor donors.[8] Nevertheless, a study of the role of RIT in pediatric cancer has recently been completed under the auspices of the Pediatric Blood and Marrow Transplant Consortium of North America.[9] The study reports favorable outcomes with RIT approaches in pediatric patients with malignant disease who were ineligible for myeloablative HCT, as long as their disease was in clinical remission (CR) at the time of HCT. These survivors are likely to have the additional benefit of reduced long-term sequelae, including possible preservation of fertility and normal growth patterns.

RIT might be a more attractive option for children with nonmalignant disease as there is no requirement for high-dose chemotherapy to eradicate malignancy; graft failure, may be a concern in certain groups[10] as many patients with nonmalignant disorders have not received prior chemotherapy, however varying degrees of immunodeficiency should make rejection less of an obstacle in children with PID. RIT has been used successfully for many years in patients with marrow aplasia, in whom myeloablation is not required.

MECHANISM OF RIT

Conventional HCT prevents rejection by the use of supralethal chemotherapy to remove host-versus-graft (HVG) reactions, create marrow space and eradicate malignancy, often achieving full donor chimerism in the early months post HCT. RIT prevents rejection by the use of pre- $\pm$ post-HCT immunosuppression to achieve tolerance and a graft-versus-marrow (GVM) reaction to create space and eradicate malignancy. In this setting a stable mixed chimerism (MC) is often achieved, which may be converted to full donor chimerism, if required, by tailing immunosuppression or donor lymphocyte infusions (DLI). Unlike in malignant disease, stable MC in the diseased cell lineage is usually sufficient to cure genetic disease.

Two general approaches have been used to develop RIT regimens.[11,12] Terminology may be confusing, but so-called reduced intensity conditioning (RIC) protocols (**Fig. 1**) have been developed by replacing myeloablative agents with more immunosuppressive and less myelosuppressive properties.[13,14] Nevertheless, such protocols still contain agents capable of ablating stem cells, for example, busulfan or melphalan, but at a reduced dose compared with conventional HCT. In contrast regimens with minimal toxicity or minimal intensity conditioning (MIC) (see **Fig. 1**) are truly nonmyeloablative and contain only immunosuppressive agents. These latter regimens, developed in animal models, initially used irradiation to induce a degree of immunosuppression pre transplant, followed by posttransplant immunosuppression given to control residual host and newly infused donor, alloreactive T cells.[15] By definition MIC procedures have been associated with less toxicity than RIC HCT; however, as MIC relies solely on a GVM reaction to make marrow space, there is a suggestion that MIC HCT may be associated with an increased incidence of graft-versus-host disease (GVHD), particularly chronic GVHD (cGVHD), especially in the unrelated donor setting.

A truly nonmyeloablative/MIC regimen should not eradicate host hematopoiesis and should allow prompt autologous hematopoietic recovery without a transplant, but be sufficient to enable at least partial donor engraftment to occur post HCT.[16] In this setting initial chimerism is often mixed. In contrast, RIC regimens require HCT for prompt hematologic recovery and if the graft is rejected, prolonged aplasia may occur. Initial chimerism following RIC HCT is frequently 100% donor, but may decline thereafter in the absence of GVM, as autologous hematopoiesis recovers.

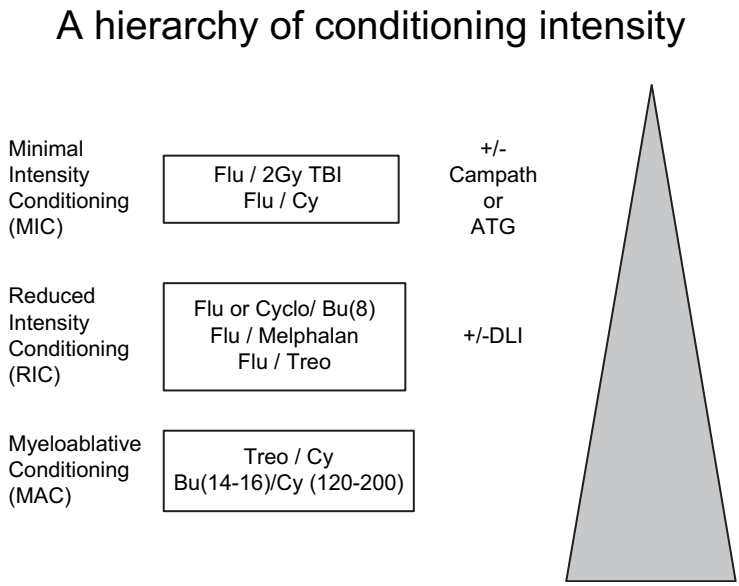


Fig. 1. A hierarchy of commonly used MIC, RIC, and MAC regimens in PID patients; Gy, gray; Flu, fludarabine; cyclo, cyclophosphamide; BU8, busulfan 8 mg/kg; BU14–16, busulfan 14–16 mg/kg; CY120–200, cyclophosphamide 120–200 mg/kg. (*From* Satwani P, Cooper N, Rao K, et al. Reduced intensity conditioning and allogeneic stem cell transplantation in childhood malignant and nonmalignant diseases. Bone Marrow Transplant 2008;41(2):174; with permission.)

RIT PROTOCOLS FOR PID

Studies reporting the use of RIT and including 5 or more patients with PID are shown in **Table 1**. Most reduced and minimal intensity protocols are based around the purine analog fludarabine, which has profound immunosuppressive and antitumor properties (see **Fig. 1**). RIC protocols combine fludarabine with a marrow ablative agent (melphalan, busulfan, or treosulfan), and MIC protocols combine fludarabine with non-marrow ablative low-dose radiation or cyclophosphamide.

RIC PROTOCOLS FOR PID

Fludarabine/Melphalan

The combination of fludarabine, melphalan, and antithymocyte globulin (ATG) (FMA) was first reported by the London group in 8 patients with severe combined immunodeficiencies (SCID) and non-SCID immunodeficiencies (see **Table 2** for definitions); despite significant comorbidities before HCT, 7 of 8 were surviving with donor cell engraftment 8 to 17 months after transplant.[17] The same group recently updated their series, reporting 113 patients with PID who had undergone RIT between 1998 and 2006.[12] Most patients (93 of 113) received a RIC regimen consisting of alemtuzumab 1 mg/kg (Campath 1H), fludarabine 150 mg/m^2, and melphalan 140 mg/m^2 (FMC), and 20 patients received MIC HCT. Donor source was mainly matched unrelated (MUD) (n = 42) and mismatched unrelated donors (mMUD) (n = 29). Eighteen patients had severe organ toxicity before transplant, including previous ventilation (n = 12), significant liver or renal impairment (n = 8), or total parental nutrition-dependent

Table 1
RIC and MIC HCT for primary immune deficiencies

Refs.	Immunodeficiency	N	Donor	Type	Conditioning	Stable Donor Chimerism	Rejection/Low-level Chimerism Requiring Further Procedure	GVHD	Survival (%)
[12a]	Various	113	MUD, mMUD, MRD, UCB	RIC (93) MIC (20)	Flu150 mg/m^2, Mel 140 mg/m^2, Camp or ATG (93) Flu120 mg/m^2, Cy40 mg/kg/anti-CD45, Camp (13)	81%	12%	2/113 died of GVHD	82
[17]	Various	8	MUD, MRD	RIC	Flu 120–150 mg/m^2, Mel 140 mg/m^2, ATG	86%	14%	1/8 limited cVHD	88
[18b]	Various	33	MUD, mMUD	RIC	Flu150 mg/m^2, Mel 140 mg /m^2, Camp or ATG	81%	19%	3/33 > grade II aGVHD, 1/33 ext cGVHD	94
[19]	Various	14	MUD, MRD	MIC	Flu 90 mg/m^2, TBI 200 cGy (10)	79% CD3 57% CD33	4/14 received second SCT/DLI/ stem cell boost	11/14 > grade II aGVHD, 8/14 ext cVHD	62
[20]	LAD	8	MUD, mMUD, MRD, UCB	RIC	Flu150 mg/m^2, Mel 140 mg/m^2, Camp (5) Flu150 mg/m^2, Treo 42 mg/m^2, Camp or ATG (3)	88%	1/8 MNC 30%, 0% myeloid, ? second SCT	3/8 > grade II aGVHD	100
[21]	SCID, WAS, HLH	5	UCB	MIC	Flu 150–180 mg/m^2, Cy 30–120 mg/kg $\pm$ VP16 900 mg/m^2, ATG	50%	2/2 HLH rejected	1/6 > grade II aGVHD	60
[23]	Various	6	MRD, MUD, UCB	RIC	Flu 180 mg/m^2, Bu (IV) 6.4 mg/kg, ATG	100%		No significant acute or ext cGVHD	67
[24c]	HLH HLH/XLP	25 10	MUD, mMUD, UCB, Haplo MUD, MRD	RIC RIC	Flu150 mg/m^2, Mel 140 mg /m^2, Camp (19) Flu, Mel, Camp	100% 100%	2/25 required DLI 4/10 required DLI	NA 3/4 > grade II aGVHD post DLI	84 100

[25]	HLH	12	mMUD, MUD, MRD Haplo	RIC	Flu150 mg/m^2, Mel 140 mg /m^2, Camp (9) Flu 150 mg/m^2, Mel 125 mg/m^2, Bu 8 mg/kg, ATG (3)	100% CD3 92% myeloid		4/12 > grade II aGVHD, 1/9 ext cGVHD	75
[26]	WAS	11	MUD, mMUD	RIC	Flu150 mg/m^2, Mel 140 mg /m^2, Camp (6) Treosulfan, Flu, Camp (5)	2/6 0% myeloid 1/5 0% myeloid	Splenectomy ×2	2/11 > grade II aGVHD, significant cGVHD	100
[27]	WAS, CGD, SCID, congenital neutropenia	6	MRD, MUD, UCB	RIC	Flu 160 mg/m^2, Bu ×16 doses targeted to steady-state concentration 600 ng/mL, ATG	100%	2/6 low-level myeloid	None	83
[28]	Various	16	MUD, mMUD, MSD, UCB	MIC	Flu 150 Cy 1200 mg/m^2, anti-CD45 MAbs ×2, Camp	88%	2 rejections, 1 second SCT, 3/14 no donor myeloid	6/16 > grade II aGVHD evolving to 2/16 ext cGVHD	81
[29]	Various	17	MSD, MUD, mMUD, UCB	RIC	Flu 150 mg/m^2, Treo 42 mg/m^2, Camp (14) or ATG (2)	88%	<50% donor in 2, ? second SCT required	2/17 > grade II aGVHD, 3/17 ext cGVHD	94
[11]	CGD	10	MSD	MIC	Flu 125 mg/m^2, Cy 120 mg/kg, ATG	80%	2 graft failures, all patients planned to receive DLIs	3/8 > grade II aGVHD, 1 evolving to ext cGVHD	70
[31]		6	MRD, MUD, mMUD	RIC	Flu 160 mg/m^2, Bu ×16 doses targeted to steady state concentration 600 ng/ml ATG (3) or Camp (3)	33%	1/6 required DLI for low level donor chimerism	1/6 grade II aGVHD evolving to ext cGVHD	100

Abbreviations: Bu, busulfan; Camp, Campath (alemtuzumab); Cy, cyclophosphamide; ext, extensive; Flu, fludarabine; Haplo, haploidentical related donor; Mel, melphalan.

[a] Includes patients from Refs.[17,18,20,24–26,29]

[b] Includes patients from Refs.[17,25,26,30]

[c] Includes patients from Cooper N, Rao K, Gilmour K, et al. Stem cell transplantation with reduced intensity conditioning for haemophagocytic lymphohistiocytosis. Blood 2006;107(3):1233–6.

Table 2
Classification of PID

■ SCID		□ WASP Deficiency
Functional	Genetic	□ C40 ligand deficiency (hyper-IGM)
T− B− NK−	ADA deficiency (AR)	
	Reticular dysgenesis (X-linked or AR)	□ XLP (Purtilo syndrome)
T− B− NK+	RAG deficiency (AR)	
	SCID with Artemis (AR)	□ Hemophagocytic syndromes
T− B+ NK−	γ deficiency (X-linked)	Immunodeficiency with partial albinism
	Jak 3 kinase deficiency (AR)	Familial HLH
T− B+NK+	IL7 Rα deficiency	Griscelli disease (partial albinism)
Unspecified		Chediak-Higashi syndrome
Other		
□ Non-SCID		□ Phagocytic cell disorders
□ T-cell immunodeficiency		
CD4 lymphopenia		Schwachman syndrome
Zap 70 kinase deficiency		Granule deficiency
MHC class II deficiency		LAD
PNP deficiency		X-linked CGD
Omenn syndrome		Kostmann disease
Severe DiGeorge complex (22q 11del)		AR-CGD
CID with skeletal dysplasia		IFN-γ receptor deficiency
Cartilage hair hypoplasia		□ Autoimmune lymphoproliferative syndrome (homozygotes) (FAS deficiency)
Other		

Abbreviations: ■, SCID; □, non-SCID; ADA, adenosine deaminase deficiency; AR CGD, chronic granulomatous disease; CID, combined immunodeficiency disease; IFN, interferon; MHC, major histocompatibility complex; PNP, purine nucleoside phosphorylase; RAG, recombinase activating gene; WASP, Wiskott-Aldrich syndrome protein.

enteropathy (n = 8). Five patients had DNA repair defects. At a median follow-up of 2.9 years (range 2 months–8 years) the overall survival (OS) for these patients was 82% (93 of 113) and 91 of 133 (81%) had stable donor engraftment. Fourteen patients (12%) had or were likely to require additional procedures, including second stem cell transplantation (SCT), marrow infusion, additional $CD34^+$ cells or gene therapy. The survival curve for each disease is shown in **Fig. 2**. Survival of more than 80% was observed in children receiving HCT for SCID, T-cell immune deficiency, X-linked lymphoproliferative disease (LPD), hemophagocytic lymphohistiocytosis (HLH), and Wiskott-Aldrich syndrome (WAS). As shown in **Fig. 3**, there was no significant difference in survival for patients transplanted from single-antigen mismatched donors compared with 10 of 10 HLA-matched donors, highlighting the possibility that RIC may allow HCT from less than ideal donors. Causes of death were as follows: multiorgan failure (n = 5); infection (n = 4); pneumonitis (n = 4); GVHD (n = 2); and recurrent disease, venoocclusive disease (VOD), transplant-related microangiopathy, and pulmonary hypertension (n = 1 each).

There are no prospective randomized studies comparing RIC HCT with conventional HCT in PID; however, the London group retrospectively compared their results in children with PID transplanted from unrelated donors using FMC-RIC HCT versus

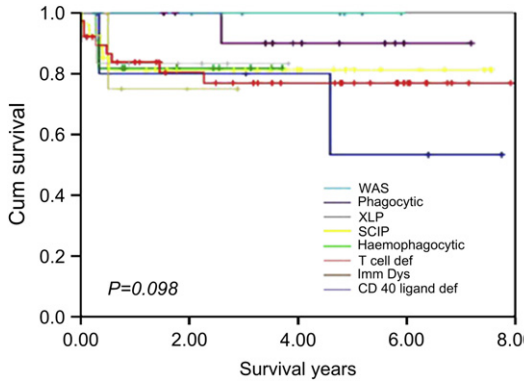


Fig. 2. OS of pediatric patients undergoing RIC SCT for PID/HLH stratified by disease. Phagocytic, neutrophil phagocytic defect; T-cell def, isolated T-cell immunodeficiencies; Imm Dys, immunodysregulatory disorders; CD40 ligand def, CD40 ligand deficiency. (*From* Satwani P, Cooper N, Rao K, et al. Reduced intensity conditioning and allogeneic stem cell transplantation in childhood malignant and nonmalignant diseases. Bone Marrow Transplant 2008;41(2):176; with permission.)

myeloablative conditioning (MAC) HCT from an earlier time cohort, and showed a decreased overall mortality (2 of 33 RIC compared with 4 of 19 MAC, $P<.01$).[18] There was no difference in the incidence of acute GVHD (aGVHD), and immune reconstitution with RIC was similar to that seen after conventional intensity conditioning with similar kinetics of CD19, CD3, and CD4 recovery (**Fig. 4**). There was an increase in viral infections/reactivations in the RIC cohort (29% for RIC compared with 21% following MAC, $P = .02$). Viral infections in those receiving RIC HCT included cytomegalovirus (CMV) (n = 3), adenovirus (n = 5), and Epstein-Barr virus (EBV) (n = 10). There was also an increased rate of MC compared with MAC HCT (45% MC, of which 13% had low-level donor chimerism for RIC versus 36% MC and 0% low-level donor

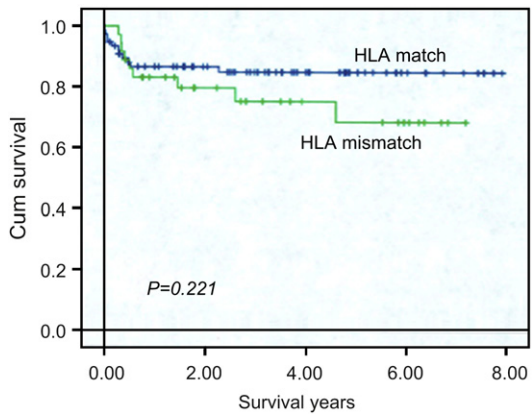


Fig. 3. OS in pediatric patients undergoing RIC HCT for PID stratified by HLA-matched versus HLA-mismatched donor. There was no significant difference in survival for HLA-matched compared with HLA-mismatched donors ($P = .2$). (*From* Satwani P, Cooper N, Rao K, et al. Reduced intensity conditioning and allogeneic stem cell transplantation in childhood malignant and nonmalignant diseases. Bone Marrow Transplant 2008;41(2):176; with permission.)

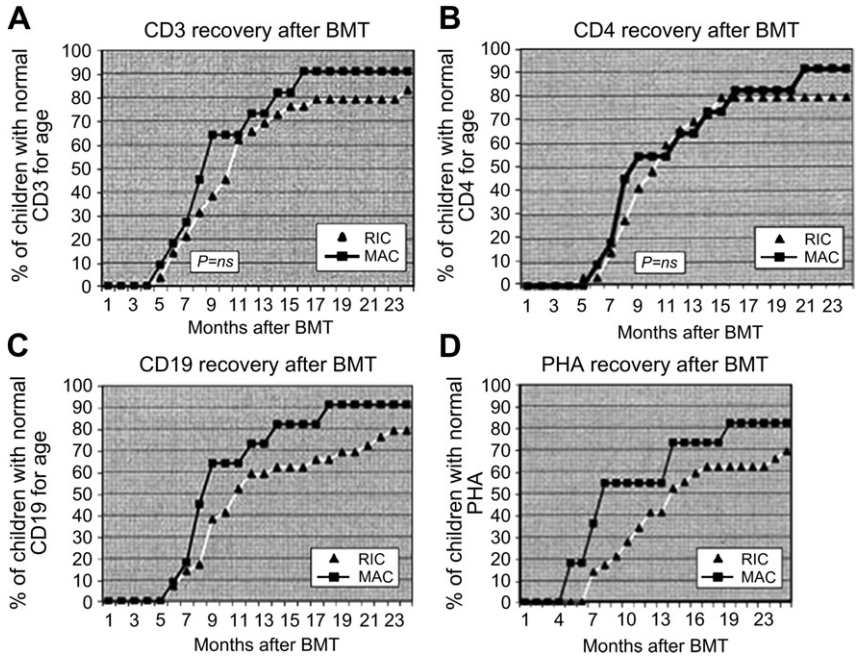


Fig. 4. Kinetics of recovery of CD3 (*A*), CD4 (*B*), CD19 (*C*) and PHA (*D*) after RIC and myeloablative transplantation (MAC) in children with primary immunodeficiencies. There was no statistical difference in speed of immune reconstitution between the 2 groups. (*From* Rao K, Amrolia P J, Jones A, et al. Improved survival after unrelated donor bone marrow transplant in children with primary immunodeficiency using a reduced intensity conditioning regimen. Blood 2005;105:884; with permission.)

chimerism for MAC); however, in general, MC after RIC appeared to stabilize or improve with withdrawal of immunosuppression, and there were low rates of recurrent disease (2 of 23 patients). OS was improved in the RIC group, mainly through improved survival in patients with non-SCID immunodeficiency (**Fig. 5**).

To assess the potential effects of the different time cohorts in this study the outcome of a larger cohort of PID patients undergoing RIC HCT from the London group was compared with that of PID patients undergoing largely MAC HCT and reported from European centers in the SCETIDE database. In this comparison (**Fig. 6**), the improvement in RIC HCT seems to be largely confined to children with T-cell deficiencies (as defined in **Table 2**).

Some of the outcomes associated with FMC/A-RIC HCT in PID have been studied further. Higher levels of viral reactivation[32] seem to relate particularly to EBV. The incidence of EBV viremia and LPD was studied in a consecutive cohort of 128 pediatric patients undergoing HCT with RIC (n = 65) or MAC (n = 68).[33] Following MAC, 6 of 68 (8%) developed viremia; all remained asymptomatic. EBV viremia (23 of 65 patients = 35%, $P<.001$) and LPD (10 of 65 = 15%, $P<.001$) were significantly more frequent following RIC. Of the 23 RIC patients who developed viremia, 8 remained asymptomatic, 5 had symptomatic viremia (fever $\pm$ rash), and 10 patients developed LPD, 2 of whom died. An absolute lymphocyte count of less than 0.3×10^9/L at the time of onset of viremia was strongly predictive of development of LPD ($P<.05$) in this group. The incidence of viremia was significantly higher in patients receiving selective T-cell

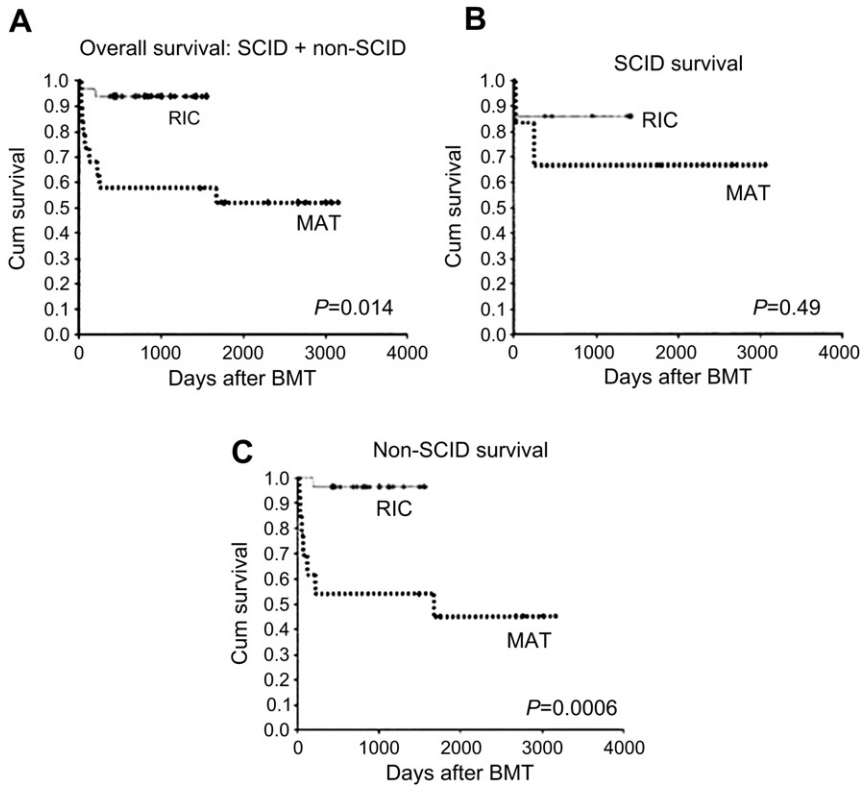


Fig. 5. Kaplan-Meier analysis comparing OS in children with primary immunodeficiencies receiving RIC or conventional conditioning (MAC or MAT) SCT. (*A*) OS in all patients was significantly better in patients who received RIC (94% OS) compared with MAC (53% OS). When divided into disease type, the improved survival following RIC was particularly marked in patients with non-SCID (who had a 54% death rate following MAC compared with a 30% death rate following MAC for SCID). (*B*) OS following either RIC or MAC in patients with SCID. (*C*) OS following RIC or MAC in patients with non-SCID. (*Reproduced from* Satwani P, Cooper N, Rao K, et al. Reduced intensity conditioning and allogeneic stem cell transplantation in childhood malignant and nonmalignant diseases. Bone Marrow Transplant 2008;41(2):176; with permission.)

depletion with ATG (15 of 43, 35%) than Campath (12 of 73, 16.4%, $P<.05$). PID and aGVHD were associated with EBV viremia in univariate analysis, but were not independent risk factors. The increased incidence of EBV viremia was believed to reflect the profound immunosuppression following RIC HCT, together with the incomplete ablation of recipient-derived B cells.[33] In contrast with this finding, the combination of FMC-RIC HCT, preemptive rituximab, and EBV-specific cytotoxic T lymphocytes was successful in curing all 8 patients with EBV-driven LPD complicating PID and immunodysregulatory syndromes,[34] suggesting that close monitoring of EBV by polymerase chain reaction and preemptive therapy mainly with rituximab can overcome complications associated with EBV viremia following RIC HCT. In adult patients a high incidence of CMV reactivation has been described following FMC-RIC HCT.[35]

Long-term chimerism (median follow-up 4.6 years, range 6 months–10.6 years) has been examined in 118 children with PID receiving FMC-RIC HCT in London (K Rao, personal communication, 2009). After prolonged follow-up donor chimerism was

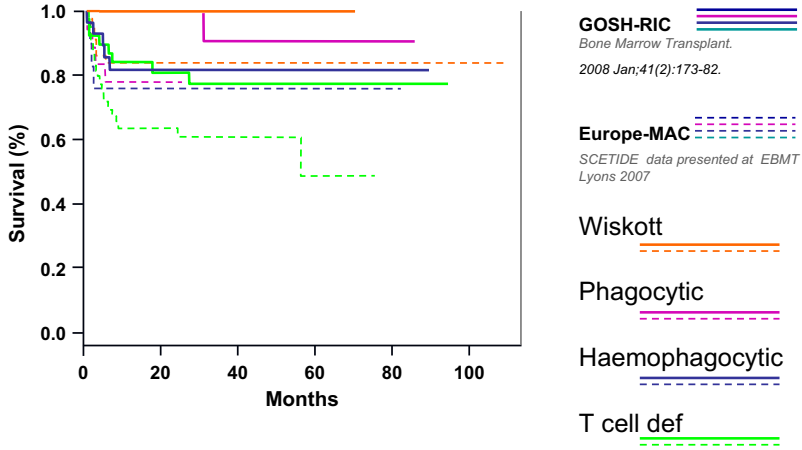


Fig. 6. Improvement in outcome of stem cell transplantation for T cell immune deficiency. GOSH-RIC, Great Ormond Street Hospital RIC HCT; Europe MAC, myeloablative HCT performed in European centers; Def, deficiency.

low (<50%) in 24 of 118 (20%) patients, 5 patients have required a second MAC HCT, 1 required a CD34+ cell top-up, 2 patients were given DLI, and 1 patient with WAS underwent a splenectomy. Twenty-one of these 24 patients are currently alive and well with stable engraftment. Two patients have died, 1 following second HCT and 1 from progressive disease, and 1 patient has continuing poor immune reconstitution. Almost all patients developing low-level donor chimerism received BM rather than peripheral blood progenitor cells (PBPC) as stem cell source and MSD and MFD had more low MC than MUDs and mMUDs (30% and 28% vs 18% and 11%). These findings have confirmed those of an earlier published study.[32] Low (<10%) donor chimerism was almost entirely limited to the myeloid series. Cyclosporin withdrawal seemed to have a positive effect on lymphoid chimerism but not on myeloid engraftment. Lymphoid chimerism changed little after the first year but myeloid chimerism did decrease further after 1 year in a few patients. Consequently, 5 years following RIC HCT for PID just less than 10% of patients have required a second procedure. This finding is probably not different from the situation following MAC HCT.

Shenoy and colleagues[36] used FMC-RIC HCT in 16 patients with nonmalignant disorders, including 2 PID patients, but gave Campath 1H 33 or 48 mg total dose early pre-HCT from day −21 to day −19. The study included sibling BM (n = 5), sibling PBSC (n = 5), unrelated BM (n = 3), and unrelated CB (n = 3). All 14 evaluable patients had complete or high-level (>50%) donor chimerism in all lineages, suggesting that lower doses or administration of Campath 1H away from the graft may increase donor chimerism in the HLA-matched setting. Further studies are under way to examine whether Campath levels taken on or around day zero may predict graft outcome in these patients (ie, high levels predicting for slow immune reconstitution and viral infections, and low levels for GVHD and complete donor chimerism). These results may better help to define the optimal method of delivering Campath in the RIT setting (Ref.[12] and S Adams, personal communication, 2007).

In addition to T cells, natural killer (NK) cells may be important in determining chimeric status post RIT. NK cells react with their target cell HLA class I molecules through killer immunoglobulinlike receptors (KIRs), which exist in inhibitory and activating forms. Following RIT, in which donor and recipient hematopoiesis may coexist,

the balance of activating/inhibitory KIR activity between donor/recipient NK cells and their targets may determine chimeric status (eg, recipients with overall lower inhibitory KIR scores have more active antidonor immune effector cells, leading to reduced donor chimerism).[37]

The benefit from FMC-RIC HCT was most evident in children more than 1 year of age. For SCID patients less than 1 year of age, treatment-related mortality (TRM) remained high even with RIC HCT (28% in the London series).[28] Occasionally, very young patients seem to develop a fatal melphalan shock syndrome with massive capillary leak within hours of receiving melphalan (K Rao, personal observation, 2008), although the mechanism of this is not understood. An alternative RIC or MIC protocol (see later discussion) might be preferable for this group of patients.

Fludarabine/Busulfan

Jacobsohn and colleagues[23] reported the outcome of RIC HCT in patients with nonmalignant disorders, using fludarabine, busulfan, and ATG (FBA) modeled after Slavin and colleagues.[13] Six children with PID underwent MSD PBSC (n = 2), MUD PBSC (n = 2), and unrelated CB (n = 2) HCT. Patients received fludarabine 180 mg/m^2, and intravenous (IV) busulfan 6.4 mg/kg in 8 doses on days −5 to −4 or pharmacokinetic monitoring to achieve an area under the curve (AUC) of 3800 to 4200 μmol/min with single daily dosing of busulfan on days −5 and −4. Two patients with X-linked hyper-IgM were phenotypically cured, off intravenous immunoglobulin, and with reversal of cholangiopathy. One had full donor and one 30% donor chimerism. One patient with X-linked lymphoproliferative disorder (XLP) was also alive and well, with 98% donor chimerism. One patient with SCID was too early to evaluate and 2 patients (1 with chronic granulomatous disease [CGD] and 1 with Omenn disease) died within 100 days of HCT. There was little aGVHD or cGVHD in evaluable patients.

Horn and colleagues[27] also reported the use of FBA in 6 children with PID. The conditioning regimen consisted of IV busulfan from day −9 to −6, to a total of 16 doses targeting continuous steady-state concentration of 600 ng/mL. Fludarabine (40 mg/m^2/d) was given from day −5 to −2 (total dose 160 mg/m^2) and rabbit ATG (thymoglobulin) 0.5 mg/kg/d on day −4 and 2.5 mg/kg on days −3 to −1 (total dose 8 mg/kg). Donors were MUD BM (3), matched related BM (2), and umbilical cord blood (UCB). Three patients achieved more than 95% donor chimerism and 3 were mixed chimeras. One patient with WAS died of CMV pneumonitis; the others are alive and disease-free. There were 13 other non-PID patients included in the study; overall MC was more common with BM as a stem cell source and graft rejection was more common in patients receiving mMUDs. Four patients experienced graft failure; all 4 patients underwent second HCT and 3 of 4 are alive and disease-free, illustrating how second HCT after failed first RIC HCT is well tolerated and frequently successful.

Further work may establish an AUC for IV busulfan that is tailored to disease, donor type and stem cell source, to achieve lineage-specific donor engraftment with the minimum amount of acute and long-term toxicity. A similar protocol was used in 5 further children with PID.[31] All are alive and disease free, one patient with chronic granulomatous disease required DLI for low level donor chimerism, the others have stable or increasing mixed chimerism not requiring intervention expect one patient with complete donor chimerism who experienced siginificant acute and chronic GVHD. Interestingly in this study investigators prolonged immunosuppression for mixed chimerism rather than tailing it as the usual course of action, this did not appear to increase graft rejection though it might have reduced donor chimerism in this group.

Fludarabin/Treosulfan

Another approach to RIT in PID has been to replace busulfan with treosulfan. Treosulfan (L-threitol-1,4-bis-methanesulphonate) is the prodrug of L-epoxybutane, an alkylating agent with myeloablative and immunosuppressive properties.[29] Recent reports in adult patients have suggested that regimens containing treosulfan provide effective HCT conditioning with reduced risk of VOD, when compared with busulfan.[38–40] In addition, there is no need for prophylactic anticonvulsant treatment and unlike busulfan, it is not necessary to measure drug levels. Phase 1 studies have suggested stable linear pharmacokinetics of treosulfan up to the clinically effective dose of 42 g/m^2.[40] Eighteen patients with PID with a mean age more than 1 year underwent HCT, with various donors and stem cell sources, using treosulfan 14 g/m^2 $\times$ 3 days + fludarabine 30 mg/m^2 $\times$ 5 days with Campath 1H (FTC) (n = 14) or ATG (FTA) (n = 2).[29] One patient received cyclophosphamide 50 mg/m^2 $\times$ 4 days and ATG. Although the latter is considered modified conditioning it should probably be classified as MAC rather than RIC (see **Fig. 1**). The median time to neutrophil recovery was 12 days (9–33 days), platelet recovery 20 days (10–145 days). Thirteen patients achieved 100% donor chimerism, which remained stable in 10 patients. Three achieved stable MC: 90% to 99% donor (n = 2); 30% donor in peripheral blood, 80% donor T cells (n = 1), which was sufficient to cure the underlying disease. Two patients achieved low-level donor chimerism (<50%) and are being considered for second HCT. Twelve patients experienced no GVHD, grade I aGVHD (n = 2), grade II aGVHD (n = 1), or grade III aGVHD (n = 1) progressing to cGVHD of skin and gut. Two patients developed de novo cGVHD (limited in one and extensive skin and gut in the second). Toxicity was tolerable, particularly given such a young group of patients, and this treatment may be preferable to FMC-RIC in this cohort; toxicity included dermatologic grade II (n = 4); gut grade III (n = 9); T-cell sequestration (n = 3); pulmonary hypertension (n = 1), and right external iliac thrombosis (n = 1). Seventeen of 18 were alive at follow-up of 429 days (156–722 days). One patient had died on day 249 with cGVHD, rotavirus, and HLH.

MIC

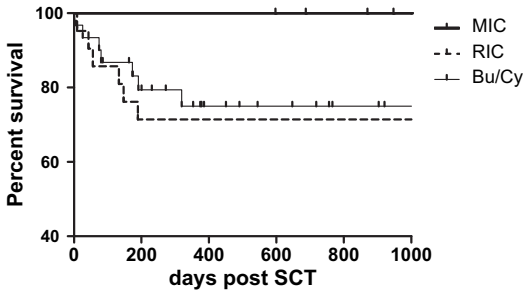
Fludarabine/Low-Dose Total Body Irradiation

The Seattle group investigated an MIC regimen in 14 patients (12 children and 2 adults) with PID and coexisting infections, organ toxicity, or other factors precluding conventional HCT.[19] Most patients received 200 cGy total body irradiation (TBI) plus fludarabine (30 mg/m^2/d; $\times$ 3 days -4 to -2) as conditioning and all patients received HLA-matched grafts with intensive postgraft immunosuppression with cyclosporin A (CsA)/mycophenolate mophetil (MMF). No serotherapy was given. Thirteen patients established mixed (n = 5) or full (n = 8) donor chimerism and 1 rejected the graft. OS at 3 years was 62%, with a TRM of 23%. Eight of 10 evaluable patients had correction of immune deficiency with stable donor engraftment. However, there was a high rate of GVHD with 11 of 14 developing significant aGVHD (mostly grade II), and extensive cGVHD in 8 patients, reflecting the use of peripheral blood as the stem cell source and the absence of serotherapy. This approach was associated with a lower incidence of viral infections/reactivations, notably EBV, than RIC regimens using serotherapy; however, the high incidence of cGVHD is a significant obstacle to broader use of this regimen in children with nonmalignant disorders.

Fludarabine/Cyclophosphamide/Monoclonal Antibodies

The London group has explored an MIC protocol combining fludarabine (30 mg/m^2 $\times$ 5 day -8 to -4) and low-dose cyclophosphamide (300 mg/m^2 $\times$ 4 on day -7 to -4)

with 2 rat anti-C45 monoclonal antibodies (MAbs) YTH 24.5/YTH 54.12 for additional myelosuppression, and serotherapy with Campath 1H either 0.6 mg/kg or 0.3 mg/kg with unrelated donor or MSD, respectively.[28] Patients were at particularly high risk from HCT-related toxicity even with RIC protocols because of severe preexisting organ toxicity, age less than 1 year, or the presence of DNA/telomere repair disorders. In total 16 patients underwent MIC HCT from MSD (5), MUD (9), and mMUD (2). Conditioning was well tolerated, with only 2 cases of grade 3 and no grade 4 toxicity. Six of 16 patients (38%) developed significant aGVHD (3 grade II skin and 3 grade III skin/gut). Five of 16 patients (31%) developed cGVHD (limited in 3 and extensive in 2), which has resolved in all cases. The incidence of GVHD was reduced when BM was used as stem cell source (2 of 10 BM recipients compared with 4 of 4 evaluable PBSC recipients developed aGVHD > grade II). Similarly the incidence of cGVHD was lower in recipients of BM (2 of 10) compared with PBSC (3 of 4). At a median of 9.5 days (range 1–15 days), 16 of 16 patients had a neutrophil count more than 0.5×10^9/L. One patient failed to engraft and had autologous recovery, and 1 patient who received a mismatched CB engrafted with stable MC after an extended period. Donor chimerism was 100% in 3 of 4 PBSC recipients, with 1 PBSC recipient rejecting the graft. Three of 10 BM recipients achieved 100% donor chimerism, 3 achieved stable high-level MC in mononuclear and granulocyte lineages, and 3 achieved donor T-cell chimerism without sustained myeloid chimerism. One achieved very-low-level donor chimerism and required a second SCT. At a median of 37 months post HCT 13 of 16 patients in this high-risk cohort were alive and cured from their underlying disease. In terms of OS, SCID patients more than 1 year of age seemed to gain particular benefit from this MIC HCT protocol (**Fig. 7**).



Number at risk						
MIC	8	8	8	8	8	8
RIC`	21	15	15	15	15	15
Bu/Cy	31	25	24	24	24	24

Fig. 7. Comparison of disease-free survival (DFS) of SCID patients more than 1 year of age transplanted using anti-CD45 MAb-based MIC, fludarabine/melphalan-based RIC and busulfan/cyclophosphamide conditioning. Kaplan-Meier curves showing DFS (days) of SCID patients aged more than 1 year conditioned with (1) CD45 MAb-based MIC regimen (n = 8, DFS 100%) (2) fludarabine/melphalan-based RIC regimen (n = 21, DFS 71.4%) and (3) busulfan/cyclophosphamide-based conditioning (n = 31, DFS 77.4%). The cohort conditioned with CD45-based MIC was transplanted between 2003 and 2007 (donor source 63% MUD, 25% MMUD, 13% MSD, 37% B^{neg} phenotype), the cohort conditioned with fludarabine/melphalan was transplanted between 1999 and 2003 (donor source 81% MUD, 19% MMUD, 57% B^{neg} phenotype) and the cohort transplanted with busulfan/cyclophosphamide was transplanted between 2003 and 2005 (donor source 57% MUD, 30% MSD, 13% MFD, 46% B^{neg} phenotype).

STEM CELL SOURCE

In children with leukemia undergoing MAC HCT from MSDs, hematopoietic recovery was faster after PBSC transplantation compared with BM, risks of grade 2 to 4 acute GVHD were similar, but chronic GVHD risk was higher after PBSC transplantation. In contrast to reports in adults, TRM, treatment failure, and mortality were higher after PBSC transplantation; risks of relapse were similar.[7] The use of PBSC as opposed to BM in RIT seems to be associated with improved donor chimerism in recipients with PID,[19,28,32] but at the cost of increased rates of GVHD; in this setting OS seems to be similar between the 2 groups. The balance of HVG and GVH/GVM reflects the complex interactions of stem cell source with disease type, conditioning regimen, serotherapy, graft content (CD34+, CD3+, NK) and GVHD prophylaxis, and is more finely balanced in RIT than MAC HCT. The optimal combinations for PID remain to be determined, but even then there is likely to remain a risk of rejection with RIT and early warning of future graft rejection as suggested by recipient chimerism status in NK-cells on day +28[41] or increasing MC greater than 30% host cells[31] might enable timely intervention by withdrawl of immune suppression or DLI.

There has been increasing interest in the use of UCB in PID but using largely myeloablative preparations (reviewed in Ref.[42]); UCB has the advantage of immediate access and a lower rate of GVHD, making it a particularly attractive stem cell source for children with PID. Several articles have been published in recent years combining RIT with UCB in more than 300 adults with malignant disease,[43] but there is considerably less experience in the use of RIT with UCB in children and even less with PID. Bradley and colleagues[21] described the outcome of 21 children, median age 9 years (range 0.33–20 years) with malignant (n = 14) and nonmalignant conditions (n = 7) transplanted using heterogeneous RIC/MIC regimens. Five patients (HLH [n = 2], SCID [n = 2], and WAS) received 4–6 of 6 HLA-matched unrelated UCB following MIC conditioning with fludarabine, cyclophosphamide, and ATG. The HLH patients received additional VP16, but both rejected; 1 underwent a successful second MAC HCT. Two of the 3 remaining patients died of viral pneumonitis and GVHD-related complications. The London group transplanted 3 patients with PID using a MIC protocol as described by Barker and colleagues.[22] Only 1 of 3 survived, 1 dying from disseminated cryptosporidiosis and the other from idiopathic pneumonitis (K Rao, personal communication, 2005). Based on only a few patients, therefore, the combination of MIC and unrelated UCB does not initially seem to offer any survival advantage to PID patients. Two centers in the UK (London and Newcastle) have performed 13 RIC UCB HCTs using fludarabine + melphalan or fludarabine + treosulfan. The outcome looks more promising, with 11 of 13 patients surviving with donor engraftment (K Rao and A Gennery, personal communication, 2009).

RIT IN SPECIFIC PID DISEASES

PID covers a large group of heterogeneous diseases (see **Table 2**). Outcomes following conventional HCT vary according to donor type and disease type: B− SCID has a poorer prognosis than B+ SCID; amongst non-SCID immunodeficiencies, T-cell deficiencies do worse than WAS, hemophagocytic diseases, and phagocytic disorders.[44] The possible advantage of RIC HCT in T-cell deficiencies has been discussed earlier, and it is likely that other specific PID types may respond differently to RIT.

HLH

Patients with HLH often have significant pretransplant comorbidities and require intensive cardiorespiratory support pre-HCT. This toxicity results in a high TRM with

conventional MAC, mostly from noninfectious pulmonary toxicity and VOD. In the HLH94 study, which advocated MAC HCT, the TRM was 30%,[45] with a 3-year OS of 71% following an MFD transplant, 70% for MUD, 54% for mMUD, and 50% for those with a haploidentical donor. The use of RIT has therefore been examined closely in HLH.[24,25] Twenty-five consecutive patients with primary HLH underwent RIT in London using MUD (n = 8), mMUD (n = 11), MFD (n = 2), and haploidentical (n = 4) donors. Patients were conditioned with fludarabine 30 mg/m^2 × 5 (days −7 to −3) and melphalan 140 mg/m^2 (day −2) in patients receiving MFD/UD transplants or 125 mg/m^2 (day −1) in patients receiving haploidentical grafts. Patients receiving MFD/UD transplants received serotherapy with Campath 1H 0.2 mg/kg × 5 (days −8 to −4) and those receiving haploidentical transplants received ATG 5 mg/kg (days −5 to −1) together with busulfan 4 mg/kg (days −9 to −8) for additional myelosuppression. One patient received a modified RIC haploidentical protocol with addition of thiotepa (10 mg/kg) to fludarabine/melphalan and OKT3 instead of ATG (P Bader, personal communication, 2007). Two patients underwent MIC HCT: one who was ventilated at the time of transplant received fludarabine 30 mg/m^2 × 3 (days −4 to −2) and 2 Gy TBI in a single fraction; and the other patient received fludarabine 120 mg/m^2, CY 30 mg/m^2, Campath 1H and 2 anti-CD45 MAbs as described earlier. Grafts were T-replete marrow (MFD/MUD) or PBSC (mMUD) and G-CSF mobilized CD34 selected or CD3/CD19 depleted PBSC (CliniMACs) for the haploidentical donors. Following RIT, 21 of 25 (84%) children are alive and in CR at a median of 36 months from transplant (range 2–105 months) with Lansky scores of 90% to 100%. There were 4 TRMs from CMV pneumonitis (n = 1), multifactorial pneumonitis following T-cell sequestration, and CMV disease on the background of previous pulmonary HLH (n = 1), parainfluenza pneumonitis (n = 1) and hepatic rupture post-transjugular liver biopsy (n = 1). No patient developed VOD. Nine patients had CMV reactivation and 9 reactivated EBV. All patients engrafted with a median of 14 days to neutrophil engraftment and a median of 16 days to an unsupported platelet count greater than 20 × 10^9/L. All patients had 100% donor cells at engraftment. Six of the 21 survivors subsequently developed MC. No patient rejected the grafts or relapsed. After this study 2 patients with progressive mixed donor chimerism received escalating DLI from their MUDs. One converted from zero to full donor myeloid chimerism, but remains 50% donor in the CD3+ fraction, and the other remained unchanged with 75% donor myeloid chimerism and 0% donor myeloid (K Rao, personal communication, 2009). Seventeen patients were alive at follow-up after more than 14 months. All of those assessed had achieved normal T-cell levels and function, as assessed by phytohemagglutinin (PHA) stimulation index, at a median of 7.5 months from SCT. One patient with X-linked lymphoproliferative syndrome had decreased NK T (CD3$^+$CD56$^+$) cells before transplant, which increased to normal levels post transplant (2.9 × 10^5/L –2.08 × 10^6/L) and remains in remission. The OS data compare favorably with historical data, particularly for patients receiving mismatched HCT (**Table 3**). In the RIT group, 7 of 8 patients (87%) transplanted from an MUD and 9 of 11 (82%) transplanted from an HLA-mismatched donor survive in CR, compared with corresponding figures of 70% and 54% in the HLH 94 study.

Further published studies of RIC HCT in patients with HLH are limited; however, an abstract presented at the Histiocyte Society Meeting 2007[46] describes 100% survival in 10 children with HLH (n = 7) or X-linked lymphoproliferative syndrome (n = 3) treated with an FMC-RIC HCT. Six patients developed MC, with 4 receiving repeated T-cell infusions. All 10 are alive and well and remain in remission at a median of 10 months. Three further patients with HLH have now undergone UD (n = 2) or RIC (n = 1) haploidentical HCT with addition of thiotepa (10 mg/kg) to fludarabine/

Table 3
Comparison of MAC versus RIC HCT for hemophagocytic lymphohistiocytosis

Donors	Historical MAC[24] (%)[a]	GOSH-RIC (%)[25]
OS	64 (86)	88 (25)
MUD	70 (33)	87 (8)
MMUD	54 (13)	82 (11)
Haploidentical	50 (16)	75 (4)
MFD	71 (24)	100 (2)

Abbreviation: GOSH, Great Ormond Street Hospital.

[a] The total number of patients in each group is described in parentheses.

Data on results with MAC are from Horne A, Janka G, Maarten Egeler R, et al. Hematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. Br J Haematol 2005;129:622–30, whereas data on RIC are adapted from Cooper N, Rao K, Goulden N, et al. The use of reduced-intensity stem cell transplantation in haemophagocytic lymphohistiocytosis and Langerhans cell histiocytosis. Bone Marrow Transplant 2008;42(Suppl 2):S48; with permission.

melphalan and G-CSF mobilized CD3/CD19 depleted PBSC (CliniMACs) and OKT3. All 3 are alive and engrafted albeit with short follow-up (K Rao and P Bader, personal communication, 2009). Fludarabine/melphalan-based RIC HCT therefore seems to be a promising approach for children with HLH, with 34 of 38 patients surviving in initial studies. RIC HCT may be particularly suitable for children with poorly responding disease.

WAS

A recent study from the European centers examined the long-term outcome of 96 WAS patients who underwent HCT following a MAC regimen between 1979 and 2001 and who survived for at least 2 years following HCT.[47] Events included in the analysis of the 96 patients included cGVHD, autoimmunity, infections, and sequelae before or after HCT. Overall, the 7-year event-free survival was 75%, and was significantly influenced by donor group: MSD HCT, 88%; UD HCT, 71% ($P = .03$); and mMRD, 55% ($P = .003$). cGVHD-independent autoimmunity in 20% of patients was strongly associated with mixed or split (donor T-cell, host myeloid, and B-cell) chimerism status, suggesting that residual host cells can moderate autoimmune disease despite coexistence of donor cells. The overall incidence of autoimmunity was 8% in patients with full donor chimerism and 71% in patients with mixed/split chimerism ($P = .001$). This finding might have significant implications for the use of RIT in WAS, as RIT has been associated with increased rates of MC.[18] Conversely, WAS patients more than 5 years old who have accumulated more comorbidities have a poorer outcome following MAC HCT,[48] and RIT may offer some advantages in this setting. Investigators in London have explored the use of RIC HCT in WAS (updated from Ref.[46]). Between 1995 and 2007, 17 patients with WAS with a median age of 27 months underwent MSD (n = 5) or UD HCT (n = 12). MAC (busulfan/cyclophosphamide) was used in 6 patients, and RIC HCT in 11: treosulfan/fludarabine (n = 5), fludarabine/melphalan (n = 6). Amongst the 11 patients receiving RIC 10 had WAS and 1 X-linked thrombocytopenia. The mean age in this group was 70 months (15–194 months) and the mean Ochs score was 4.8. Donor source was MUD (n = 10) and mMUD (n = 1). Eight patients received BM and 3 patients PBSC. All patients survive, with a median follow-up of 4 years. Five of the 17 patients have mixed/split chimerism (details shown in **Table 3**) all following UD HCT: 1 of 2 following MAC UD HCT, and 4 of 11 (36%) following RIC UD HCT. All 4 of these patients received

in vivo T-cell depletion with Campath 1H 1 mg/kg total dose day −8 to day −4. Only 1 of these patients has so far developed definite autoimmune disease (**Table 4**). Three subsequent patients underwent UD HCT with RIT with reduced Campath 1H 0.6 mg/kg total dose day −8 to day −6, and all achieved 100% donor chimerism, with only 1 patient experiencing aGVHD grade II skin. Three of four patients with MC developed aGVHD higher than grade II, as opposed to 3 of 15 with full donor chimerism ($P<.05$). Comparative incidence of mixed/split chimerism following MAC HCT in other studies is 28%[47] and 38%.[49] RIC HCT protocols may be suitable for UD HCT in WAS, particularly in older children with comorbidities; however, some GVM reaction is required to secure 100% donor chimerism in all patients.

CGD

Horwitz and colleagues[50] reported 10 patients with CGD who underwent MIC HCT comprising cyclophosphamide (120 mg/kg), fludarabine (125 mg/m^2) and ATG (160 mg/kg), followed by transplant of CD34+-selected peripheral blood mononuclear cells from MSDs. Delayed DLI was given at intervals of 30 or more days to increase the level of donor chimerism. After a median follow-up of 17 months donor myeloid chimerism in 8 of 10 patients ranged from 33% to 100%, a level that could be expected to provide normal host defense. In 2 patients graft rejection occurred. Significant aGHVD developed in 3 of 4 adult patients with engraftment, 1 of whom

Table 4
Patients with WAS who became mixed chimeras after HCT

Presentation Ochs Score	Donor	Conditioning	Donor Chimerism (%)	Autoimmune Disease
Petechiae AHA Rituximab Infections 5	MUD BM	Treosulfan 42 g/m^2 Fludarabine 150 mg/m^2 Campath 1H 1.0 mg/kg	CD3 76 CD15 0 CD19 29	No splenectomy
Petechiae Eczema Infections 4	MUD BM	Melphalan 140 mg/m^2 Fludarabine 150 mg/m^2 Campath 1H 1.0 mg/kg	CD3 100 WB <5	AHA Splenectomy
Petechiae Infections Arthritis Splenectomy 5	MUD BM	Melphalan 140 mg/m^2 Fludarabine 150 mg/m^2 Campath 1H 1.0 mg/kg	CD3 80 CD15 0 CD19 52	No
Petechiae GI bleed Cerebral bleed Splenectomy 5	mMUD PBPC	Treosulfan 42 g/m^2 Fludarabine 150 mg/m^2 Campath 1H 1.0 mg/kg	CD3 100 CD15 63	No
IC bleed GI bleed Retuximab Splenectomy 5	MUD PBSC	Busulfan 16 mg/kg Cyclophos 200 mg/kg Campath 1H 1.0 mg/kg	CD3 62 CD15 58 CD19 53	No

Abbreviations: AHA, autoimmune hemolytic anemia; cyclophos, cyclophosphamide; GI, gastrointestinal; IC, intracranial.

subsequently had extensive cGVHD. Seven patients were reported to have survived from 16 to 26 months. Two patients died of transplant-related complications, and 1 patient who rejected the graft died after a second HCT.

As a comparison RIC HCT using FBA, busulfan 8 to 10 mg/kg (adjusted with busulfan kinetics in pediatric patients), fludarabine 180 mg/m^2, and ATG 40 mg/kg and matched donors (MSD = 5, MUD = 3) in 8 high-risk CGD patients led to 90% to 100% donor chimerism at a median follow-up of 26 months.[51,52] This is despite the use of BM in 7 of 8 cases. Seven patients are alive and well, and all active inflammatory and infectious foci are cured. One adult patient who had received PBSC from a CMV-negative MUD died of CMV pneumonitis on day +150. Another type of RIC HCT (4 Gy of TBI, cyclophosphamide 50 mg/kg, and fludarabine 200 mg/m^2) followed by 2 mismatched unrelated CB units in a single adult McLeod phenotype CGD patient with invasive aspergillosis also resulted in full donor engraftment and cure.[53] All 5 CGD patients who received FMC-RIC HCT survived, but sustained donor engraftment was achieved in only 2 of 5 (T Gungor, personal communication, 2008). RIC HCT using the FBA combination may be particularly suitable for high-risk patients with CGD.[30]

Leukocyte Adhesion Deficiency

The transplant experience for 36 children with leukocyte adhesion deficiency (LAD) undertaken at 14 centers worldwide between 1993 and 2007 was recently surveyed.[20] At a median follow-up of 62 months OS was 75%. MAC was used in 28 patients, and the remaining 8 patients received RIC (FMC = 5, FTC/A = 2) Survival after MFD and UD transplants was similar, with 11 of 14 MFD and 12 of 14 UD recipients surviving; mortality was greatest after haploidentical HCT, in which 4 of 8 children did not survive. Full donor chimerism was achieved in 17 of the survivors, mixed multilineage chimerism in 7 patients, and mononuclear cell restricted chimerism in a further 3 patients. Causes of death in the 9 patients who died included pneumonitis (n = 2), infection (n = 5), VOD (n = 3), and malignancy (n = 1); some had more than 1 contributing factor and all had received MAC HCT. Overall, the use of RIC regimens seemed to be associated with reduced toxicity, with all 8 patients surviving, although 2 patients have low-level donor chimerism, not requiring second HCT to date.

FERTILITY AND LATE EFFECTS

One major impetus for performing RIT in children is the avoidance or reduction of long-term sequelae associated with MAC HCT, including growth failure, gonadal failure, secondary malignancies, and myelodysplasia.[54] However, the true incidence of late effects following RIT in children with PID awaits well-planned and well-executed follow-up studies as the first cohorts of survivors approach adulthood. Intact fertility and uncomplicated pregnancies have been reported in dogs with canine LAD following MIC HCT.[55] There have been several reports of successful pregnancies in adults following FMC- and FBA-RIC protocols for malignant disease. One adult CGD patient fathered a child after FBA[51]; however the impact of the same drugs on the pediatric gonadal and endocrine systems may be different. The avoidance of busulfan on the developing brain might have been considered to have a beneficial effect on cognitive function and improve IQ, but conditioning type seemed to have no impact on these parameters in the PID population.[56]

SUMMARY

Studies so far indicate that RIT may have an important role in treating patients with PID. Unlike more standard approaches, such regimens can be used without severe

toxicity in patients with severe pulmonary or hepatic disease. RIT also offers the advantage that long-term sequelae such as infertility or growth retardation may be avoided or reduced. Prospective randomized studies are required to define the true benefit of RIT versus MAC in any given type of PID; such studies are unlikely given the small number of patients and physician and patient/family preferences. On the present evidence the use of RIT seems to be most appropriate for those patients with significant comorbidities (eg, T-cell deficiencies) and those undergoing UD HCT. More studies are required using pharmacokinetic monitoring (eg, busulfan and Campath 1H) and varying stem cell sources to optimize GVM reactions and minimize GVHD. In certain PID patients RIT will be the first step toward establishing donor cell engraftment; second infusions of donor stem cells, DLI, or a second MAC HCT (which seems to be well tolerated) may be required in some patients with low-level donor chimerism or graft rejection.

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