

## Review

# Reduced-intensity allogeneic hematopoietic stem cell transplantation for acute leukemias: ‘what is the best recipe?’

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### Summary:

**Reduced-intensity stem cell transplantation (RIST) has been shown to be a safe and useful alternative transplant method for patients including elderly and medically unfit patients. RIST conditioning regimens vary widely in the intensity of myeloablation, immunoablation, and anti-leukemia effects, and thus optimal regimen for each disease entity is yet to be determined. Most reports on RIST to date are small, single-institution experiences or retrospective studies with heterogeneous patient populations and primary diseases, complicating any direct comparison between studies. In acute myeloid leukemia (AML), moderate-intensity regimens may be effective, achieving 30–70% 1-year disease-free survival in various series, but minimal-intensity regimens are associated with high relapse rates. In acute lymphoblastic leukemia (ALL), not even moderate-intensity regimens are effective and most patients with advanced ALL relapse post transplant. Thus, the risk/benefit ratios of graft-versus-host disease/graft-versus-leukemia effect differ among diseases. Larger, prospective, multi-center clinical trials are needed to determine the best use of RIST in hematologic malignancies.**

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Reduced-intensity stem cell transplantation (RIST)<sup>1–4</sup> has made allogeneic hematopoietic stem cell transplantation (HSCT) a possible therapeutic option for patients with hematologic malignancies who are unable to tolerate standard high-dose chemotherapy and/or high-dose total-body-irradiation (TBI) regimens because of old age, intensive pretreatment, compromised organ function, or active infections. RIST has recently become a more popular

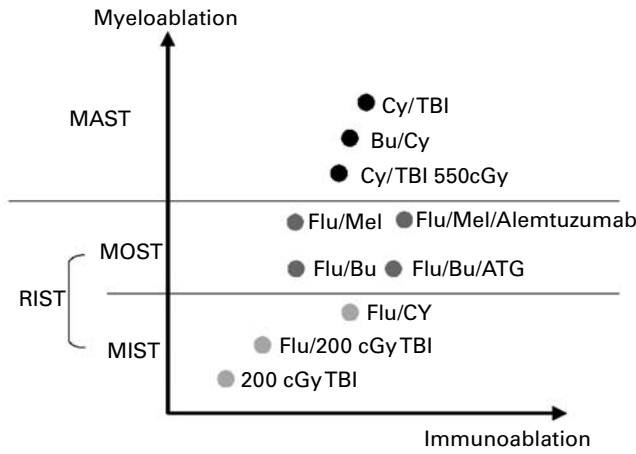
treatment option for acute leukemias,<sup>1–10</sup> but its precise role within an overall treatment strategy has not yet been well defined. RIST relies on a graft-versus-leukemia (GVL) effect for its principal antitumor activity.<sup>10</sup> The GVL effect was first described by Barnes and Loutit in 1957<sup>11</sup> in animal models, and indirect evidence for its existence was apparent in clinical studies in the 1980s, when lower relapse rates of acute leukemia were observed in patients with graft-versus-host disease (GVHD).<sup>8,12–15</sup> In the 1990s, direct clinical evidence of GVL effects came from complete remissions following donor lymphocyte infusion (DLI) in patients with relapsed chronic myeloid leukemia (CML).<sup>7,9</sup>

### Different preparative regimens

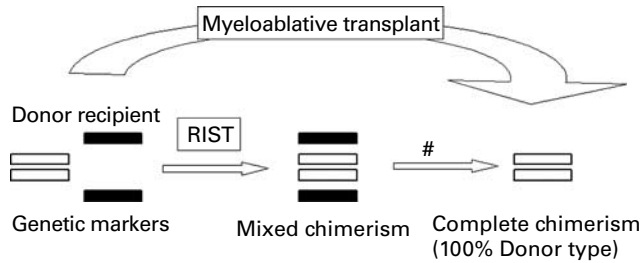
In this review, any transplantation that uses a conditioning regimen less than myeloablative is called ‘RIST’. A subset of RIST that uses a minimal-intensity regimen is called ‘Minimal-Intensity Stem Cell Transplantation (MIST)’. MIST regimens are truly nonmyeloablative, that is, the patient’s own hematopoiesis can recover if donor stem cells are not infused. Examples of MIST conditioning regimens are fludarabine (Flu)/cyclophosphamide (Cy)<sup>5,6,16–18</sup> and 200 cGy TBI with or without Flu.<sup>2,19,20</sup> The other, larger subset of RIST is ‘Moderate-intensity Stem Cell Transplantation (MOST)’. Examples of MOST conditioning regimens are Flu or cladribine (Cla)/busulfan (Bu) with or without anti-thymocyte globulin (ATG),<sup>3,4,21</sup> and Flu/melphalan (Mel) with or without alemtuzumab.<sup>1,22–24</sup> For transplantation using intensive, myeloablative conditioning regimens, we use the term ‘Myeloablative Stem Cell Transplantation (MAST)’. Figure 1 displays the intensity of these different regimens according to myeloablation and immunoablation.

An interesting early observation was the persistence of host cells for long periods after RIST, resulting in mixed donor/host chimerism (Figure 2). As different conditioning regimens were employed, the speed of conversion to complete donor type chimerism in different hematopoietic lineages was noted to vary among protocols. MAST conditioning regimens almost always cause complete donor chimerism in all hematopoietic lineages promptly after transplants, and the clinical courses following different MAST conditioning regimens are similar. RIST regimens vary widely in the intensity of myeloablation, immunoabla-

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**Figure 1** Diagram showing intensity of each regimen. The x-axis indicates the degree of immunoablation, and the y-axis of myeloablation. RIST: reduced-intensity stem cell transplantation, MIST: minimal-intensity stem cell transplantation, MOST: moderate-intensity stem cell transplantation, MAST: myeloablative stem cell transplantation.



**Figure 2** Schematic diagram of mixed chimerism. It turned out that stable mixed chimerism, which requires donor lymphocyte infusion (#) to be converted to complete donor chimerism, is relatively rare.

tion, and antitumor effects. Their toxicities vary widely, as does the rate of achieving complete donor hematopoietic chimerism. The mucosal toxicity of MOST regimens such as Flu/Mel 180 mg/m<sup>2</sup> is significant,<sup>25</sup> whereas a MIST regimen such as Flu/TBI 200 cGy may obviate the need for transfusions.<sup>26</sup> GVHD after MIST may also be less intense.<sup>27</sup> The characteristics of these regimens are summarized in Table 1.

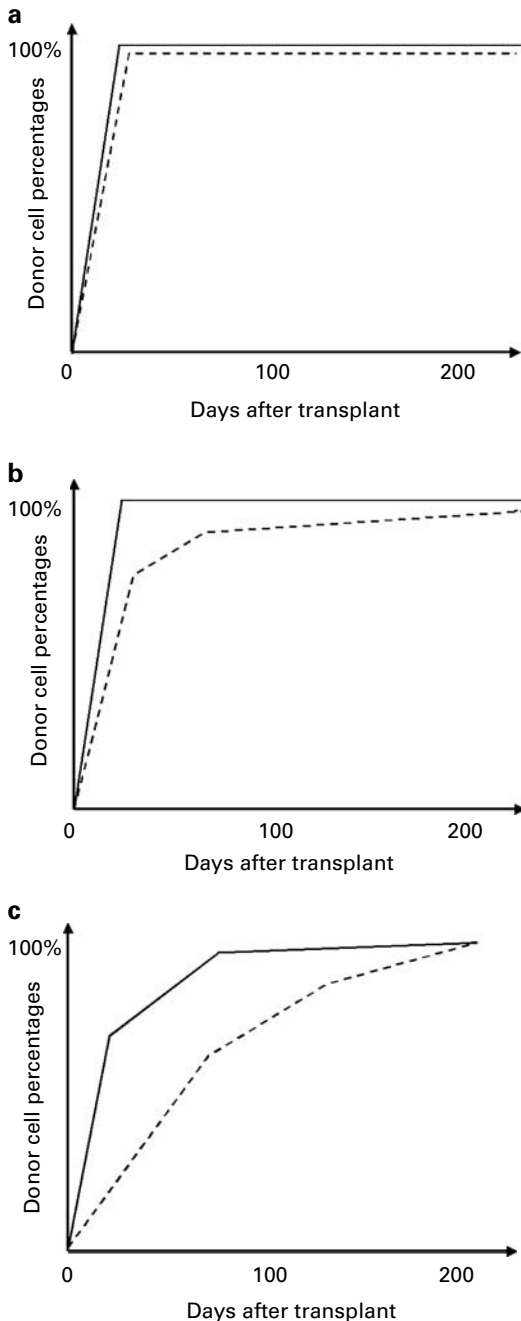
### Hematopoietic chimerism, RIST, and DLI

Initial clinical results suggested that persistent mixed chimerism after RIST was inevitable and, thus, additional DLI was considered to be necessary in order to achieve complete donor chimerism. Indeed, some MIST regimens do not completely eradicate host hematopoiesis<sup>2,20</sup> and some protocols incorporate DLI from the outset.<sup>28</sup> Additional clinical experience suggested, however, that DLI was often not necessary to achieve complete donor chimerism following MOST regimens. Thus, MOST is similar to MAST in not needing DLI. DLI also caused toxicities, including severe GVHD.<sup>29,30</sup> Marks *et al*<sup>30</sup> reported a 25% incidence of grades II–IV acute GVHD after DLI, and 15% of grades III–IV. As a consequence, at most institutions,

**Table 1** Comparison of transplantation

Type of transplant	Examples	If stem cells were not infused	Intensity of regimen	Antileukemia activity	Regimen-related toxicity	Time to achieve complete chimerism	Case stayed in mixed chimera	DLI needed except relapse
Myeloablative stem cell transplantation (MAST)	CY/TBI BU/CY (CY/TBI 550 cGy)	Pancytopenia, Host hematopoiesis will not recover	Intense	Strong	High	Complete donor type when engrafted both in myeloid and T cells	Very rare	Rare
Reduced-intensity stem cell transplantation (RIST)	Moderate-intensity stem cell transplantation (MOST)	Pancytopenia, Host hematopoiesis may recover	Moderate	Moderate	Intermediate	Relatively short (about 1 month, at least in myeloid)	Rare	Rare
	Minimal-intensity stem cell transplantation (MIST)	Host hematopoiesis recovers within 1 month	Weak	Weak	Low	May take 3–6 months	More common	More often

RIST = reduced-intensity stem cell transplantation; MIST = minimal-intensity stem cell transplantation; MOST = moderate-intensity stem cell transplantation; MAST = myeloablative stem cell transplantation; Cy = cyclophosphamide; Bu = busulfan; TBI = total body irradiation; ATG = antithymocyte globulin; Mel = melphalan.



**Figure 3** Diagram of chimerism status after stem cell transplantation using each regimen. (a) Myeloablative stem cell transplantation (MAST). (b) Moderate-intensity stem cell transplantation (MOST). (c) Minimal-intensity stem cell transplantation (MIST) with fludarabine/TBI 200 cGy. A solid line represent for myeloid lineage, a broken line for T-cell lineage.

DLI is currently used only following relapse or after an increase of host cells during a period of mixed chimerism. If T-cell depletion is performed *in vitro* or *in vivo*, the probability of incomplete donor-type chimerism is higher and, in such cases, DLI may be necessary.<sup>31,32</sup>

Kinetics of achieving complete donor chimerism varies among transplant regimens. MAST regimens usually achieve complete donor chimerism in all lineages within 1

**Table 2** Factors affecting donor–host chimerism

Factors affecting donor–host chimerism	Effect on donor complete chimerism
Heavy treatment before transplant	↑
Intensive conditioning	↑↑
GVHD	↑↑
Tapering immune suppression post transplant	↑
DLI	↑↑
More T cells transplanted	↑↑
More CD34 cells transplanted	↑↑
T-cell depletion (donor T cells)	↓
ATG or alemtuzumab to host	↓ (controversial)

GVHD = graft-versus-host disease; DLI = donor lymphocyte infusion; ATG = anti-thymocyte globulin.

month (Figure 3a). In MOST, complete donor chimerism in the myeloid lineage is almost always achieved promptly, although host T cells may persist, causing mixed chimerism for up to 2–3 months<sup>33–35</sup> (Figure 3b). With MIST, complete myeloid engraftment can be somewhat slower, taking as long as 3 months to achieve (Figure 3c). In one study, complete donor T-cell chimerism preceded complete donor myeloid chimerism after MIST,<sup>6</sup> but it is unclear whether this difference is clinically important. Mohr *et al*<sup>36</sup> reported that a variety of factors, including the number of transplanted CD34 cells, the conditioning regimen, and the number of previous chemotherapy regimens may all determine the kinetics of achieving complete donor chimerism (Table 2).

### Does GVHD decrease with RIST compared to MAST?

The severity of GVHD is related to the intensity of the conditioning regimens and, thus, some authors predicted milder GVHD after RIST.<sup>37</sup> In addition, stable mixed chimerism after RIST infers the tolerance of donor cells to host elements, and one study reported a low GVHD rate in the setting of mixed chimerism.<sup>38</sup> In a second study, early complete donor T-cell chimerism was associated with higher incidence of grades II–IV GVHD.<sup>35</sup> The incidence of GVHD thus appears to be less in MIST than in MAST,<sup>27</sup> but equivalent between MAST and MOST.<sup>10,39,40</sup>

In animal models, the induction of GVHD requires host antigen-presenting cells (APCs).<sup>41–43</sup> It is thus possible that mixed chimerism in APC populations may induce more GVHD than complete donor chimerism.<sup>44</sup> Such mixed chimerism might help to explain why GVHD is similar after MOST despite the decreased intensity of conditioning.

Given the risk of GVHD after MOST regimens, some centers have added ATG or anti-CD52 antibody (alemtuzumab) to the preparative regimen. Slavin *et al*<sup>4</sup> added ATG to Flu/Bu, and reported excellent results, but the Dresden group observed comparable engraftment rate without ATG, suggesting that it was not necessary.<sup>21</sup> ATG or alemtuzumab has now been used in many RIST regimens.<sup>3,22,24,29,32,39,45–48</sup> These agents have a very long half-life and, thus, suppress not only host immunity responsible for graft rejection but also act as ‘*in vivo* T

depletion' of the graft. As the results of studies vary widely, it is unclear whether these agents affect rates of acute GVHD,<sup>32,46–48</sup> chronic GVHD,<sup>32,46–48</sup> donor engraftment,<sup>32,36,47</sup> infections,<sup>32,46</sup> or relapse.<sup>46,49</sup> Although some studies claim that the use of ATG is associated with a poor prognosis,<sup>45,46</sup> other studies have not found such an association.<sup>32,48</sup> In a few studies, the use of ATG increased relapse.<sup>46,49</sup> A reasonable approach would be to use ATG only in patients at low risk for relapse. The best use of those potent agents in the context of RIST will need to account for dose, timing of administration, and disease status.

### RIST for acute myeloid leukemia (AML)

To date, many studies of RIST have included a mixture of diseases. In addition to the difference in efficacy of chemotherapeutic agents for different malignancies, the potency of GVL effects also varies from disease to disease. Early reports of RIST focused on patients with, primarily, myeloid diseases, because the GVL effect was generally thought to be stronger in myeloid diseases.<sup>1–4,21,23</sup>

In AML, most published reports of RIST have used MOST regimens. In one report of 19 elderly patients (median age 64)<sup>50</sup> with advanced AML (median blast percentage was 50%), 1-year overall survival (OS) was 68% and 1-year disease-free survival (DFS) was 61%. Martino *et al*<sup>51</sup> reported a 66% 1-year DFS in 37 patients (17 AML and 20 myelodysplastic syndrome (MDS)). Sayer *et al*<sup>52</sup> reported 1-year OS and DFS of 47% in 113 patients, most of whom received Flu/Bu. Hamaki *et al*<sup>49</sup> used a Flu or Cla/Bu with or without ATG regimen in 36 AML and MDS patients, with 1-year DFS of 64% in high-risk patients and of 85% in low-risk patients. Using unrelated donors and Flu/Mel conditioning, Wong *et al*<sup>25</sup> reported 1-year OS and DFS of 44 and 37%. The St Louis group used unrelated donors and a 550 cGy TBI and Cy regimen and reported 72% 1-year survival in first CR AML.<sup>53,54</sup>

The only available results with MIST in AML are from the Seattle group.<sup>20</sup> A total of 18 patients in CR1 received 200 cGy TBI with or without Flu and transplants from human leukocyte antigen (HLA)-matched sibling donors. The high relapse rate of 39% and 1-year DFS of 42% suggested that a more intensive regimen was needed.

The MDACC group<sup>40</sup> first used a MIST regimen (FAI) and then a MOST regimen (Flu/Mel) for AML. As expected, the F/M regimen produced more regimen-related toxicity, but less relapse than the FAI regimen (relapse rate was 61% with FAI and 30% with FM). Overall, long-term survival results were comparable between regimens (the 3-year OS was 35% with FM and 30% with FAI).

These studies mentioned above as well as other studies from which AML cases can be extracted are summarized in Table 3.<sup>55–57</sup>

### Acute lymphoblastic leukemia (ALL)

After MAST, the GVL effect is less potent in ALL compared to other diseases.<sup>7</sup> A GVL effect in ALL may be evident only with significant GVHD, as opposed to

other diseases such as CML.<sup>58,59</sup> The results of RIST for ALL are also not that impressive.<sup>59,60</sup> Martino *et al*<sup>59</sup> reported a 2-year OS of 31% in 27 cases of advanced ALL, with a relapse rate in patients with GVHD. Another report claimed that RIST is effective treatment only for early stage ALL (CR1) but not for advanced ALL (Table 4).<sup>60,61</sup> Currently, it is believed that RIST may not be sufficient as a treatment of ALL.

### Other malignancies

CML is one of the diseases for which RIST may be most effective, because the GVL effect is very potent in CML.<sup>7,9</sup> CML patients have a large tumor burden, however, and thus some cytoreduction is required.<sup>62</sup> The best results in CML have been reported after a MOST regimen using Flu/Bu with ATG.<sup>63</sup>

For some lymphoid diseases, myeloablation may not be needed. In lymphomas, particularly low-grade-lymphomas, early complete donor chimerism may not be critical, because malignancy progresses slowly, and cytoreduction can be achieved with specific agents such as Rituximab.<sup>17</sup> The MDACC group has published the results of MIST in low-grade lymphomas with excellent long-term disease control.<sup>17,18</sup>

### Does relapse increase after RIST compared to MAST?

Intuitively, less intensive conditioning regimens would cause less cytoreduction of tumor and may result in higher relapse rates. The relapse rates after MOST, however, are not much different from those observed after MAST (Table 2). In one study, the relapse rate was related to the incidence of GVHD, regardless of the intensity of conditioning, again suggesting the importance of GVL as the primary antitumor effect of allogeneic HSCT.<sup>39</sup> The relapse rate of AML after MIST, however, appears very high,<sup>2,20</sup> suggesting a need for moderate intensity in conditioning for AML. If the GVL effect acts as consolidation or maintenance therapy after the induction of the conditioning regimen, that induction should be of sufficient intensity to control the disease until the consolidation becomes effective.

Both GVL effect and GVHD are observed after RIST, and an optimal balance between these two phenomena is still elusive. We have recently reported more relapse associated with grade II GVHD than with grade I GVHD.<sup>58</sup> One explanation for this seeming paradox is that systemic steroid treatment may compromise GVL. Thus, prediction of steroid responsiveness at the time of GVHD onset may help tailor immunosuppression in selected cases in order to preserve GVL. Basic and clinical research in this direction is warranted.

Stable mixed chimerism infers an incomplete eradication of host elements, which would imply an increased risk of relapse. In addition, during stable mixed chimerism, donor-derived T cells must be tolerant of host hematopoietic cells, and this lack of alloreactivity may offer less protection against relapse. Mixed chimerism

**Table 3** Representative reports of RIST for AML/MDS

<i>Series mainly consisted of AML/MDS</i>											
Author	N	Disease	Age (range)	Alt. donor	Regimen	Adv. diseases	OS (y)	DFS (y)	Comments	Relapse/ all death	Ref. #
Wong	29	AML (13) MDS (7) CML (9)	59 (55–69)	All MUD	Flu/Mel (23), Flu/BU (5), FAI (1)	7/13 Ref AML	44% (1 y)	37% (1 y)		2/9	25
Feinstein	18	AML	59 (36–73)	None	TBI 200 cGy (n = 10) Flu/TBI 200 cGy (n = 8)	All CR1	54% (1 y)	42% (1 y)	Relapse rate 39%	7/10	20
de Lima	94	AML (68) MDS (26)	61 (27–74) FAI 54 (22–75) FM	1-Ag MM (6) in FAI MUD (29), 1-Ag MM (8) in FM	FAI (n = 32) Flu/Mel (n = 62)	18/32 NR (FAI) 52/62 NR (FM)	FAI 30% (3 y) FM 35% (3 y)		Relapse 61% FAI, 30% FM		40
Hamaki	36	AML (24) MDS (12)	55 (27–67)	None	Flu or Cla/BU (28) Flu or Cla/BU/ ATG (8)	22/36		64% (HR 1 y) 85% (SR 1 y)	CR1 AML 6/6 AinCR Other AML 9/18 AinCR	1/10	49
Bertz	19	AML	64 (60–70)	12 MUD	Flu/Mel/BCNU	10/19	68% (1 y)	61% (1 y)		2/6	50
Martino	37	AML (17) MDS (20)	57 (22–66)	None	Flu/BU	22/37 (57%)		66% (1 y)			51
Sayer	113	AML	51 (16–67)	50 MUD, 13 mm Rel	Flu/BU (93) Flu/TBI (4–8 Gy) (20)	85/113 non-CR	32% (2 y) 47% (1 y)#	29% (2 y) 47% (1 y)#	52% 2Y-DFS for CR1 40% for CR2–3 39% 3 y-DFS for CR other than CR1	29/61	52
Hallemeier	32	AML	47 (32–60)	All MUD	TBI 550 cGy/ CY	All CR (CR1 n = 15)	55% (3 y, CR1) 72% (1 y, CR1)#	57% (3 y, CR1) 67% (1 y, CR1)#			53
Malladi	16	AML (10) AML/MDS (2) MDS (4)	47 (27–66)	None	Flu/Mel	5/16	79% (1 y)#	79% (4 y) 79% (1 y)#			55
Giralt	86	AML (34) MDS (9) CML (27) ALL/NHL (16)	52 (22–70)	MUD (40), 1-AgMM (7) Rel	FM180 (66) FM140 (12) Cla/Mel (8)	42/43	39.1% (1 y, AML/MDS)	34.7% (1 y, AML/MDS)	NRM day 100 39.8%	5/41 (all cases)	56
Taussig	16	AML	54 (37–66)	None	Flu/CY or Flu/Mel	None	69% (2 y) 69% (1 y)#	56% (2 y) 56 (1 y)#			57
<i>Series in which AML cases can be extracted</i>											
Author	N	Age (range)	Alt. Donor	Regimen	Adv. AML cases	AML cases	Comments	Ref. #			
McSweeney	45	56 (36–72)	None	TBI 200 cGy (44) Flu/TBI 200 Gy (1)	4/11	5/11 AinCR Median FU 482 days	Some cases overlap with Reference 45	2			
Slavin	26	31 (1–61)	None	Flu/BU/ATG	None	5/8 AinCR		4			
Niederweiser	52	48 (6–65)	All UR BM 15 (29%) mm 13 BM, 39 PBSC	Flu/TBI 200 cGy	CR1 (2) CR2 (1) More adv. (10)	4/13 AinCR Median FU 722 days		98			

**Table 3** Continued

Author	N	Age (range)	Alt. Donor	Regimen	Adv. AML cases	AML cases	Comments	Ref. #
Bornhauser	24	47 (25-65)	None	Flu/BU	5/10	7/10 AInCR Median FU 242 days		21
Chakraverty	47	45 (18-62)	All UR BM UR PBSC (1)	Flu/Mel/ alemtuzumab	CR2 (5), Non-CR (1)	4/6 AInCR Median FU 15 months		22

OS = overall survival; DFS = disease-free survival; Flu = fludarabine; Bu = busulfan; Mel = melphalan; Cla = cladribine; TBI = total body irradiation; ATG = antithymocyte globulin; FAI = Flu/Ara-C/Idarubicin; FM = Flu/Mel; MUD = matched unrelated donor; 1-AgMM = 1-antigen mismatch; AInCR = alive in CR; NRM = nonrelapse mortality; # = 1-year survival rate estimated from figures; y = year(s); NR = high risk; SR = standard risk; Rel = relative; FU = follow up; Adv = advanced; mm = mismatched; Ref = refractory, UR = unrelated.

in natural killer (NK) cells may be associated with graft rejection after RIST,<sup>35</sup> but it is not known whether such chimerism affects relapse or GVHD. Early complete T-cell donor chimerism is associated with less relapse, less graft rejection, and better survival in one study.<sup>64</sup> In fact, most reports indicate fewer relapses in complete donor-type chimeras,<sup>65-73</sup> although this finding is not universal.<sup>74,75</sup> Representative studies are summarized in Table 5.

Some studies have shown that the treatment before transplant may affect the engraftment and relapse rate after RIST.<sup>76</sup> Additional treatment after remission may suppress the disease, as well as host hematopoiesis and host T cells. If the suppression of host T cells results in earlier and more stable engraftment of donor cells, particularly donor T cells, early donor-type chimerism may be achieved, and relapse rate may decrease.<sup>64</sup> Although intensive treatment before transplant tends to increase regimen-related toxicity (RRT) after MAST, RRT is lower after RIST and the concern decreases. Pre-transplant therapy before MAST does not improve post transplant survival in first-remission AML,<sup>77</sup> but the impact of pre-transplant therapy for RIST needs to be assessed.

### Conclusions and future directions

To date, most studies of RIST for acute leukemia are small, single-institution studies or retrospective multi-institution studies. Larger, prospective, multicenter studies are needed, particularly in AML where a comparison of RIST and MAST for patients who are eligible for full-intensity HSCT. RIST is not advised as treatment for ALL outside of a clinical trial.

The use of RIST is also being explored for myelofibrosis,<sup>78-80</sup> solid tumors,<sup>5,81,82</sup> aplastic anemia,<sup>83,84</sup> paroxysmal nocturnal hemoglobinuria (PNH),<sup>85-87</sup> thalassemia,<sup>88</sup> sickle cell anemia,<sup>88,89</sup> benign nonhematological conditions such as autoimmune diseases.<sup>90,91</sup> Future studies may also attempt to 'target' the kinetics of complete donor T-cell chimerism according to the need for immediate disease control. The indications for RIST may therefore expand beyond those of MAST. The variety of RIST regimens may permit risk stratification according to the severity and the refractoriness of each disease. In addition, RIST using alternative donor sources, such as cord blood<sup>92,93</sup> or HLA-mismatched donors,<sup>94,95</sup> deserves investigation.

To take advantage of strong GVL potential in unrelated transplantation,<sup>96-98</sup> RIST from an unrelated donor may be preferred to a matched sibling donor, if GVHD can be better controlled. Research in this area enhances efforts to separate GVL from GVHD. The creation of an optimal regimen for each disease entity will also likely include disease-specific agents in the future. Such approaches need to be validated in large, prospective, multi-institutional studies with significant length of follow up in order to make firm conclusions regarding the optimal RIST regimens in each disease.

**Table 4** Representative reports of RIST for ALL

Series mainly consisted of ALL									
Author	N	Disease	Age (range)	Alternative donor	Regimen	High risk cases	OS (year)	Comments	Ref. #
Martino	27	ALL	50 (18–63)	MUD (8), 1-Ag MM relative (4)	Various	12 (44%) refractory, 11 (41%) Ph positive	31% (2 years)	Progression with/without GVHD at 2 years, 35/70%	59
Arnold	22	ALL	38 (21–58)	MUD (8), 1-Ag MM relative (1)	Mainly Flu/ BU or Flu/ BU/ATG	16 (73%) advanced, 11 (50%) Ph positive	4 alive in CR	Poor results in advanced cases	60

Ph = Philadelphia chromosome; OS = overall survival; AinCR = alive in CR.

**Table 5** Comparison of reports that claimed mixed chimerism predisposed relapse (A) or not (B)

Author	Diagnosis	N	Chimerism	Outcome/ relapsed	Follow-up (months)	P	Comments	Ref. #	
<i>A. Reports claiming mixed chimerism predisposes to relapses</i>									
Bader	AML20, ALL21, MDS14	55	36 CC 18 MC, 1 rejection	7 10				66	
Bader	AML	81	62 CC 19 MC	8 9		<0.005	Children	68	
Mattsson	AML, MDS	30	16 CC 14 MC (PB or BM) >1 month 22 CC 8 MC in PB >1 month	2 10 4 8	30	= 0.01		70	
Molloy	ALL	36	23 CC 13 MC	All in CR 5	24		Children, MUD, TCD	71	
Wasch	AML39, CML31, ALL18, and others	101	78 CC 20 MC	10 5	15	= 0.18		72	
Zetterquist	B-ALL	12	7 CC 5 MC in CD19 cells	All in CR 4	17	<0.01		73	
<i>B. Reports claiming mixed chimerism does not predispose to relapses</i>									
Valcarcel	Mainly Flu/Mel for lymphoid, Flu/BU for myeloid	68	40 Flu/Mel, fast T cell CC 28 Flu/BU, slow T cell CC	MC not predict relapse				74	
van Leeuwen	Various	53	30 CC 9 transient MC 14 stable MC	12 4 4				75	

AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; MDS = myelodysplastic syndrome; CR = complete remission; CC = complete chimera; MC = mixed chimera; MUD = matched unrelated donor; TCD = T-cell-depleted transplant.

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