

## REVIEW

# Reduced-intensity conditioning for acute myeloid leukemia: is this strategy correct

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**Allogeneic stem cell transplantation for acute myeloid leukemia (AML) using reduced-intensity conditioning (RIC) is based on the strategy of attaining donor cell engraftment with immunosuppressive agents. This approach, which relies predominantly on donor effector cells for anti-leukemic or graft-versus-leukemia effect, is being used with increased frequency. Treatment-related mortality appears less with RIC than that observed with conventional myeloablative regimens. Available data support the fact that a myeloablative regimen is not required for successful engraftment and some patients appear to be cured of their disease. Despite the plethora of clinical reports, however, no prospective studies have been conducted that establish this procedure as the preferred option in AML. On the other hand, patients formerly excluded from a myeloablative procedure such as the 'elderly' and those with significant comorbid conditions, often may be RIC transplant candidates. By using prospective controlled clinical trials, we will determine whether these encouraging RIC data are applicable to a nonselect population of AML. The transplant community now is poised to design and complete investigations to ascertain the true role of RIC in the treatment of AML.**

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## Introduction

Myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) is a curative modality for many advanced hematologic malignancy patients, including acute myeloid leukemia (AML). Treatment-related mortality due to the toxic effects of cytotoxic therapy and graft-versus-host disease (GVHD), however, continue to plague this therapy. In particular, elderly patients, those with comorbid conditions, patients whose disease is advanced or refractory, and those who have experienced relapse after an autologous HSCT experience poor survival, in part due to treatment-related mortality after a myeloablative allogeneic HSCT. The transplant community in the past decade has systemically begun to utilize a new strategy for allografts, designed to reduce the regimen-related toxicity of conventional myeloablative allografts yet preserving antileukemia effect.<sup>1–4</sup> These clinical results are in keeping with the elegant and pioneering preclinical canine model of Storb *et al.*<sup>5</sup> The fundamentals of this novel approach are two-fold. The first strategy combines the antileukemic potential of using reduced-dose cytotoxic conditioning with the immunological aspects of

the graft-versus-tumor effect. Usually, patients are given a purine analog such as fludarabine, in combination with another agent such as busulfan, melphalan, idarubicin and cytarabine or cyclophosphamide. In these protocols, donor engraftment is achieved with different degrees of myelosuppression ranging from minimal to severe. The second strategy is based on preclinical studies in the canine model and involves low-dose total body irradiation (TBI) 2 Gy either alone or in combination with fludarabine followed by immunosuppression with cyclosporine and mycophenolate mofetil. This latter approach relies almost exclusively on immunological mechanisms.

Various investigators have termed this paradigm 'mini-transplants', 'nonmyeloablative transplants' and 'reduced-intensity conditioning transplants'. While there is an abundance of data, there are almost no controlled, prospective studies making it difficult to arrive at definitive recommendations. This review will address this strategy, review selected studies, compare outcomes with myeloablative allogeneic transplants and attempt to provide a look at future concepts for AML.

## Definitions

A 'traditional' or 'conventional' allogeneic HSCT utilizes sufficient chemotherapy with or without TBI so that if the recipient is not 'rescued' with hematopoietic stem cells from an allogeneic donor, the patient will die of fatal infection or bleeding due to irreversible bone marrow aplasia. This approach exploits the maximum tolerated doses of cytotoxic agents in order to eliminate the largest number of AML cells in the host but, as such, may inflict serious injury to visceral organs, termed regimen-related toxicity. The frequency of fatal toxicities in the course of a myeloablative allogeneic HSCT for AML increases with age. Unfortunately, the vast majority of AML patients who would benefit from an allograft are older and therefore usually ineligible for such treatment.<sup>6</sup> While various investigators have made attempts to reduce regimen-related toxicities by using several pharmacologic agents thought to interfere with pathophysiologic mechanisms including amifostine,<sup>7</sup> defibrotide<sup>8</sup> and palifermin,<sup>9</sup> to name a few, most of these efforts usually have not translated into significant clinical benefit.

More recently the intensity of the conditioning regimen administered before a HSCT has been reduced and a number of different definitions have been used to identify regimens with differing intensities. A Bacigalupo and co-workers on behalf of the European Bone Marrow Transplant (EBMT) Group<sup>10</sup> have suggested a series of specific definitions as a function of the regimen intensity. Many argue that the term 'mini-transplant' conceptually is incorrect as it mixes together the intensity of the conditioning with the propensity for risk of the transplant. Further, this term may be misleading as it implies that the disease can be cured without use of high-dose chemo-radio-

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**Table 1** Proposed definitions for allogeneic HSCT preparative regimens that provide less-than-myeloablative intensity (A Bacigalupo and CIBMTR, personal communication)

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Conventional intensity conditioning (CIC): These regimens cause prolonged pancytopenia, and require stem cell rescue. When given without stem cell support these regimens usually cause irreversible pancytopenia and are therefore lethal. The intensity of myelo-immuno suppression is high, close to the maximum tolerated dose.
Minimally intensive conditioning (MIC): A regimen which will cause no cytopenia, and does not require stem cell support for blood counts to recover. The intensity of myelo-immuno ablation is minimal.
Reduced-intensity conditioning (RIC): All other conditioning regimens which do not qualify for either <i>conventional</i> or <i>minimally intensive</i> . Many of these regimens will indeed require stem cell support to be clinically useful, although if stem cell support is withheld, peripheral blood counts may recover only after many weeks.

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therapy and that the transplant course will be uneventful yet the reported transplant-related mortality, in fact, ranges between 10 and 20% (*vida infra*). Finally, this term implies that financial costs may be reduced when compared to a myeloablative HSCT, often not the case (*vida infra*). As a result, the EBMT Workshop<sup>10</sup> has suggested that the term mini-transplant be discouraged.

A series of working definitions has been proposed by the Center for International Blood & Marrow Transplant Research (CIBMTR) (Table 1) that is based on the anticipated duration of cytopenias in the host and the requirement for stem cell support. Use of such a terminology may improve communication when comparing approaches. For the purpose of this review, we will use the terms reduced-intensity and nonmyeloablative conditioning in a 'generic' sense to contrast with the term myeloablative transplant.

#### *Are GVHD rates reduced for reduced-intensity compared to myeloablation?*

As GVHD is mediated, in part, due to an increase in host inflammatory mediators after cytotoxic exposure, the likelihood of developing this syndrome is anticipated to be reduced after use of a nonmyeloablative regimen.<sup>11</sup> Further, a less intense preparative regimen is likely to be associated with incomplete or mixed chimerism early after the transplant, a situation that favors delay in onset of acute GVHD.<sup>12,13</sup> The mixed chimerism syndrome may be a reflection of the choice of conditioning regimen that can favor myeloid versus lymphoid engraftment. For example, a regimen such as a fludarabine-cyclophosphamide-containing approach may be lymphoid ablative that can result in a 100% donor T-cell engraftment; GVHD may not be mitigated in these patients. In fact, the remaining host myeloid antigen presenting cells can contribute well to stimulating GVHD by effectively presenting host antigens. In contrast, the regimens that allow slow T-cell recovery result in a reduced incidence of GVHD early yet use of donor lymphocyte infusion (DLI) can result in full donor chimerism.

Finally, due to concerns for an increased relapse rate with reduced-intensity conditioning, some investigators have intensified the approach leading to GVHD rates that are not dissimilar from myeloablative regimens.<sup>14-16</sup> Although on theoretical grounds the risk of developing GVHD is lower, a number of investigators have utilized either long-acting immunosuppressive agents such as antithymocyte globulin (ATG) or more recently, Campath-1H, that may reduce GVHD risk as well as likelihood of engraftment failure by 'purging' donor cells *in vivo* and blunting recipient response.<sup>14,17</sup> Of concern with this approach is a propensity to allow relapse, an observation reported by some investigators.<sup>18</sup>

#### *Limitations and proposed solutions for non-myeloablative allografts*

Table 2 addresses problems inherent in using reduced-intensity conditioning for AML patients. For the most part, the published results are derived from small, single-center, often retrospective trials reporting that hampers drawing conclusions. Also, patients and treatments are very heterogeneous further limiting interpretation of results. The use of a less-intensive approach with cytotoxic agents clearly results in a lower leukemia cell kill than with a myeloablative regimen that may lead to a higher relapse rate in such patients. Further, the use of less cytotoxic agent therapy may provide a less intense immunosuppression of host immunity resulting in a higher incidence of engraftment failure. On the other hand, infusion of allogeneic hematopoietic and donor effector cells still may result in the development of GVHD even if prophylactic agents are utilized. These problems may be addressed by the incorporation of targeted agents into the reduced-intensity conditioning regimen, including <sup>188</sup>Rh- or <sup>90</sup>Yt-monoclonal antibodies.<sup>19</sup> Other strategies to improve this approach include the use post-transplant of monoclonal antibodies such as gemtuzumab ozogamicin<sup>20</sup> or to utilize DLI to induce a graft-versus-leukemia effect. The use of new immunomodulating monoclonal antibodies such as Campath may help reduce GVHD in this setting.

#### *Reduced-intensity conditioning results for AML patients*

Table 3 presents the results of 14 relatively recent published experiences of using reduced-intensity conditioning in trials that enrolled at least 15 AML patients.<sup>19,21-38</sup> In general, most of the trials were conducted during the periods from 1998 through 2004 but the publications reported heterogeneous patients with respect to disease status at transplant (CR1, CR2, relapse, refractory disease). Further, the reports often differed as to whether the studies were retrospective analyses versus prospective trials. Many of the trials are modest in size with respect to numbers of AML patients. Corradini *et al.*<sup>24</sup> enrolled 150 patients of which only 17 were AML patients. Gómez-Núñez and associates<sup>31</sup> published a 145 patient trial that included only 20 AML subjects. Baron *et al.*<sup>25</sup> reported the Fred Hutchinson Cancer Research Center prospective experience of 322 patients that enrolled 46 AML patients. Schmid *et al.*<sup>27</sup> reported a large experience that involved 75 subjects; most were median age in the fifth decade, although some were in the seventh decade. The trial reported by Baron *et al.*<sup>25</sup> included pediatric patients. Sayer,<sup>33</sup> for the Cooperative German Transplant Study Group, retrospectively analyzed data from a variety of centers employing different inclusion criteria for predictive factors for 113 AML patients receiving reduced-intensity conditioning before an allograft; Hegenbart *et al.*<sup>34</sup> published a prospective study involving the same centers and inclusion criteria, the largest AML reduced-intensity conditioning trial published to date.

**Table 2** Limitations (administrative, practical and scientific) and proposed solutions for using reduced-intensity conditioning for AML

Issue	Solution	Comment
Small single-center reports, or larger multicenter yet retrospective trial reporting; inability to extricate data on AML patients from pooled various other disease types	Prospective, multi-center study design and execution	Obvious difficulties due to investigator bias (which regimen preferred), patient heterogeneity and acceptance
Insufficient antileukemia effect in preparative regimen	Addition of more cytotoxics use of targeted agents in regimen	Increases morbidity and potential mortality <sup>188</sup> Re-CD166 or <sup>90</sup> Yt-CD166 <sup>17</sup>
High relapse rate	Use of post-transplant therapy such as gemtuzumab ozogamicin <sup>18</sup> Induction of GVL effect	Potentially less toxic after reduced-intensity conditioning than after myeloablative conditioning withdrawal of immunosuppression or use of DLI
Unclear benefit of using of using conventional cytotoxic agents immediately before initiating preparative regimen ('pretransplant cytoreduction')	Initiation of controlled trials to define risk:benefit of pretransplant conventional cytotoxic agents	Difficult task given marked patient heterogeneity and investigator and patient preferences
Possible higher incidence of engraftment failure	Agents to target marrow microenvironment use of increased cell dose or boost graft	Difficult concept; possibly short-lived radioimmunoconjugates difficult logistically
GVHD incidence and severity rates similar to myeloablative transplants, especially chronic GVHD	Use of immune modulators such as Campath	Intriguing results from Tauro <i>et al.</i> <sup>24</sup>

Abbreviations: AML, acute myeloid leukemia; GVL, graft-versus-leukemia; DLI, donor lymphocyte infusion.

A purine analog such as fludarabine or 2-chlorodeoxyadenosine (2-CDA) usually was administered with or without low-dose TBR and monoclonal antibodies such as Campath or antithymocyte globulin (ATG). Claxton *et al.*<sup>35</sup> reported a novel approach that included the use of sirolimus that appeared to add antileukemia effect to the GVHD prophylaxis regimen. Hallemeier *et al.*<sup>32</sup> described a 32 patient study conducted using unrelated donor grafts, including three mis-matched donors, using a cyclophosphamide and 5.5 Gy single fraction TBR regimen. Excellent results were obtained but it is unclear if this approach qualifies as a reduced-intensity conditioning approach. Some of the trials also included an alkylating agent such as melphalan. The trials reported the use of only sibling-matched allogeneic donors as the graft source or a mix of alternative donors and sibling-matched donors. Bertz *et al.*<sup>30</sup> reported a study confined to older AML and myelodysplastic patients and thought that the addition of ATG to those receiving matched-unrelated donor grafts increased the safety margin in this population. Treatment-related mortalities, in general, were relatively low in the 10–20% range, although a trial by Martino *et al.*<sup>29</sup> reported a 5% 1-year treatment-related mortality. On the other hand, 59% of patients in one study<sup>29</sup> previously received an autograft a median (range) of 14 (2–83) months earlier and treatment-related mortality approached 60% in subjects age at least 60 years who had an ECOG performance status 2–3. Similarly, Sayer *et al.*<sup>33</sup> showed a 53% 2-year nonrelapse mortality, highest in the unrelated donor group ( $P=0.002$ ). GVHD rates were not dissimilar from those seen with myeloablative regimens with the exception of a study by Ringhoffer *et al.*<sup>19</sup> in which particularly low acute and chronic GVHD rates were noted. Conclusions regarding this study, however, are limited by the small number of patients analyzed and reported.

Notably, engraftment failure rates in these series were surprisingly low. Several studies reported no engraftment failure rates and overall ranged from 0% to a maximum of 7% in three studies.<sup>25,27,36</sup> On the other hand, relapse rates were quite high exceeding 30% in four of the 10 studies to a maximum of 45% reported by Ringhoffer<sup>19</sup> and 40% at 2 years reported by van Besien *et al.*<sup>21</sup> Finally, leukemia-free survival and overall survival rates were reasonable given the fact that many of these

patients previously had failed autograft procedures and had significant comorbidities. The highest leukemia-free survival or progression-free survival rates were reported by Hamaki *et al.*<sup>22</sup> who noted one year rates of 85% in low-risk and 64% in high-risk patients. A recent publication by Platzbecker *et al.*<sup>38</sup> showed an excellent 3-year disease-free and overall survival rate of 63%. The trial with the longest follow-up, reported by Corradini *et al.*,<sup>24</sup> observed 5-year leukemia-free and overall survival rates of 32 and 38%, respectively. Once again, heterogeneity in the patient populations in these trials make comparisons very difficult to interpret.

Obviously the comparisons between reduced-intensity conditioning and myeloablative allografts in AML may present difficulties (Table 4). Some of the 'so-called' nonmyeloablative regimens contain alkylating agents and as such may be more modest intensity rather than low intensity conditioning. Also, an inherent selection bias is demonstrated by investigators and practitioners who 'assign' patients myeloablative versus nonmyeloablative conditioning. Further, these trials include many non-AML patients; even in the trials restricted to 'myeloid malignancies', investigators often do not distinguish between *de novo* and treatment-related AML or myelodysplasia; often it is unclear whether the patient is in first complete remission, subsequent complete remission, relapse or has primary refractory disease. Patients characteristics vary markedly, including differences in cytogenetic risk, the time from diagnosis to transplant, the extent of disease and prior therapy, whether the patients were given pretransplant cytoreduction before proceeding to a nonmyeloablative regimen, and heterogeneity in the type of preparative regimen that may or may not include alkylating agents, TBR or monoclonal antibody therapy. The graft source varies from blood versus bone marrow and matched-related versus alternative donor transplants although most nonmyeloablative reports utilize blood in contrast to myeloablative transplants that often use marrow as the stem cell source. Finally, GVHD prophylaxis therapies certainly differ and in most situations the follow-up after reduced-intensity conditioning transplants is considerably shorter compared to myeloablative transplants. Also, the T-cell content of the graft may vary considerably impacting upon the risk of GVHD. To

**Table 3** Comparison of recent RIC allograft trials that included at least 15 AML patients

Author/period	No. Patients. Total/(AML)	Median age (range)	Regimen	Donor type	TRM/NRM	AGVHDgr II-IV/ CGVHD	Graft failure	Relapse	LFS/PFS	OS
VanBes 2001–2004 <sup>21</sup>	52 (41)	52 yr (17–71)	FLUD+MEL+Campath	MRD 27, MUD 25	2-yr 33%	1-yr 33%/1-yr 18%	4%	2-yr 40%	2-yr 31%	2-yr 39%
Hamaki 1999–2002 <sup>22</sup>	36 (24)	55 yr (27–67)	2-CDA or Bu plus FLUD±ATG	MRD 36	100-day 3%	48%/82%	3%	22%	1-yr 85% low risk; 1-yr 64% high risk	NS
Gupta 2000–2004 <sup>23</sup>	24 (16)	64 yr (60–71)	FLUD+TBI 2Gy	MRD 24	2-yr 25%	45%/74%	NS	27%	2-yr 44%	2-yr 52%
Corradini 1998–2004 <sup>24</sup>	150 (17)	52 yr (20–69)	Thio+FLUD+CY	MRD 150	10% for AML and MDS	**III–IV: 30%/50%	0	NS	5-yr 32% (AML/ MDS)	5-yr 38% (AML/MDS)
Baron 1998–2003 <sup>25</sup>	322 (46)	54 yr (5–72)	TBI 2Gy±FLUD	MRD 192, MUD 130	NS	58%/extensive 56%	7%	34%	3-yr 39%	3-yr 50%
Ringhofer 1999–2004 <sup>19</sup>	20 (16)	63 yr (56–67)	<sup>188</sup> Re or <sup>90</sup> Yt anti- CD66+FLUD±MEL	MRD 11, MUD 9	2-yr 25%	5%/15%	0	45%	NS	30 months- 17%
Tauro 1998–2004 <sup>26</sup>	76 (56)	52 yr (18–71)	FLUD+MEL+Campath	MRD 35, MUD 41	1-yr 19%	0 gr III–IV; 28% I–II/11%	3%	36%	3-yr 37%	3-yr 41%
Schmid 1999–2002 <sup>27</sup>	75	52 yr (19–66)	Sequential FLUD+AraC+AMSA, then TBI 4Gy+ATG+CY	MRD 31, MUD 44	1-yr 33%	49%/35%	7%	17%	2-yr 40%	2-yr 42%
Ho NS <sup>28</sup>	62 (23)	53 yr (22–70)	FLUD+Bu+Campath	MRD 7, MUD 16,	1-yr 15%	NS	3%	NS	1-yr 62%	1-yr 74%
Martino 1998–2002 <sup>28</sup>	37 (17)	57 yr (22–66)	FLUD+Bu	MRD 37	1-yr 5%	19%/extensive at 1-yr 43%	0	1-yr 28%	1-yr 66%	NS
Bertz <sup>30</sup> (NS)	19 (15)	64 yr (60–70)	FLUD+BCNU+MEL	MRD 7, MUD 12,	1-yr 22%	59%/extensive 41%	0	21%	1-yr 61%	1-yr 68%
Gomez 1999–2002 <sup>31</sup>	145 (20)	54 yr (19–67)	FLUD+either MEL or Bu	MRD 145,	1-yr 20%	34%/1-yr 41%	NS	NS	1-yr 52%	1-yr 60%
Hallemeier 1997–2002 <sup>32</sup>	32	47 yr (32–60)	CY+TBI 5.5Gy	MUD 29, MM 3	28%	** III–IV 3%/ extensive 54%	0	22%	3-yr CR1: 57% 3-yr ≥CR2:39%	3-yr CR1: 55% 3-yr ≥CR2: 39%
Sayer 1998–2000 <sup>33</sup>	113	51 yr (16–67)	(1) Bu+FLUD±CY (2) TBI 4–8 Gy+FLUD	MRD 50, MUD 50, MM 13	53%	42%/33%	5%	NS	2-yr 29%	2-yr 32%
Hegenbart 1998–2002 <sup>34</sup>	122	57.5 yr (17–74)	TBI 2Gy±FLUD	MRD 58, MUD 64	2-yr 16%	40%/extensive 36%	5%	2-yr 39%	2-yr 44%	2-yr 48%
Claxton 2001–2004 <sup>35</sup>	23	59 yr (28–72)	FLUD+CY+ sirolimus±ATG	MRD 6, MUD 11, MM 6	8%	43%/77%	0	NS	NS	2-yr 50%
Chen 2000–2004 <sup>36</sup>	34	49 yr (30–66)	ECP+Pento+TBI 4–6 Gy	MRD 18, MUD 16	32%	11%/53%	7%	26%	29%	31%
Shimoni (NS) <sup>37</sup>	36 (15)	58 yr (55–66)	FLUD plus: Bu or Treo or MEL; plus ATG or Campath	MUD 31, MM 6	1-yr 39%	31%/45%	0	28%	1-yr 43%	1-yr 52%
Platzbecker 1998–2005 <sup>38</sup>	26	49 yr (17–68)	FLUD+Bu or MEL	MRD 11, MUD 15	2-yr 15%	54%/64%	NS	11%	3-yr 63%	3-yr 63%

Abbreviations: AGVHD, grade II–IV acute graft-versus-host disease; AraC, cytarabine; AMSA, amsacrine; ATG, anti-thymocyte globulin; CGVHD, chronic graft-versus-host disease; CR1, first complete remission; ≥CR2, second remission or beyond; CY, cytophosphamide; ECP, extracorporeal phototherapy; FLUD, fludarabine; MEL, melphalan; MUD, matched-unrelated donor; MRD, matched-related donor; MM, mis-matched donor; NS, not stated; Pento, pentostatin; Thio, thiotepa; Treo, treosulfan; Yr, year.

\*\*Grade III–IV acute GVHD.

**Table 4** Problems comparing RIC and myeloablative allograft trials in AML

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Definition problems for RIC, NST, mini, etc
Inherent selection bias by investigators/practitioners
Mixing of AML ( <i>de novo</i> and t-AML) and MDS in series
Variability in stage of the disease, for example, complete remission, relapse, primary refractory
Variability in patient characteristics, for example, age and comorbidities
Variability in the definition of refractory AML
Variability in cytogenetic risk, time to transplant, stage, prior therapy, use/absence of pretransplant cyto-reduction, and preparative regimens
Variability in graft type, for example, blood versus marrow, matched-related versus matched-unrelated donor as well as greater likelihood of using blood in non-Myeloablative compared to myeloablative transplants that often use marrow
Variability in GVHD prophylaxis therapies, for example, cyclosporine ± mycophenolate mofetil (reduced-intensity conditioning) versus Cyclosporine/methotrexate or tacrolimus/methotrexate in myeloablative conditioning
Shorter reported follow-up after transplant for RIC compared to myeloablative
No prospective comparison trials

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date, there are no prospective comparison trials that have been reported.

*Advantages and disadvantages for reduced-intensity conditioning allografts*

Table 5 depicts the theoretic advantages versus disadvantages of reduced-intensity conditioning compared to myeloablative allografts. Elderly patients who otherwise are in good health often are excluded from myeloablative transplants. In addition, patients who have comorbid conditions may not be deemed appropriate candidates for such therapy. Several groups are in the process of developing more accurate comorbidity scoring systems that may lend clarity to the dilemma of choosing the intensity of the conditioning regimen.<sup>39</sup> Finally, some patients and physicians are not accepting of the increased risk of the myeloablative approach and elect a reduced-intensity conditioning transplant. As noted above, nonmyeloablative transplants appear to be associated with a lower treatment-related mortality and possibly a delayed onset and ‘less virulent’ course of acute GVHD. In one study involving 52 elderly patients receiving matched-unrelated or mis-matched transplants, acute GVHD affected 63% of subjects yet only 9% died of this complication.<sup>40</sup> Explanations for this ‘attenuated’ form of GVHD (onset often when immunosuppression was being tapered) in an older patient group at high risk for fatalities probably reflect lack of tissue injury and cytokine storm from the reduced-intensity conditioning and the situation of initial mixed donor–host chimerism.

While there has been a suggestion that costs may be lower, this has not been borne out in practice.<sup>41</sup> On the other hand, engraftment failure rates may be higher and tempo to develop an antileukemic effect may be slower, the latter a potentially catastrophic situation if the transplant is not undertaken when the patient’s disease is in complete remission. The graft-versus-leukemia effect may be disease-specific, for example, stronger in chronic myeloid leukemia and multiple myeloma when compared to AML and acute lymphoblastic leukemia. Finally, DLI may not be available for matched unrelated donor transplants and clearly is not an option available for umbilical cord blood transplants. Late relapses also may be more common after reduced-intensity conditioning allografts.

*Myeloablation versus reduced-intensity conditioning: what are the data?*

At present comparisons between myeloablative and reduced-intensity conditioning allograft trials are quite difficult. Investigators initially used reduced-intensity conditioning in patients

**Table 5** ‘Advantages’ and ‘disadvantage’ of reduced-intensity conditioning compared to myeloablative for AML

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<i>‘Advantages’</i>
‘Elderly’ AML (age > 50 years) now ‘allograft-eligible’
Association of comorbid conditions does not exclude otherwise eligible patients
Better patient acceptance of the procedure compared to myeloablative approach
‘Apparent’ lower treatment-related mortality
Possible lower incidence of GVHD
‘Anticipated’ lower financial cost
Greater potential for conducting transplant in an outpatient setting
<i>‘Disadvantages’</i>
Increased risk of engraftment failure
Slower tempo to anti-leukemia effect; added risk especially if patient is not in complete remission
Apparent disease-specific graft-versus-leukemia effect (GVL): CML > MM > AML > ALL
Potentially DLI-dependent for engraftment and GVL (often not available; MUD or UCB)
Increased potential for late relapse due to reduced intensity

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Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; DLI, donor lymphocyte infusion; GVHD, graft-versus-host disease; GVL, graft-versus-leukemia; MM, multiple myeloma; MUD, matched unrelated donor; UCB, unrelated cord blood.

not eligible for conventional allografts due to advanced age or comorbid conditions. Additionally, important risk factors for survival in AML including cytogenetics and secondary versus *de novo* AML have not necessarily been taken into account before treatment assignments were made. In Table 6, we review the data from five retrospective comparisons, some quite large, in which the investigators compared myeloablative to reduced-intensity conditioning; communications that enrolled less than 20 AML patients were excluded. Aoudjane *et al.*<sup>42</sup> recently reported in preliminary fashion a comparison of 315 given reduced-intensity conditioning versus 407 myeloablative allografts. The incidence of grade II–IV acute GVHD was statistically higher in the myeloablative-treated patients and chronic GVHD rates also were higher. Treatment-related mortality correspondingly was lower at 18% in the reduced-intensity group ( $P=0.0001$ ) but relapse rates were statistically higher in the reduced-intensity group (41 versus 24%,  $P=0.003$ ). As a result, leukemia-free and overall survival essentially were the same in both groups.

Another preliminary communication (Herr A-L *et al.*, *Blood*, 2005; **17a**, abstract) involved nearly 1200 patients but was comprised of retrospective data and contained considerably less

**Table 6** Retrospective comparison trials of myeloablative versus reduced-intensity conditioning (at least 20 AML patients)

Author	Period	RIC	Comment	Myelo	P-value
Aoudjane <sup>42</sup>	1997–2003				
	No. patients	N = 315	Retrospective registry survey: age ≥50 years	N = 407	
	Median age	57 years		54 years	—
	II–IV AGVHD	22%		31%	0.003
	CGVHD	48%		56%	0.64
	RR CGVHD	0.69		0.94	0.02
	TRM	18%		32%	0.0001
	Relapse	41%		24%	0.0001
LFS	40%	44%		0.8	
OS	47%	46%	0.43		
Herr A-L	1997–2003				
	No. patients	204		954	—
	Median age	58 years		57 years	
	Cytogenetics	'worse'			<0.05
	TRM	15%		8%	0.002
	1-year relapse	34%		40%	NS
	1-year LFS	50%		52%	NS
1-year OS	62%		66%	NS	
Kojima <sup>43</sup>	1998–2002				
	No. patients	<sup>a</sup> 70 (33)	Restriction: age limit 50–59 years	<sup>a</sup> 137 (56)	<0.01
	Median age	57 years		52 years	—
	II–IV AGVHD	56%		43%	—
	CGVHD	65%		58%	—
	1-year NRM	15%		31%	0.0062
	TRM	<sup>a</sup> 8/33 (24%)		<sup>a</sup> 19/56 (34%)	—
	2-year PFS	56%		30%	—
2-year OS	69%		39%	—	
Alyea <sup>44</sup>	1997–2002				
	No. patients	71 (21)	Restriction: age limit above 50 years	81 (13)	—
	Median age	58 years		54 years	—
	II–IV AGVHD	29%		27%	—
	NRM	32%		50%	0.01
	2-year OS	38%		29%	NS
2-year PFS	36%		25%	NS	
Scott <sup>45</sup>	1998–2003				
	No. patients	38 (20)	Restriction: only t-AML (N = 55 total); mostly MDS	112 (35)	—
	Median age	62 years		53 years	—
	II–IV AGVHD	54%		78%	—
	ECGVHD at 2 years	55%		64%	—
	NRM	39%		32%	—
	Tumor progression at 3 years	31%		23%	NS
	3-year OS	28%		48%	NS
	3-year PFS	27%		44%	NS

AGVHD, acute graft-versus-host disease; CGVHD, chronic graft-versus-host disease; ECGVHD, extensive chronic graft-versus-host disease; NRM, non-relapse mortality; OS, overall survival; RR, relative risk; LFS, leukemia-free survival; TRM, treatment-related mortality.

<sup>a</sup>Refers to AML patients only in the overall series.

detailed information. Inexplicably, treatment-related mortality in those patients undergoing reduced-intensity conditioning was higher (15 versus 8%,  $P=0.002$ ), although it is the unusually low mortality in the myeloablative cohort that is out of line with other published data. Relapse, leukemia-free survival and overall survival rates did not differ significantly between the two approaches.

In a much smaller study, Kojima *et al.*<sup>43</sup> compared 70 patients receiving reduced-intensity versus 137 receiving myeloablative treatment. This comparison was restricted to those aged 50–59 years. Both acute and chronic GVHD rates were higher in the reduced-intensity conditioning group (56 versus 43 and 65 versus 58%, respectively). The authors did not indicate if these data were of statistical significance. Nonrelapse mortality at one

year, however, was statistically higher at 31% in the myeloablative group compared to only 15% in the reduced-intensity group ( $P=0.0062$ ). Two-year progressive-free survival and overall survival appeared to be superior in the reduced-intensity group, 56 versus 30 and 69 versus 39%, respectively.

Alyea *et al.*<sup>44</sup> reported a 152-patient comparison but only 34 of the patients had AML. There were no differences in the rates of acute GVHD. Nonrelapse mortality was lower at 32% in the reduced-intensity group compared to 50% in the myeloablative group ( $P=0.01$ ), but progression-free survival and overall survival rates were the same in the two groups. Finally, Scott *et al.*<sup>45</sup> reviewed data in secondary AML patients comparing myeloablative versus nonmyeloablative transplants. Both acute and extensive chronic GVHD rates were higher in the myeloablative group (54 versus 78 and 55 versus 64%), but treatment-related mortality, relapse rates and 3-year progression-free and overall survival rates did not differ among the two approaches. As stated previously, the lack of prospective data and the enormous patient and disease heterogeneity in select and historic comparisons make it almost impossible to confidently interpret the significance of these data.

#### Financial cost comparisons

Cordonnier *et al.*<sup>41</sup> evaluated the financial costs in a small series for myeloablative versus nonmyeloablative transplants in AML patients (Table 7). The initial hospitalization (mean days) was longer in the myeloablative group, but the nonmyeloablative group had more mean readmission days. As the costs of nonmyeloablative transplants were higher in the second 6 months after transplant, the early cost savings were negated. At 1 year there was no statistical difference in the financial costs (in Euros) of performing a myeloablative transplant compared to a reduced-intensity conditioning transplant.

#### Future considerations and conclusions (Table 8)

It seems clear that reduced-intensity conditioning transplants are a 'fact of life' and are 'here to stay'. This development took place in a selective and uncontrolled fashion that may have hindered our ability to interpret confidently the significance of what may be a truly significant advance in the therapy of AML. On the other hand, one can argue that this exploratory period has fostered a great diversity of regimens and intensities to be explored. Investigators in this field now are poised to design, execute and report the results of more rigorous and large, multicenter, prospective, randomized trials comparing myeloablative versus nonmyeloablative conditioning in patients eligible for both approaches. A number of patient-, disease- and treatment-related factors are critical in the design of trials comparing conventional myeloablative to reduced-intensity conditioning allografts. These variables include patient and donor age, presence or absence of comorbid conditions, leukemic cytogenetics, *de novo* versus secondary AML, disease

state at transplant, donor graft type (matched-related versus matched-unrelated versus mismatched as well as blood versus marrow), preparative regimen including TBI versus non-TBI and GVHD prophylaxis approach.

In the interim, a number of strategies can be implemented to improve reduced-intensity conditioning regimens in the allograft setting for AML. One obvious area of investigation is to determine the optimal timing and regimen for pretransplant intensification with cytotoxic agents. To date, the approach of additional chemotherapy has been associated subsequently with an increase in nonrelapse mortality during the reduced-intensity conditioning transplant.<sup>46–48</sup> Use of disease-specific agents for AML as part of the pretransplant intensification may facilitate this approach. Targeted therapy to a specific blood concentration with a parenterally administered agent such as IV busulfan also may increase the therapeutic ratio.<sup>49</sup> DLI appears to be effective only in a minority of AML patients when used as salvage for relapsed disease.<sup>50</sup> On the other hand, some have postulated that prophylactic DLI may be of benefit at time of low leukemia cell burden. Given the observation by Marks *et al.*<sup>51</sup> that DLI were associated with a significant incidence of acute GVHD (25% grade II–IV and 15% grade III–IV), this maneuver may require additional manipulations such as thymidine-kinase suicide gene transfer of donor lymphocytes.<sup>52</sup> Other investigators are developing antileukemic vaccinations while Fontaine *et al.*<sup>53</sup> have proposed use of cytotoxic T-cell infusions as a means of preventing relapse. Other investigators have addressed risk-directed GVHD prophylaxis and others are targeting the leukemia using monoclonal antibodies.

Lowsky *et al.*<sup>54</sup> recently reported a small series of 13 AML and 24 lymphoid malignancy patients given a novel nonmyeloablative conditioning regimen comprised of 8 Gy total lymphoid irradiation (TLI) in 10 fractions plus ATG followed by matched-related donor ( $N=23$ ) and matched-unrelated donor ( $N=14$ ) allografts. Only two patients (both lymphoid malignancy) developed acute GVHD (one each grade I and grade III) while only three AML patients developed chronic GVHD (all

**Table 8** Future considerations for investigations utilizing reduced-intensity conditioning regimens

Design, execution and reporting of large, multicenter, prospective, randomized trials comparing myeloablative versus nonmyeloablative conditioning in eligible patients
Systematically explore the role of pretransplant induction or cytotoxic agent therapy
Prophylactic donor lymphocyte infusions
Ant-leukemia vaccinations
Cytotoxic T-cell infusions <sup>55</sup>
Risk-directed GVHD prophylaxis
More efficacious and targeted components of the preparative regimen, for example, IV busulfan <sup>51</sup> and <sup>188</sup> Re and <sup>90</sup> Yt anti-CD66 monoclonal antibodies <sup>19</sup>
Expanded use of alternative donor grafts

**Table 7** Retrospective comparison of financial cost of conventional myeloablative versus nonmyeloablative allografts in AML patients: 2001 costs in France (Euros)<sup>42</sup>

	Myeloablative (N = 12)	Non-myeloablative (N = 11)	P-value
Mean initial hospital days	48 days	22 days	0.004
Mean readmission days	16 days	34 days	0.07
Median cost day -8 to +179	€55 900	€40 300	0.34
Median cost day 180–365	€5900	€16 900	0.03
Median first year cost	€64 600	€60 000	0.75

extensive). Ten of 13 AML patients are alive, nine in CR a median (range) of 446 (215–1041) days after allograft. They attributed these dramatic results, in part, to the use of TLI that appeared to induce a marked increase in CD4<sup>+</sup> donor lymphocyte-derived IL-4.

One unique aspect of reduced-intensity conditioning transplant is the potential for exploiting a greater GVL effect when an unrelated donor is used as demonstrated by a few investigators.<sup>55–57</sup> Several trials have examined this concept with umbilical cord blood and HLA-mis-matched donors.<sup>58–61</sup>

Several attempts by the U S cooperative oncology groups, notably the Southwestern Oncology Group (SWOG), failed to complete a prospective evaluation of this modality due to lack of patient accrual to such protocols. For unclear reasons, many physicians appear reluctant to study reduced-intensity conditioning in a controlled fashion. Currently, plans to remedy this situation are underway within the Blood & Marrow Transplant Clinical Trials Network (BMT CTN) in conjunction with the major oncology cooperative groups. In such a study, elderly AML patients will receive reduced-intensity conditioning allografts to demonstrate proof of principle that this modality can provide extended disease-free survival in an extremely poor-patient group. On the other hand, even an optimally designed study may fail due to the compromise between the desire to minimize intensity and gain survival versus the goal of using maximal intensity and greater antileukemia effect. If successful in the elderly, however, a prospective trial likely should be undertaken in younger patients who are eligible for either a myeloablative or a reduced-intensity conditioning allograft. Other groups who already have initiated studies in this area include the trial by the OSHO/HOVONS/SAKK group in which patients age 60–75 years with a related or matched-unrelated donor receive a TBI 2 Gy-based regimen after first consolidation and their outcome is compared to those given chemotherapy only.

In a short time, the nonmyeloablative conditioning approach has grown exponentially. For example, the frequency for centers performing reduced-intensity allogeneic transplants has increased dramatically from <1% in 1998 to 27% in 2001.<sup>62</sup> Although this strategy similarly is plagued by treatment-related mortality, GVHD and relapse, the results of therapy in a considerably poor-risk patient group are comparable to those using a myeloablative regimen. While much work remains to be carried out, we anticipate that the field will move forward and complete trials in AML patients that will establish the appropriate use of this technology.

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