Chapter 17
Nonmyeloablative Transplantation
Frédéric Baron and Brenda M. Sandmaier

Word counts:
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1. Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) for hematological malignancies was developed in the late 1960s as a way to deliver supra-lethal doses of chemotherapy and/or total body irradiation (TBI) with the aim of eradicating the underlying disease while marrow was infused to restore hematopoiesis. However, confirming observations made in mice 20 years prior [1],...
Weiden, et al. recognized in the late 1970s that the allograft itself conferred immune-mediated antileukemic effects [2, 3]. Indeed, patients who developed acute and/or chronic Graft-versus-Host Disease (GVHD) had lower risks of relapse than those who did not [2, 3]. This antileukemic effect of GVHD was termed the "Graft-versus-Tumor effect." The existence of Graft-versus-Tumor effects was then supported by several observations demonstrating higher risk of relapse in patients given syngeneic HSCT, compared to those receiving grafts from allogeneic donors [4] and in those given T cell-depleted grafts [5]. Furthermore, it was found that immune-mediated effects of donor lymphocyte infusions (DLI) were sufficient to eradicate the malignancy in a number of patients who relapsed with chronic or acute myeloid leukemias after allogeneic HSCT [6].

The myeloablative doses of chemotherapy and/or TBI given during the conditioning regimen for conventional allogeneic HSCT can produce significant morbidity and mortality, particularly in older patients, those with medical comorbidities, or those who have failed a myeloablative HSCT [7, 8]. Because of these toxicities, the use of myeloablative allogeneic HSCT has been restricted to younger patients in good medical condition, while median patient age at diagnosis for acute or chronic myeloid leukemia, chronic lymphocytic leukemia, Non-Hodgkin's Lymphoma and multiple myeloma ranges from 65 to 71 years [SEERS (surveillance, Epidemiology and End Results) data [9]].

2. Nonmyeloablative and Reduced-Intensity Conditioning

Given the increasingly recognized power of Graft-versus-Tumor effects, several groups of investigators explored the feasibility of nonmyeloablative or reduced-intensity conditioning regimens that would allow engraftment of both donor hematopoietic stem cells and donor T cells, and then eradicate the malignancies mainly towards Graft-versus-Tumor effects [10–16]. While Giralt, et al. proposed criteria for reduced-intensity conditioning (1) reversible myelosuppression within 28 days without stem cell support, 2) mixed chimerism (i.e., coexistence of hematopoietic cells of donor and host origin) in a proportion of patients at time of first assessment, and 3) low rates of non-hematologic toxicity) [17], practical definitions for reduced-intensity conditioning regimen varied from one study to another (Table 17-1).

Further, separating what constitutes a nonmyeloablative versus a reduced-intensity conditioning has been somewhat arbitrary (Fig. 17-1). Reduced-intensity conditioning regimens have combined fludarabine (used mainly for its immunosuppressive activity) with consequent (but nonmyeloablative) doses of alkylating agents such as melphalan (140 mg/m²) [18], thiotepa (≤ 10 mg/kg) or busulfan (4–8 mg/kg) [19], given to produce significant antitumor effects with the objective of both debulking and controlling the malignancy before the occurrence of Graft-versus-Tumor effects. In contrast, nonmyeloablative conditionings have used potent immunosuppressive regimens to overcome Host-versus-Cell reactions (graft rejection) [15, 16, 20], allowing engraftment of donor hematopoietic and immune cells, and eradication of host-derived hematopoiesis and tumor cells almost exclusively via Graft-versus-Tumor effects. The distinction of what constitutes a nonmyeloablative and what constitutes a reduced-intensity conditioning is clinically relevant.
Table 17-1. Practical definitions for reduced-intensity conditioning.

<table>
<thead>
<tr>
<th>CIBMTR/NMDP [17]</th>
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<tbody>
<tr>
<td>≤ 5 Gy TBI</td>
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<tr>
<td>≤ 9 mg/kg total busulfan dose</td>
</tr>
<tr>
<td>≤ 140 mg/m² total melphalan dose</td>
</tr>
<tr>
<td>≤ 10 mg/kg total thiolepa dose</td>
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<td>usually includes a purine analog</td>
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<table>
<thead>
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<th>EBMT (1) [82]</th>
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<tr>
<td>Fludarabine associated with:</td>
</tr>
<tr>
<td>≤ 4 Gy TBI</td>
</tr>
<tr>
<td>≤ 10 mg/kg total busulfan dose</td>
</tr>
<tr>
<td>≤ 140 mg/m² total melphalan dose</td>
</tr>
<tr>
<td>≤ 10 mg/kg total thiotepa dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EBMT (2) [46]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludarabine associated with:</td>
</tr>
<tr>
<td>&lt; 3 Gy TBI</td>
</tr>
<tr>
<td>≤ 8 mg/kg busulfan</td>
</tr>
<tr>
<td>or other nonmyeloablative drugs</td>
</tr>
</tbody>
</table>

CIBMTR, Center for International Blood and Marrow Research; NMDP, National Marrow Donor Program; EBMT, European Group for Blood and Marrow Transplantation; TBI, total body irradiation

Fig. 17-1. Commonly used conditioning regimens in relation to their immunosuppressive and myelosuppressive properties. Please note that this classification is not based on direct experimentation and is, thus, hypothetical. TBI, total body irradiation; TLI, total lymphoid irradiation; F, fludarabine; Cy, cyclophosphamide; Cy 120, cyclophosphamide 120 mg/kg; Cy 200, cyclophosphamide 200 mg/kg; M, melphalan, M 140; melphalan 140 mg/m²; M 180; melphalan 180 mg/m²; Flag-Irda, fludarabine/cytosine arabinoside/irudubicin; TT, thiotepa; ATG, anti-thymocyte globulin; Ale, alemtuzumab; Bu8, busulfan 8 mg/kg; Bu16, busulfan 16 mg/kg. Reprinted from Molecular Therapy, 12:26–41, copyright 2006; F. Baron and R. Storb, “Allogeneic hematopoietic cell transplantation following nonmyeloablative conditioning as treatment for hematologic malignancies and inherited blood disorders (Review),” with permission from Elsevier.
since nonmyeloablative conditioning has been associated with a lower degree of donor engraftment, higher risk of graft rejection, decreased risk of non-relapse mortality, and higher risk of relapse compared with reduced-intensity regimens as observed in a study performed at the M.D. Anderson Cancer Center (MDACC) [21].

3. Engraftment Kinetics

By definition, nonmyeloablative and reduced-intensity conditioning regimens usually lead to an initial state of mixed chimerism [22]. Several factors have been associated with kinetics of donor engraftment after nonmyeloablative conditioning. Factors associated with faster donor T cell engraftment included high intensity of the conditioning regimen [21, 22], having had previous myelosuppressive chemotherapy [23, 24], the use of peripheral blood stem cells (PBSC) instead of marrow as a stem cell source [25–27], a high number of CD34+ and T cells in the graft [23, 26, 27], and intense post-grafting immunosuppression [28].

High levels (>50%) of donor T and NK-cell chimerism one month after HSCT have each been associated with a lower risk of graft rejection [15, 24]. When analyzed as a continuous variable, higher levels of donor T cell chimerism one month after HSCT were associated with increased risks of grade II–IV acute GVHD [24] (Fig. 17-2A). Further, achievement of full donor T cell chimerism was associated with a lower risk of relapse (Fig. 17-2B). Finally, in patients with acute myeloid leukemia and myelodysplastic syndromes, the risk of subsequent relapse was substantially higher in patients with < 90 percent donor chimerism levels among marrow CD34+ cells on day 28 after HSCT than in those with > 90 percent [29].

4. Transplant-Related Toxicities after Nonmyeloablative versus Myeloablative Conditioning

Transplant-related toxicities and infections occurring after myeloablative allogeneic HSCT have been thought to be the consequence of the intense conditioning, of Graft-versus-Host reactions, or of both. A number of retrospective studies compared transplant-related toxicities and infections after HSCT following nonmyeloablative versus myeloablative conditioning with to determine the relative contributions of conditioning intensity to these complications.

Not unexpectedly, the hematological changes after nonmyeloablative conditioning were milder than that seen after myeloablative conditioning [30], and patients given nonmyeloablative or reduced-intensity conditioning required less platelet and red blood cell transfusions than those given myeloablative conditioning (reviewed in reference [31]). Similarly, liver, kidney, gastrointestinal, and lung toxicities were significantly reduced with nonmyeloablative conditioning [32–35].

Junghanss, et al. compared the incidence of post-transplant infections in 56 nonmyeloablative recipients to that in 112 matched controls given myeloablative conditioning [36, 37]. The 30- and 100-day incidences of bacteremia were 9 percent and 27 percent in nonmyeloablative recipients versus 27 percent (P=0.01) and 41 percent (P=0.07) in myeloablative recipients, respectively.
In contrast, invasive aspergillosis occurred at a similar rate (15% versus 9% at one year; \( P=0.30 \)). The onset of CMV disease was significantly delayed among nonmyeloablative compared to myeloablative recipients (medians of 130 versus 52 days; \( P=0.02 \)) due to the persistence of host-derived CMV immunity early after HSCT in nonmyeloablative recipients [38]. However, the one-year probability of CMV disease for high risk CMV patients was comparable in the two groups.
5. Graft-versus-Host Disease and Graft-versus-Tumor Effects After Nonmyeloablative Conditioning

The biology of reconstitution of donor-derived immunity after nonmyeloablative conditioning differs from what occurs after myeloablative conditioning in several aspects. First, nonmyeloablative conditionings generally lead to an initial state of mixed donor-host chimerism that might favor both Host-versus-Graft and Graft-versus-Host tolerance and, thus, limit GVHD [39]. Secondly, the intensity of the preparative regimens has been shown to contribute to acute GVHD physiopathology, presumably by inducing tissue damage and the release of a "cytokine storm" [40, 41]. In contrast, the number of recipient-derived antigen presenting cells (APC) might be higher after nonmyeloablative than myeloablative conditioning. Since recipient-derived APC are thought to play a major role in the initiation of acute GVHD [42], their persistence in an increased number after nonmyeloablative regimen might favor acute GVHD.

A number of reports have compared incidences of acute and chronic GVHD after nonmyeloablative or reduced-intensity conditioning. Most have shown lower incidences of acute GVHD and similar or lower incidences of chronic GVHD after nonmyeloablative versus myeloablative conditioning [43–47], including one study analyzing age-matched patients treated in a single institution [43]. However, although relatively less frequent, GVHD with or without associated infections has remained the leading cause of non-relapse mortality after nonmyeloablative HSCT.

GVHD incidence could be decreased by the use of anti-thymocyte globulin (ATG) or alemtuzumab, a humanized monoclonal antibody recognizing CD52 that is expressed on lymphocytes and NK cells, but not on hematopoietic stem cells [12, 20, 48]. However, these strategies were associated with increased risk of disease relapse/progression [48, 49].

Another approach aimed at reducing the incidence of acute GVHD has been developed by the Stanford University group. Based on murine experiments [50], the authors investigated a novel nonmyeloablative regimen that favored the presence of a high proportion of regulatory NK-T cells [50]. This regimen consisted of total lymphoid irradiation (TLI, 8 Gy) and ATG (Thymoglobulin, 7.5 mg/kg total dose), and post-grafting immunosuppression with MMF and CSP. First results in 37 patients with various hematological malignancies indicated that this regimen was indeed associated with a low incidence of grade II–IV acute GVHD (one of 37 patients), while Graft-versus-Tumor effects were apparently preserved [20].

As mentioned earlier, GVHD occurrence is strongly associated with Graft-versus-Tumor effects in patients given myeloablative conditioning [3]. Since nonmyeloablative regimens rely nearly exclusively on Graft-versus-Tumor effects for tumor eradication, several groups of investigators looked at the impact of GVHD on HSCT outcomes after nonmyeloablative or reduced-intensity conditioning.

First, Martino, et al. showed that patients with acute myeloid leukemia (n=17) or myelodysplastic syndrome (n=20) who experienced acute and/or chronic GVHD had significantly lower risks of relapse than those who did not (P=0.008) [51]. Kroger, et al. analyzed data from 120 patients with multiple
myeloma who were given allogeneic grafts after reduced-intensity conditioning [52]. While occurrence of acute GVHD was found to have no impact on relapse risks, occurrence of chronic GVHD was associated with significantly lower risk of relapse (P=0.02) in a time-dependent Cox analysis [52]. Similar observations were made by Crawley, et al. in a cohort of patients given allogeneic grafts after nonmyeloablative or reduced-intensity conditioning at various European Group for Blood and Marrow Transplantation (EBMT)-affiliated centers as treatment for multiple myeloma [49]. More recently, Blaise, et al. analyzed outcomes of 33 patients with acute myeloid leukemia in first complete remission receiving allogeneic HSCT from HLA-identical siblings following reduced-intensity conditioning [53]. In a landmark analysis starting on day 100, occurrence of chronic GVHD was associated with a lower risk of relapse (0% versus 44%, P=0.007) and better leukemia-free survival (95% versus 53%, P=0.007).

We analyzed the impact of acute and chronic GVHD on HSCT outcomes in a cohort of 322 patients given nonmyeloablative HSCT as treatment for hematological malignancies [54]. Grades II and III–IV acute GVHD were not significantly associated with lower risks of progression/relapse, but were instead associated with increased non-relapse mortality and lower progression-free survival. In contrast, the occurrence of chronic GVHD correlated with a lower risk of relapse in multivariate time-dependent analyses (HR=0.4, P=0.006) and was associated with significantly better progression-free survival (HR=0.5, P=0.003) (Fig. 17-3).

Taken together, these observations suggested that new approaches aimed at reducing the incidence of grade II–IV acute GVHD without suppressing chronic GVHD might improve progression-free survival after nonmyeloablative or reduced-intensity conditioning.

![Fig. 17-3. Impact of acute and chronic GVHD and of achievement of full donor T cell chimerism (FDC) on progression-free survival (PFS) 322 patients reported in ref. [54] given grafts after 2 Gy TBI with or without fludarabine](image_url)
6. Results in Specific Diseases

Tables 17-2 and 17-3 show the results of a number of phase I–II studies assessing post-HSCT outcomes in patients with hematological malignancies who were given nonmyeloablative or reduced-intensity conditioning. Since inclusion criteria varied between the studies, the efficacy of each regimen cannot be compared.

Encouraging results have generally been observed in patients with acute myeloid leukemia in first or second complete remissions (two-year overall survival ranging from 40% to 75%) [46, 53, 55–57] (Fig. 17-4), as well as in patients with myelodysplastic syndrome with < 5 percent blasts at HSCT (two-year overall survival ranging from 33% to 60%) [58, 59], chronic myeloid leukemia (two-year overall survival ≥ 70% for patients in first chronic phase [10, 60, 61]), chronic lymphocytic leukemia (two-year overall survival ranging from 50% to 80%) [62–66], or indolent or chemotherapy-sensitive aggressive Non-Hodgkin’s Lymphoma (two-year overall survival ranging from 50% to 80%) [12, 14, 67–70] (Tables 17-2 and 17-3). Conversely, results in patients with advanced aggressive diseases (such as acute leukemias not in complete remission, chemotherapy-insensitive high-grade Non-Hodgkin’s Lymphoma or multiple myeloma, or advanced myelodysplastic syndromes) have been less impressive.

7. Consolidative Allografts Following Planned Autografts

Since Graft-versus-Tumor effects may not be sufficiently fast enough to eradicate large volume disease in patients with aggressive malignancies, an elegant strategy has been to follow a “debunking” autologous HSCT (which can be administered with transplant-related mortality rates of less than 5%) with a nonmyeloablative allogeneic HSCT. This strategy, pioneered by Carella, et al. in patients with refractory lymphoma [71], was evaluated by Maloney, et al. in patients with refractory lymphoma [71], was evaluated by Maloney, et al. in...

![Fig. 17-4. Overall survival in 122 acute myeloid leukemia patients following nonmyeloablative HSCT according to disease status at time of HSCT](image-url)
Table 17-2. Recent results in patients given HSCT after nonmyeloablative/reduced-intensity conditioning for myeloid malignancies.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Disease</th>
<th>Regimen</th>
<th># Pts.</th>
<th>Median Pt. Age</th>
<th>% Pts. with MRD</th>
<th>% GVHD Grade III–IV</th>
<th>% GVHD Acute</th>
<th>% GVHD Chronic</th>
<th>NRM %</th>
<th>Follow-up (mos)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDACC [21]</td>
<td>AML+MDS</td>
<td>FAI</td>
<td>32</td>
<td>61</td>
<td>81</td>
<td>11</td>
<td>27</td>
<td>29</td>
<td>36</td>
<td>3-yr OS 30%</td>
<td>3-yr PFS 19%</td>
</tr>
<tr>
<td>MDACC [21]</td>
<td>AML+MDS</td>
<td>FM</td>
<td>62</td>
<td>54</td>
<td>40</td>
<td>19</td>
<td>39</td>
<td>52</td>
<td>36</td>
<td>3-yr OS 35%</td>
<td>3-yr PFS 32%</td>
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<tr>
<td>CGTP [97]</td>
<td>AML</td>
<td>Various</td>
<td>113</td>
<td>51</td>
<td>44</td>
<td>27</td>
<td>33</td>
<td>53</td>
<td>24</td>
<td>2-yr EFS 29%</td>
<td>2-yr EFS 52%</td>
</tr>
<tr>
<td>King’s College London [59]</td>
<td>AML+MDS</td>
<td>FBC</td>
<td>62</td>
<td>53</td>
<td>39</td>
<td>0 (MRD)-9 (URD)</td>
<td>NR</td>
<td>15</td>
<td>12</td>
<td>1-yr OS 74%</td>
<td>1-yr DFS 62%</td>
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<tr>
<td>Queen Elizabeth Hospital [56]</td>
<td>AML+MDS</td>
<td>FMC</td>
<td>76</td>
<td>52</td>
<td>46</td>
<td>0</td>
<td>11</td>
<td>19</td>
<td>12</td>
<td>3-yr DFS 37%</td>
<td>3-yr DFS 42%</td>
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<td>(all patients)</td>
<td>(CR1, CR2 or CR3)</td>
</tr>
<tr>
<td>University of Chicago [98]</td>
<td>AML+MDS</td>
<td>FMC</td>
<td>52</td>
<td>52</td>
<td>44</td>
<td>10</td>
<td>18</td>
<td>33</td>
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<td>1-yr OS 48%</td>
<td>1-yr PFS 38%</td>
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<tr>
<td>Marseille [53]</td>
<td>AML-CR1</td>
<td>FB+ATG</td>
<td>33</td>
<td>52</td>
<td>100</td>
<td>12</td>
<td>64</td>
<td>5</td>
<td>24</td>
<td>2-yr OS &amp; DFS 76%</td>
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<tr>
<td>HOVON/SAKK/OSHO [57]</td>
<td>AML-CR1</td>
<td>Flu/TBI</td>
<td>83</td>
<td>62</td>
<td>65</td>
<td>NR</td>
<td>23</td>
<td>22</td>
<td>24</td>
<td>2-yr DFS 51% (MRD) / 65% (URD)</td>
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<td></td>
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<td></td>
<td></td>
<td>2- yr DFS 39% (MRD) / 54% (URD)</td>
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<tr>
<td>Seattle consortium [99]</td>
<td>AML</td>
<td>Flu/TBI</td>
<td>122</td>
<td>58</td>
<td>48</td>
<td>12</td>
<td>36</td>
<td>16</td>
<td>24</td>
<td>2-yr OS 51% (CR1) / 61% (CR2)</td>
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<td></td>
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<td></td>
<td>2- yr DFS 44% (all pts)</td>
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<tr>
<td>EBMT [46]</td>
<td>AML</td>
<td>Various</td>
<td>315</td>
<td>57</td>
<td>100</td>
<td>8</td>
<td>48</td>
<td>18</td>
<td>24</td>
<td>2-yr OS 53% / 60% (CR1/CR2)</td>
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<tr>
<td>FHCRC [47]</td>
<td>MDS</td>
<td>Flu/TBI</td>
<td>38</td>
<td>62</td>
<td>68</td>
<td>22</td>
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<td>41</td>
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<td>3-yr OS 28%</td>
<td>3-yr PFS 27%</td>
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<td>EBMT [82]</td>
<td>MDS</td>
<td>Various</td>
<td>215</td>
<td>56</td>
<td>100</td>
<td>15</td>
<td>45</td>
<td>22</td>
<td>36</td>
<td>3-yr OS 41%</td>
<td>3-yr PFS 33%</td>
</tr>
<tr>
<td>Hadassah-Hebrew University [10]</td>
<td>CML-CP1</td>
<td>FB+ATG</td>
<td>24</td>
<td>35</td>
<td>79</td>
<td>29</td>
<td>55</td>
<td>15</td>
<td>60</td>
<td>5-yr OS &amp; DFS 85%</td>
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(continued)
Table 17-2. (continued)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Disease</th>
<th>Regimen</th>
<th># Pts.</th>
<th>Median Pt. Age</th>
<th>% Pts. with MRD</th>
<th>% GVHD</th>
<th>NRM</th>
<th>Follow-up (mos)</th>
<th>Survival</th>
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<td>Seattle consortium [60]</td>
<td>CML</td>
<td>Flu/TBI</td>
<td>24</td>
<td>58</td>
<td>100</td>
<td>12</td>
<td>32</td>
<td>21</td>
<td>36</td>
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<tr>
<td>EBMT [61]</td>
<td>CML</td>
<td>Various</td>
<td>186</td>
<td>50</td>
<td>61</td>
<td>9</td>
<td>42</td>
<td>19</td>
<td>24</td>
</tr>
</tbody>
</table>

OS, Overall survival; DFS, disease free survival; PFS, progression-free survival; MRD, HLA-matched related donor; URD, unrelated donor; MDACC, MD Anderson Cancer Center; CGTG, Cooperative German Transplant study Group; EBMT, European Group for Blood and Marrow Transplantation; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; CML, chronic myeloid leukemia; CR, complete remission; CP, chronic phase; Flu, fludarabine; TBI, total body irradiation; FAI, Flu 120mg/m² + cytarabine 4 g/m² + idarubicin 36 mg/m²; FM, Flu 100–150mg/m² + melphalan 140–180 mg/m²; FBC, Flu 150mg/m² + busulfan 8 mg/kg + alemtuzumab 100mg; FMC, Flu 150mg/m² + melphalan 140mg/m² + alemtuzumab 100 mg; FB + ATG, Flu 180mg/m² + busulfan 8 mg/kg + ATG; Flu/TBI, 2 Gy TBI ± Flu 90mg/m²
### Table 17-3. Recent results in patients given HSCT after nonmyeloablative/reduced-intensity conditioning for lymphoid malignancies.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Disease</th>
<th>Regimen</th>
<th># Pts.</th>
<th>Median Pt. Age</th>
<th>% Pts. with MRD</th>
<th>% GVHD Grades III–IV Acute</th>
<th>Chronic</th>
<th>NRM %</th>
<th>Follow-up (mos)</th>
<th>Survival</th>
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<td>Royal Free and University College London [12]</td>
<td>LG/MCL/HG</td>
<td>FMC</td>
<td>88</td>
<td>48</td>
<td>72</td>
<td>5</td>
<td>7</td>
<td>(LG)-38 (HG)</td>
<td>36</td>
<td>3-yr OS 55% (all pts)</td>
</tr>
<tr>
<td>EBMT [68]</td>
<td>LG/MCL/HG/HL</td>
<td>Various</td>
<td>188</td>
<td>40</td>
<td>89</td>
<td>NR</td>
<td>16</td>
<td>26</td>
<td>12</td>
<td>2-yr OS 50% 2-yr PFS 65%</td>
</tr>
<tr>
<td>Seattle consortium [69]</td>
<td>HG</td>
<td>Flu/TBI</td>
<td>42</td>
<td>50</td>
<td>69</td>
<td>19</td>
<td>57</td>
<td>15</td>
<td>12</td>
<td>1-yr OS 63% 1-yr PFS 49%</td>
</tr>
<tr>
<td>MDACC [14]</td>
<td>LG</td>
<td>FC ± Rituximab</td>
<td>20</td>
<td>51</td>
<td>100</td>
<td>5</td>
<td>64</td>
<td>16</td>
<td>24</td>
<td>2-yr OS 84% 2-yr DFS 84%</td>
</tr>
<tr>
<td>MDACC [70]</td>
<td>MCL</td>
<td>FluCy + Rituximab / FCC</td>
<td>18</td>
<td>57</td>
<td>72</td>
<td>0</td>
<td>36</td>
<td>11</td>
<td>36</td>
<td>3-yr OS 86% 3-yr PFS 82%</td>
</tr>
<tr>
<td>Seattle consortium [67]</td>
<td>MCL</td>
<td>Flu/TBI</td>
<td>16</td>
<td>54</td>
<td>60</td>
<td>30</td>
<td>64</td>
<td>24</td>
<td>24</td>
<td>2-yr OS 65% 2-yr DFS 60%</td>
</tr>
<tr>
<td>Institutio Nazionale Tumori Milan [100]</td>
<td>TCL</td>
<td>FluCyThio</td>
<td>17</td>
<td>41</td>
<td>82</td>
<td>12</td>
<td>50</td>
<td>6</td>
<td>24</td>
<td>3-yr OS 81% 3-yr PFS 64%</td>
</tr>
<tr>
<td>EBMT [101]</td>
<td>HL</td>
<td>Various</td>
<td>311</td>
<td>31</td>
<td>71</td>
<td>NR</td>
<td>20</td>
<td>27</td>
<td>24</td>
<td>2-yr OS 46% 2-yr PFS 26%</td>
</tr>
<tr>
<td>Royal Free and University College London [102]</td>
<td>HL</td>
<td>FMC</td>
<td>49</td>
<td>32</td>
<td>63</td>
<td>4</td>
<td>14</td>
<td>16</td>
<td>24</td>
<td>4-yr OS 56% 4-yr PFS 39%</td>
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<tr>
<td>Hospital de la Santa Creu, Barcelona [103]</td>
<td>HL</td>
<td>FM</td>
<td>40</td>
<td>35</td>
<td>93</td>
<td>NR</td>
<td>47</td>
<td>25</td>
<td>12</td>
<td>2-yr OS 48% 2-yr PFS 32%</td>
</tr>
<tr>
<td>Berlin [64]</td>
<td>CLL</td>
<td>FB+ATG</td>
<td>30</td>
<td>50</td>
<td>43</td>
<td>20</td>
<td>75</td>
<td>15</td>
<td>24</td>
<td>2-yr OS 72% 2-yr PFS 67%</td>
</tr>
<tr>
<td>MDACC [63]</td>
<td>CLL</td>
<td>FluCy ± Rituximab</td>
<td>17</td>
<td>54</td>
<td>100</td>
<td>12</td>
<td>60</td>
<td>22</td>
<td>24</td>
<td>2-yr OS 80% 2-yr DFS 60%</td>
</tr>
<tr>
<td>Seattle consortium [62]</td>
<td>CLL</td>
<td>Flu/TBI</td>
<td>64</td>
<td>56</td>
<td>69</td>
<td>19</td>
<td>50</td>
<td>22</td>
<td>24</td>
<td>2-yr OS 60%</td>
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</table>

(continued)
<table>
<thead>
<tr>
<th>Study Group</th>
<th>Disease</th>
<th>Regimen</th>
<th># Pts.</th>
<th>Median Pt. Age</th>
<th>% Pts. with MRD</th>
<th>% GVHD Grades III-IV Acute</th>
<th>% GVHD Chronic</th>
<th>NRM %</th>
<th>Follow-up (mos)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham Heartlands Hospital [66]</td>
<td>CLL</td>
<td>FMC</td>
<td>41</td>
<td>54</td>
<td>58</td>
<td>10</td>
<td>13</td>
<td></td>
<td>26</td>
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<td></td>
<td></td>
<td></td>
<td>2-yr OS 51%</td>
<td>2-yr PFS 45%</td>
</tr>
<tr>
<td>Dana-Farber Cancer Institute [65]</td>
<td>CLL</td>
<td>FB</td>
<td>46</td>
<td>53</td>
<td>33</td>
<td>19</td>
<td>38</td>
<td></td>
<td>17</td>
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<td></td>
<td></td>
<td></td>
<td>2-yr OS 54%</td>
<td>2-yr PFS 34%</td>
</tr>
<tr>
<td>EBMT [49]</td>
<td>MM</td>
<td>Various</td>
<td>229</td>
<td>52</td>
<td>78</td>
<td>NR</td>
<td>50</td>
<td></td>
<td>26</td>
<td>24</td>
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<td></td>
<td></td>
<td></td>
<td>3-yr OS 41%</td>
<td>3-yr PFS 21%</td>
</tr>
<tr>
<td>Seattle consortium [72]</td>
<td>MM</td>
<td>TBI*</td>
<td>54</td>
<td>52</td>
<td>100</td>
<td>7</td>
<td>46</td>
<td></td>
<td>2</td>
<td>3</td>
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<td></td>
<td></td>
<td></td>
<td>2-yr OS 78%</td>
<td>2-yr PFS 55%</td>
</tr>
</tbody>
</table>

OS, Overall survival; DFS, disease free survival; PFS, progression-free survival; MRD, HLA-matched related donor; URD, unrelated donor; MDACC, MD Anderson Cancer Center; EBMT, European Group for Blood and Marrow Transplantation; LG, low-grade non-Hodgkin lymphoma; HG, high-grade Non-Hodgkin’s Lymphoma; MCL, mantle cell lymphoma; HL, Hodgkin’s Lymphoma; TCL, T-cell lymphoma; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; Flu, fludarabine; TBI, total body irradiation; FMC, Flu 150 mg/m² + melphalan 140 mg/m² + alemtuzumab 100 mg; FM, Flu 150 mg/m² + melphalan 140 mg/m²; FB + ATG, Flu 180 mg/m² + busulfan 8 mg/kg + ATG 20–40 mg/kg; Flu/TBI, 2 Gy TBI ± Flu 90 mg/m²; FluCy, Flu 90–125 mg/m² + cyclophosphamide 2000–2250 mg/m²; FCC, Flu 60 mg/m² + cisplatin 100 mg/m² + cytarabine 2 g/m²; FluCyThio, Flu 60 mg/m² + cyclophosphamide 60 mg/kg + Thiothepa 10 mg/kg; TBI, 2 Gy TBI; FB, Flu 120 mg/m² + i.v. busulfan 3.2 mg/kg; * tandem autologous/allogeneic HSCT.
54 patients with multiple myeloma. Patients were first given autologous HSCT after a cytoreductive dose of 200 mg/m² melphalan; this was followed 1.3–7.6 (median two) months later by allogeneic HSCT from HLA-identical sibling following 2 Gy TBI [72]. The 100-day mortalities after autologous and allogeneic HSCT were 2 percent each. Two-year overall and progression-free survivals were 78 percent and 55 percent, respectively. A large phase III study comparing tandem autologous HSCT with tandem autologous/allogeneic HSCT is currently ongoing in patients with multiple myeloma (BMT-CTN 01–02).

8. Nonmyeloablative HSCT After Failed Autologous HSCT

The outcomes for patients with relapse or secondary myelodysplastic syndromes after autologous HSCT were poor. A second myeloablative HSCT from an allogeneic donor has been a potentially curative option, but this approach has been limited by non-relapse mortality rates of 50 to 80 percent [8]. This prompted several groups of researchers to investigate the feasibility of allogeneic HSCT with nonmyeloablative or reduced-intensity conditioning in patients who had failed autologous HSCT. As shown in Table 17-4, most studies found lower non-relapse mortality, compared to what was seen following myeloablative allogeneic HSCT, and relatively encouraging results in patients with chemo-sensitive disease at HSCT [73–79].

We recently analyzed data from 147 patients who had treatment failure with myeloablative autologous (n=135), allogeneic (n=10) or syngeneic (n=2) HSCT and underwent HLA-matched related (n=62) or unrelated (n=85) HSCT following conditioning with 2 Gy TBI with or without added fludarabine, to determine factors that predict HSCT outcomes [80]. Three-year incidences of non-relapse mortality, relapse and overall survival were 32 percent, 48 percent and 27 percent, respectively, for patients given grafts from related donors, and 28 percent, 44 percent and 44 percent, respectively, for unrelated graft recipients. The best outcomes were seen in patients with Non-Hodgkin’s Lymphoma, while patients with Hodgkin’s Lymphoma and multiple myeloma had poor outcomes due to high incidences of relapse/progression (Fig. 17-5). Being in partial or complete remission at HSCT (P=0.002), and developing chronic GVHD (P=0.03) were associated with lower risks of relapse/progression. Further, being in partial or complete remission at HSCT (P=0.01), absence of comorbidity at HSCT (P=0.03) and lack of acute GVHD after HSCT (P=0.06) were associated with better overall survival.

9. Outcomes with Myeloablative versus Nonmyeloablative Conditioning

Alyea, et al. performed a retrospective analysis of 152 patients (> 50-years-old) with hematological malignancies undergoing HSCT after reduced-intensity (n=71) or myeloablative (n=81) conditioning [81]. Reduced-intensity conditioning consisted of fludarabine (120 mg/m²) and intravenous busulfan (3.2 mg/kg), while myeloablative conditioning included mainly cyclophosphamide (3.6 g/m²) plus TBI (14 Gy). With a median follow-up of 18 months, the cumulative incidences of relapse and non-relapse mortality were 46 percent and 32 percent, respectively, in the reduced-intensity conditioning group, versus 30 percent
Table 17-4. Recent results in patients given HSCT after nonmyeloablative/reduced-intensity conditioning after failed myeloablative HSCT.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Disease</th>
<th>Regimen</th>
<th># Pts.</th>
<th>Median Pt. Age</th>
<th>% Pts. with MRD</th>
<th>% Grades III–IV Acute</th>
<th>% Grades Chronic</th>
<th>% GVHD</th>
<th>NRM</th>
<th>Follow-up (mos)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massachusetts General Hospital Boston [74]</td>
<td>HM CyATG-ThyRx</td>
<td>13</td>
<td>38</td>
<td>100</td>
<td>38</td>
<td>40</td>
<td>1 pt.</td>
<td>11</td>
<td></td>
<td>2-yr OS 45%</td>
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<td></td>
<td></td>
<td>2-yr DFS 38%</td>
<td></td>
</tr>
<tr>
<td>Christie Hospital Manchester [104]</td>
<td>Lymphoproliferative malignancies</td>
<td>FMC</td>
<td>38</td>
<td>44</td>
<td>100</td>
<td>0</td>
<td>15</td>
<td>20</td>
<td>14</td>
<td>14-mo OS 53%</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>14-mo PFS 50%</td>
<td></td>
</tr>
<tr>
<td>MDACC [76]</td>
<td>Chemo-sensitive NHL</td>
<td>FluCy + Rituximab (n=16) or FCC (n=4)</td>
<td>20</td>
<td>51</td>
<td>90</td>
<td>0</td>
<td>50</td>
<td>5</td>
<td>36</td>
<td>3-yr OS/PFS 95%</td>
<td></td>
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<td></td>
<td></td>
<td>3-yr DFS 80%</td>
<td></td>
</tr>
<tr>
<td>City of Hope Cancer Center, Duarte [77]</td>
<td>HM FM (n=24) or Flu/TBI (n=4)</td>
<td>28</td>
<td>47</td>
<td>50</td>
<td>21</td>
<td>67</td>
<td>21</td>
<td>3</td>
<td>2-yr OS 57%</td>
<td></td>
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<td></td>
<td></td>
<td>2-yr DFS 41%</td>
<td></td>
</tr>
<tr>
<td>Hospital de la Santa Creu, Barcelona [78]</td>
<td>HM FM</td>
<td>46</td>
<td>47</td>
<td>100</td>
<td>24</td>
<td>73</td>
<td>24</td>
<td>12</td>
<td></td>
<td>1-yr OS 63%</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-yr PFS 57%</td>
<td></td>
</tr>
<tr>
<td>Hadassah-Hebrew University [73]</td>
<td>HM FB+ATG</td>
<td>12</td>
<td>33</td>
<td>75</td>
<td>17</td>
<td>33</td>
<td>1 pt</td>
<td>3</td>
<td></td>
<td>3-yr OS 56%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-yr DFS 50%</td>
<td></td>
</tr>
<tr>
<td>Seattle consortium [80]</td>
<td>HM Flu/TBI</td>
<td>147</td>
<td>46</td>
<td>42</td>
<td>19</td>
<td>56</td>
<td>30</td>
<td>36</td>
<td></td>
<td>3-yr PFS 20% (MRD)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-yr PFS 28% (URD)</td>
<td></td>
</tr>
</tbody>
</table>

OS, Overall survival; DFS, disease free survival; PFS, progression-free survival; MRD, HLA-matched related donor; URD, unrelated donor; MDACC, MD Anderson Cancer Center; NHL, Non-Hodgkin’s Lymphoma; HM, Hematological malignancies; CyATG-ThyRx, Cyclophosphamide 150–200 mg/kg + ATG + Thymic irradiation (7 Gy); Flu, fludarabine; TBI, total body irradiation; FMC, Flu 150 mg/m² + melphalan 140 mg/m² + alemtuzumab 100 mg; FM, Flu 150 mg/m² + melphalan 140 mg/m²; FB + ATG, Flu 180 mg/m² + busulfan 8 mg/kg + ATG 20–40 mg/kg; Flu/TBI, 2 Gy TBI ± Flu 90 mg/m²; FluCy, Flu 90–125 mg/m² + cyclophosphamide 2000–2250 mg/m²; FCC, Flu 60 mg/m² + cisplatin 100 mg/m² + cytarabine 2 g/m²
Fig. 17-5. Cumulative incidences of relapse (A) and overall survival (B) in 147 patients given nonmyeloablative HSCT after failed myeloablative HSCT according to diagnosis category group: HL, Hodgkin’s Lymphoma; MM, multiple myeloma; Myeloid, myeloid malignancies including acute myeloid leukemia (n=16), myelodysplastic syndromes (n=12), chronic myeloid leukemia (n=3), and myeloproliferative disorders (n=2); NHL-A, aggressive Non-Hodgkin’s Lymphoma (n=24); NHL-I, indolent Non-Hodgkin’s Lymphoma (n=12); NHL-MCL, mantle cell lymphoma (n=14) (C). Progression-free survival in 147 patients given nonmyeloablative HSCT after failed myeloablative HSCT according to disease status at HSCT. Reprinted from F. Baron, et al., “Factors associated with outcomes in allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning after failed myeloablative hematopoietic cell transplantation.” J Clin Oncol 2006; 24:4150–4157. Reprinted with permission from the American Society of Clinical Oncology.”
(P=0.05) and 50 percent (P=0.01), respectively, in the myeloablative group. Better overall survival was seen in the nonmyeloablative than in the myeloablative group at two years (39% versus 29%; P=0.056).

Scott, et al. compared results of allogeneic HSCT following either nonmyeloablative (2 Gy TBI with or without added fludarabine; n=38) or myeloablative (busulfan 16 mg/kg, targeted to 800–900 ng/mL and cyclophosphamide 120 mg/kg, n=112) conditioning in patients with myelodysplastic syndrome over 40 years of age [47]. In multivariate analyses, three-year progression-free survival (HR=1.1, P=0.60), progression incidence (HR=1.3, P=0.43) and non-relapse mortality (HR=1.0, P=0.94) were comparable between nonmyeloablative and myeloablative patients. Further, in the subgroup of patients with transformed acute myeloid leukemia in morphological complete remission after chemotherapy, progression-free survival (HR=1, P=0.93) and progression rate (HR=0.7, P=0.64) were similar in patients given nonmyeloablative versus myeloablative conditioning. These observations suggest that Graft-versus-Tumor effects are more important than conditioning intensity in preventing relapse in this group of patients.

Martino, et al. compared HSCT outcomes in 836 patients who received HLA-identical grafts from siblings at various EBMT-affiliated centers after nonmyeloablative (n=215) or myeloablative (n=621) conditioning [82]. Nonmyeloablative/reduced-intensity conditioning included fludarabine with intermediate doses of 1–2 alkylating agents (i.e., ≤10 mg/kg p.o. busulfan; ≤140 mg/m² i.v. melphalan; or ≤10 mg/kg i.v. thiotepa) or low-dose (2–4 Gy) TBI. Three-year incidences of relapse, non-relapse mortality and progression-free survival were 45 percent, 22 percent and 33 percent, respectively, in nonmyeloablative recipients, versus 27 percent, 32 percent and 41 percent, respectively, in those given myeloablative conditioning. In multivariate analysis, nonmyeloablative recipients had a higher incidence of relapse (HR=1.64, P=0.001), but a lower incidence of non-relapse mortality (HR=0.61, P=0.015), leading to a similar probability of progression-free survival (P=0.9).

Aoudjhane, et al. analyzed data from 722 patients with de novo acute myeloid leukemia over 50 years of age and given allogeneic HSCT after either reduced-intensity (n=315) or myeloablative (n=407) conditioning among EBMT-affiliated centers [46]. Reduced-intensity conditioning regimens were defined as fludarabine combined with low-dose TBI (<3 Gy), or busulfan (total dose ≤8 mg/kg) or other nonmyeloablative drugs. Two-year probabilities of leukemia-free survival for patients in first complete remissions at HSCT (n=416) were 44 percent in patients given reduced-intensity conditioning versus 54 percent (P=0.26) in patients given myeloablative conditioning. For patients in second complete remissions at HSCT (n=104), the figures were 55 percent versus 47 percent (P=0.81), respectively. In multivariate analyses, the use of reduced-intensity versus myeloablative conditioning was associated with a higher risk of relapse (RR 1.8, P=0.0003), a lower risk of non-relapse mortality (RR 0.48, P<0.0001) and comparable leukemia-free survival (RR 1.15, P=0.24).

Finally, Dreger, et al. compared data from 155 patients with chronic lymphocytic leukemia who were given reduced-intensity conditioning after either reduced-intensity (n=73), or myeloablative conditioning (n=82) [83]. Two-year rates of relapse, non-relapse mortality and event-free survival were 28 percent, 19 percent and 58 percent, respectively, in nonmyeloablative recipients, versus
11 percent, 26 percent and 62 percent, respectively, in those given myeloablative conditioning. In multivariate analysis, nonmyeloablative recipients had a higher incidence of relapse (HR=2.46, P=0.08), but a lower incidence of non-relapse mortality (HR=0.40, P=0.03), leading to a similar probability of event-free survival (HR=0.69, P=0.22).

Taken together, these studies suggest that nonmyeloablative/reduced-intensity conditioning achieved their goal of reducing early non-relapse mortality, but at the cost of a higher risk of relapse. Prospective studies comparing nonmyeloablative/reduced-intensity versus myeloablative conditioning are needed to define whether there is a role as well for nonmyeloablative/reduced-intensity conditioning in patients eligible for conventional myeloablative HSCT.

10. Impact of Comorbidities on the Selection of Conditioning Regimens

Since short-term results seem comparable in patients given either nonmyeloablative or myeloablative conditioning, an important question is whether it is possible to determine which patients might benefit from a nonmyeloablative or reduced-intensity conditioning, and which others could safely receive myeloablative regimens. In an effort to answer this question, Sorror, et al. assessed the effect of comorbidities (scored with the Hematopoietic Cell Transplantation-specific comorbidity index (HCT-CI) [84]) on outcomes among patients with acute myeloid leukemia or myelodysplastic syndromes receiving allogeneic grafts after either nonmyeloablative (n=87) or myeloablative (n=360) conditioning [85]. Survival for patients with low risk disease (defined as acute myeloid leukemia in first complete remission or myelodysplastic refractory anemia) and/or no/few comorbidities (HCT-CI scores of 0–1) was similar among the two groups. However, nonmyeloablative recipients with high risk disease and HCT-CI scores of ≥2 had less non-relapse mortality (HR=0.35, P=0.006), and better overall survival (HR=0.55, P=0.01) than comparable patients given myeloablative conditioning, suggesting that nonmyeloablative conditioning should be preferentially used in such patients.

The same group investigated the impact of comorbidities on HSCT outcomes in patients with B-cell malignancies given allogeneic HSCT after either nonmyeloablative or myeloablative conditioning [86]. Among patients without comorbidity at HSCT (HCT-CI = 0), survival was comparable for patients given nonmyeloablative or myeloablative conditioning (P=0.7). In contrast, among patients with comorbidities (HCT-CI score ≥1) at HSCT, the use of nonmyeloablative conditioning was associated with lower non-relapse mortality (HR=0.5, P=0.03) and better overall survival (HR=0.6, P=0.05).

11. Does Nonmyeloablative HSCT Improve Survival over Chemotherapy in Patients with Hematological Malignancies?

It has been difficult to compare the results of phase I–II studies assessing nonmyeloablative/reduced-intensity conditioning to those obtained in comparable patients given conventional chemotherapy, since one could argue that only fitter patients were referred to transplantation centers and offered HSCT. This
underlines the interest of analyses comparing outcomes in patients who have an HLA-identical sibling donor (and could potentially receive a HSCT) in comparison to those who do not.

**11.1 Acute Myeloid Leukemia**

Mohty, et al. investigated whether allogeneic HSCT after reduced-intensity conditioning improved progression-free survival in adults with newly diagnosed acute myeloid leukemia who achieved complete remissions after induction chemotherapy, but were ineligible for conventional HSCT because of age or medical comorbidities [87]. Ninety-five consecutive patients (median age 52 (range, 26–65) years old) were retrospectively analyzed. Thirty-five patients had HLA-identical sibling donors (donor group), while 60 did not (no donor group). Twenty-five of 35 patients included in the donor group (71%) could received the allogeneic HSCT, while 10 patients with an identified donor did not receive allogeneic HSCT because of patient or donor refusals \( (n=6) \), early relapse \( (n=2) \) or psychiatric disorders \( (n=2) \). The four-year probability of progression-free survival was 54 percent in the donor group, versus 30 percent in the non-donor group \( (P=0.01) \). This was due to a significantly lower risk of relapse in patients who received an allogeneic HSCT (12% at four years), than in those who did not (54% at four years, \( P<0.001 \)).

The Groupe Ouest Est d’Etude des Leucémies et Autres Maladies du Sang (GOELAMS) recently reported the first results of a phase III study comparing outcomes of patients with acute myeloid leukemia in first complete remission receiving either autologous or allogeneic HSCT [88]. A search to identify an HLA-identical sibling was performed for each patient as they received a first course of consolidation therapy. After a second course of consolidation chemotherapy, patients with an HLA-matched sibling donor were scheduled to undergo an HSCT after either myeloablative (if age \( \leq 50 \); consisting of 12 Gy TBI and cyclophosphamide 120 mg/kg) or reduced-intensity (if age 51–60; consisting of busulfan 4–8 mg/kg, fludarabine 120 mg/m\(^2\), and ATG) conditioning. Among patients younger than 50 years, disease free survival was significantly better in patients included in the allogeneic arm \( (n=111) \), than in those included in the autologous arm \( (71\% \text{ versus } 52\%, P=0.007) \). Among patients aged 50- to 60-years-old, there was better disease free survival in patients given reduced-intensity allogeneic HSCT, than in those given autologous HSCT \( (62\% \text{ versus } 50\%, P=0.27) \).

**11.2. Multiple Myeloma**

The Intergroupe Francophone du Myelome compared autologous HSCT followed by dose-reduced allograft \( (n=65) \) with tandem autologous HSCT \( (n=219) \) in high risk de novo multiple myeloma (defined as deletion 13 and/or \( \beta2 \) microglobulin >3 mg/L) [89]. The reduced-intensity conditioning regimen consisted of busulfan (4 mg/kg), fludarabine (125 mg/m\(^2\)) and ATG (Imtix; 12.5 mg/kg). Nineteen of the 65 patients with a sibling donor did not receive the allogeneic HSCT because of progressive disease \( (n=7) \), donor/patient refusal \( (n=5) \), ongoing infection \( (n=4) \) or unknown causes \( (n=3) \). On an intent-to-treat basis, survival \( (P=0.27) \) and event-free survival \( (P=0.56) \) did not differ between studies. However, the lack of improved survival in the allogeneic arm might be due to the high-dose ATG used that abrogated Graft-versus-Tumor
effects. Further, the choice of including busulfan instead of melphalan in the conditioning regimen was controversial. Indeed, the use of busulfan in the conditioning regimen was associated with inferior survival (P=0.01) in the multiple myeloma EBMT study [49]. Results of the ongoing BMT-CTN 01–02 multiple myeloma study will help to better define the role for nonmyeloablative HSCT in patients with multiple myeloma.

12. Conclusions and Perspectives

Reduced-intensity conditioning and nonmyeloablative regimens have allowed older patients, those who had failed a high-dose HSCT, and those with comorbidity to benefit from the potentially curative Graft-versus-Tumor effects. Remarkably, minimally toxic regimens of 2 Gy TBI with or without fludarabine, or TLI plus ATG each followed by post-grafting immunosuppression with MMF and CSP have assured engraftment rates almost similar to those after myeloablative conditioning [15, 20]. Antitumor responses in some disease types require extended periods of time, with some patients achieving complete remissions more than one year after HSCT [15, 54].

Ongoing efforts are directed at better preventing acute GVHD, at increasing the use of nonmyeloablative regimens in patients given haploidentical grafts [90] or unrelated cord blood [91] and at increasing Graft-versus-Tumor effects by combining nonmyeloablative conditioning with disease-targeted therapy such as imatinib, thalidomide, bortezomib, rituximab or radiolabeled monoclonal antibodies [63, 92–95]. For example, encouraging results have been achieved by combining the anti-CD45 radiolabeled monoclonal antibody with nonmyeloablative conditioning in patients with acute myeloid leukemia not in complete remission at HSCT or with advanced myelodysplastic syndromes [93]. Other groups of investigators are focusing on identifying patients at high risk of relapse early after HSCT and treating them with preemptive DLI or rapid taper of post-grafting immunosuppression [29]. Finally, further progress in adoptive transfer of T cell populations with relative tumor specificity are likely to improve HSCT’s effectiveness after reduced-intensity or nonmyeloablative regimens [96].

References


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