Outcome and prognostic factors in patients with mantle-cell lymphoma relapsing after autologous stem-cell transplantation: a retrospective study of the European Group for Blood and Marrow Transplantation (EBMT)


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Background: Autologous stem-cell transplantation (autoSCT) is considered a standard treatment of non-frail patients with mantle cell lymphoma (MCL), but little is known about outcome of MCL patients relapsing after autoSCT. We therefore sought to analyse the outcome after autoSCT failure and the efficacy of a rescue stem-cell transplantation (SCT) in this setting.

Patients and methods: Patients with MCL were eligible if they had relapsed after autoSCT performed between 2000 and 2009. A total of 1054 patients could be identified in the EBMT registry. By contacting the transplant centres, a full dataset could be retrieved for 360 patients.

Results: Median overall survival (OS) after relapse of the whole study group was 19 months. A long (>12 months) interval between autoSCT and relapse (P<0.001, hazard ratio (HR) 0.62), primary refractory disease (P<0.02, HR 1.92), prior high-dose ARA-C treatment (P=0.04, HR 1.43), and the year of relapse (P=0.02, HR 0.92) significantly influenced OS from relapse in multivariate analysis.

Eighty patients (22%) received a rescue allogeneic SCT (alloSCT). Relapse incidence, non-relapse mortality, and OS 2 years after alloSCT was 33% (confidence interval 21% to 45%), 30% (95% CI 19% to 42%), and 46% (95% CI 33% to 59%), respectively. Remission duration after autoSCT was the only variable significantly affecting the outcome of salvage alloSCT. In contrast, rescue autoSCT was not associated with long-term disease control. However, individual patients survived long term even without salvage transplantation.

Conclusions: MCL recurrence within 1 year after autoSCT has an extremely dismal outcome, while the prognosis of patients with longer remission durations after autoSCT is significantly better. AlloSCT may offer the possibility of durable survival when
Key words: mantle cell lymphoma relapse, autologous stem-cell transplantation, allogeneic stem-cell transplantation

introduction

The prognosis of patients with mantle cell lymphoma (MCL) has improved considerably during recent years [1]. The refinement of dose-intensified approaches such as autologous stem-cell transplantation (autoSCT) for younger patients (<60 years) with MCL has contributed significantly to this development. In particular, the addition of high-dose ARA-C and rituximab to the induction treatment before autoSCT were identified as important factors [2, 3].

Although a significant proportion of patients with MCL enjoy long-term disease control after autoSCT, relapse remains the main cause of treatment failure. The prognosis of patients with MCL recurrence after autoSCT appears to be extremely poor, especially if occurring early after transplant [4]. So far, there is no standard salvage treatment of MCL relapse after autoSCT, and therapy decisions are usually based on individual patient conditions. Despite the advent of novel agents such as mTOR- [5] proteasome- [6] or brutons-tyrosine-kinase [7] inhibitors allogeneic stem-cell transplantation (alloSCT) seems to be the only option for long-term disease control in this setting [4]. Although experience with alloSCT in MCL is accumulating [8–10], published series are mostly small and patients who received an autoSCT before alloSCT are generally pooled with patients in other disease stages. Apart from a small single-centre retrospective study [4], separate analyses of patients receiving alloSCT for failure of autotransplant are sparse.

Taking advantage of the largest patient sample analysed to date, the present retrospective registry-based study investigates the outcome of patients who experienced MCL recurrence after autoSCT. The results suggest that the prognosis of patients with MCL relapse after autoSCT is dismal, in particular if disease recurs early. While the best prognosis is observed in those patients who relapse later than 1 year after autoSCT and manage to proceed to a salvage allotransplant, a minority of patients may enjoy long-term survival even without aggressive treatment.

patients and methods

patient eligibility

Eligible patients were aged 18 years or more who underwent a first autoSCT for MCL between 2000 and 2009, subsequently relapsed, and were registered with the EBMT database. Baseline information and transplantation characteristics of eligible patients were downloaded, and centres were contacted to provide information on relapse treatment and updated follow-up data as well as written histopathology reports of the original diagnosis.

statistical analysis

Details of the statistical analysis are described in the supplementary Material, available at Annals of Oncology online. In brief, overall survival (OS) was calculated from relapse after autoSCT to death. Probabilities of OS were calculated using the Kaplan–Meier estimate. Survival curves were compared using the log-rank test and multivariate analysis for OS was done by Cox regression analysis (Table 1). Median observation time was calculated by the reversed Kaplan–Meier estimate. Relapse incidence after alloSCT was calculated as time from alloSCT to relapse, and non-relapse mortality (NRM) incidence was calculated as time from alloSCT to death in the absence of prior relapse or progression. Relapse and NRM events were considered as competing risks.

results

patient selection

A total of 1054 patients meeting the eligibility criteria could be identified in the EBMT registry. Of these, the requested additional dataset could be retrieved for 376 patients. Seven patients had to be excluded due to loss of follow-up and three due to falsely reported relapse (supplementary Figure S1, available at Annals of Oncology online). On request, we received histology reports for 246 (73%) patients, resulting in exclusion of six patients (2.5%) because of a diagnosis other than MCL. We did not receive histology reports for the remaining 120 patients and therefore compared their outcome to the 246 patients for whom histology reports were available. Because outcome of both groups was not significantly different [P = 0.15, hazard ratio (HR) 1.2, 95% confidence interval (95% CI) 0.9–1.6,

<table>
<thead>
<tr>
<th>Covariate</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Time to relapse (per 12 months)</td>
<td>&lt;0.0001</td>
<td>0.62</td>
<td>0.54–0.72</td>
</tr>
<tr>
<td>Salvage autoSCT versus first-line autoSCT (reference category first-line autoSCT)</td>
<td>0.16</td>
<td>1.26</td>
<td>0.91–1.73</td>
</tr>
<tr>
<td>Refractory versus sensitive MCL before autoSCT (reference category-sensitive disease)</td>
<td>0.02</td>
<td>1.92</td>
<td>1.10–3.33</td>
</tr>
<tr>
<td>Age at relapse (per 10 years)</td>
<td>0.58</td>
<td>0.97</td>
<td>0.98–1.03</td>
</tr>
<tr>
<td>Year of relapse calculated from 2000 onwards (per year)</td>
<td>0.02</td>
<td>0.94</td>
<td>0.86–0.99</td>
</tr>
<tr>
<td>Rituximab before autoSCT (reference category no rituximab treatment)</td>
<td>0.53</td>
<td>1.15</td>
<td>0.56–1.35</td>
</tr>
<tr>
<td>ARA-C before autoSCT (reference category no ARA-C treatment)</td>
<td>0.04</td>
<td>1.43</td>
<td>0.50–0.99</td>
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</tbody>
</table>

HR, hazard ratio; CI, confidence interval; autoSCT, autologous stem-cell transplantation; MCL, mantle cell lymphoma; ARA-C, high-dose cytarabine.
supplementary Figure S2, available at *Annals of Oncology* online, the analysis was performed with all 360 patients
(Figure 1).

**patient and relapse characteristics**

Sixty-three percent had undergone autoSCT as part of first-line therapy; 67% and 50% had documented exposure to rituximab and high-dose ARA-C before autoSCT; and 8% had refractory disease at autoSCT. Median time from autoSCT to relapse was 20 months (range: 0.4–117 months). One-third of the relapsed patients experienced their progression within the first year after autoSCT (33%), whereas only 21 relapses (6%) occurred beyond 5 years after autoSCT. Patient characteristics of early relapses (<12 months) versus late relapses (>12 months) are compared in

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Overall survival (OS) of mantle cell lymphoma patients who have relapsed after autologous stem-cell transplantation (autoSCT). (A) Median OS of 360 patients with mantle cell lymphoma calculated from relapse after autoSCT was 19 months. (B) OS after autoSCT failure stratified by the progression-free interval after first autoSCT (≤12 months: solid line versus >12 months: dashed line), *P* < 0.001; hazard ratio (HR) 0.26; 95% confidence interval (95% CI) 0.18–0.36. (C) OS after autoSCT failure stratified by timing of first autoSCT (first line: solid line versus salvage SCT: dashed line), *P* = 0.006; HR 0.7; 95% CI 0.42–0.82. (D) OS after autoSCT failure stratified by refractory disease (sensitive: solid line versus refractory: dashed line) at autoSCT, *P* = 0.005; HR 1.93; 95% CI 1.03–3.06. (E) OS after autoSCT failure stratified by calendar year of relapse (2000–2003: solid line versus 2004–2007: dashed line versus 2008–2011: dotted line), *n* = 360. (F) OS calculated from the 3 month's landmark after autoSCT failure stratified by response to first-salvage regimen given for relapse (CR: solid line versus PR: dashed line versus SD/PD: dotted line), *n* = 212, *P* < 0.0001.
outcome after relapse

With a median observation time of 40 months [95% confidence interval (95% CI) 34–44 months], median OS after relapse of the whole study group was 19 months (95% CI 15–23 months, Figure 1A). Baseline patient and treatment variables were analysed to identify risk factors for OS after relapse. By univariate analysis, a long (>12 months) interval between autoSCT and relapse was associated with superior OS after relapse (P < 0.001, HR 0.26; Figure 1B). Similarly, first-line autoSCT (P = 0.006, HR 0.7; Figure 1C), refractory disease at autoSCT (P = 0.005, HR 1.9; Figure 1D) and calendar year of relapse (P < 0.0001, HR per year 0.88, 95% CI 0.83–0.92; Figure 1E) significantly influenced OS from relapse. The survival benefit of late relapse was also observed in the favourable subsets who achieved a CR and received an first-line autoSCT (P < 0.001, HR 0.20, 95% CI 0.13–0.34; P = 0.007, HR 0.38, 95% CI 0.15–0.96). In contrast, the year of first autoSCT, age, gender, high-dose AraC pre-treatment, rituximab pre-treatment (supplementary Figure S3, available at Annals of Oncology online) and the use of TBI did not significantly affect on survival after relapse.

Ki67 percentages of tumour biopsies were available for a small subset of 46 patients. Interestingly, a Ki67 percentage above 30% was associated with early relapse after autoSCT [P = 0.0027, odds ratio (OR) 8, 95% CI 2.06–31.12] and also poor survival after relapse (P = 0.0047, HR 2.90, 95% CI 1.52–5.56).

By multivariate analysis, refractory disease at autoSCT (HR = 1.92), remission duration after autoSCT (HR per 12 months 0.62) and calendar year of relapse starting from 2000 onwards (HR per year 0.92) were confirmed to be independent predictors for OS. In addition and in contrast to the results of the univariate analysis, high-dose AraC pre-treatment (P = 0.04, HR 1.43) adversely affected OS from relapse (Table 2).

salvage treatment of relapse after autoSCT

Information on first-salvage regimens that were used to treat relapse after autoSCT and corresponding responses were only available in 231 patients. The first-salvage regimen after relapse was predominantly chemotherapy based in 190 patients (82%, supplementary Table S2, available at Annals of Oncology online). Only a minority of patients were not treated (n = 4, 2%). As expected, the percentage of chemotherapy-refractory disease after autoSCT failure was much higher than before autoSCT. Only 8% of all relapsed patients had been chemo-refractory before first autoSCT. This proportion increased to 41% after post-transplant disease recurrence (supplementary Table S2, available at Annals of Oncology online) and was associated with a significantly worse survival (P < 0.0001; Figure 2F). In logistic regression analysis, only timing of autoSCT beyond first remission (0.0076, OR 2.36, 95% CI 1.26–4.44) was associated with chemotherapy-refractory disease after relapse, but not year of autoSCT, age, AraC-, Rituximab- or TBI-pre-treatment.

outcome of patients without rescue SCT

Two- and 5-year survival of all patients after autoSCT failure who did not receive an alloSCT were 37% (95% CI 32–44) and 16% (95% CI 9–23) (Figure 2A), respectively. A long remission duration after first autoSCT was again associated with a significant survival benefit (Figure 2B). Two-year survival in the subgroup of chemotherapy-sensitive patients with a progression-free interval of more than 1 year after first autoSCT was 82% (95% CI 71% to 92%) but dropped to 29% (95% CI 9% to 50%) at 5 years.

Of note, there was a small number of patients (n = 10) who survived longer than 5 years after relapse without alloSCT. To exclude the possibility that these patients had a primary diagnosis other than MCL, we were able to confirm the diagnosis of MCL in all of the nine long-term survivors who had a histology report available.

outcome of patients after rescue SCT

A rescue transplant was performed in 87 of 360 patients (24%). Only seven patients (2%) received a rescue autoSCT. Survival after relapse for these patients was poor. Five of seven patients rapidly relapsed after rescue autoSCT and died soon thereafter. Only one long-term survivor was observed after rescue autoSCT.

Eighty patients (22%) received an alloSCT for relapse after autoSCT (supplementary Table S3, available at Annals of Oncology online). The outcome of patients after rescue SCT was predominantly chemotherapy based in 57 patients (71%), supplementary Table S4, available at Annals of Oncology online). Only a minority of patients were not treated (n = 27, 34%). As expected, the percentage of chemotherapy-refractory disease after autoSCT failure was much higher than before autoSCT. Only 8% of all relapsed patients had been chemo-refractory before first autoSCT. This proportion increased to 41% after post-transplant disease recurrence (supplementary Table S2, available at Annals of Oncology online) and was associated with a significantly worse survival (P < 0.0001; Figure 2F). In logistic regression analysis, only timing of autoSCT beyond first remission (0.0076, OR 2.36, 95% CI 1.26–4.44) was associated with chemotherapy-refractory disease after relapse, but not year of autoSCT, age, AraC-, Rituximab- or TBI-pre-treatment.

Table 2. Multivariate cox regression analysis of patients (n = 80) who received an alloSCT after autoSCT failure

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Relapse</th>
<th>Non-relapse mortality</th>
<th>Overall survival</th>
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<tbody>
<tr>
<td></td>
<td>P</td>
<td>HR* 95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Age at alloSCT (10 years)</td>
<td>0.57</td>
<td>0.78 0.35–1.80</td>
<td>0.43</td>
</tr>
<tr>
<td>Donor (UD versus RD) reference category RD</td>
<td>0.41</td>
<td>0.67 0.26–1.76</td>
<td>0.12</td>
</tr>
<tr>
<td>TCD (TCD versus no TCD) reference category no TCD</td>
<td>0.27</td>
<td>0.59 0.24–1.49</td>
<td>0.65</td>
</tr>
<tr>
<td>Conditioning (RIC versus MAC) reference category RIC</td>
<td>0.32</td>
<td>0.63 0.26–1.55</td>
<td>0.20</td>
</tr>
<tr>
<td>Time to relapse (12 months)</td>
<td>0.05</td>
<td>0.67 0.44–0.99</td>
<td>0.58</td>
</tr>
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</table>

Relapse and non-relapse mortality were considered as competing risks.
*Sub-distribution hazard ratio.
HR, hazard ratio; CI, confidence interval; RD, related donor; UD, unrelated donor; TCD, T-cell depletion (anti-thymocyte globulin and alemtuzumab); MAC, myeloablative conditioning; RIC, reduced intensity conditioning.
Of note, the vast majority (91%) of patients proceeding to allografting did so after reaching PR or CR following salvage therapy. Most patients underwent alloSCT after one salvage therapy line (76%). Only 19% and 5% received two and three salvage attempts before alloSCT, respectively.

Median observation time after rescue alloSCT was 32 months (95% CI 19–41 months). Two- and 5-year survival after alloSCT was 46% (95% CI 33% to 59%) and 34% (95% CI 19% to 49%), respectively (Figure 2C). AlloSCT performed for late relapse (>12 months) after autoSCT was associated with superior OS compared with patients who received an allograft following a shorter remission duration after autoSCT (P = 0.01; HR 0.32; 95% CI 0.12–0.87).

Thus, 2- and 5-year survival in the subgroup of chemotherapy-sensitive patients with a progression-free interval of more than 1 year after first autoSCT was both 60% (95% CI 35% to 85%).

Relapse incidence and NRM 2 years after alloSCT was 33% (95% CI 21% to 45%) and 30% (95% CI 19% to 42%) respectively. Relapse incidence (P = 0.01, HR 4.3) but not incidence of NRM was significantly higher in patients with early relapse (≤12 months) after autoSCT (supplementary Figure S4A–D, available at Annals of Oncology online). Neither donor choice, T-cell depletion by ATG or alemtuzumab nor conditioning intensity had a significant influence on any end point incidence after alloSCT (Table 2).

**Figure 2.** Overall survival with and without allogeneic stem-cell transplantation. (A) OS after autoSCT failure of patients who never received an alloSCT, n = 280, 2-year survival after relapse was 37%. (B) OS after autoSCT failure of patients who never received an alloSCT stratified by the progression-free interval after first autoSCT (≤12 months: solid line versus >12 months: dashed line), n = 280, P < 0.001; HR 0.27; 95% CI 0.20–0.39. (C) OS after alloSCT carried out for relapse after autoSCT, n = 80, 2-year survival after alloSCT was 48%. (D) OS after alloSCT carried out for relapse after autoSCT stratified by the progression-free interval after first autoSCT (≤12 months: solid line versus >12 months: dashed line), n = 80, P = 0.001; HR 0.32; 95% CI 0.12–0.87.

**Discussion**

The results presented here confirm in a large cohort that the outcome of patients with MCL relapsing after autoSCT is generally dismal. With a median of 19 months, survival was in line with that observed in a small retrospective study, where the median OS after autoSCT failure was comparably poor at 23 months [4]. However, in contrast to our previous study which included patients of only three German referral centres, it has to be taken into account that surveillance strategies of all 82 participating centres of the current registry study are not known in detail which may lead to inaccuracies of calculating progression-free intervals. The present study demonstrates that outcome of MCL relapse after autoSCT has improved significantly over the last decade suggesting that relapse strategies for these patients have become more effective. Despite the advent of novel agents such as mTOR-, [5] proteasome- [6] or bruto-s-tyrosine kinase [7] inhibitors, the majority of patients reported in this study received a chemotherapy-based treatment as first-line therapy after autoSCT failure. As many as 40% of patients were refractory to the first-salvage treatment after auto-transplant when compared with only 8% chemotherapy-refractoriness before autoSCT within the same patient cohort. These results indicate that evolving chemotherapy-refractory MCL clones significantly
contribute to the poor outcome of MCL relapse after autoSCT. Validation of promising new therapeutic approaches, such as BH3-mimetics or B-cell receptor kinase inhibitors, is therefore urgently awaited [7].

High-dose ARA-C treatment before autoSCT has been suggested to improve outcome after autoSCT [2, 3], which was recently confirmed in a prospective randomized study [11]. In this context, the finding that high-dose ARA-C treatment was associated with a worse outcome after autoSCT failure is intriguing, suggesting an enrichment of the more aggressive clones in patients who relapse after high-dose ARA-C treatment. In contrast, rituximab pre-treatment was not associated with a survival disadvantage after autoSCT failure. However, it has to be taken into account that only 35 patients in our study did not receive rituximab prior autoSCT.

Twenty-four percent of patients in our retrospective study received a rescue SCT after initial autoSCT failure. Only seven patients received another autoSCT as second transplant, but there was only one long-term survivor among these patients. Although conclusions on only seven patients are difficult to draw, these results do not encourage a rescue autoSCT as reasonable salvage strategy in this situation. In contrast, a significant proportion of the 80 patients who underwent alloSCT as a rescue transplant achieved a durable remission. Single-centre experiences predominantly report better results with a 3-year OS of 59% in Heidelberg [4] or 65% in the Fred Hutchinson Cancer Research Center [12] and a 3-year OS of 85% in the MD Anderson Cancer Centre [13]. However, a follow-up study of MD Anderson Cancer Centre patients reported a 6-year survival of 53% after alloSCT [10]. In addition, multi-centre retrospective or registry studies report equivalent OS rates of 50% after 2 years or 37% [14] after 5 years [9].

Our analysis was not designed to evaluate if allogeneic transplantation is the optimum treatment strategy after autoSCT failure in MCL. Although alloSCT seems to be the only modality capable of providing sustained disease control in a significant proportion of patients in this setting, it must be kept in mind that patients receiving a secondary allotransplant most likely represent a favourable subgroup. Moreover, long-term remissions after alloSCT were almost exclusively seen in patients who have remained in remission for more than a year after autoSCT achieving a plateau at ~50%. Thus, it remains to be shown that alloSCT indeed is superior to non-transplant strategies in good-risk patients (e.g. chemosensitive late relapses in patients with transplant-eligible performance status). This is even more important in the emerging era of targeted molecular treatments for MCL [15]. In patients with a short progression-free interval of <12 months after first autoSCT, the benefit of an alloSCT is even less clear, albeit the 23% 3-year survival observed in our 13 patients is similar to that seen for patients undergoing alloSCT in a refractory state [16]. However, in the absence of prognostic indicators and established non-transplant therapies, an alloSCT should be considered for eligible patients with MCL recurrence more than 1 year after autoSCT.

In conclusion, patients with MCL who relapse within one year of an autoSCT have an extremely poor outcome even with alloSCT. In contrast, about half of the patients who have MCL recurrence beyond 1 year after autoSCT and can undergo salvage alloSCT experience long-term survival. It remains to be shown in future studies if a similarly good outcome can be achieved without alloSCT in this more favourable subgroup of patients. A second autoSCT does not appear to be a promising option in patients with MCL failing a first autoSCT.

disclosure

The authors have declared no conflicts of interest.

references