ORIGINAL RESEARCH ARTICLE

Prolonged survival after second autologous transplantation and lenalidomide maintenance for salvage treatment of myeloma patients at first relapse after prior autograft

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Abstract
Autologous stem cell transplantation (ASCT) as part of the primary therapy in multiple myeloma (MM) is standard practice. In contrast, the role of a second ASCT (ASCT2) and subsequent lenalidomide maintenance for relapsed disease remains unclear. In this study, we analysed 86 consecutive MM patients with a first relapse after prior ASCT receiving either a second ASCT or conventional chemotherapy. After a median follow-up of 37.7 months since first relapse, 54 (62.8%) patients were still alive and 29 (33.7%) without progression. Sixty-one (71.0%) patients received ASCT2 and had better progression-free survival (PFS) (30.2 versus 13.0 mo; \( P = .0262 \)) and overall survival (OS) rates (129.6 versus 33.5 mo; \( P = .0003 \)) compared with 25 (29.0%) patients with conventional treatment. Patients relapsing later than 12 months after ASCT1 benefitted from a second ASCT with better PFS2 (\( P = .0179 \)) and OS2 (\( P = .0009 \)). Finally, lenalidomide maintenance after ASCT2 was associated with longer PFS (41.0 vs 21.6 mo; \( P = .0034 \)) and better OS (not yet reached vs 129.6 mo; \( P = .0434 \)) compared with patients without maintenance. Our data suggest that a second ASCT and lenalidomide maintenance given at first relapse in MM after prior ASCT are associated with better survival rates.

KEYWORDS
autologous, chemotherapy, high-dose, lenalidomide, maintenance, myeloma, relapse, salvage, stem cell, survival, transplant

1 | INTRODUCTION

Autologous stem cell transplantation (ASCT) after high-dose melphalan chemotherapy (HDCT) is part of the first-line standard treatment algorithm for patients with symptomatic multiple myeloma (MM) up to the age of 70 years.\(^1\)\(^-\)\(^9\) With the incorporation of novel agents into this strategy, progression-free survival (PFS) and overall survival (OS) rates of such patients have markedly improved within the last decade.\(^10\)\(^-\)\(^15\) However, almost all patients with MM will ultimately relapse at some stage following initial therapy, the majority within 3 years after ASCT, and no plateau is observed in their OS.\(^2\)\(^,\)\(^3\)\(^,\)\(^6\)\(^,\)\(^16\)

The optimal treatment for MM patients relapsing after first-line treatment including ASCT is less clear. The introduction of a rapidly increasing number of novel compounds in the last decade has resulted in markedly improved response and survival rates in MM patients relapsing after prior autograft, thereby continuously enlarging the complexity of guidelines for the management of relapsed MM.\(^10\)\(^-\)\(^12\)\(^,\)\(^17\)

One treatment option (among others) for relapsing MM patients is a second ASCT, particularly when a frozen autograft is available, and several reports have demonstrated the feasibility of this strategy.\(^1\)\(^,\)\(^5\)\(^,\)\(^6\)\(^,\)\(^14\)\(^,\)\(^16\)\(^,\)\(^18\)\(^-\)\(^21\) However, such data are available mainly from retrospective single-centre studies reporting experiences from mostly small numbers of selected patients, with PFS rates ranging between 7 to 22 months.\(^1\)\(^,\)\(^18\)\(^,\)\(^22\) Prognostic factors associated with prolonged PFS in these reports included quality and duration of response to the first high-dose therapy (ASCT1), the number of lines of therapy before salvage ASCT (ASCT2), younger age, and lower β-2-microglobulin at diagnosis.\(^5\)\(^,\)\(^6\)\(^,\)\(^14\)\(^,\)\(^23\)\(^,\)\(^24\) The BSBMT/UKMF myeloma X trial for relapsed MM patients represents so far the only prospective study that compared salvage ASCT with continued conventional chemotherapy.
In this retrospective single-centre study, we compared consecutive MM patients who relapsed after first-line treatment including ASCT1 and who received salvage therapy consolidated either by a second ASCT (ASCT2) or by continued treatment including novel agents. Furthermore, we also assessed the effect of lenalidomide maintenance after salvage ASCT. Our data suggest that MM patients relapsing after prior ASCT benefit from salvage ASCT2 as compared with continued conventional treatment including novel agents. In addition, lenalidomide maintenance after ASCT2 was associated with longer PFS2 and OS2 rates.

2 | METHODS

2.1 | Patients

This retrospective single-centre study analysed patients with MM with a first relapse treated between 01/2002 and 12/2016 at the University Hospital Bern. Patients were eligible for the study if they had received melphalan-based HDCT with ASCT as part of their first-line treatment and subsequently had a first relapse as defined by either increasing myeloma parameters and/or occurrence of new myeloma-related organ damages including renal failure, anaemia, hypercalcaemia, or bone lesions. The centre followed a policy that myeloma patients with a remission duration of at least 24 months after the first ASCT should be offered the option of a second ASCT at first relapse. This study was approved by the ethics committee of Bern, Switzerland, with the decision number #381/15.

Patients were summarized in 2 cohorts. The +HD2 group comprised MM patients who received a second ASCT (ASCT2) for consolidation of salvage treatment, whereas MM patients in the −HD2 group were treated with continued conventional regimens including novel agents. Patients in the +HD2 group were further analysed whether they had lenalidomide maintenance until progression or intolerance (+HD2+R) or no maintenance treatment after ASCT2 (+HD2-R).

2.2 | Treatment

In relapsing patients without frozen autografts, non-myelosuppressive chemotherapy with vinorelbine or gemcitabine together with G-CSF was used for mobilization of autologous stem and progenitor cells. At least 3 × 10⁶ CD34+ cells/kg body weight (b.w.) were aimed to be collected per stem cell transplantation. Patients ≤70 years were administered full-dose melphalan (200 mg/m²), whereas patients above 70 years received a reduced dose (140 mg/m²). The dose of melphalan was lowered to 140 mg/m² for patients with reduced renal function with a creatinine-clearance between 40 and 50 mL/min, and to 100 mg/m² for patients with a creatinine-clearance below 40 mL/min.

2.3 | Definitions

OS2 was assessed from the beginning of relapse treatment until death of any cause or last follow-up. PFS2 was calculated from the beginning of relapse treatment until disease progression or death, whichever occurred first. Response to treatment was assessed according to the European Group for Blood and Marrow Transplantation Criteria and to the criteria of the International Myeloma Working Group. Accordingly, complete remission (CR) was defined as a negative immunofixation in serum and urine and less than 5% plasma cells in the bone marrow. A ≥90% reduction of serum M-protein and urine M-protein <100 mg per 24 hours or a serum and urine M-protein detectable only by immunofixation, but not electrophoresis, was defined as very good partial response (VGPR); and a reduction of ≥50% of serum M-protein was considered partial response (PR). Progression (PD) was defined as an increase of at least 25% in measurable monoclonal immunoglobulin in serum or urine or an increase of ≥25% in urinary light chains.

2.4 | Statistical analysis

The analysis of PFS and OS was calculated using the Kaplan-Meier method. The log-rank method was performed for comparison of survival. Comparisons of median values between 2 groups were analysed using the Mann-Whitney test, and the Kruskal-Wallis test was applied for comparisons of 3 groups. The correlation of 2 variables was assessed by the rank-based estimation for linear models and multivariate analysis. All reported P values were 2-sided, and P values below .05 were considered significant. The statistical analysis was performed applying GraphPad Prism Version 7.0 (GraphPad Software, La Jolla, California).

3 | RESULTS

3.1 | Patients

We included all 86 MM patients who relapsed after a single high-dose melphalan-based chemotherapy with ASCT and received salvage treatment between 01/2002 and 12/2016 at the University Hospital Bern, Switzerland. Patient characteristics at first diagnosis of MM are summarized in Table 1. The median age at first diagnosis of MM was 58 years with a range from 30 to 68 years.

3.2 | Relapse after ASCT1

The median duration between ASCT1 and first relapse was 28.9 months (range, 2.8-187.5) in the +HD2 group as compared with the −HD2 group with only 14.3 months (0.9-58.6 mo, respectively; \( P = .0012 \)). Thus, ASCT2 was rather given to relapsing myeloma patients with a longer remission duration after ASCT1 and with better response rates after ASCT1 (CR1 in 67% vs 36%; \( P = .0151 \)), whereas other parameters were comparable as summarized in Tables 1 and 2. Diagnosis of relapse was based on progressive myeloma parameters (M-gradient and/or involved light-chain) in 70 patients (81%), new osteolytic lesions (17 pts; 20%), and myelosuppression because
of bone marrow infiltration (23 pts, 27%) as depicted in Table 2. All re-induction regimens were either bortezomib- or lenalidomide-based.

### Outcome after the second ASCT (ASCT2)

Sixty-one (71%) patients (+HD2) received a second ASCT at relapse, and 25 (29%) patients (−HD2) had conventional treatment without ASCT2. The conditioning chemotherapy with melphalan and the transplantation procedure applied for ASCT2 were identical as for first-line HDCT/ASCT. The median duration between ASCT1 and ASCT2 was 38 (8-192) months, and the median age of the patients at ASCT2 was 60 years (37-73). A median of 3.6 × 10⁶/kg CD34+ stem and progenitor cells were transplanted, which was similar as in ASCT1. After median 11 days, neutrophils recovered above 0.5 × 10⁹/L, and after 12 days, the platelet levels exceeded 20 × 10⁹/L (Table 3).

The further course of the disease differed between the 2 groups: After a median follow-up of 37.7 months since the first relapse, 54 (62.8%) patients were still alive, and 29 (33.7%) patients remained without second progression (Table 2). The PFS (PFS2) after start of relapse treatment until progression or second relapse was better in the +HD2 group with 30.2 months compared with 13 months in the −HD2 group (Figure 1A; P = .0262). Also, a better OS of 129.6 months was observed in the +HD2 group compared with 33.5 months in the −HD2 group (Figure 1B; P = .0003). There was no treatment-related mortality associated with the ASCT2. After ASCT2, 16 (26%) patients reached a CR2, 16 (26%) had VGPR2, 11 (18%) had PR2, and 1 patient (2%) had PD2, whereas the definite information on the remission

### Table 1 Patient characteristics at first diagnosis and at first ASCT (HDCT1 and ASCT1)

<table>
<thead>
<tr>
<th></th>
<th>Group −HD2 (N = 25)</th>
<th>Group +HD2 (N = 61)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, median (range)</td>
<td>58 (30-68)</td>
<td>57 (32-67)</td>
<td>n.s.</td>
</tr>
<tr>
<td>MM subtype</td>
<td></td>
<td></td>
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<tr>
<td>IgG, n (%)</td>
<td>14 (56)</td>
<td>38 (62)</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgA, n (%)</td>
<td>7 (28)</td>
<td>15 (25)</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgM, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>Kappa light chain, n (%)</td>
<td>11 (44)</td>
<td>42 (69)</td>
<td>.0497</td>
</tr>
<tr>
<td>Lambda light chain, n (%)</td>
<td>14 (56)</td>
<td>18 (30)</td>
<td>.0279</td>
</tr>
<tr>
<td>Asecretory, n (%)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>...</td>
</tr>
<tr>
<td>Light chain only, n (%)</td>
<td>4 (16)</td>
<td>7 (11)</td>
<td>n.s.</td>
</tr>
<tr>
<td>BM infiltration, median % (range)</td>
<td>70 (20-100)</td>
<td>65 (10-100)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hypercalcaemia, n (%)</td>
<td>5 (20)</td>
<td>12 (20)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Renal failure, n (%)</td>
<td>9 (36)</td>
<td>19 (31)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Median creatinine, μmol/L</td>
<td>103.5</td>
<td>94.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anaemia, n (%)</td>
<td>9 (36)</td>
<td>11 (18)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Median Hb, g/L</td>
<td>97</td>
<td>108</td>
<td>n.s.</td>
</tr>
<tr>
<td>Osteolytic lesion, n (%)</td>
<td>20 (80)</td>
<td>46 (75)</td>
<td>n.s.</td>
</tr>
<tr>
<td>β2-microglobulin &gt; 3.5 mg/L, n (%)</td>
<td>11 (44)</td>
<td>21 (34)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL, n (%)</td>
<td>7 (28)</td>
<td>12 (20)</td>
<td>n.s.</td>
</tr>
<tr>
<td>LDH, median U/L</td>
<td>396</td>
<td>328</td>
<td>n.s.</td>
</tr>
<tr>
<td>Collected stem cells, median (range)</td>
<td>10 (4-24)</td>
<td>10.9 (2-41)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Transplanted stem cells, median (range)</td>
<td>3.5 (2-10)</td>
<td>3.7 (2-9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Haematological recovery in days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils &gt;0.5 G/L, median (range)</td>
<td>12 (10-28)</td>
<td>12 (10-17)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Platelets &gt;20 G/L, median (range)</td>
<td>14 (0-30)</td>
<td>13 (0-24)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Remission after ASCT1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>...</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>7 (28)</td>
<td>4 (7)</td>
<td>.0120</td>
</tr>
<tr>
<td>VGPR, n (%)</td>
<td>8 (32)</td>
<td>15 (25)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>9 (36)</td>
<td>41 (67)</td>
<td>.0151</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>...</td>
</tr>
<tr>
<td>Maintenance with lenalidomide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After ASCT1, n (%)</td>
<td>9 (36)</td>
<td>18 (30)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration, months (range)</td>
<td>6.1 (1-23.3)</td>
<td>10.2 (2-32.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Relapse during maintenance, n (%)</td>
<td>7 (28)</td>
<td>10 (16)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Anaemia, Hb < 100 g/L; ASCT, autologous stem cell transplantation; BM, bone marrow; collected/transplanted stem cells, ×10⁶/kg/KG; CR, complete remission; Hb, haemoglobin; hypercalcaemia, calcium > 2.6 mmol/L; IgG/IgA/IgM, immunoglobulin type G, A, M; LDH, lactate dehydrogenase; n.s., not significant; PD, progressive disease; PR, partial remission; SD, stable disease; VGPR, very good partial remission.
status after ASCT2 remained unclear in 17 (28%) patients because the concept of VGPR was not yet introduced in the early years of the study period (Table 3).

### 3.4 Outcome depending on interval between ASCT1 and first relapse

In patients with a first relapse occurring before 12 months after ASCT1 (17 patients; 20%), the median PFS2 rates were 21.9 months (+HD2) and 7 months (−HD2) (Figure 2A; P = .2895), and the median OS rates were 37.1 months (+HD2) and 10.5 months (−HD2) (Figure 2B; P = .3900), respectively. For patients relapsing before 18 months after ASCT1, the PFS rates were 22 months and 13 months (Figure S2A; P = .1268), and the OS rates were 62.6 months and 24.9 months (Figure S2B; P = .0524), respectively. Patients with a PFS1 longer than 18 months had better PFS2 rates in the +HD2 group with 30.3 months versus 13.9 months (Figure 2E; P = .0731), and the OS rates were 165 months and 45.7 months (Figure 2F; P = .256).

In patients relapsing between 12 and 18 months after ASCT1, PFS was not different while we observed a better OS in the +HD2 group (129.6 months) compared with 35.15 months (P = .0358) in the −HD2 group (Figure 2C,D). Finally, significant differences for PFS2 and OS2 were identified for all patients with PFS1 longer than 12 months since ASCT1: The median PFS2 rates were 30.3 months (+HD2) and 15 months (−HD2) (Figure S1A; P = .0179), and the median OS rates were 129.6 months (+HD2) and 40.8 months in −HD2 patients (Figure S1B; P = .0009). These data propose that patients relapsing later than 12 months after ASCT1 have better survival rates if treated again with (salvage) ASCT2 after prior ASCT.

### 3.5 Lenalidomide maintenance after ASCT2

Twenty-seven of 86 patients (31%), including 18 of 61 +HD2 patients (30%) and 9 of 25 −HD2 patients (36%), received lenalidomide maintenance after first-line ASCT, with a median treatment duration of 8.3 (1-32.4) months. In the −HD2 group, 7 of 9 patients (78%) relapsed during first-line lenalidomide maintenance compared with 10 of 18 (56%) in the +HD2 group (P = .0434). At first relapse, 28 of 61 patients (46%) received lenalidomide maintenance treatment (+HD2+R) after ASCT2, and 33 patients (54%) had no lenalidomide maintenance after ASCT2 (+HD2-R). Lenalidomide maintenance after ASCT2 (vs no maintenance after ASCT2) was associated with longer PFS2 (41 mo vs 21.2 mo; Figure 3A; P = .0034) and better OS2 (not yet reached vs 129.6 mo; Figure 3B; P = .0434), respectively.

The patient characteristics at initial diagnosis of MM in the 2 groups +HD2−/+R were comparable, with both groups achieving similar remission rates after ASCT1 (Table S1). More patients in the +HD2-R group previously had already lenalidomide maintenance after ASCT1 (15 of 33 patients, 45%) compared with the +HD2+R patients (3 of 28 patients, 11%). The time to first relapse after ASCT1 was not different between the +HD2-R and the +HD2+R groups. The median duration until second progression after start of relapse treatment was shorter...
in +HD2 R patients with 19.6 (5.3–85.8) months compared with 25.3 (18.5–57.2) months in +HD2+R patients, respectively (Table 2). A total of 12 (43%) of the 28 +HD2+R patients received lenalidomide already at least once before ASCT2, either as maintenance after ASCT1 (3 patients) or as part of their re-induction treatment (9 patients). Compared with the 16 (57%) +HD2+R patients, who never had lenalidomide before ASCT2, no differences assessed from the time of ASCT2 for PFS (P = .741) and OS (P = .7679) were observed (Figure S3A,B).

Furthermore, we compared patients with ASCT2 but without subsequent lenalidomide maintenance (n = 33) with patients without ASCT2 (n = 25) and without lenalidomide maintenance to analyse whether ASCT2 per se improved the outcome independently from subsequent lenalidomide maintenance. We found that PFS rates were 21 months (+HD2-R) and 13 months (-HD2-R; Figure 3C; P = .6348), and OS was 129.6 months and 33.5 months (Figure 3D; P = .0250), respectively.

Finally, we performed a multivariate analysis for OS (Table S2) including the following factors: Age above 60 years, ASCT2 given, CR2/VGPR2 achieved after salvage treatment before ASCT2, gender, year of start of salvage treatment for first relapse before 2012 versus after 01/2012; and lenalidomide maintenance given as part of treatment of first relapse. The analysis indicated that ASCT2 (P = .031), lenalidomide maintenance (P = .018), and the achievement of at least VGPR2 after salvage treatment before ASCT2 (P = .027) were independent risk factors for better OS.

### Discussion

Multiple myeloma remains an incurable disease for most patients. For younger MM patients, the standard of care for first-line treatment involves induction therapy consolidated with HDCT and autologous peripheral blood stem cell (ASCT) rescue followed by maintenance treatment. Almost all patients with MM will relapse following initial therapy, the majority within 3 years after an ASCT. The role of a second ASCT (ASCT2) for relapse treatment is less established. Clinicians opting for ASCT2 after re-induction therapy face the dilemma of lacking randomized controlled trial data or a systematic outcome analysis in this setting. Consequently, there is a lack of clear guidance and criteria for selection of patients who may benefit from this approach. Results reported in this retrospective single-centre analysis of MM patients with a first relapse after prior ASCT indicate that a second ASCT after re-induction therapy face the dilemma of lacking randomized controlled trial data or a systematic outcome analysis in this setting. Consequently, there is a lack of clear guidance and criteria for selection of patients who may benefit from this approach. Results reported in this retrospective single-centre analysis of MM patients with a first relapse after prior ASCT indicate that a second ASCT after re-induction therapy face the dilemma of lacking randomized controlled trial data or a systematic outcome analysis in this setting. Consequently, there is a lack of clear guidance and criteria for selection of patients who may benefit from this approach. Results reported in this retrospective single-centre analysis of MM patients with a first relapse after prior ASCT indicate that a second ASCT after re-induction therapy face the dilemma of lacking randomized controlled trial data or a systematic outcome analysis in this setting.

![Kaplan-Meyer survival curves comparing (A) progression-free survival and (B) overall survival of multiple myeloma patients receiving ASCT2 at relapse (green line) and multiple myeloma patients without ASCT2 at relapse (black line). Progression-free survival (A) and overall survival (B) are calculated since start of relapse treatment.](Colour figure can be viewed at wileyonlinelibrary.com)
Until recently, treatment of MM patients with a first relapse comprised either lenalidomide/dexamethasone (RD) or bortezomib/dexamethasone (VD) based combinations. However, lenalidomide and bortezomib are both applied in frontline treatment, and many patients become resistant to these agents early in the course of their disease. In addition, a substantial number of new second-line agents including pomalidomide, carfilzomib, ixazomib, panobinostat, elotuzumab, and daratumumab offer alternative treatment options for relapsing patients. Furthermore, randomized studies have indicated that triple combinations incorporating one of these new agents to the RD or VD regimens were superior to the double combinations in terms of response rate and PFS.38-44 The choice of the appropriate salvage regimen is usually aiming at achieving best PFS, and it is based on lenalidomide/bortezomib resistance, availability of the compounds, and costs. In this treatment landscape, ASCT2 can be considered in younger patients if not used upfront, but also after prior autograft. In this study, we present the outcome of a large cohort of MM patients relapsing after prior ASCT who underwent an ASCT2 as part of their salvage management, and we compared them to a cohort of MM patients with a first relapse treated with RD- or VD-based regimens during the same period at our institution. We observed that a second ASCT demonstrated superior PFS and OS compared with chemotherapy treatment alone, with a PFS2 of 30.2 months and an OS of 129.6 months after initiation of relapse treatment. Importantly, these survival rates compare not only very favourably with previously published small studies in this setting6,14,18,22,35,36 but also to the results

**FIGURE 2** Kaplan-Meyer survival curves comparing (A, C, E) progression-free survival and (B, D, F) overall survival of multiple myeloma patients with (green line) or without (black line) ASCT2, relapsing before 12 months, within 12 to 18 months, and later than 18 months after ASCT1. Progression-free survival (A, C, E) and overall survival (B, D, F) are calculated since start of relapse treatment [Colour figure can be viewed at wileyonlinelibrary.com]
of randomized studies investigating prolonged administration of triple combinations involving novel compounds as described above.38-44

We found that the time to progression (TTP) after the first ASCT was the most important factor predicting both PFS and OS after diagnosis of relapse, which is consistent with previous reports of salvage ASCT.6,14,16,18,21-23,37,45 In our group of patients, an initial TTP after ASCT1 of less than 12 months was associated with a median survival of only 37.1 months, compared with 129.6 months in patients with an initial TTP of at least 12 months. This is consistent with other reports of ASCT2, where TTP after first remission of 12, 18, or 24 months was identified as a prognostic parameter. A similar observation was made in our cohort where a TTP of less than 12 months after ASCT1 was predictive of shorter OS irrespective of subsequent therapies (ASCT2 or non-transplant treatment) given at relapse. Finally, it is not surprising that patients achieving a CR after ASCT2 tended to benefit the most in terms of duration of response in our cohort.

The benefit of a second lenalidomide maintenance treatment after ASCT2 given to treat first relapse after prior autograft followed already by lenalidomide maintenance is hardly studied.14,46 One might argue that repeating an identical approach might promote outgrowth of resistant myeloma subclones. Our results indicate that patients relapsing after prior autograft with or without lenalidomide maintenance both benefit from lenalidomide maintenance after ASCT2 for PFS (P = .0034) and OS (P = .0434). We found a PFS rate of 41 months vs 21.6 months and an OS rate not yet reached vs 129.6 months. This result is consistent with previous studies suggesting that lenalidomide maintenance after salvage ASCT favorably affects the duration of response,14,46 whereas others failed to demonstrate this effect.6 An interesting observation of our study was that patients with previous lenalidomide maintenance similarly benefitted from a second lenalidomide maintenance as patients receiving lenalidomide maintenance only after ASCT2.

Given the obvious limitations of the retrospective design of our analysis and the selection bias of a single-centre study, we cannot ultimately compare the outcomes among those who had an ASCT2 with those who had non-ASCT-based salvage therapies. However, our data suggest a significant benefit of ASCT2 given after prior ASCT, but the small patient numbers in our study do not allow to draw definite conclusions. Furthermore, because of its retrospective nature, this study does not provide any information regarding quality of life issues that would be crucial in deciding between ASCT2 and non-ASCT options. Hence, when balancing the decision between ASCT2 for relapsed myeloma in comparison with other salvage treatment options, the answer remains unclear and difficult to discern in the absence of comparative trials. Until then, we can use studies such as ours to assist in this decision process.

In conclusion, we consider that ASCT2 has a favourable risk/benefit profile, and it should be considered as an option in relapsed/refractory patients who have had at least a 12-month disease-free interval after ASCT1. However, the debate on the role of an ASCT2 versus novel agents as salvage therapy in relapsed disease continues. Even though it is neither appropriate nor effective in comparing results from different studies, the overall response rates of ASCT2 in our study was 97%, which is comparable to those reported with prolonged use of salvage regimens with novel agents. Hence, with comparable efficacy between novel agents and ASCT2, it is crucial to offer therapies that
strike a balance between intensity and duration of therapy with the goal of reducing toxicity. ASCT2 has an initial risk of significant toxicity, but it may also provide the potential of having a shorter time of treatment in appropriately selected patients. On the other hand, novel agents are associated with a higher risk of grade III or IV toxicities such as neuropathy, myelosuppression, thrombosis, and others. Hence, providers and patients may prefer the transient toxicity associated with ASCT2 in place of the continuous toxicities of novel agents. There is no evidence that the efficacy of future novel agent salvage therapies may be compromised by the prior sequence of salvage transplantation therapy. Moreover, with the increasing cost of novel agent-based regimens in terms of drugs and prophylaxis costs, considering an ASCT2 as a salvage regimen could be cost-effective and safe while at the same time capable of providing durable benefit in appropriately selected patients such as those who have had a prolonged TTP after their ASCT1.

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**CONFLICT OF INTEREST**

All authors declare no conflict of interest.

**AUTHORSHIP AND CONTRIBUTION**

U.G. performed research and analysed data; B.J., U.N., D.B., T.E., and T. Z. contributed vital material; B.M. and U.B. contributed vital data; T.P. designed research and analysed data; all authors participated in drafting or reviewing the report, and all authors approved the submitted version.

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**REFERENCES**


SUPPORTING INFORMATION

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