Which is the best treatment strategy before autologous peripheral blood stem cell transplantation in POEMS syndrome?

by Francesco Autore, Stefania Bramanti, Federica Lessi, Idanna Innocenti, Eugenio Galli, Serena Rocchi, Rossella Ribolla, Daniele Derudas, Stefania Oliva, Paola Stefanoni, Magda Marcatti, Angelo Schenone, Giorgio La Nasa, Claudia Crippa, Elena Zamagni, Marcello Riva, Rita Mazza, Daniele Mannina, Simona Sica, Andrea Bacigalupo, and Luca Laurenti

Received: June 12, 2023.
Accepted: August 21, 2023.

Citation: Francesco Autore, Stefania Bramanti, Federica Lessi, Idanna Innocenti, Eugenio Galli, Serena Rocchi, Rossella Ribolla, Daniele Derudas, Stefania Oliva, Paola Stefanoni, Magda Marcatti, Angelo Schenone, Giorgio La Nasa, Claudia Crippa, Elena Zamagni, Marcello Riva, Rita Mazza, Daniele Mannina, Simona Sica, Andrea Bacigalupo, and Luca Laurenti. Which is the best treatment strategy before autologous peripheral blood stem cell transplantation in POEMS syndrome?

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in a regular issue of the journal. All legal disclaimers that apply to the journal also pertain to this production process.
Which is the best treatment strategy before autologous peripheral blood stem cell transplantation in POEMS syndrome?

Francesco Autore*1, Stefania Bramanti*2, Federica Lessi3, Idanna Innocenti1, Eugenio Galli1, Serena Rocchi4, Rossella Ribolla6, Daniele Derudas7, Stefania Oliva8, Paola Stefanoni9, Magda Marcatti10, Angelo Schenone11,12, Giorgio La Nasa7, Claudia Crippa6, Elena Zamagni4,5, Marcello Riva3, Rita Mazza3, Daniele Mannina3, Simona Sica1,13, Andrea Bacigalupo1,13, Luca Laurenti1,13

* equally contributed

1 Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Roma,
2 Istituto Clinico Humanitas IRCCS, Rozzano,
3 Azienda Ospedale Università Padova, Padova,
4 IRCCS Azienda Ospedaliere-Universitaria di Bologna, Istituto di Ematologia “Seràgnoli”, Bologna,
5 Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna,
6 Spedali Civili, Brescia,
7 SC di Ematologia e CTMO - Oncologico Oncologico di Riferimento Regionale "A. Businco" - ARNAS "G. Brotzu" - Cagliari,
8 S. Giovanni Battista, Torino,
9 ASST Papa Giovanni XXIII, Bergamo,
10 San Raffaele, Milano,
11 Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal and Infantile Sciences (DINOGMI), University of Genoa
12 IRCCS San Martino Hospital, Genova
13 Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma.

Abstract word count: 232
Text word count: 2263
Number figures: 1
Number tables: 3
Short running title: Treatment strategy before aPBSCT in POEMS

Keywords: POEMS, aPBSCT, mobilization, cyclophosphamide

Authors’ contributions: FA and LL performed research, SB FL II SR RR DD SO PS MM AS GLN CC EZ MR DM collected data, EG performed data analysis, FA EG AB and LL wrote the manuscript, SB SS AB supervised the study.

Correspond to:
Francesco Autore, MD, PhD
Fondazione Policlinico Universitario A. Gemelli IRCCS,
Largo Agostino Gemelli 8, I-00168 Rome, Italy.
Phone number: +39-06-30155300
Fax number: +39-06-3017319
Abstract
Autologous peripheral blood stem cell transplantation (aPBSCT) provides optimal outcomes in POEMS syndrome but the definition of the best treatment before aPBSCT remains to be defined, because of the disease rarity and the heterogeneity of published case series.
We collected clinical and laboratory data of patients with POEMS syndrome undergoing aPBSCT from 1998 to 2020 in 10 Italian centres. The primary endpoint of the study was to evaluate the impact of prior therapies and mobilizing regimen on outcome.
We divided patients in three groups: patients who did not receive any treatment before transplant (15 patients, group A: front-line), pre-treated patients with other agents (14 patients, group B) and patients treated with cyclophosphamide as mobilizing regimen (16 patients, group C). The three groups did not show differences in terms of demographic and clinical characteristics.
All 45 patients underwent aPBSCT after high dose melphalan conditioning regimen, with a median follow-up of 77 months (37-169 months). The responses were not statistically different between the 3 groups (p 0.38). PFS and OS rates at 6 years were 65% (49-85) and 92% (84-100), respectively and did not differ in the 3 groups. The cumulative incidence of transplant related mortality and relapse was respectively 4% and 36%.
In conclusion, in a relatively large number of patients with POEMS syndrome, undergoing an autologous transplant, pre-treatment and disease status at transplant did not appear to have an impact on major transplant outcomes.

Introduction
POEMS syndrome is a rare paraneoplastic condition associated with an underlying plasmacellular disorder. The acronym POEMS referred to the main features of this syndrome: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma-cell disorder, and skin changes.\(^1\-3\)

Treatment recommendations are based on limited trial data: the disease is so rare that literature consists mainly of small retrospective studies or case series.
Main experience in the treatment has been with alkylating-based therapy with autologous peripheral blood stem cell transplantation (aPBSCT). Reports on the use of cyclophosphamide-based therapies are interesting with excellent hematologic clinical responses, good achievement of neurologic improvement and also vascular endothelial growth factor (VEGF) reduction allowing optimal progression-free survival (PFS) and overall survival (OS).\(^4\-16\)
For patients fit to undergo a transplant, in the absence of organ dysfunction, high dose chemotherapy and aPBSCT appear to be the best strategy. The dose of melphalan in the conditioning has ranged from 140 to 200 mg/m\(^2\), with very high and long-lasting responses, though relapses have also been reported.\(^10,11,15,17-21\) Tandem transplant has been applied
anecdotally, and few information are available regarding any added value of the second transplant.  

For unfit patients, for whom high-dose chemotherapy is not recommended, many therapeutic approaches have been suggested, included steroids, low-dose alkylating agents associated with steroids or radiotherapy.

Other promising treatments are lenalidomide, thalidomide, bortezomib, and drugs with anti-VEGF and anti-TNF effects. Single agent intravenous immunoglobulin and plasmapheresis are not helpful to cure patients with POEMS syndrome.

A recent retrospective study on the best first-line treatment in POEMS, conducted on 347 patients focused the attention on three options: melphalan plus dexamethasone, aPBSC or lenalidomide plus dexamethasone. The highest response rates were seen with aPBSC, followed by lenalidomide plus dexamethasone, and melphalan plus dexamethasone. Although all these three treatments had reasonable responses and survivals, patients at higher risk may benefit more from aPBSC.

In the setting of aPBSC, reports on clinical outcome of patients with advanced disease and poor performance status are few and appropriate patient selection remains an important issue regarding the risk-benefit ratio associated with the procedure.

The best protocol to collect PBSC in patients with POEMS syndrome remains to be defined because the efficacy of different treatments has not previously been compared in large patient cohorts, and the rarity of the disease makes it difficult to conduct randomized controlled trials. Cyclophosphamide plus granulocyte colony stimulating factor (G-CSF) mobilizes more CD34+ cell and reduces incidence of engraftment syndrome in patients with POEMS syndrome, although it potentially increases the risks related to the procedure, without a significant tumour mass reduction.

Several published series reported successful mobilization and collection through chemo-mobilization, as well as with the use of the G-CSF alone. Because of the disease rarity and the heterogeneity of published case series the best treatment before aPBSC remains to be defined. Therefore, we decided to collect data on patients with POEMS syndrome underwent to aPBSC in different Italian centres to evaluate response and survival of the treatment before the transplantation and of the transplant itself.

Methods

We collected clinical and laboratory data of patients with POEMS syndrome from 10 Italian centres, including all the consecutive patients who underwent to aPBSC from January 1998 to December 2020.

We divided our population in 3 different groups: patients who did not receive any treatment before transplant (group A, front-line), pre-treated patients with other agents (group B) and patients treated with cyclophosphamide as mobilizing regimen (group C).

Before transplant patients of group A received G-CSF 10 mg/kg/day alone for 5 consecutive days as mobilizing regimen; patients of group C cyclophosphamide 2-4 g/m² followed by G-CSF 5 mg/kg/day. Group B included patients treated with Len-Dex (lenalidomide 10–25 mg on days 1–21, dexamethasone 40 mg on days 1, 8, 15, 22), Vel-Dex (bortezomib 1 mg/m² on days 1, 4, 8 and 11, plus dexamethasone 20 mg on days 1–4 and 8–11) or radiotherapy; all these patients were mobilized with G-CSF 5-10 mg/kg/day for 5 consecutive days.
Patients of all the groups were treated with melphalan as conditioning regimen at the dose of 140–200 mg/m\(^2\). G-CSF was used after transplant from day +6 to engraftment of neutrophils \(>1000/mmc\). No patient received maintenance therapy after aPBSCT. All patients provided informed consent. The study was approved by the Institutional Review Board and conducted following the ethical guidelines of the Declaration of Helsinki.

Patients were evaluated for responses (clinical, hematologic, and radiologic), toxicity, PFS and OS. Hematologic response was defined by the response criteria for POEMS syndrome. Complete remission (CR) was assessed by negative bone marrow, negative immunofixation of the serum and of the urine, normalized VEGF; very good partial remission (VGPR) was defined by 90\% reduction in M-protein or immunofixation positive only as long as M-protein was at least 0.5 g/dL at baseline, VEGF improved by at least 50\%; partial remission (PR) by 50\% reduction in M-protein or immunofixation positive as long as baseline M-protein was at least 1.0 g/dL. Progressive disease (PD) was assessed by more than 50\% increase in these proteins or the reappearance of the proteins after CR; stable disease (SD) was considered as all the statuses other than CR, VGPR, PR, and PD.

A first evaluation of the response was made before transplantation for group B and C. After the transplant we evaluated the best response for patients of all the groups using clinical, serologic and radiologic exams.

Toxicities were defined per the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0).

**Statistical analysis**

PFS was the time from treatment to recurrence, the reappearance of clinical symptoms, or death. OS was defined as the time from treatment to death. Patients lost to follow-up were censored on the day of the last follow-up visit.

The chi square test, or Fisher's exact test when appropriate, was used to determine the significance of differences in the values of categorical variables. Continuous variables were compared by discrete categorization variables (e.g. groups) using the Equal-Variances T-test or with the Mann-Whitney test if the distribution was not normal. p-values < 0.05 were considered significant. Cut-off determination for a continuous variable to predict an event was explored with the ROC analysis. PFS and OS were calculated with Kaplan-Meier log-rank test. Tests were performed with NCSS 2020 Statistical Software (2020). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ncss.

**Results**

Our data set consisted of 45 patients with POEMS syndrome who underwent aPBSCT; patients’ baseline characteristics are shown in Table 1. The median age at the time of the diagnosis was 53 years (range 38-71); 49\% were men. Polyneuropathy was present in all the patients, gammopathy in 95\% of the patients (monoclonal IgA in 64\%).

We conducted the analysis dividing the cohort in 3 different subgroups: 15 patients in group A, 14 patients in group B and 16 patients in group C. No differences were shown in terms of demographic and clinical characteristics, except for the level of haemoglobin (lower in group A) and white blood cell counts (higher in group C), as shown in Table 2.

Data on stem cell mobilization showed a median of collected CD34+ cell of 5.98 x10\(^6\)/kg overall (6.4 for group A, 6.2 for group B and 5.3 for group C, p=0.11) with a median of one single procedure per mobilization (range 1-3). Use of plerixafor was allowed but it was necessary in only
7 patients (3 of group A and 4 of group B). The procedure was generally good in terms of effectiveness and safety in all the groups.

Evaluation of response before transplant highlighted that the patients achieved VGPR in 14% and 13%, PR in 29% and 25% of the cases of group B and C, respectively, achieving a good response rate by the treatment before aPBSCT.

Data on conditioning and transplantation are represented in Table 3. Use of Mel200 was the choice in 87% of the patients, other 6 patients were conditioned with Mel140 for physician choice based on patients’ fitness status.

aPBSCT was complicated by febrile neutropenia in 62% of all the patients, gastrointestinal toxicity in 47% and infections in 42%; a median of 2 red blood cells unit/patient (range 0-13) and 3 platelets unit/patient (range 0-10) was the transfusion need during the hospitalization. Polymorphonuclear PMN counts >500 x10⁹/L were reached at a median of 14 days, platelets count >25 x10⁹/L at a median of 14 days. Median days of hospitalization after transplantation were 22 days (range 13-69). No significant differences were noted between the three groups in terms of complications, toxicity, blood support, engraftment and hospitalization.

The best response rates after aPBSCT were as follow: CR in 46%, VGPR in 23%, PR in 18%, SD in 8% and PD in 5% evaluated at a median time of 5.5 months (95% range 5.3-19). When comparing the response rate (CR vs VGPR/PR vs SD/PD) between the 3 groups any difference was found (p = 0.38). Considering that patients of group A were not treated before transplant and the outcomes were similar in the 3 subgroups, we did not find significant difference also when evaluating patients in responsive versus progressive disease at transplant. In 10 cases it was necessary a re-admission in hospital: in 5 cases for relapse and in 5 for infectious complications.

Median follow-up was 77 months (range 37-169): seventeen patients (37.8%) experienced disease progression without a statistical difference between the three groups. The overall 6-year PFS rate was 70% (CI 55-85). The 3 groups did not show significant differences; there was a tendency to unfavourable PFS for patients of group C (PFS at 6 years of 63% for group C vs 78% for group A and 68% for group B; p = 0.3), but no variable was found to negatively affect PFS, neither the treatment chosen before transplantation (Fig 1a).

Overall 6-year TTR was 73% and did not differ among the treatment groups (p=0.29) (Fig. 1b). The retreatment choice was lenalidomide plus dexamethasone in most of the cases (12 out of 17 patients); other choices were cyclophosphamide, radiotherapy, daratumumab added to lenalidomide and steroids or rituximab.

Overall 6-year OS was 91% and it did not differ among the treatment groups (p=0.35) (Fig. 1c). Seven out of 45 patients (15.6%) died, 4 for progressive disease and 3 for transplant infectious complications.

**Discussion**

Our data showed that pre-transplant therapy, both cyclophosphamide and other agents, did not have an impact on the outcome of the transplant. The results were in fact impressive in terms of PFS, TTR and OS for patients affected by POEMS syndrome who underwent to transplant, confirming aPBSCT as an effective and safe procedure in POEMS independently by the mobilizing treatment.

Recently Zhao concluded that aPBSCT was the best first-line treatment in POEMS, better than lenalidomide plus dexamethasone and melphalan plus dexamethasone. The rarity of POEMS syndrome makes it difficult to conduct randomized trials. Consequently, comparison between patients treated with different protocols evaluated in a multicentre cohort could be an option to debate about open questions in POEMS. In literature many papers reported
favourable outcomes in patients underwent to aPBSCT with similar results from retrospective studies: CR rate over 45% of cases, improvement of neurological signs, low rates of complications and transplant-related mortality.\textsuperscript{11,15,17,18,21}

The best protocol to collect PBSC remains to be defined in patients with POEMS syndrome, even if PBSC mobilization was optimal in all our three groups. To solve the question of the best mobilizing regimen between G-CSF and alkylating agents we recently published a report. In 25 patients both the approaches for mobilization of peripheral blood progenitors were able to harvest a sufficient CD34+ cell dose and allow good and rapid engraftment.\textsuperscript{45}

We noted that in patients of group C plerixafor was not used, so treatment with cyclophosphamide was able to collect a sufficient dose of PBSC only with G-CSF. Our previous study registered only few poor mobilizers, equally distributed between G-CSF and cyclophosphamide group, so this finding could be better confirmed in a larger population of patients.

The present analysis showed that no significant differences in terms of clinical and laboratory characteristics between pre-treated patients and patients who underwent front-line aPBSCT were noted. Sometime the previous treatment with cyclophosphamide served as a purging therapy to ameliorate fitness of patients, leading them to the transplant procedure. Other papers looked at purging therapies before transplant with cyclophosphamide as a promising approach in POEMS syndrome with disseminated bone marrow involvement.\textsuperscript{3} We noted in fact a role of chemotherapy in terms of eligibility to transplant for patients initially unfit for the procedure, so that patients not candidate for aPBSCT, after the pre-treatment achieved a better condition to be suitable and perform the transplant.

All our patients were conditioned with melphalan: Mel200 is the best option and no differences in toxicity were noted compared to Mel140. In literature there is a consensus about the use of Mel: rates over 90-95% were registered for the use of melphalan.\textsuperscript{11,18,21} Considering the main case series reported in literature we calculated that 460 patients were treated with Mel200/Mel140 and less than 10 patients were treated with other conditioning regimes, mainly BEAM (carmustine, etoposide, cytarabine, and melphalan).\textsuperscript{11,15,17,18,20,21,45,47} Engraftment was similar into our three groups of patients and also transplant complication as infections, hospitalization and transfusion support did not show differences between the 3 groups.

In conclusion, all the three schemes of treatment (front-line without pre-treatment, cyclophosphamide or other agents) had reasonable responses with significant improvement in symptoms, durable PFS and impressive OS in newly diagnosed patients with POEMS syndrome who underwent to aPBSCT. Our study is one of the largest national series of patients with POEMS treated with aPBSCT in Europe. Patients unsuitable to receive aPBSCT front-line for comorbidity could be rescued with cyclophosphamide as therapeutic and mobilizing agent.
References


### Table 1. Patients' characteristics

<table>
<thead>
<tr>
<th></th>
<th>ALL N 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53</td>
</tr>
<tr>
<td>Gender male</td>
<td>22 (49)</td>
</tr>
<tr>
<td>VEGF baseline median, range</td>
<td>3882 (258-30000)</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>34 (75)</td>
</tr>
<tr>
<td>Organomegaly</td>
<td>38 (84)</td>
</tr>
<tr>
<td>Gammopathy</td>
<td>43 (95)</td>
</tr>
<tr>
<td>Monoclonal IgA</td>
<td>29 (64)</td>
</tr>
<tr>
<td>Monoclonal others</td>
<td>14 (31)</td>
</tr>
<tr>
<td>Skin</td>
<td>31 (69)</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>19 (42)</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>14.1</td>
</tr>
<tr>
<td>PLTs (10^9/L)</td>
<td>476</td>
</tr>
<tr>
<td>PLTs &gt; 500 x10^9/L</td>
<td>17 (47)</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>7.6</td>
</tr>
</tbody>
</table>

VEGF: Vascular Endothelial Growth factor; Hb: hemoglobin; PLTs: platelets; WBC: white blood cells
Table 2. Patients Group A-B-C characteristics.

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>GROUP A</th>
<th>GROUP B</th>
<th>GROUP C</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td>53</td>
<td>56</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td><strong>Gender (male)</strong></td>
<td></td>
<td>22 (49)</td>
<td>12 (80)</td>
<td>11 (79)</td>
<td>9 (56)</td>
</tr>
<tr>
<td><strong>Median year diagnosis</strong></td>
<td>2013</td>
<td>2011</td>
<td>2014</td>
<td>2012</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Median year transplant</strong></td>
<td>2013</td>
<td>2012</td>
<td>2017</td>
<td>2012</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>VEGF</strong></td>
<td>3556</td>
<td>2938.5</td>
<td>4840</td>
<td>4164</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Gammopathy</strong></td>
<td>43</td>
<td>14 (93)</td>
<td>13 (93)</td>
<td>16 (100)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Gammopathy IgA</strong></td>
<td>29</td>
<td>8 (53)</td>
<td>8 (57)</td>
<td>13 (81)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Gammopathy others</strong></td>
<td>14</td>
<td>6 (40)</td>
<td>5 (34)</td>
<td>3 (19)</td>
<td>na</td>
</tr>
<tr>
<td><strong>Polyneuropathy</strong></td>
<td>45</td>
<td>15 (100)</td>
<td>14 (100)</td>
<td>16 (100)</td>
<td>na</td>
</tr>
<tr>
<td><strong>Bone lesions</strong></td>
<td>27</td>
<td>7 (47)</td>
<td>10 (71)</td>
<td>10 (62)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Endocrinopathy</strong></td>
<td>34</td>
<td>11 (73)</td>
<td>9 (64)</td>
<td>14 (87)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Skin lesions</strong></td>
<td>31</td>
<td>9 (60)</td>
<td>10 (71)</td>
<td>12 (75)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Fluid overload</strong></td>
<td>19</td>
<td>6 (40)</td>
<td>6 (43)</td>
<td>7 (44)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Organomegaly</strong></td>
<td>38</td>
<td>14 (93)</td>
<td>10 (71)</td>
<td>14 (87)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Hb (g/dl)</strong></td>
<td>14.1</td>
<td>11.5</td>
<td>14.4</td>
<td>14.4</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>PLTs (10^9/L)</strong></td>
<td>476</td>
<td>358</td>
<td>401</td>
<td>508</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>PLTs&gt;500 × 10^9/L</strong></td>
<td>17(47)</td>
<td>3 (20)</td>
<td>4 (28)</td>
<td>10 (62)</td>
<td>0.035</td>
</tr>
<tr>
<td><strong>WBC (10^9/L)</strong></td>
<td>7.6</td>
<td>5.7</td>
<td>4.7</td>
<td>15.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

VEGF: Vascular Endothelial Growth Factor; Hb: hemoglobin; PLTs: platelets; WBC: white blood cells
Table 3. Conditioning and transplant

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>GROUP A</th>
<th>GROUP B</th>
<th>GROUP C</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N 45</td>
<td>No treatment N 15</td>
<td>Other treatments N 14</td>
<td>Cyclophosphamide N 16</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>53</td>
<td>51</td>
<td>54</td>
<td>54</td>
<td>-</td>
</tr>
<tr>
<td>Conditioning Mel 140</td>
<td>6(13)</td>
<td>3 (20)</td>
<td>1 (7)</td>
<td>2 (12)</td>
<td>0.59</td>
</tr>
<tr>
<td>Conditioning Mel 200</td>
<td>39(87)</td>
<td>12 (80)</td>
<td>13 (93)</td>
<td>14 (88)</td>
<td></td>
</tr>
<tr>
<td>CD34+</td>
<td>4.01</td>
<td>3.95</td>
<td>4.22</td>
<td>3.91</td>
<td>0.52</td>
</tr>
<tr>
<td>G-CSF (days)</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td>0.23</td>
</tr>
<tr>
<td>GI toxicity</td>
<td>21(47)</td>
<td>7 (50)</td>
<td>9 (64)</td>
<td>5 (31)</td>
<td>0.19</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>28(62)</td>
<td>9 (64)</td>
<td>8 (57)</td>
<td>11 (69)</td>
<td>0.80</td>
</tr>
<tr>
<td>Infections</td>
<td>19(42)</td>
<td>7 (50)</td>
<td>5 (36)</td>
<td>7 (44)</td>
<td>0.75</td>
</tr>
<tr>
<td>RBC transfusions</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>0.15</td>
</tr>
<tr>
<td>PLTs transfusions</td>
<td>3</td>
<td>3.5</td>
<td>2</td>
<td>3</td>
<td>0.43</td>
</tr>
<tr>
<td>PMN &gt; 500x10^6/μL</td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>14</td>
<td>0.47</td>
</tr>
<tr>
<td>PLTs 25 x 10^9/μL</td>
<td>14</td>
<td>14</td>
<td>14.5</td>
<td>14</td>
<td>0.29</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>27</td>
<td>29.5</td>
<td>27</td>
<td>23.5</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Mel: melphalan; G-CSF: granulocyte colony-stimulating factor; GI: gastrointestinal; RBC: red blood cells; PMN: polymorphonuclear cells; PLTs: platelets.
Figures 1. Survival outcomes in the three groups (A: no treatment; B: other treatment; C: cyclophosphamide): Progression Free Survival PFS (figure 1A), Time to Retreatment TTR (figure 1B) and Overall Survival OS (figure 1C).