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Article type: Original article

Received: December 2, 2019.

Accepted: January 7, 2020.

Published online: January 14, 2020.

ISSN: 1897-9483

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Autologous stem cell transplantation in the treatment of multiple myeloma patients with 17p deletion

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The authors have no conflicts of interest to declare.

What is new

Autologous stem cell transplantation (ASCT) is a standard of treatment for younger patients with myeloma. It is based on administration of high – dose chemotherapy followed by stem cell support. On the other hand, it is known that the patients with confirmed deletion of chromosome 17p are not responding to any chemotherapy. In this circumstance it is unclear why they should respond to chemotherapy given in very high doses. Our opinion is that misleading information came from the studies where all the patients with high – risk disease were put together despite the biology of the disease. Our data confirmed that this procedure is not providing expected benefit for patients so can be even potentially harmful. Further prospective studies are required.
ABSTRACT

Introduction: Deletion of chromosome 17p (del(17p)) in multiple myeloma patients is associated with a poor prognosis. The high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains standard of treatment in this group of patients.

Objectives: The aim of the study was to compare results of treatment with high-dose chemotherapy and ASCT with standard treatment in the patients with 17p deletion.

Patients and methods: We collected information from 12 Polish centers between 2011 and 2017. The data from 97 patients with p53 deletion was analyzed. 29 were treated with autologous stem cell transplant, and the remaining 68 received standard treatment only.

Results: 45 patients died during the observation period, the overall survival for the whole group was 33 months (range, 1–66 months) with a median progression-free survival (PFS) of 13 months (range, 1–46 months). The prognostic factors of overall survival (OS) in multivariable analysis were: calcium level at the concentration at diagnosis within normal range (HR: 0.24; 95%CI: 0.12–0.48), and at least partial remission (PR) achieved after first-line treatment (HR: 0.25; 95% CI: 0.12–0.51). Treatment with ASCT was an important factor in improving survival (HR: 3.23; 95% CI: 1.52–6.84). Abnormal kidney function at the time of diagnosis shortened PFS (HR: 0.46; 95%CI 0.22–0.94). When the analysis was limited only to patients who could be an ASCT candidate, the survival advantage of the procedure was lost (p=0.21).

Conclusions: We conclude that there is no benefit from high-dose chemotherapy in patients with 17p deletion.

Keywords: Autologous stem cell transplantation, multiple myeloma, 17p deletion
INTRODUCTION

Deletion of chromosome 17p (del(17p)) is found in 10% of newly diagnosed multiple myeloma (MM) patients at diagnosis and there is a higher prevalence in more advanced disease[1-3]. Its presence is associated with poor prognosis and resistance to chemotherapy [4, 5]. These patients tend to present with relatively frequent extramedullary and central nervous system involvement [6-8]. The International Myeloma Working Group (IMWG) currently recommends FISH (fluorescence in situ hybridization) as the standard approach for identification of the primary genetic event [9]. Currently, there is no consensus on the appropriate FISH-positivity cut-off value for defining the presence of del(17p) and it is not known what minimum percentage of del(17p)-positive cells is associated with a poor prognosis [10]. The significance of p53 mutation in myeloma requires additional and at present can be used only in the context of clinical trials [3, 9]. To treat patients with high-risk cytogenetics, including patients with del(17p), the IMWG recommends bortezomib-based induction followed by high-dose therapy with double ASCT and post-transplant bortezomib maintenance [9]. It is based mostly on the results of the combined Haemato Oncology Foundation for Adults in the Netherlands and German-Speaking Myeloma Multicenter Group - HOVON-65/GMMG-HD4 study [11].

The role of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) remains controversial. The clinical outcome in patients treated with novel drugs compared to a matched control group without p53 deletion showed significantly worse survival in del(17p) group [12]. However, because there are few stratified clinical trial results, high-dose chemotherapy followed by double ASCT is still recommended as a standard approach in this high-risk group of patients [9].
In this study we analyzed real-world data from multiple myeloma (MM) patients with del(17p) who were treated with or without ASCT. The aim of this study is a real-world analysis of the effectiveness of high-dose treatment in the context of this high-risk genetic abnormality.

PATIENTS AND METHODS
From 12 Polish centers, we collected data from patients who were proven to carry del(17p), based on results from FISH studies. These were identified by searching hospital records, including cytogenetic laboratory records from 2011 to the end of 2017. FISH analysis was determined locally from fresh bone marrow aspirates using probes containing DNA sequences that were specific to the p53 gene and mapped to the 17p13.1 region of chromosome 17. A cut-off value of 20% of cells was used to confirm FISH positivity. Data concerning patient demographics, disease characteristics, treatment regimens, and clinical endpoints for the chemo and ASCT groups are summarized in Table 1. Initially the standard first-line treatment for all patients was cyclophosphamide or malphalan, thalidomide, and dexamethasone - CTD/MPT and the second-line treatment was bortezomib, cyclophosphamide/thalidomide and dexamethasone - VCD/VTD. Since 2015, the first-line treatment was VCD/VTD. The initial treatment in both groups was similar in chemotherapy and ASCT group: thalidomide only containing regimen was given to: 42% vs. 46%, velcade only containing regimen received: 30% vs. 29% and velcade and thalidomide together containing regimen: 19% vs 20%.

Abnormal kidney function was defined as creatinine level >2 mg/dl, as in the Durie-Salmon staging system [13].

Prognostic features and treatment response were assessed according to the International Myeloma Working Group Uniform Response Criteria [14]. The characteristics of patients undergoing the ASCT are presented in Table 1. The median time to transplant was 373 days (range, 176–1040 days). Post-transplant analysis was performed at day 100 for patients treated with ASCT. Because only three patients received maintenance therapy, no separate analysis was performed in this group.
Statistical analysis

Overall survival (OS) was calculated from the time of diagnosis to the time of death using the Kaplan–Meier method. For progression-free survival (PFS), death or progression was considered an event. Pearson’s $\chi^2$ and Fisher’s tests were used to compare differences between categorical variables. The rank-sum test was used to compare the distribution of continuous variables. Cox proportional hazard regression analysis was used to compare OS and PFS between patient groups to identify risk factors of those who underwent the ASCT and others. Factors found to be significant at the $P=0.20$ level were then included in a multivariable analysis. In order to determine the significance of treatment on survival, a proportional hazards regression analysis was carried out which included the treatment group adjusted for other prognostic factors. All P-values are two sided. Confidence intervals refer to 95% boundaries. Because the model is not ATF (Accelerated Failure Time) model so the conclusions about shorter or longer survival are indirect ones. Analyses were performed using Statistica 13.1 software (2016, Dell Inc., Tulsa, OK).

RESULTS

We summarized data from 97 patients with the p53 deletion, 29 of whom were treated with autologous stem cell transplantation as a part of their initial treatment. The remaining 68 received standard treatment without high-dose chemotherapy; 45 patients died during observation period, and the overall survival for the group was 33 months (range, 1–66 months) with a median PFS of 13 months (range, 1–46 months; Figs 1 and 2)

Ethics

All the patients provided written informed consent to participate in the study. Ethics committee approval was not required at the time of the study.
ASCT group

In the high-dose group, 22 (93%) patients responded to the initial standard treatment, achieving minimum PR or better at the time of transplantation (Table 1). Because of ASCT, only one patient was left with progressive disease and one other patient progressed from partial remission (PR) to complete remission (CR). At the time of analysis, there were 11 deaths in the ASCT group. The median OS was 42 months (range, 9–68 months; Figure 1), the median PFS was 12 months (range, 2–46 months; Figure 2). Six patients underwent double transplantation (Table 1). One of the patients achieved CR from PR as a result of the second high-dose treatment. There was no difference in OS between the single and double transplant group (HR: 0.43; 95%CI: 0.17–1.12).

Standard treatment group

Among the patients who achieved CR (9%) at the end of the first-line treatment, ten (15%) were in VGPR (very good partial response), 18 in PR (27%), and the remaining 23 patients (34%) were assessed as less than PR. The data from 11 (16%) patients was missing or was not assessed. There were 34 deaths in this group, the median OS was 13 months (range, 1–49 months; Figure 1), and the median PFS was 4 months (range, 1–19 months; Figure 2).

Univariable and multivariable analysis

To determine which prognostic factors were statistically significant, we performed univariable analysis. The following factors were not significant: age >65 or >70 years, the type of heavy and light chain, presence of osteolytic lesions, or the type of first-line treatment including thalidomide, bortezomib, or both. The following five factors were found to be significant for OS: creatinine level: normal or increased HR: 0.37; 95%CI 0.20–0.68); calcium level normal or increased (HR: 0.30; 95%CI 0.17–0.55); response to the initial treatment: PD/SD (progressive disease/stable disease)
versus PR (partial response), VGPR (very good partial response), CR (complete response), or sCR (straighten complete response) (HR: 0.24; 95% CI 0.13–0.47); and initial treatment without or including ASCT (HR: 3.22; 95% CI 1.52–6.82).

There was only one factor (abnormal kidney function at the time of diagnosis) that was significant for PFS (HR: 0.46; 95% CI 0.22–0.94).

The following three factors remained significant for OS in the multivariable analysis: no increase in the calcium level at the time of diagnosis (HR: 0.24; 95% CI: 0.12–0.48); minimum PR achieved as a result of a first-line treatment (HR: 0.25; 95% CI: 0.12–0.51); and a worse prognosis was seen in patients with no ASCT as a part of initial treatment (HR: 3.22; 95% CI: 1.52–6.83).

In a subsequent analysis, we investigated if patients benefited most from high-dose therapy, so we included in the analysis only patients who could be a candidate for ASCT treatment. When the comparison was limited only to patients who obtained the minimum PR as a result of the initial treatment and were no older than 70 years, there was no longer a survival benefit in transplanted patients (p=0.21).

DISCUSSION
Despite remarkable progress in the treatment of MM, adverse genetic risk continues to have a significant impact on survival. This applies particularly to patients with del(17p). However, the first question is how del(17p) should be defined. Cut-off values up to 60% from a single cell were accepted in different studies [15, 16]. The issue related to the FISH-positivity cut-off value was recently discussed at length[17]. The conclusion was that there was no consensus on the appropriate FISH-positivity cut-off value for defining the presence of del(17p). In our study 20% cut off was
made based on the standard criteria, which were in use during the defined period. Additionally, the optimal management of this group of patients remains controversial [18]. Recently, some new data suggested cancer clonal fraction cut off of 0.55 of mutated or deleted 17p as the best method to discriminate high-risk population [19]. We did not include 17p mutated group into our study. Among patients with del(17p) only 18 had cancer clonal fraction >0.55. No difference was found between >0.2 and <0.55 and >0.55 groups, most probably due to very small population. Obviously no difference between chemo and ASCT treated group could not be found either.

In an early report, Chang et al. presented data denying the effectiveness of ASCT in genetic high-risk groups including del(17p) [20]. The Intergroupe Francophone du Myelome (IFM) trial IFM-2005-01, which reported the comparison of bortezomib plus dexamethasone versus vincristine, doxorubicin, and dexamethasone followed by auto-HSCT, failed to confirm a benefit of the new treatment in a sub-group of patients with 17p deletion [21]. However, the current IMWG recommendation for treating patients with high-risk cytogenetics, including patients with del(17p), is prolonged bortezomib-based treatment followed by high-dose therapy with double ASCT [11]. This is based mostly on the results of the randomized phase III HOVON-65/GMMG-HD4 study, where newly diagnosed symptomatic myeloma patients were randomly assigned to receive induction therapy with vincristine, doxorubicin, and dexamethasone or bortezomib, doxorubicin, and dexamethasone followed by high-dose melphalan and autologous stem-cell transplantation maintenance consisting of thalidomide or bortezomib for 2 years. The significant advantage of bortezomib-based treatment was observed in patients with the deletion 17p13, who have a median PFS of 12 compared to 22 months and median overall survival of 24 months compared to not reached at 54 months (HR, 0.36; 95% CI, 0.18 to 0.74). In the University of Arkansas study, 441 patients were treated with Total Therapy 3, which incorporated bortezomib, thalidomide, and dexamethasone induction followed by consolidation and maintenance treatment. In contrast to the
previous Total Therapy 2, Total Therapy 3 results did not show any negative influence affecting the rate or duration of the complete response or survival coming from presence of p53 haplo-insufficiency [22]. The benefit of bortezomib, thalidomide, and dexamethasone followed by double ASCT in this high-risk group was also observed in the Italian Group for Hematological Disease in Adults (GIMEMA) study [23]. A recently published meta-analysis by Liu et al. suggested that there was improved survival of patients with the del(17p) if they were treated with a combination of carfilzomib or elotuzumab and revlimid/pomalidomide with dexamethasone followed by bortezomib maintenance [24].

The recommendation for a double ASCT procedure is based on a meta-analysis of four European trials [25]. These studies include high-risk patient groups with del(17p) but also with the translocation t(4; 14). The overall 4-year survival rate was 76% in the tandem transplant group and 33% in patients who received single procedures only. The advantage of tandem transplantation in myeloma was not confirmed in prospective studies. In the Bologna 96 study, Cavo et al. observed higher complete remission rates after double ASCT (47% vs. 33%, p<0.01) in high-risk groups, but failed to show prolonged overall survival [26]. There was no prospective study focused on the effectiveness of ASCT limited only to patients with the deletion del(17p13) deletion. In a case-matched study where patients with del(17p) were compared with standard-risk patients from the University of Texas MD Anderson Cancer Center database, no benefit of ASCT was found in the group of patients who were treated initially with proteasome inhibitors or immunomodulatory drugs [12].

Our study confirmed the poor prognosis observed in patients with del(17p). Similar to some previous studies, our results did not confirm the statistically significant effectiveness of the high-dose treatment compared with the standard therapy based on novel drugs. Cohen et al., in a multicenter
analysis from eight centers in Israel, noticed improved survival after ASCT only in patients who were in remission for a minimum of 6 months [27]. The report presented by Kroger et al. showed that only use of the combination of autologous-allogenic tandem transplantation can overcome the negative prognostic effect of del(17p13) in the group of patients with complete molecular remission [28].

Besides ASCT as part of the treatment and the response to the initial treatment, hypercalcemia was found to remain significant in the era of novel drugs. This observation has been recently confirmed by other groups [29]. Additionally, there is extensive literature focusing on kidney failure as a risk factor for myeloma and ASCT [30-33].

Our data confirms that there is no benefit of ASCT in MM. Because of the limitations related to the retrospective nature of this analysis, the question should be addressed by a prospective, possibly randomized study.


Contribution statement:

JC and AJ conceived the concept of the study, JC analyzed the data, all authors were involved in data collection edited and approved the final version of the manuscript.

Table 1

Patient’s characteristic in whole group, standard chemotherapy and high – dose chemotherapy (ASCT) treated subgroups

<table>
<thead>
<tr>
<th></th>
<th>All patients N=97</th>
<th>ASCT N=29</th>
<th>Chemo N=68</th>
<th>ASCT vs chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>63 (range 38 – 84)</td>
<td>59 (range 38 -67 years)</td>
<td>64.5 (range 43 – 84 years)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>42 (43%)</td>
<td>14 (48%)</td>
<td>28 (41%)</td>
<td>p=0.19</td>
</tr>
<tr>
<td>Male</td>
<td>55 (57%)</td>
<td>15 (52%)</td>
<td>40 (59%)</td>
<td></td>
</tr>
<tr>
<td>Myeloma subtype:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (52%)</td>
<td>32 (47%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (31%)</td>
<td>18 (26%)</td>
<td></td>
<td>p=0.27</td>
</tr>
<tr>
<td>Light-chain only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (10%)</td>
<td>16 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-secretory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (7%)</td>
<td>1 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light chain type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kappa</td>
<td>56 (58%)</td>
<td>17 (59%)</td>
<td>39 (57%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (29%)</td>
<td>11 (38%)</td>
<td>7 (10%)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------</td>
<td>----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>ISS</td>
<td>2</td>
<td>29 (30%)</td>
<td>11 (38%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>34 (35%)</td>
<td>2 (7%)</td>
<td>32 (47%)</td>
</tr>
<tr>
<td></td>
<td>unknown</td>
<td>16 (16%)</td>
<td>5 (17%)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Best response to the initial treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>1 (1%)</td>
<td>1 (3%)</td>
<td>-</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>CR</td>
<td>12 (12%)</td>
<td>6 (21%)</td>
<td>6 (9%)</td>
<td></td>
</tr>
<tr>
<td>VGPR</td>
<td>23 (24%)</td>
<td>13 (45%)</td>
<td>10 (15%)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>25 (26%)</td>
<td>7 (24%)</td>
<td>18 (26%)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>3 (3%)</td>
<td>-</td>
<td>3 (4%)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>22 (23%)</td>
<td>2 (7%)</td>
<td>20 (29%)</td>
<td></td>
</tr>
<tr>
<td>Single transplant</td>
<td>22 (76%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tandem transplant</td>
<td>7 (24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Results of the transplant

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>CR</td>
<td>7</td>
<td>24%</td>
</tr>
<tr>
<td>VGPR</td>
<td>12</td>
<td>41%</td>
</tr>
<tr>
<td>PR</td>
<td>7</td>
<td>24%</td>
</tr>
<tr>
<td>PD</td>
<td>1</td>
<td>3%</td>
</tr>
<tr>
<td>Missing/Not assessed</td>
<td>1</td>
<td>3%</td>
</tr>
</tbody>
</table>

### Results of the second transplant

<table>
<thead>
<tr>
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<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>VGPR</td>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>25%</td>
</tr>
</tbody>
</table>

1sCR+CR+VGPR+PR vs PD

(sCR - stringent complete response, CR – complete response, VGPR – very good partial response, PR – partial response), PD – progressive disease
Figure 1

Patient’s characteristic in whole group, standard chemotherapy and high – dose chemotherapy (ASCT) treated subgroups
Figure 2
Comparison the progression-free survival of patients treated with ASCT and without high-dose chemotherapy

List of abbreviations:

autologous stem cell transplantation (ASCT)
complete response (CR)
cyclophosphamide, thalidomide, and dexamethasone (CTD)
deletion of chromosome 17p (del(17p))

German-Speaking Myeloma Multicenter Group (GMMG)
Haemato Oncology Foundation for Adults in the Netherlands (HOVON)
International Myeloma Working Group (IMWG)
Intergroupe Francophone du Myelome (IFM)

Italian Group for Hematological Disease in Adults (GIMEMA)

malphalan, thalidomide, and dexamethasone (MPT)

multiple myeloma (MM)

partial response (PR)

straighten complete response (sCR)

very good partial response (VGPR)