Short Communication

High levels of circulating CD34+ cells at autologous stem cell collection are associated with favourable prognosis in multiple myeloma

J Raschle1, D Ratschiller1, S Mans1, BU Mueller2 and T Pabst*,1
1Department of Medical Oncology, University Hospital and University of Berne, Berne, Switzerland; 2Department of Internal Medicine, University Hospital and University of Berne, Berne, Switzerland

BACKGROUND: High-dose chemotherapy with autologous stem cell transplantation is a cornerstone in the first-line treatment of multiple myeloma patients. However, only few factors have been identified affecting the outcome in such patients. We hypothesised that varying levels of mobilised CD34+ cells confer prognostic information in myeloma patients undergoing high-dose chemotherapy.

METHODS: We determined circulating CD34+ cells at the day of peripheral stem cell collection in 158 consecutive myeloma patients between January 2001 and August 2010. Patients were stratified into two groups (super vs normal mobilisers) with a cutoff of 100,000 peripheral CD34+ cells per ml.

RESULTS: We found that patients with more than 100,000 peripheral CD34+ cells per ml had a better overall survival (P = 0.005) and a prolonged time to progression (P = 0.0398) than patients with CD34+ cell counts below 100,000 CD34+ cells per ml. High levels of CD34+ cells were an independent marker for better overall survival and time to progression in a multivariate analysis that included disease stage, response at transplant, light-chain subtype, age, sex, and height.

CONCLUSION: Our results suggest that high levels of mobilised peripheral CD34+ cells are associated with favourable outcome in myeloma patients undergoing autologous transplantation.

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Keywords: myeloma; autologous; transplantation; stem cells; CD34; prognosis

A variety of factors have been reported to affect prognosis in patients with multiple myeloma including cytogenetic abnormalities, molecular markers, cytokine profiling, and clinical parameters (Kyle and Rajkumar, 2009; Rajkumar, 2009; Barlogie et al., 2010; Dingli and Rajkumar, 2010; Munshi et al., 2011). In particular, clinical features such as high lactate dehydrogenase levels, IgA subtype, presence of extramedullary disease, renal failure, high levels of serum-free light chains or of the serum k/l free light-chain ratio, plasmablastic disease, or presentation as primary plasma cell leukaemia have been identified to confer unfavourable prognostic information (Munshi et al., 2011). Accordingly, risk stratification models have been established in multiple myeloma (Greipp et al., 2005; Rajkumar and Kyle, 2005; Kyle and Rajkumar, 2009; Rajkumar, 2010).

With growing insights into the genetic heterogeneity of multiple myeloma, additional prognostic factors have been proposed allowing stratification of myeloma patients into different risk categories, possibly paving the way towards a more risk-adapted therapeutic approach (Rajkumar, 2009). Such an evolving risk assessment can be based on molecular and cytogenetic abnormalities detected by conventional karyotyping, fluorescent in situ hybridisation, and/or gene expression profiling (Fermand et al., 2005; Greipp et al., 2005; Rajkumar and Kyle, 2005; Kyle and Rajkumar, 2009; Chang et al., 2010; Hose et al., 2011; Munshi et al., 2011).

High-dose chemotherapy followed by autologous stem cell transplantation is a cornerstone within the current standard treatment for symptomatic myeloma patients fit for intensive treatment (Child et al., 2003; Terpos et al., 2003; Barlogie et al., 2004; Blade et al., 2005; Fermand et al., 2005; Rajkumar and Kyle, 2005; Wang et al., 2007; Palumbo et al., 2009; Rajkumar, 2009; Lonial, 2010; Cavo et al., 2011). In fact, a number of studies have established the benefit of autologous transplantation for myeloma patients in prolonging the time to progression and, at least in some of them, also in improving overall survival (Attal et al., 1996; Child et al., 2003; Barlogie et al., 2004; Blade et al., 2005; Cavo et al., 2011).

In this retrospective study, we investigated the level of circulating CD34+ cells at the day of peripheral stem cell collection as a prognostic marker in myeloma patients. We hypothesised that excellent stem cell mobilisation is associated with an intact bone marrow homeostasis and thus confers favourable prognostic information. In fact, we found that levels of circulating CD34+ cells below 100,000 per ml at the day of stem cell collection were associated with shorter time to progression and overall survival.
STUDY DESIGN

Patients

A total of 158 consecutive myeloma patients underwent stem cell collection with subsequent autologous stem cell transplantation as a component of their first-line treatment between January 2001 and August 2010 at the Department of Medical Oncology, University Hospital in Bern, Switzerland. Clinical characteristics at diagnosis and mobilisation, regimens used for induction and mobilisation, and the course of the disease of the study population are summarised in Table 1 and Supplementary Figure S1. All patients had G-CSF in addition to chemotherapy for mobilisation. Chemotherapy was high-dose cyclophosphamide until December 2005 and vincristine since January 2006 (Bargetzi et al, 2003). No patient received a CXCR4 antagonist, and no CD34 selection was performed.

Statistical analysis

Patients were stratified into one group with more than 100 000 peripheral CD34+ cells per ml (super mobilisers), and a group with less than 100 000 circulating CD34+ cells per ml (normal mobilisers) at the day of apheresis. Overall survival was defined as the time from the day of stem cell harvest until death or last follow-up whichever occurred first. The time until first progression was the time from the day of apheresis until first progression or death, whichever occurred earlier, or until last follow-up if the patient remained in remission. Curves depicting overall survival and time to progression were performed using the Kaplan–Meier method. The survival analysis was performed using log-rank test. To evaluate the effects of parameters on outcome, the two groups were compared using the χ²-test or Fisher’s exact test, and differences in the mean values in case of continuous variables were tested using t-test. The Cox proportional hazard regression was applied to analyse various risk factors on survival. Results were considered significant if the P-value was below 0.05. All statistical analyses and graphs were performed using graph pad prism program 5.04 (1992–2010; GraphPad Software, Inc., La Jolla, CA, USA) and Statview 5.0.1 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 158 consecutive myeloma patients undergoing autologous transplantation during their first-line treatment were stratified into two groups based on the level of circulating peripheral CD34+ cells per ml (super mobilisers), and a group with less than 100 000 circulating CD34+ cells per ml (normal mobilisers) at the day of apheresis. Overall survival was defined as the time from the day of stem cell harvest until death or last follow-up whichever occurred first. The time until first progression was the time from the day of apheresis until first progression or death, whichever occurred earlier, or until last follow-up if the patient remained in remission. Curves depicting overall survival and time to progression were performed using the Kaplan–Meier method. The survival analysis was performed using log-rank test. To evaluate the effects of parameters on outcome, the two groups were compared using the χ²-test or Fisher’s exact test, and differences in the mean values in case of continuous variables were tested using t-test. The Cox proportional hazard regression was applied to analyse various risk factors on survival. Results were considered significant if the P-value was below 0.05. All statistical analyses and graphs were performed using graph pad prism program 5.04 (1992–2010; GraphPad Software, Inc., La Jolla, CA, USA) and Statview 5.0.1 (SAS Institute, Cary, NC, USA).

Mobilised stem cells and outcome in myeloma

| Super mobilisers | Normal mobilisers | All | P-value |
|------------------|-------------------|-----|---------|
| n                | 69                | 89  | 158     |
| Age at diagnosis (years) Mean ± s.e.m. | 55.42 ± 0.8917 | 56.52 ± 0.7661 | 56.04 ± 0.5810 |
| Range            | 32–71             | 30–69 | 30–71  |
| Cytogenetics†    |                   |      |         |
| Not done         | 53                | 65   | 118     |
| Done             | 16                | 24   | 40      |
| Normal           | 5                 | 8    | 13      |
| del 13q          | 11                | 13   | 24      |
| t(11;14)         | 1                 | 0    | 1       |
| del (17p)        | 1                 | 2    | 3       |
| +3/+7;+9         | 0/00              | 1/21 | 1/21    |
| t(4;14)          | 0                 | 3    | 3       |
| Light chainb     |                   |      |         |
| aκ/λ            | 44/23             | 58/28 | 102/51 |
| Stage at diagnosis (ISS)c | 15/17/32 | 22/26/38 | 37/43/70 |
| Subtypesd       |                   |      |         |
| IgG/IgA          | 47/10             | 59/14 | 106/24 |
| Light chain only | 6                 | 10   | 16      |
| Asecreatory      | 3                 | 2    | 5       |
| Mean follow-up (months) | 35.84      | 29.83 | 32.46  |
| Progression      |                   |      |         |
| Yes/no           | 27/42             | 43/46 | 70/88  |
| Dead†           |                   |      |         |
| Yes/no           | 12/57             | 30/59 | 42/116 | 0.0289 |
| Median time between apheresis and transplantation (d) Mean ± s.e.m. | 32.46 ± 4.938 | 26.20 ± 2.247 | 28.94 ± 2.503 |
| Range            | 7–24              | 8–100 | 7–242  |
| First-line treatment† | 52/17       | 72/17 | 124/34 |
| 1 line > 2 line  |                   |      |         |
| VAD              | 36                | 45   | 81      |
| Bortezomib/dex. | 17                | 27   | 44      |
| Thalidomide/dex. | 11                | 8    | 19      |
| dex.             | 3                 | 6    | 9       |
| Melphalan/pred.  | 2                 | 3    | 5       |
| Single/tandem transplantation | 29/40 | 25/64 | 54/104 |
| Response to induction† |            |      |         |
| Complete remission | 4               | 7    | 11      |
| VGPR             | 12                | 16   | 28      |
| Partial remission | 51                | 62   | 113     |
| Stable disease   | 1                 | 3    | 4       |
| Radiotherapy before stem cell collection |             |      |         |
| Yes/no           | 10/59             | 16/73 | 26/132 |
| Mobilisation chemotherapy |        |      |         |
| Vinorelbine      | 34                | 48   | 82      |
| Cyclophosphamide | 33                | 30   | 63      |
| Bortezomib/dex. | 0                 | 9    | 9       |
| VAD              | 2                 | 2    | 4       |
| Peripheral leucocytes at day of stem cell collection (g/l) Mean ± s.e.m. | 25.76 ± 1.874 | 16.56 ± 1.165 | 20.56 ± 1.107 |
| Range            | 4.1–52.7          | 1.2–52.7 | 1.2–52.7 |

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Table I (Continued)

|                         | Super mobilisers | Normal mobilisers | All       | P-value  |
|-------------------------|------------------|-------------------|-----------|----------|
| circulating peripheral CD34+ cells at day of stem cell collection (cells per ml) |                 |                   |           |          |
| Mean ± s.e.m.           | 179.609 ± 10.937 | 44.381 ± 2602     | 103.436 ± 7309 | <0.0001  |
| Range                   | 103.740–608.760  | 2800–99120        | 2800–608.760 |          |
| Total number of collected CD34+ cells (cells kg⁻¹) |                 |                   |           |          |
| Mean ± s.e.m.           | 18.17 ± 1.022    | 10.37 ± 0.5541    | 13.78 ± 0.6243 | <0.0001  |
| Range                   | 2.4–49.4         | 2.04–26.35        | 2.04–49.4   |          |
| CD34+ cells re-infused (cells kg⁻¹) |                 |                   |           |          |
| Mean ± s.e.m.           | 5.773 ± 0.2419   | 4.381 ± 0.04      | 4.824 ± 0.1625 | 0.0055   |
| Range                   | 2.3–12.6         | 2.01–10           | 2.01–12.6   |          |
| Neutrophil engraftment (days) |                 |                   |           |          |
| Mean ± s.e.d.           | 11 ± 0.2698      | 11.26 ± 0.2615    | 11.14 ± 0.1882 |          |
| Range                   | 1–17             | 4–18              | 1–18       |          |

Abbreviations: del = deletion; dex = dexamethasone; Ig = immunoglobulin; ISS = international staging system; pred = prednisone; t = translocation; VAD = vincristine, adriamycin, dexamethasone; VGPR = very good partial response. Some of the patients had several cytogenetic abnormalities. The information on the light-chain subtype was not available in five patients. The information on the ISS stage at diagnosis in eight patients. The information on subtype in seven patients. Causes of death were all due to myeloma progression, with the exception of three patients in the normal mobiliser group (heart failure; infection; suicide: one patient each) and one patient in the super mobiliser group (infection). No patient had a first-line treatment with lenalidomide. The information on the response to induction in two patients.

normal mobiliser group (P = 0.0289). The median overall survival of all myeloma patients was 72 months (Supplementary Figure S1). Although the group of super mobilisers did not yet reach the median survival, the group of normal mobilisers had a median survival of 50 months (P = 0.0050; Figure 1).

A total of 70 patients in our cohort had a first progression of their disease after autologous transplantation, with 27 patients progressing in the super mobiliser and 43 patients in the normal mobiliser group. The group of super mobilisers showed a longer time to progression, with a median time to progression of 46 months compared with 33 months in the normal mobiliser group (P = 0.0050; Figure 1).

The favourable effect of high levels of circulating CD34+ cells at the day of stem cell collection was observed independent from the type of chemotherapy regimen used for induction, and it was also independent from the chemotherapy (cyclophosphamide or vinorelbine) used for mobilisation (data not shown). Better OS and TTP in the group of super mobilisers were also observed across the ISS stages, with the favourable effect reaching significance (P = 0.0039 and P = 0.011) for patients with ISS stage III at diagnosis (data not shown). We did not observe that the number of CD34+ cells infused at transplantation-affected OS or TTP, with P = 0.754 and P = 0.899, respectively, for patients below vs above the mean value of infused CD34+ cells (data not shown).

In a multivariate analysis, the level of circulating CD34+ cells turned out to be an independent prognostic factor for OS (P = 0.0011) and TTP (P = 0.0228). This multivariate analysis also included light-chain subtype, sex, age, height, and disease stage at diagnosis, as well as the type of response at transplant (Table 2).

**DISCUSSION**

To our knowledge, this is the first report identifying varying levels of circulating CD34+ cells at the day of stem cell collection to be a prognostic marker in myeloma patients. Although previous studies indicated that patients with various lymphoid malignancies mobilising large numbers of CD34+ cells (‘super mobilisers’) enjoy improved survival following autologous stem cell transplantation (Stockler-Goldstein et al, 2006; Gordan et al, 2003; Bolwell et al, 2007; Hiwase et al, 2008), such data are lacking so far for myeloma patients. A small study including 39 myeloma patients found no difference in outcome (Kakihana et al, 2010). As the two groups of super vs normal mobilisers in our cohort did not differ in clinical characteristics, we can exclude one or several of such parameters, to have affected the conclusion of this analysis. With regards to the retrospective character of this study, we consider a prospective evaluation of the effect of levels of mobilised CD34+ cells on outcome to be desirable, and we are in the process of initiating such a study.

The reason for the better clinical course of myeloma patients with large numbers of circulating CD34+ cells at the day of stem cell collection remains to be elucidated. One hypothesis is that patients with a high number of circulating CD34+ cells might have ‘intact’ stem cell niches with conservation of the number of stem cells and their regulation of self-renewal and differentiation (Scadden, 2006). This intact stem cell niche status might enable such patients to mobilise large numbers of CD34+ cells during the stem cell stimulation procedure (Wilson and Trumpp, 2006). Bone marrow infiltration by malignant plasma cells at diagnosis or at stem cell collection might serve as a surrogate marker for altered stem cell homeostasis. However, we observed no difference in the mean bone marrow infiltration between the groups of super vs normal mobilisers (data not shown).

Another factor possibly affecting the conclusion of this study is the number of CD34+ cells used at autologous transplantation. Patients in the super mobiliser group in this study received higher numbers of CD34+ cells during autologous transplantation (P = 0.0055). In fact, the composition of the infused cellular
Table 2: Multivariate analysis for overall survival and progression-free survival

| P-value | Hazard ratio | Lower 95% | Upper 95% |
|---------|--------------|-----------|-----------|
| Overall survival | | | |
| Light chain (k vs λ) | 0.0159 | 1.912 | 1.009 | 3.002 |
| Sex (male vs female) | 0.8444 | 1.112 | 0.622 | 1.925 |
| CD34 + cells (super vs normal mobilisers) | 0.0011 | 4.382 | 1.973 | 9.288 |
| Age (> vs < mean age) | 0.9886 | 0.980 | 0.552 | 1.801 |
| Height (> vs < mean height) | 0.7865 | 1.282 | 0.675 | 2.442 |
| CR and VGPR vs PR and SD | 0.0164 | 3.865 | 1.608 | 6.084 |
| ISS stage (III vs I and II) | 0.2922 | 0.695 | 0.358 | 1.312 |
| Time to progression | | | |
| Light chain (k vs λ) | 0.0422 | 1.751 | 1.006 | 2.944 |
| Sex (male vs female) | 0.5205 | 1.185 | 0.724 | 2.002 |
| CD34 + cells (super vs normal mobilisers) | 0.0228 | 1.884 | 1.061 | 3.012 |
| Age (> vs < mean age) | 0.7486 | 0.892 | 0.622 | 1.382 |
| Height (> vs < mean height) | 0.7880 | 0.912 | 0.572 | 1.533 |
| CR and VGPR vs PR and SD | 0.0330 | 3.926 | 1.722 | 5.258 |
| ISS stage (III vs I and II) | 0.1566 | 0.652 | 0.423 | 1.284 |

**Abbreviations:** CR = complete remission; PR = partial remission; SD = stable disease; VGPR = very good partial remission. Multivariate analysis investigating overall survival and time to progression using the Cox proportional-hazard regression model.

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**Conflict of interest**

The authors declare no conflict of interest.

**Author contributions**

JR performed research, analysed data and wrote the paper; DR analysed data; SM performed research; BM analysed data; and TP designed research, analysed data and wrote the paper. All authors have read and approved the report in its final version.

**Supplementary Information** accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)
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