Intravenous injection of bortezomib, melphalan and dexamethasone in refractory and relapsed multiple myeloma

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Background: A combination of bortezomib (1.3 mg/m²), melphalan (5 mg/m²), and dexamethasone (40 mg) (BMD), with all three drugs given as a contemporary intravenous administration, was retrospectively evaluated.

Patients and methods: Fifty previously treated (median 2 previous lines) patients with myeloma (33 relapsed and 17 refractory) were assessed. The first 19 patients were treated with a twice-a-week (days 1, 4, 8, 11, ‘base’ schedule) administration while, in the remaining 31 patients, the three drugs were administered once a week (days 1, 8, 15, 22, ‘weekly’ schedule).

Results: Side-effects were predictable and manageable, with prominent haematological toxicity, and a better toxic profile in ‘weekly’ schedule (36% versus 66% in ‘base’ schedule). The overall response rate was 62%. After median follow-up of 24.5 months (range 2.7–50 months), the median progression-free survival (PFS) was 21.6 with no difference between the two schedules and the median overall survival (OS) was 33.8 months. Independently from the adopted schedule, we found that also in a cohort of relapsed/refractory patients achieving at least partial remission improved PFS (35.2 versus 9 months) and OS (unreached median versus 18 months).

Conclusion: Taken together, our observations suggest that BMD is an effective regimen in advanced myeloma patients with acceptable toxicity.

Key words: intravenous therapy, multiple myeloma, salvage therapy

Introduction

Encouraging reports have been recently published regarding the improvement of progression-free survival (PFS) and overall survival (OS) in patients affected by multiple myeloma (MM) [1, 2]. This outcome was mainly attributed to the new targeted therapy approach though the contribution of old drugs, such as melphalan, has been recognized as well [3].

Melphalan has been used at different doses ranging from low oral doses (0.25 mg/kg/day for 4 days) to intermediate i.v. (25 mg/m²) [4–6], to high i.v. (up to 200–240 mg/m²), doses as preparative regimen for autologous transplant [7].

At the lower doses, melphalan is usually combined with steroids. In the past, the association of oral melphalan with prednisone (MP) has been considered the standard regimen for patients not eligible to autologous transplantation [8, 9]. Dexamethasone combined to melphalan produced the similar overall response rate (ORR) and even better results in terms of complete response (CR) [10, 11]. Actually, the combination of melphalan and steroids is considered the backbone for the addition of one or more of the new drugs, such as lenalidomide and bortezomib [12–14].

In vitro studies have shown that bortezomib enhances sensitivity of myeloma cells to melphalan and does not greatly affect the growth of normal haemopoietic cells [15]. In vivo, the combination of standard melphalan–prednisone associated with bortezomib has been successfully tested in either relapsed or previously untreated patients [16–18]. However, in most clinical studies, bortezomib has been added to the classic MP scheme (oral melphalan 0.2 mg/kg/day + oral prednisone 2 mg/kg/day day1–4, 9 courses at 6-week intervals) on days 1, 4, 8, and 11 [17, 18] losing the potential synergic effect showed in vitro when both drugs are contemporary present in the culture medium.

Several clinical pharmacokinetic studies have shown that melphalan has a short half-life in the plasma, and its absorption from the gastrointestinal tract is extremely variable [19–21]. In addition, if we consider the frequency of
bortezomib-related gastrointestinal toxicity, it is reasonable to hypothesize that bortezomib could also hamper the melphalan absorption thus reducing its activity [22]. As the safety of i.v. melphalan administration has been documented [23], we added i.v. melphalan to the combination of bortezomib and dexamethasone (BMD) should ensure that all the drugs are present in the plasma at the same time and at the most effective concentrations.

In the present report, we retrospectively evaluate the data to obtain information on the efficacy and safety of intravenous and contemporary administration of standard doses of bortezomib (1.3 mg/m²), intermediate doses of melphalan (5 mg/m²), and high doses of dexamethasone (40 mg).

**patients and methods**

**patient selection**

Relapsed/refractory symptomatic MM patients with measurable disease [24] no longer eligible for a bone marrow transplant procedure were treated if they had an ECOG performance status [25] less than 3 months and a life expectancy of more than 3 months. Most of patients were relapsed (66%), with stable disease for at least 6 months after their last line of treatment (median 10 months, range 6–39) and one-third resistant to previous chemotherapy (Table 1).

Median number of the previous lines of treatment was 2 (range 1–6). Nine patients (18%) had already received bortezomib alone or in combination, and 35 patients (70%) had already received melphalan (17 at high dose as conditioning regimen for autologous stem cell transplantation and 18 as part of a standard melphalan-prednisone regimen), as summarized in Table 2.

Because of high-dose steroids and bortezomib, the only exclusion criteria were psychiatric diseases or grade 2 or higher peripheral neuropathy.

All participants provided written informed consent before enrolment, in accordance with the Declaration of Helsinki.

**Table 1.** Characteristics of the 50 patients included in BMD study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 50)</th>
<th>'Base' schedule (N = 19)</th>
<th>'Weekly' schedule (N = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>67 (45–83)</td>
<td>71 (59–80)</td>
<td>64 (45–83)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>22 (44)</td>
<td>9 (47)</td>
<td>13 (42)</td>
</tr>
<tr>
<td>Paraproteins (isotype), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin G</td>
<td>28 (56)</td>
<td>9 (47)</td>
<td>19 (61)</td>
</tr>
<tr>
<td>Immunoglobulin A</td>
<td>13 (26)</td>
<td>4 (21)</td>
<td>9 (29)</td>
</tr>
<tr>
<td>Light chain only</td>
<td>8 (16)</td>
<td>6 (32)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Relapsed/refractory</td>
<td>33 (66)</td>
<td>11 (58)</td>
<td>22 (71)</td>
</tr>
<tr>
<td>Median time to relapse in months (range)</td>
<td>10 (6–39)</td>
<td>8 (6–27)</td>
<td>12 (9–39)</td>
</tr>
<tr>
<td>Median ECOG PS (range)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Baseline haemoglobin, g/l (range)</td>
<td>10.5 (8.8–10.8)</td>
<td>10.3 (8.8–10)</td>
<td>10.6 (8.9–10.8)</td>
</tr>
<tr>
<td>Baseline platelet count, 10⁹ (range)</td>
<td>166 (75–190)</td>
<td>156 (75–185)</td>
<td>168 (95–190)</td>
</tr>
<tr>
<td>Bone marrow infiltration &gt;50%, n (%)</td>
<td>22 (44)</td>
<td>9 (47)</td>
<td>13 (42)</td>
</tr>
<tr>
<td>C-reactive protein, mg/l (range)</td>
<td>5 (&lt;5–76)</td>
<td>5 (&lt;5–72)</td>
<td>5 (&lt;5–76)</td>
</tr>
<tr>
<td>Lactate dehydrogenase, U/l (range)</td>
<td>375 (125–915)</td>
<td>390 (125–875)</td>
<td>360 (125–915)</td>
</tr>
<tr>
<td>β2-microglobulin, mg/l</td>
<td>4.8 (3.8–7.6)</td>
<td>5.2 (3.8–7.2)</td>
<td>4.8 (4.0–7.6)</td>
</tr>
<tr>
<td>Serum albumin, g/dl (range)</td>
<td>3.8 (2.5–4.2)</td>
<td>3.7 (2.6–4.0)</td>
<td>4.0 (2.5–4.2)</td>
</tr>
</tbody>
</table>

ECOG PS, performance status according to Eastern Cooperative Oncology Group (ECOG) score.

**Table 2.** Characteristics of previous treatments

<table>
<thead>
<tr>
<th>Prior therapy</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 50 (%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>50 (100)</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>48 (96)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>13 (26)</td>
</tr>
<tr>
<td>Low dose melphalan</td>
<td>18 (36)</td>
</tr>
<tr>
<td>High dose melphalan and ABMT</td>
<td>17 (34)</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Thalidomide/lenalidomide</td>
<td>17/2 (34/4)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Median number of regimens (range)</td>
<td>2 (1–6)</td>
</tr>
</tbody>
</table>

ABMT, autologous bone marrow transplantation.

**drug administration**

Between May 2006 and December 2006, 19 patients received the ‘base’ schedule (days 1, 4, 8, and 11). Between January 2007 and December 2008, after an interim evaluation indicating frequent toxicity, further 31 patients received the ‘weekly’ schedule at days 1, 8, 15, and 22.

‘Base’ schedule consisted of i.v. bortezomib at the dose of 1.3 mg/m² and melphalan at the dose of 5 mg/m² on days 1, 4, 8, and 11. Dexamethasone 40 mg was administered i.v. on the day of bortezomib and melphalan (days 1, 4, 8, and 11) and orally the day after each injection (days 2, 5, 9, and 12). In ‘weekly’ schedule, bortezomib and melphalan were administered at the same dosage on days 1, 8, 15, and 22 and dexamethasone on days 1–2, 8–9, 15–16, and 22–23 (Figure 1).

Each cycle was proposed every 28 days (‘base’ schedule) or 35 days (‘weekly’ schedule) for six planned courses.

**concomitant medications**

All patients received treatment with bisphosphonates every 4 weeks during the study. An antibiotic and antiviral prophylaxis was carried out with cotrimoxazole (800 mg twice a day, twice a week) and acyclovir 400 mg/die twice a day. Supportive therapy with erythropoietin (EPO) and granulocyte...
colony-stimulating factor (G-CSF) was administered accordingly to ASH/ASCO guidelines [26, 27].

safety and efficacy assessment
Each patient’s medical history was recorded on day 1 of each cycle. Physical examinations were conducted, and blood was collected for haematology, renal and liver function tests on each day of i.v. drug administration.

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC) criteria [28].

Efficacy assessment was recorded after cycle 2 and every other cycle thereafter: myeloma protein evaluation by measuring serum and urine M component, β2-microglobulin, albumin, and C-reactive protein (C-RP); at the end of planned cycles: bone marrow examination, documentation of extramedullary plasmocytomas, and assessment of disease response according to the criteria of the International Myeloma Working Group [24, 29].

Disease response was defined as complete remission (CR), very good partial remission (VGPR), partial remission (PR), stable disease (SD), progression disease (PD); not valuable, according to Refs. [24, 29].

statistical analysis
Descriptive statistics were generated for analysis of results and P value under 0.05 was considered significant. Qualitative results were summarized in counts and percentages. ORR was defined as PR or better (CR + VGPR + PR). Toxicity rates were compared between the two schedule cohorts by two tailed Fischer’s exact test, confidence interval 95%. OS and PFS were analysed with Kaplan–Meier tests. Standard errors were calculated by the method of Greenwood, the 95% confidence intervals are computed as 1.96 times the standard error in each direction.

PFS was calculated from the time of inclusion until the date of progression, relapse, death or the date the patient was last known to be in remission. OS was calculated from the time of inclusion until the date of death for any cause or the date the patient was last known to be alive. Fisher’s exact test was used to compare these end points according to schedule (‘weekly’ versus ‘base’) and treatment response (CR/VGPR/PR versus SD/PD). All calculations were carried out using Graph Pad Prism version 5.00 for Windows, Graph Pad Software, San Diego, CA, www.graphpad.com.

results

treatment
The median number of administered cycles was 4 in the ‘base’ schedule and 5 in ‘weekly’ schedule (range 1–6), with a mean duration of treatment of 4.5 ± 0.7 months in the ‘base’ schedule and 6.1 ± 0.5 months in the ‘weekly’ schedule.

Delivery of planned doses was as follows: 60% of patients received all doses of BMD, 30% missed from two to four doses, and 10% missed five or more doses. Four patients failed to complete the first cycle (early death for myocardial infarction in a cardiopathic patient, progression disease in one case and withdrawal of informed consent in one case in the base cohort, kidney failure in one case of the weekly cohort).

In the ‘base’ schedule cohort, seven patients discontinued the treatment after at least two cycles for the following reasons: early death for stroke (1), withdrawal of consent (1), progression disease (2), toxicity (2), and infection (1). Three of 19 patients (16%) required drug reduction of 75% for 3/6 cycles and 4/19 patients (21%) received dexamethasone at 50% of dosage. Three patients shifted to the weekly schedule after two cycles and thus completed the planned treatment.

In the ‘weekly’ schedule cohort, 10 patients discontinued the treatment of toxicity (n = 3), infection (n = 3), and disease progression (n = 4, including two disease related deaths). No drug reduction was required for the other patients of the ‘weekly’ schedule cohort.

toxicity
The most common adverse events occurred during chemotherapy administration are shown for both schedules in Figure 2.

In the ‘base’ group, 55 of 92 (60%) cycles were complicated by grade 3–4 haematological toxicity. Thrombocytopenia was the most common haematological toxicity, with grades 3–4 in 31 cycles (34%). Platelet transfusion support was required in 9.8% of cycles, and red blood cells were transfused in 13% of cycles, despite of EPO support. G-CSF administration was needed to support 27 cycles (29%). Nausea and vomiting were mild, affecting 10% of cycles. Constipation was most
commonly reported, especially at first two courses. Peripheral neurotoxicity, never exceeding grade 3, referred in 13% of cycles.

In the ‘weekly’ group, we observed significant lower toxic effects (Figure 3). Of 137 cycles evaluated, 49 (36%) were complicated by haematological grade 3–4 toxicity. Again, thrombocytopenia was the most common (16%) side-effect, but only in one case platelet transfusion support was required. EPO was used in 31.3% of cycles, as well as GCSF in 11%.

Variation in haematological values due to toxicity is reported for each cycle and each schedule in Figure 3. Even if grade 3–4 neutropenia was common in both cohorts, only one case of fever of unknown origin and one case of diarrhoea with documented Candida infection were recorded.

Despite the concomitant antibiotic and antiviral prophylaxis, 4/50 patients had Herpes Zoster reactivation (therapy not continuously taken) and 1/50 patient had P. Carinii–related pneumonia (cotrimoxazole not given for allergy).

BMD did not affect the renal function and the single patient who entered the study (treated with ‘weekly’ schedule) with renal impairment had stabilization of serum creatinine.

efficacy

After six cycles, the ORR (CR + VGPR + PR) was 62%, including 26% of negative immunofixation CR. In 10 cases, the maximal response was achieved within the first two cycles. The response rate at second cycle was 60%, with only two cases of CR. The quality of achieved response improved in patients receiving all planned cycles, independently from the schedule adopted. However, it was not predictive of better OS and PFS (data not shown).

Among nine bortezomib-refractory patients, four achieved VGPR and five PR. There was no difference in the response rate among patients receiving BMD as second line salvage compared with those heavily pre-treated (>3 lines). Among the 23 patients treated only with MP before being treated with BMD, we registered 1 (4%) CR, 2 (8%) VGPR, 7 (31%) PR, and 13 (57%) SD/PD.

At the end of treatment, no significant difference in the quality of achieved response was detectable between the two groups (P = 0.74); therefore, a global response analysis has been carried out.

After median follow-up of 24.5 months (range 2.7–50 months), the median PFS was 21.6 with no difference between the two schedules (Figure 4A). The median OS was 33.8 months (29.8 and 38.2 in the ‘weekly’ and ‘base’ schedule respectively, P = ns, Figure 4B).

discussion

Here, we report the results of a treatment used for relapsed and refractory MM patients. BMD scheme was adopted to take advantage of the i.v. contemporary administration of bortezomib, melphalan, and dexamethasone, known for their synergistic in vitro effect, to obtain at each administration an appropriate plasma level of each drug mimicking as much as possible the in vitro setting.

Indeed, when used in in vitro setting, bortezomib was able to restore melphalan sensitivity in resistant cell lines and to synergize in reducing myeloma cells viability [14]. Similarly, association of melphalan and dexamethasone has well-known effects on cell growth, cell cycle, cell loss, and DNA cross-links as reported in in vitro studies and clinical trials [10].

In vivo combination of full dosage of bortezomib 1.3 mg/m² with oral low dosage of melphalan (0.025 or 0.1 mg/kg) is safe and effective, obtaining ORR (including minimal remission,
MR) of 70% (35% VGPR or better) in relapsed patients [30]. Equally, when used as first line in elderly patients, the combination of melphalan–bortezomib was effective and well tolerated, achieving ORR of 89%, according to the European Bone Marrow Transplantation (EBMT) criteria [31], with durable responses. The VISTA trial [16, 17] has recently identified the combination of bortezomib, melphalan, and prednisone as the gold standard for first-line treatment in patients not candidate to autologous transplant.

However, in the abovementioned trials, melphalan and prednisone were given orally during the first 4 days, while bortezomib was administered by i.v. injection, according to the 1-4-8-11 schedule. We used the contemporary i.v. administration of bortezomib, melphalan, and prednisone to optimize their synergistic actions. Other groups have already explored the i.v. administration of melphalan in combination with new drugs for relapsed patients. In particular, two studies [12, 32] adopted the strategy of a single melphalan injection while bortezomib was given at days 1, 4, 8, and 11 with repeated infusions. Palumbo [12] combined thalidomide plus prednisone with i.v. injection of melphalan (20 mg/m²) reaching an ORR (nCR + PR) of 42%, with a PFS of 9 months, after a median follow-up of 14 months. Popat [32] reported 68% ORR (CR + VGPR + PR) in a series of relapsed patients treated with i.v. combination of melphalan, bortezomib and dexamethasone. In this study, melphalan was given once per cycle at intermediate dosage (7.5 mg/m²) and patients experienced a PFS and OS, respectively, of 10 and 28 months, after a median follow-up of 17 months.

In the present study, we obtained a CR rate of 26% and an ORR (CR, VGPR, and PR) of 66% results, which are not different from those obtained by Palumbo [12] and Popat [32] in terms of the response rate. However, in our series, we obtained a higher prolongation of PFS (21.6 months) and OS (33.8 months) compared with the two other studies, and these results are supported by a longer follow-up of 24.5 months. Moreover, unlike the other studies, our series included not only relapsed but also refractory patients with poor prognosis.

Figure 3. Haematological toxicity of BMD. Mean ± SEM of haemoglobin level (A), platelet count (B) and leukocyte count (C) for each cycle in the ‘weekly’ (grey) and ‘base’ cohort (black).

Figure 4. OS and PFS analysis of BMD. Kaplan–Meier plots of (A) OS and (B) PFS by schedule (‘weekly’ in red, ‘base’ in black) are reported.
These results suggest that (i) melphalan can be given i.v. at intermediate dosage (20 mg/m² per cycle) but a sufficient interval (at least 1 week) is needed between its administrations; (ii) the repeated infusions could induce good quality responses which are more durable than those obtained after administration of a single infusion per cycle. Multiple administrations of melphalan per cycle are probably able of hitting the plasma cells soon after their re-growth, especially when combined with bortezomib and dexamethasone.

As expected [2], better OS was associated by achieving CR or VGPR, independently from the administered schedule and the number or type of prior therapies. Unfortunately, we were unable to identify any clinical mark useful to predict response before the start of treatment. In particular, it was not possible to predict the final response to the treatment based on the early evaluation after the second cycle, differently from other series of relapsed/refractory patients reported before [33]. Further biological markers of response to treatment are worth investigating to identify clinical subset to apply our protocol to improve the quality and duration of the response.

In our study, the improved PFS and OS were obtained at the price of a consistent but acceptable toxicity, and we did not record any drugs-related death. Actually, toxicity of ‘base’ schedule was high and, for this reason, we modified it with a ‘weekly’ schedule after first 19 patients were enrolled. Switching from ‘base’ to ‘weekly’ schedule was sufficient to bring toxicity to a quite manageable and predictable level. The most important toxicity was haematological with thrombocytopenia and anaemia, which required in some cases platelet and red cells transfusions.

Patients’ quality of life, even if not formally measured, was reduced due to many admissions to the hospital for both i.v. administration and side-effects management, including transfusions. In future investigations, we strongly recommend to consider formal measurements of quality of life and comorbidities that can affect feasibility of chemotherapeutic protocols, even if series of relapsed/refractory patients reported before [33].

In conclusion, our study indicates that, in relapsed/refractory heavily pre-treated myeloma patients, the contemporary i.v. administration of bortezomib, melphalan, and dexamethasone is very effective and may produce high rate of response with very durable remission. Owing to its modalities of administration and its side-effects, this schema should be proposed to motivated patients with a good bone marrow reserve.

acknowledgements

A.R., A.C., and F.D.R. designed the research; A.R., U.C., G.A.P., and F.D.R. analysed and interpreted data; A.R. and S.F. carried out statistical analysis. All authors recruited patients, provided clinical data, reviewed, and approved the manuscript.

disclosure

F.D.R. has received honoraria from Janssen-Cilag. The remaining authors have declared no conflicts of interest.

references

Efficacy of abbreviated Stanford V chemotherapy and involved-field radiotherapy in early-stage Hodgkin lymphoma: mature results of the G4 trial


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Patients and methods: Patients with untreated nonbulky stage I–IIA supradiaphragmatic HL were eligible for the G4 study. Stanford V chemotherapy was administered for 8 weeks followed by radiation therapy (RT) 30 Gy to involved fields (IF). Freedom from progression (FFP), disease-specific survival (DSS) and overall survival (OS) were estimated.

Results: All 87 enrolled patients completed the abbreviated regimen. At a median follow-up of 10 years, FFP, DSS and OS are 94%, 99% and 94%, respectively. Therapy was well tolerated with no treatment-related deaths.

Conclusions: Mature results of the abbreviated Stanford V regimen in nonbulky early-stage HL are excellent and comparable to the results from other contemporary therapies.

Key words: abbreviated Stanford V regimen, early-stage Hodgkin lymphoma, involved-field radiotherapy

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