Frontline chemotherapy with bortezomib-containing combinations improves response rate and survival in primary plasma cell leukemia: a retrospective study from GIMEMA Multiple Myeloma Working Party

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Background: The best therapeutic approach for primary plasma cell leukemia (PPCL) remains unknown so far. In very limited studies, the poor clinical outcome of this aggressive variant of multiple myeloma seemed to be ameliorated by the use of the proteasome inhibitor bortezomib. Aiming to provide more consolidated data, this multicenter retrospective survey focused on unselected and previously untreated PPCL patients who had received bortezomib as frontline therapy.

Patients and methods: Twenty-nine patients with PPCL were collected. Bortezomib was given at standard doses and schedules, in various combinations with dexamethasone, thalidomide, doxorubicin, melphalan, prednisone, vincristine, and cyclophosphamide.

Results: An overall response rate of 79% was observed, with 38% of at least very good partial remission. Grade 3–4 hematological, neurological, infectious, and renal toxic effects occurred in 20%, 21%, 16%, and 4% of patients, respectively. After a median follow-up of 24 months, 16 patients were alive (55%), 12 of whom were in remission phase and 4 relapsed. The best long-term results were achieved in patients who received stem-cell transplantation after bortezomib induction.

Conclusion: Bortezomib, used as initial therapy, is able to increase the percentage and the quality of responses in PPCL patients, producing a significant improvement of survival.

Key words: bortezomib, chemotherapy, multiple myeloma, primary plasma cell leukemia

introduction

Plasma cell leukemia (PCL) is a rare and aggressive variant of multiple myeloma (MM), representing ~0.3%–1.3% of all MM, with peculiar clinical and biological characteristics. PCL exists in two forms: (i) primary plasma cell leukemia (PPCL), ~60% of cases, presenting as de novo, without previous evidence of MM; (ii) secondary plasma cell leukemia (SPCL), which accounts for the remaining 40% of cases, consisting of a leukemic transformation occurring in ~1% of patients with a previously diagnosed MM [1, 2].

PPCL is diagnosed by the presence of 20% clonal plasma cells in peripheral blood [if white blood cell (WBC) < 10⁹/l] and/or an absolute number of circulating clonal plasma cells > 2 × 10⁹/l (if WBC > 10⁹/l), producing a monoclonal paraprotein in a patient without a previous history of MM [3, 4].

The best therapeutic approach for PPCL remains unknown so far and the prognosis is still poor. Patients treated with standard chemotherapy showed an overall response rate (ORR) of <50%, with a median survival of few months [5–13]. Transplant procedures may partially improve the clinical outcome of PPCL; overall, however, the long-term results remain largely unsatisfactory [14–16].

We recently showed that the first-in-class proteasome inhibitor bortezomib might be an effective agent for selected
patients within a heterogeneous series of PCL, mainly in the setting of untreated PPCL [17].

Aiming to confirm and extend these promising but preliminary data, in the present study, we conducted a multicenter retrospective survey focused on unselected PPCL patients who had received bortezomib exclusively as first-line therapy for the treatment of their disease, outside of clinical trials.

**patients and methods**

Twenty-nine previously untreated patients with PPCL (17 male, 12 female; M/F ratio 1.4) were collected in 19 hematologic Italian institutions participating in the GIMEMA (Gruppo Italiano Malattie Ematologiche dell’Adulto) Multiple Myeloma Working Party from January 2006 to June 2010. This study was approved by the Ethical Committee of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) ‘Centro di Riferimento Oncologico della Basilicata’ in Rionero in Vulture, Italy.

The mean age at diagnosis was 62 years (range 42–82). The mean number of WBC count was 14.3 $\times 10^9$/l (range 2.2–81 $\times 10^9$/l) and the mean percentage of circulating plasma cells was 39% (range 10%–95%). Variable degrees of renal impairment were observed in 14 patients (48%), while 7 patients (24%) had concomitant extramedullary disease. Cytogenetic abnormalities, detected by FISH, were observed in 14 of 17 evaluated patients, the most frequent resulting in complex karyotypes, including various combinations of t(4;14), t(11;14), t(14;16), del(17), and del13q.

Bortezomib was generally given using the standard schedule of 1.3 mg/m² on days +1, +4, +8, and +11, with an interval of 10 days between cycles. Appropriate dose reductions were applied, according to the manufacturer indications when side-effects occurred. Nine patients received bortezomib in combination with dexamethasone and thalidomide (VTD regimen); seven with dexamethasone alone (BD regimen); seven with doxorubicin and dexamethasone (PAD regimen); two with oral melphalan and prednisone (VMP regimen); two with doxorubicin, dexamethasone, and vincristine (PAD-V regimen); one with melphalan, prednisone, and thalidomide (VMPT regimen); and one with cyclophosphamide and dexamethasone (VCD regimen). A few patients received a maintenance treatment with bortezomib every 2 weeks after response.

Responses were graded according to the published International uniform response criteria [18]. Progression-free survival (PFS) and overall survival (OS) were evaluated beginning with the first month of treatment with bortezomib.

**results**

A total number of 104 cycles were administered (mean 3.7, range 1–9). After bortezomib-containing treatments, 12 (41%) partial remissions (PRs), 3 (10%) very good partial remissions (VGPRs), and 8 (28%) complete remissions (CRs) were achieved (ORR 79%; Table 1). Serum creatinine levels improved or returned to normal values in 10 (91%) of 11 patients who had abnormal renal function at baseline. Circulating plasma cells were rapidly cleared in all responding patients. After bortezomib-containing induction therapies, seven patients underwent double (four) or single (three) autologous stem-cell transplantation (AuSCT), four patients underwent AuSCT followed by reduced-intensity allogeneic stem-cell transplantation (Allo-SCT), one of which from an unrelated donor, while one patient underwent myeloablative Allo-SCT. One patient failed to mobilize circulating stem cells.

Grade 3–4 hematological, neurological, infectious, and renal toxic effects occurred in five (20%), six (21%), four (16%), and one (4%) patient, respectively (Table 1). No case of tumor lysis syndrome was observed.

One patient with preexisting renal damage died of progressive disease after 3 months, developing more severe renal failure. Another patient died in CR 10 months after diagnosis, while carrying out Allo-SCT, due to pseudomonas sepsis. After a median follow-up of 24 months, 16 patients were alive (55%); 12 of them remained in remission phase and 4 relapsed after 4, 11, 16, and 31 months, respectively. Eleven (84%) of the 13 deceased patients did not receive stem-cell transplantation (SCT). Figures 1 and 2 show OS and PFS, respectively, of this series.

**discussion**

The prognosis of PPCL is very poor and there are no standard curative therapies. The treatments usually given are derived from those used to treat MM, with the aim to both prolong

**Table 1. Response and survival**

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Number (Percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>79%</td>
</tr>
<tr>
<td>Complete remission</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>Very good partial remission</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Partial remission</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>Alive patients</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>In remission</td>
<td>12</td>
</tr>
<tr>
<td>Relapsed</td>
<td>4</td>
</tr>
<tr>
<td>Transplanted patients</td>
<td>12</td>
</tr>
<tr>
<td>Alive</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>Not-transplanted patients</td>
<td>17</td>
</tr>
<tr>
<td>Alive</td>
<td>6 (35%)</td>
</tr>
</tbody>
</table>

*Median follow-up: 24 months.*

Figure 1. Overall survival in all patients with PPCL. PPCL, primary plasma cell leukemia.
on the use of bortezomib to treat a heavily pretreated patient with primary plasma cell leukemia. 

In particular, patients treated with melphalan–prednisone had a survival of 4.1 months with a median OS of only 8 months [19]. Tiedemann et al. reported a median OS of 11.2 months in 51 cases of PPCL. In particular, patients treated with melphalan–prednisone had a survival of 4.1 months with respect to 15.4 months for patients that received more complex drug combinations [20].

Moreover, the median OS reported by the Surveillance, Epidemiology and End Results database analysis of 291 patients with PPCL in the United States was only 4 months [21]. Slightly better results were found in patients aged <60 years than >60 years (7 versus 3 months, respectively).

Finally, the multicenter retrospective study of 73 PPCL Italian patients reported a median OS of 12.6 months [22], which was significantly longer in the first-line therapy responders as compared with nonresponders (26.4 versus 4.2 months, respectively).

In the last years, new drugs, such as the immunomodulatory agents thalidomide and lenalidomide and the proteasome inhibitor bortezomib, have modified the clinical scenario of MM, significantly increasing the percentage and the quality of responses, as well as PFS and OS. As a consequence, these drugs have been also used in PCL [19]. However, due to the rarity of the disease, few data have been published so far in this specific setting.

Bortezomib compares favorably with other agents in patients with high-risk MM as defined by chromosomal abnormalities. Therefore, this drug may be an active agent in patients with PPCL as well since they commonly present with adverse chromosomal abnormalities. Esparis-Ogando et al. [23] were the first to report on the use of bortezomib to treat a heavily pretreated patient with SPCL, severe anemia, and thrombocytopenia. After treatment, circulating plasma cells disappeared and peripheral blood counts returned to be normal.

After this, several case reports and small series have described the successful use of bortezomib in both PPCL and SPCL [1, 17, 24–36].

Musto et al. [17] reported a retrospective survey of 12 unselected cases of SPCL or PPCL treated with bortezomib for one to six cycles, as monotherapy or variously combined with other drugs. Three patients were treated with bortezomib as frontline therapy. An ORR of 92%, with a PFS and an OS of 8 and 12 months, respectively, was achieved. Responses did not appear to be influenced by previous treatments or by other clinical or biologic parameters, including chromosome 13 deletion or the combination of bortezomib with other drugs. For eight patients with PPCL, the median PFS and OS were not reached after 21 months of follow-up. Eight patients remained alive 6–21 months after bortezomib treatment, four of whom were in VGPR or CR. Grade 3–4 hematological or neurological toxic effects occurred in nine and one patient, respectively, while six patients experienced possible or documented infections.

Pagano et al. [22] carried out a retrospective analysis of 73 patients with PPCL treated with different chemotherapy regimens, all including steroids (vincristine, adriamycin, cyclophosphamide, melphalan, bortezomib, thalidomide ± bortezomib). It showed an ORR of 55% (mean duration of response: 16.4 months) and an OS of 12.6 months. The best results, however, were observed in patients treated with bortezomib and AuSCT.

The present study reported the retrospective analysis of 29 patients with PPCL seen in 19 hematologic Italian institutions. To our knowledge, this is the largest series of PPCL patients treated with bortezomib-containing combinations as frontline therapy. A response rate of 79% was observed, with 38% of patients achieving VGPR or CR. These results clearly indicate that bortezomib is effective in inducing high rates of significant responses in patients with PPCL. Moreover, toxicity was found to be acceptable, with, in particular, ~20% of patients experiencing hematological or neurological side-effects. Interestingly, 91% of patients with renal impairment displayed an improvement to normal value of creatinine serum levels, while no case of tumor lysis syndrome was diagnosed [37]. Finally, at a median follow-up of 24 months, 55% of patients were alive, with 75% of them maintaining a remission phase. These results compare favorably with all other previous PPCL series reported. The best outcomes, however, were observed in patients who received SCT as consolidation after induction with bortezomib-based regimens, while other patients generally had a shorter remission phase.

The prognosis of PPCL remains generally poor, especially in patients not eligible for SCT. However, our results, despite the clear limits of the retrospective nature of the study and those related to the heterogeneous combinations applied, seem to confirm the capacity of bortezomib in increasing ORR and, likely, OS in patients with PPCL when used as frontline therapy. Bortezomib, however, should be integrated, when possible, within intensive therapeutic programs, including SCT. It will be interesting, in the near future, to explore new therapeutic strategies, for example the safety and efficacy of
bortezomib in combination with other new agents, such as lenalidomide [38] and the role of newer drugs, such as carfilzomib and pomalidomide.

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disclosure
The authors declare no conflict of interest.

references