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Cytogenetic and clinical marks for defining high-risk myeloma in the context of bortezomib treatment

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Multiple myeloma (MM) is a heterogeneous disease, and the benefit from bortezomib treatment is not uniform among all patients subgroups. Currently, little information is available to predict patients response to bortezomib treatment. In this study, we aimed to identify patients benefiting minimally from bortezomib as part of first-line therapy and to define high-risk MM in the context of bortezomib treatment. We compared the effect of a bortezomib-based treatment (arm B) with that of a treatment without bortezomib (arm A) on different genetic patient subgroups in a series of 273 cases of newly diagnosed MM. These patients were enrolled in a prospective, non-randomized clinical trial (BDH 2008/02). A subgroup of patients exhibiting little benefit from bortezomib treatment was identified. These patients had at least one of the following characteristics: del(17p13), 1q21 gain, or high lactate dehydrogenase levels. In this subgroup, survival of patients treated with bortezomib was comparable (progression-free survival: 14.0 vs. 15.0 months, $p = 0.992$; overall survival: 21.0 vs. 14.0 months, $p = 0.472$) to that of patients undergoing thalidomide-based treatment. We propose that all patients with newly diagnosed MM should be evaluated for these three markers before bortezomib treatment. Other novel drugs and alternative therapeutic strategies are needed for patients with such markers.

Over the past few years, the introduction of novel agents into therapy for multiple myeloma (MM) has revolutionized the treatment paradigm, resulting in a significant improvement in response rates and overall survival (OS) [1]. Bortezomib, a direct inhibitor of the 26S proteasome, is the first-in-class proteasome inhibitor to enter clinical trials. It is now one of the most important components of anti-myeloma therapy and part of standard therapy regimens for the treatment of newly diagnosed patients whether they are transplant eligible or transplant ineligible [2,3]. Unfortunately, the beneficial effect of bortezomib is not consistent, and a small proportion of patients do not derive significant benefit from bortezomib-based therapy [4]. These facts underscore the reality that MM is not a single genetically distinct disease, but one with different molecular subtypes and significant differences in drug responses. The differential effects of different genetic patient subgroups in response to bortezomib remain unexplored.

Although there remains a paucity of data regarding the clinical impact of novel therapeutics, it appears that bortezomib can overcome the poor prognosis conferred by some of the high-risk markers [5,6]. Although in some patients bortezomib is not able to overcome the negative prognostic impact of the high-risk prognostic factors, it could improve outcome compared with standard treatments in the same high-risk patient subgroup [7]. However, in some cases bortezomib is not even able to improve outcome, and further treatment options are needed to target this group. Therefore, the identification of genetic and clinical features in

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patients benefiting minimally from bortezomib treatment is important to their receiving appropriate treatment. To date, there are no validated markers to predict the responsiveness of patients with MM to bortezomib therapy.

To design a treatment plan for patients, it is important that the physician know how the patient will likely respond to different treatments [8]. The aim of our study was to define high-risk MM in the context of bortezomib treatment using simple and widely available markers evaluated at the time of diagnosis. Our results indicated that high-risk MM was related to three independent prognostic variables: del(17p13), 1q21 gain, and lactate dehydrogenase (LDH) higher than normal. The outcome of patients with any of these adverse prognostic factors did not improve with bortezomib treatment.

Methods

Patients

This study was a prospective, non-randomized clinical trial. The trial was done in accordance with the Declaration of Helsinki (Version 1996) and was approved by the local ethics committee of our institutions. At their request, patients were assigned to either thalidomide-based (arm A) treatment or bortezomib-based (arm B) treatment (Supplementary Table E1, online only, available at www.exphem.org). Arm A consisted of four cycles of induction treatment with TAD (thalidomide 200 mg/day, adriamycin 9 mg/m^2 intravenously on days 1 through 4, and dexamethasone 20 mg/day orally or intravenously on days 1 through 4 and 9 through 12) or TCD (thalidomide 200 mg/day, cyclophosphamide 300 mg/m^2 intravenously on days 1 and 8, and dexamethasone 20 mg/day orally or intravenously on days 1 through 4 and 9 through 12). Arm B consisted of four cycles of induction treatment with BCD (bortezomib 1.3 mg/m^2 intravenously or subcutaneously on days 1, 4, 8, and 11; cyclophosphamide 300 mg/m^2 intravenously on days 1 and 8; and dexamethasone 20 mg/day orally or intravenously on days 1, 2, 4, 5, 8, 9, 11, and 12) or PAD (bortezomib 1.3 mg/m^2 intravenously or subcutaneously on days 1, 4, 8, and 11; adriamycin 9 mg/m^2 intravenously on days 1–4; and dexamethasone 20 mg/day orally or intravenously on days 1, 2, 4, 5, 8, 9, 11, and 12). After at least four cycles of treatment, patients with partial remission or better response underwent consolidation therapy, which took the form of either autologous stem cell transplant (ASCT) or chemotherapy with their original regimens, according to their wishes. Subsequently, patients were treated with thalidomide (100–150 mg/day) for 1 year to maintain the response. When necessary, some patients also received supportive treatment with zoledronic acid every 1–2 months and erythropoietin or granulocyte colony-stimulating factor. All patients underwent prophylactic acyclovir treatment.

Interphase fluorescence in situ hybridization analyses

All MM samples were purified using Miltenyi technology (Miltenyi Biotec, Paris, France) with anti-CD138-coated magnetic beads before fluorescence in situ hybridization analysis as previously reported [9]. Plasma cells were then analyzed using DNA probes specific for the following chromosomal aberrations: del(13q14), del(17p), t(11;14), t(4;14), and t(14;16). Gain of 1q21 was assessed using a bacterial artificial chromosome probe at 1q21 (RP11-307C12) [10]. A total of 200 interphase nuclei were analyzed. The cutoff values recommended by the European Myeloma Network (EMN) were used: For deletions and numerical aberrations, the cutoff level was set at 20%; for translocations in the IgH locus as well as other translocations, the cutoff level was set at 10% [11].

Statistical analyses

Progression-free survival (PFS) was calculated from the initiation of therapy to the date of death, progression, or last follow-up. OS was measured from the initiation of treatment to date of death or last follow-up, according to the international uniform response criteria [12]. The two-sided Fisher exact test was used to assess associations between categorical variables, with a confidence coefficient of 95%. Survival curves were plotted using the Kaplan–Meier method, with differences assessed with the log-rank test. Results were considered significant if p values were ≤ 0.05.

Results

Patient characteristics

A total of 273 patients with newly diagnosed symptomatic MM were enrolled in the present study between January 2008 and December 2012. One hundred thirty patients were included in arm A, among whom 20 patients underwent ASCT. One hundred forty-three patients were included in arm B, and 22 of them underwent ASCT. The median follow-up time for all patients from diagnosis was 36 months.

The median age of the patients was 58 years (range: 26–83 years). The distribution of International Staging System (ISS) stages was as follows: stage I, 14.3%; stage II, 33.3%; stage III, 47.3% (missing data, 5.1%). High LDH was defined as a LDH level above the institutional upper limit of normal (220 U/L). Our results indicated that serum LDH was elevated in 18.5% (47/254) of newly diagnosed MM patients. There were no significant differences among the groups in clinical characteristics except for a high frequency of elevated LDH in arm B (Table 1).

Frequency of chromosomal aberrations

Because of the small numbers of purified plasma cells in some specimens and the failure of fluorescence in situ hybridization in several cases, we were not able to test the full set of probes in all patients. Two hundred fifty-five patients were analyzed for 1q21 gain, 266 were analyzed for del(13q), 267 were analyzed for del(17p), 266 were analyzed for 14q32 rearrangement, 261 were analyzed for t(11;14), 258 were analyzed for t(4;14), and 252 were analyzed for t(14;16). Interphase fluorescence in situ hybridization analysis of CD138-enriched plasma cells revealed gain of chromosome regions 1q21 (47.8%), del(13q14) (48.1%), and del(17p13) (10.1%). Furthermore, the IgH translocations t(11;14), t(4;14), and t(14;16) were observed at frequencies of 24.9%, 23.6%, and 4.4%, respectively. According to the Intergroup Francophone du