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ORIGINAL REPORT

Bortezomib Plus Dexamethasone Induction Improves Outcome of Patients With t(4;14) Myeloma but Not Outcome of Patients With del(17p)

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See accompanying articles on pages 4621 and 4635

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ABSTRACT

Purpose
Cytogenetics is an important prognostic parameter in multiple myeloma (MM). Patients presenting with either t(4;14) or del(17p) are known to have a short event-free survival (EFS) and overall survival (OS). Some preliminary data suggest that bortezomib is able to overcome these prognostic parameters.

Patients and Methods
A series of 507 patients with newly diagnosed MM who received four cycles of bortezomib-dexamethasone induction therapy before high-dose melphalan were analyzed for both t(4;14) and del(17p).

Results
We found that both t(4;14) and del(17p) remain prognostic parameters, even in the context of bortezomib treatment. However, it is important to note that bortezomib significantly improves the prognosis (in terms of both EFS and OS) of patients with t(4;14), compared with patients treated with vincristine, doxorubicin, and dexamethasone induction therapy. In contrast, no improvement was observed for del(17p) patients.

Conclusion
Short-term bortezomib induction improves outcome of patients with t(4;14) but not the outcome of patients with del(17p). However, both abnormalities remain prognostic factors predicting both EFS and OS despite bortezomib induction.

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INTRODUCTION

Multiple myeloma (MM) is characterized by a huge heterogeneity in biologic and clinical presentation. Whereas some patients encounter a long relapse-free survival (> 10 to 15 years), others present inexorable clinical evolution, leading to death in a few months. Many prognostic parameters have been described including C-reactive protein levels,[1] proliferation based on plasma cell labeling index[2] or karyotype abnormality,[3,4] and β_2-microglobulin or albumin level, which is the basis of the International Staging System (ISS) model.[5] More recently, chromosomal abnormalities have been shown to play an important prognostic role. Interphase fluorescence in situ hybridization (FISH) techniques, focused on identified plasma cells, revealed that some specific abnormalities such as del(13), t(4;14), del(17p), and t(14;16) displayed a specific poor outcome.[6,7] This specific prognostic value has been shown independently of treatment modalities, including high-dose therapies.

More recent data suggested that novel therapies (eg, thalidomide, bortezomib, lenalidomide) may overcome the poor prognosis associated with chromosomal changes.[4,8-11] Preliminary data suggested that bortezomib may negate the poor prognosis conferred by del(13).[12,13] These data have been extended to t(4;14) and del(17p).[9-11] However, these data are limited to small numbers of patients or to specific treatment modalities. To address this issue, we analyzed a large series of young (age < 65 years) patients with newly diagnosed MM who were treated with induction therapy of four cycles of bortezomib-dexamethasone before high-dose melphalan and who were prospectively analyzed for t(4;14) and del(17p).

PATIENTS AND METHODS

Patients

Patients younger than age 65 years were treated with bortezomib (Velcade; Millennium Pharmaceuticals, Cambridge, MA) and dexamethasone (Vel/Dex) induction before high-dose melphalan with hematopoietic stem-cell support. Bortezomib was administered as a four-course induction of 1.3 mg/m^2 on days 1, 4, 8, and 11. After induction, an intensification based on melphalan 200 mg/m^2 was administered. Patients were treated within the Intergroupe Francophone du Myélome (IFM) 2005-01 trial (n = 235) or according to this trial after trial closing (n = 272). To specifically address the question of outcome of patients with t(4;14) and del(17p), we updated the follow-up of patients with these chromosomal changes. Five hundred seven patients were analyzed over a 3-year period. This population was then compared with a series of 512 patients treated with induction therapy consisting of four cycles of vincristine, doxorubicin, and dexamethasone (VAD) within the same period and also specifically updated for patients with t(4;14) and del(17p). Subsequently, 30% of the Vel/Dex population and 26% of the VAD population were enrolled onto the IFM 2005-02 trial. This prospective trial, which enrolled 614 patients, compared lenalidomide maintenance with placebo until relapse, after a short-term lenalidomide consolidation in both arms.

FISH Analysis

For all the patients, bone marrow specimens were collected and shipped overnight to a central laboratory. On receipt, plasma cells were sorted using anti-CD138–coated magnetic beads (StemCell Technologies, Vancouver, British Columbia, Canada), according to previously reported methods.[7] After sorting, plasma cells were hybridized with specific t(4;14) and del(17p) probes (Abbott Molecular, Les Moines, IL).

RESULTS

Patient demographics and clinical characteristics are listed in Table 1. Patients with t(4;14) or del(17p) displayed similar median age (57 years), similar median hemoglobin level (10 g/dL), and similar sex ratio. In contrast, we found significantly different isotype repartition, including immunoglobulin A (IgA) in 44% of patients with t(4;14) versus 19% of patients with no chromosomal abnormality ($P < .001$) and light chains only in 31% of patients with del(17p) versus 16% of patients with no abnormality ($P < .001$), in agreement with previous publications. Patients with either t(4;14) or del(17p) presented with a higher ISS stage [41% stage III for t(4;14) and 44% stage III for del(17p) *v* 24% stage III for no abnormality; $P < .001$ for both). Twenty-seven patients presented with both t(4;14) and del(17p). Similar to patients with a single abnormality, these patients presented with a higher incidence of ISS stage III (35%), and 32% had immunoglobulin A myeloma.

Five hundred seven patients treated with Vel/Dex induction were analyzable. Among them, 106 patients presented a t(4;14), and 54 patients presented a significant (> 60%) del(17p). This cutoff for del(17p) has been calculated according to patient outcome, testing multiple cutoffs (every 5%). As previously published,[7] we found that patients with del(17p) in a low percentage of their plasma cells displayed a similar outcome as patients lacking del(17p) (Appendix Fig A1, online only). This population was then compared with a population of 512 patients treated with four cycles of VAD induction. With a median follow-up of 24 months, a significantly higher percentage of t(4;14) patients treated with Vel/Dex experienced relapse (41%) compared with patients lacking t(4;14) (36%; $P < .02$; Fig 1A). Regarding

Table 1. Patient Demographics and Clinical Characteristics According to Cytogenetics

Demographic or Clinical Characteristic	No Abnormality*	t(4;14)†	del(17p)	t(4;14) and del(17p)	*P*
Age, years					NS
Median	57	58	57	56	
Range	31-65	27-65	27-65	34-64	
Male, %	52	55	57	52	NS
IgA, %	19	44	19	32	
IgG, %	55	42	55	53	< .001
Light chains, %	16	12	31	15	
Hb, g/dL					NS
Median	11	10	10.2	9.1	
Range	5.9-16.3	5.5-14.8	5.5-14.2	6-14	
ISS stage, %					< .001
I	38	25	19	30	
II	38	31	41	35	
III	24	44	40	35	

Abbreviations: NS, not significant; IgA, immunoglobulin A; IgG, immunoglobulin G; Hb, hemoglobin; ISS, International Staging System.
*No t(4;14) and no del(17p). Six patients were positive for immunoglobulin D, and two patients were positive for immunoglobulin M.
†Two patients were positive for immunoglobulin D.

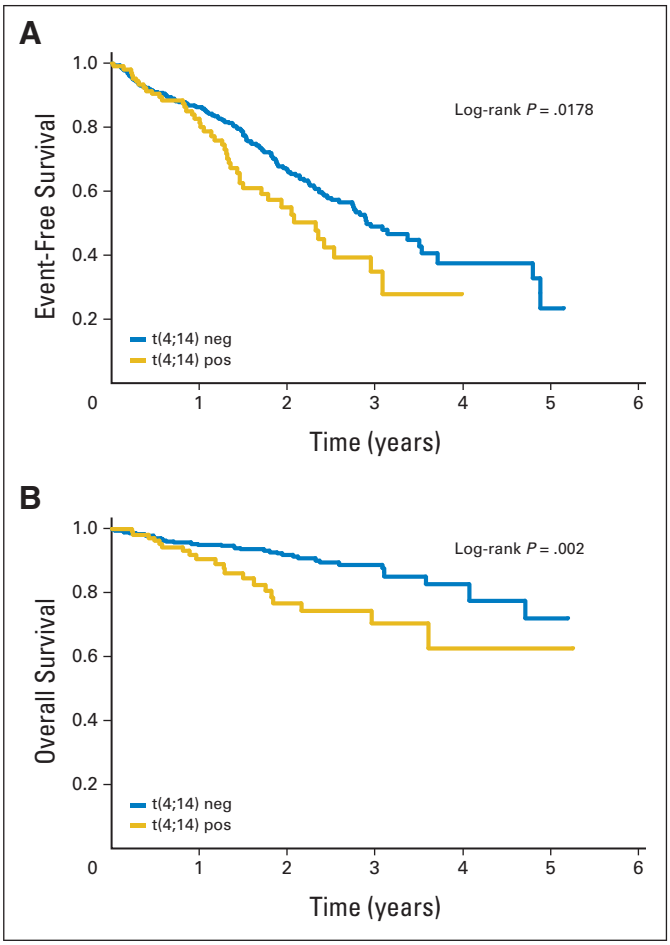

Fig 1. (A) Event-free survival (EFS) and (B) overall survival (OS) in patients with t(4;14) (n = 106) or without t(4;14) (n = 401) treated with bortezomib-dexamethasone induction (EFS and OS in years; $P < .02$ for EFS; $P = .002$ for OS).

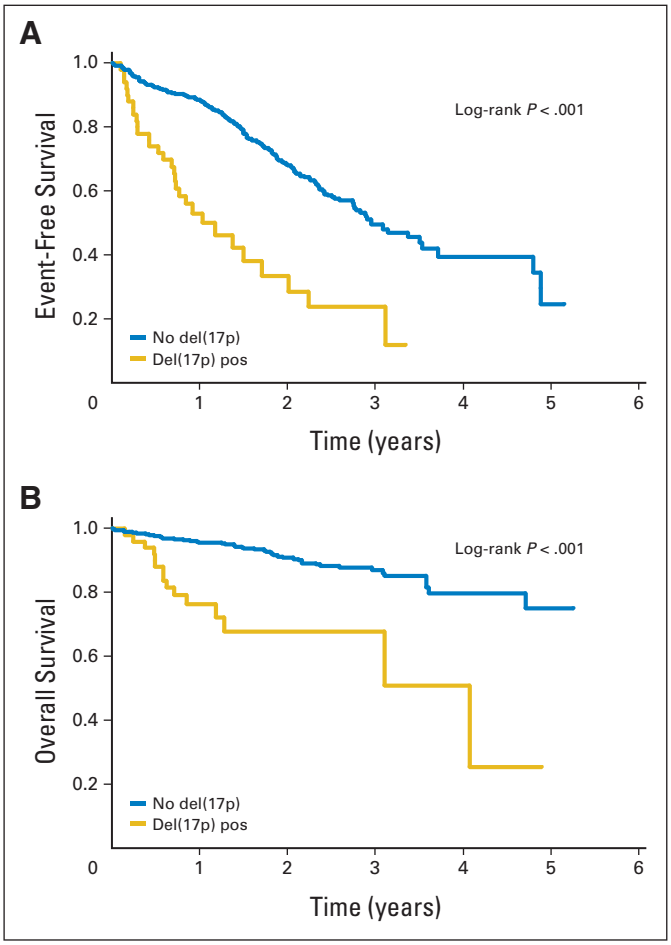

Fig 2. (A) Event-free survival (EFS) and (B) overall survival (OS) in patients with del(17p) (n = 54) or without del(17p) (n = 453) treated with bortezomib-dexamethasone induction (EFS and OS in years; $P < .001$ for EFS and OS).

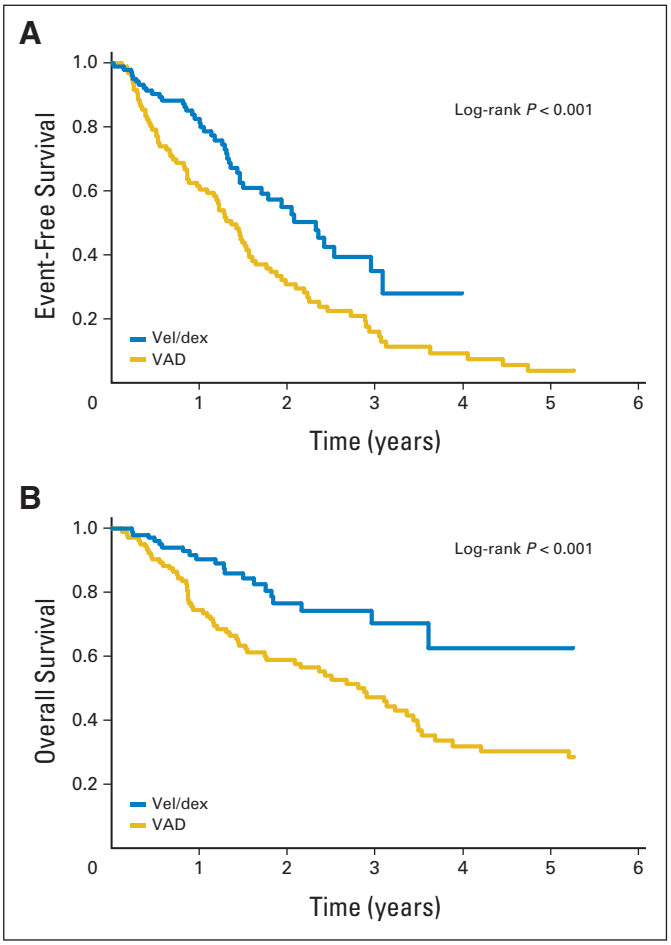

Fig 3. (A) Event-free survival (EFS) and (B) overall survival (OS) in patients with t(4;14) treated with bortezomib-dexamethasone (Vel/Dex) induction (n = 106) or vincristine, doxorubicin, and dexamethasone (VAD) induction (n = 98; EFS and OS in years; $P < .001$ for EFS and OS).

overall survival (OS), a significantly higher death rate was observed among patients with t(4;14) compared with patients lacking this abnormality ($P = .002$; Fig 1B). Similar data were observed according to del(17p). Median event-free survival (EFS) time was 14 months for patients with del(17p) in more than 60% of the plasma cells compared with 36 months for patients lacking del(17p) or with del(17p) in less than 60% of the plasma cells ($P < .001$; Fig 2A); similar results were observed regarding OS (4-year OS: 79% *v* 50%, respectively; $P < .001$; Fig 2B). The analysis of the subgroup with both t(4;14) and del(17p) showed a similar poor outcome but not worse than that of patients with isolated del(17p). The small number of patients prevented any statistical analysis.

We then compared t(4;14)-positive patients treated with Vel/Dex induction (n = 106) with a similar number of patients treated with VAD induction (n = 98). The median EFS was 28 months for patients treated with Vel/Dex compared with 16 months for patients treated with VAD induction ($P < .001$; Fig 3A). A similar OS improvement was observed, with a 4-year OS of 63% for patients treated with Vel/Dex compared with 32% for patients treated with VAD ($P < .001$; Fig 3B).

Regarding patients with del(17p), the analysis was based on 54 patients with del(17p) observed in more than 60% of plasma cells and treated with Vel/Dex induction versus 119 patients treated with VAD. No difference was observed between the two groups for both EFS ($P = .32$) and OS ($P = .49$; Appendix Figs A2A and A2B, online only).

DISCUSSION

Although the prognosis of MM has remained desperately poor for many years, the introduction of novel drugs such as thalidomide, bortezomib, and lenalidomide markedly changed the disease spectrum. The introduction of these drugs in clinic dramatically improved patient outcome, both at relapse and at first treatment. Whether these novel drugs modify prognostic factors is still a matter of debate. Conflicting results have been reported with lenalidomide; some reports suggest that lenalidomide overcomes the poor prognosis associated with del(13) and t(4;14), but not that of del(17p), whereas others show opposite results.[8,14,15] Recent encouraging data suggest that bortezomib is able to overcome the poor prognosis associated with unfavorable genetics.[9-11] To address this issue, we conducted a retrospective study based on a large series (> 500) of patients uniformly treated with Vel/Dex induction before high-dose melphalan. Patients younger than 65 years of age with newly diagnosed MM received an

induction treatment with bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, combined with dexamethasone. All patients underwent FISH analysis at diagnosis, performed on highly purified plasma cells, based on t(4;14) and del(17p). We show that both abnormalities remain strong prognostic factors that are not abrogated by bortezomib-based induction. Patients with t(4;14) displayed both a shorter EFS ($P < .02$) and OS ($P = .002$). Similar data were observed regarding del(17p) ($P < .001$ for EFS and $P < .001$ for OS). However, when compared with patients treated with a VAD induction within the same period, bortezomib did improve both EFS and OS of patients with t(4;14) ($P < .001$ and $P < .001$, respectively). In contrast, no improvement was observed regarding del(17p), which remains a poor prognostic parameter, even in the novel drug era. We want to stress here that del(17p) is not prognostic in all patients. Patients presenting del(17p) in less than 60% of their plasma cells did not display a specific poor outcome (Appendix Figs A1A and A1B).

Because approximately one third of the patients were subsequently enrolled onto the IFM 2005-02 trial, we looked at the specific outcome of these patients. Globally, patients enrolled onto this trial, independently of the treatment arm, encountered a better outcome (Appendix Figs A3A and A3B, online only). However, in patients who were not enrolled onto the trial, Vel/Dex induction significantly improved the outcome of patients with t(4;14) compared with VAD (Appendix Figs A4 and A5, online only). In contrast, no improvement was observed for patients with del(17p).

Our data are in conflict with some reports suggesting that bortezomib was able to totally overcome the prognostic impact of t(4;14) and del(17p). In the VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment With Melphalan and Prednisone) trial, 26 patients displayed high-risk genetics—t(4;14), t(14;16), or del(17p).[9] However, because of the small number of patients, we think these data are not really evaluable. More recently, Pineda-Roman et al[10] and Shaughnessy et al[11] reported on the improvement of prognosis in patients with t(4;14) or del(17p) by the introduction of bortezomib in the Total Therapy 3 program. How do we reconcile these apparently conflicting results? One interpretation is that data are not comparable, either because of small numbers (VISTA trial) or because of a totally different therapeutic strategy (Total Therapy). Another interpretation regards the number of bortezomib injections. In the IFM experience, only four cycles (16 injections) of bortezomib were administered. In the VISTA trial, the theoretical number of bortezomib injections was 52. In the Total Therapy 3 program, patients were supposed to receive almost 150 injections of bortezomib. Thus, a possible explanation is that only long-term administration of bortezomib is able to overcome the poor prognosis of t(4;14) and del(17p). Prospective trials addressing this question are urgently needed.

In conclusion, this study shows that short-term induction with Vel/Dex before high-dose melphalan significantly improves the outcome of patients with t(4;14). This schema should become a standard of care for these patients. In contrast, it does not modify the outcome of patients with del(17p), for whom a standard has still to be found.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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