SUPPLEMENTARY APPENDIX

Retrospective matched-pairs analysis of bortezomib plus dexamethasone versus bortezomib monotherapy in relapsed multiple myeloma

Meletios A. Dimopoulos,[1] Robert Z. Orlowski,[2] Thierry Facon,[3] Pieter Sonneveld,[4] Kenneth C. Anderson,[5] Meral Beksac,[6] Lotfi Benboubker,[7] Huw Roddie,[8] Anna Potamianou,[9] Catherine Couturier,[10] Huaibao Feng,[11] Ozlem Ataman,[12] Helgi van de Velde,[13] and Paul G. Richardson[5]

[1]Department of Clinical Therapeutics, University of Athens School of Medicine, Greece; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Hôpital Claude-Huriez, Lille, France; [4]Department of Hematology, Erasmus Medical Centre, University Hospital Rotterdam, The Netherlands; [5]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [6]Hematology Department, The Ankara University School of Medicine, Turkey; [7]Centre Régional de Cancérologie Henry Kaplan (CHRU de Tours), and Hôpital Bretonneau, Tours, France; [8]Haematology Department, Western General Hospital, Edinburgh, Scotland, UK; [9]Janssen-Cilag Pharmaceutical SACI, Athens, Greece; [10]Janssen-Cilag, Issy Les Moulineaux, France; [11]Janssen Research & Development, LLC, Raritan, NJ, USA; [12]Janssen-Cilag UK, High Wycombe, England, UK; and [13]Janssen Research & Development, Division of Janssen Pharmaceutica NV, Beerse, Belgium

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Correspondence: mdimop@med.uoa.gr

Online supplementary information

Supplementary Methods

Patients, treatment, and assessments

All three studies contributing to this matched-pairs analysis (MMY-2045[1] [NCT00908232], APEX[2] [NCT00048230], and DOXIL-MMY-3001[3] [NCT00103506]) were international, multicenter studies. MMY-2045 enrolled patients at 49 sites in 10 European countries from May 2008 to December 2009 (data cut-off date: April 2, 2011), APEX was conducted at 93 centers in the USA, Canada, Europe, and Israel from June 2002 to October 2003 (data cut-off date: September 2005), and DOXIL-MMY-3001 enrolled patients at 123 centers worldwide from December 2004 to March 2006 (data cut-off date: November 28, 2006).

In all studies, patients received bortezomib 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11 of 21-day cycles, for up to eight cycles. In APEX, patients could then receive three 35-day cycles of bortezomib 1.3 mg/m^2 on days 1, 8, 15, and 22. In MMY-2045, patients also received dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

In MMY-2045, responses were assessed by investigators applying International Myeloma Working Group uniform criteria.[4] Response assessments, which were based on serum and urine M-protein levels, were evaluated at baseline, on day 1 of each cycle until the end of treatment, and monthly thereafter until progression/relapse. Follow-up for survival was then every other month until the last enrolled patient had been followed for 1 year.

In APEX and DOXIL-MMY-3001, response rates and time to progression were determined by a computer-programmed algorithm (validated by an independent review committee), according to European Group for Blood and Marrow Transplantation criteria.[5] In APEX, response was evaluated every 3 weeks for 39 weeks with follow-up every 6 weeks until disease progression, and every 3 months thereafter. In DOXIL-MMY-3001, patients were followed for progression with assessments every 3 weeks for 42 weeks, and every 6 weeks thereafter.

Matched-pairs analysis

In the initial matched-pairs analysis, 13 parameters identified as being related to study drug exposure or clinical outcome were included in the matching exercise. These were: age; body surface area; Eastern Cooperative Oncology Group (ECOG) score; type of myeloma; percent of plasma cells in the bone marrow; presence of extramedullary plasmacytomas; prior stem cell transplantation; prior exposure to immunomodulatory drugs (IMiDs); prior exposure to dexamethasone; hemoglobin level; platelet count; creatinine clearance; and albumin level. Variables not included in the matching, either due to not being related to study drug exposure or clinical outcome, or due to not being collected consistently across the three clinical studies, were: region; sex; race; weight; height; time since initial diagnosis; time since last MM treatment; serum M-protein; urine M-protein; presence of lytic bone lesions; cytogenetic abnormalities; vital signs; corrected calcium; lactate dehydrogenase level; β_2-microglobulin level; glucose; and other laboratory parameters.

Among 384 patients included in the analysis, the 13 identified continuous and categorical variables were compared between treatment groups using the standard *t*-

test and Chi-square test, respectively. Standardized differences were also used to compare baseline characteristics between groups.[6,7] A propensity score model was estimated using the 13 identified variables. For propensity score estimation, a logistic regression model was used in which treatment group was regressed on the 13 identified baseline characteristics. Patients in the two groups were matched on the logit of the propensity score using calipers of width equal to 0.3 of the standard deviation of the logit of the estimated propensity score.[7] The means and prevalence of the continuous and dichotomous baseline covariates were then compared between treatment groups in the matched sample; the standardized difference and variance ratio were used to quantify differences between groups.[6,7]

In the second, confirmatory matched-pairs analysis, only eight consistently-collected parameters related to clinical outcome were included in the matching exercise. These were: age; ECOG score; type of myeloma; percent of plasma cells in the bone marrow; prior exposure to dexamethasone; hemoglobin level; creatinine clearance; and albumin level. Five variables that were mainly associated with bortezomib exposure (i.e. predominantly influencing bortezomib dosing, such as body surface area and platelet count, or influencing bortezomib-related efficacy, such as prior stem cell transplantation,[8] prior IMiDs,[8,9] and presence of extramedullary plasmacytomas),[10,11] were excluded from the second matched-pairs analysis.

Statistical analyses

For statistical inference with the propensity score-matched sample, methods that account for the matched nature of the sample were used. For overall response rate, the Cochran-Mantel-Haenszel test, stratified on the matched pair, was used to estimate the odds ratio and 95% confidence interval of achieving a response with bortezomib-dexamethasone *versus* single-agent bortezomib. For time-to-event endpoints, including time to progression, progression-free survival, and overall survival, Kaplan-Meier curves were estimated separately for the two groups. The stratified (by matched pair) log-rank test was used to assess the statistical significance of treatment effects, and the stratified (by matched pair) Cox proportional hazard model was used to estimate the hazard ratio and 95% CI for bortezomib-dexamethasone *versus* single-agent bortezomib. In order to explore the potential loss of efficiency for analysis stratified by matched pairs, an additional analysis of progression-free survival was conducted with stratification by propensity score quintile.

Two sensitivity analyses were performed, using all 384 patients available for possible inclusion in the initial matched-pairs analysis. A covariate-adjusted regression analysis was conducted, with the 13 identified variables included in the regression models as covariates. A propensity score-weighted regression analysis was also conducted, in which the propensity score was calculated for each patient using a logistic regression model including the 13 identified variables, and the inverse of the propensity score was used in the weighted regression models.

Supplementary references

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