Cytogenetics and Survival of Multiple Myeloma: Isolated and Combined Effects

Theodoros N. Sergentanis,[1,2] Efstathios Kastritis,[2] Evangelos Terpos,[2] Meletios A. Dimopoulos,[2] Theodora Psaltopoulou[1]

Abstract

In a large cohort of unselected patients with multiple myeloma (n = 432), the presence of del(13q), t(4;14), and del(17p) was independently associated with poorer overall survival, after adjustment for a variety of clinical and laboratory parameters. The poor prognosis seemed more pronounced among patients with combinations of 2 adverse cytogenetic abnormalities.

Background: A variety of clinical and laboratory prognostic factors for multiple myeloma (MM) have been addressed in published studies. The prognostic significance of cytogenetic abnormalities is also under investigation. **Patients and Methods:** The present study evaluated the potential prognostic role of cytogenetic events and their combinations in terms of overall survival in a large cohort of unselected patients with MM (n = 432). Multivariate Cox regression analysis was performed, adjusting for age, gender, Chronic Kidney Disease Epidemiology Collaboration Kidney Disease: Improving Global Outcomes classification, International Staging System score, Eastern Cooperative Oncology Group performance status, serum lactate dehydrogenase, serum calcium, platelet count, and blood hemoglobin. **Results:** The presence of del(13q) (adjusted hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.18-2.47), t(4;14) (adjusted HR, 2.00; 95% CI, 1.19-3.35), and/or del(17p) (adjusted HR, 2.03; 95% CI, 1.22-3.37) was independently associated with poorer overall survival. The poor prognosis seemed more pronounced among patients harboring combinations of 2 adverse cytogenetic abnormalities. In contrast, t(14;16), t(11;14), and add(1q21) were not associated with overall survival. The effect of bortezomib seemed rather minimal in the modification of the prognostic role mediated by del(17p). **Conclusion:** The presence of del(13q), t(4;14), and del(17p), singly or in combination, seems to be an independent poor prognostic factor for patients with MM.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 16, No. 6, 335-40
Keywords: Bortezomib, del(13q), del(17p), t(4;14), t(14;16)

Introduction

Multiple myeloma (MM) is a B-cell neoplastic proliferative disease and is the second most common hematologic malignancy after non-Hodgkin lymphoma.[1] Anemia, hypercalcemia, renal insufficiency, and osteolytic bone disease are the hallmark sequelae of MM.[2] The 5-year relative survival rate has been estimated at approximately 40%,[3] with a median survival of 3 to 4 years after conventional treatments and 5 to 7 years after high-dose treatment followed by autologous stem cell transplantation.[4] An increase in survival rates has been noted in recent decades owing to the development of novel anti-MM agents.[5]

A variety of clinical and laboratory prognostic factors for MM have been addressed in published studies. The International Staging System (ISS), integrating serum β_2-microglobulin and albumin levels, is a well-established prognostic factor.[6] Younger age has been associated with more favorable features and better prognosis,[7] and better performance status (PS) also seems to signal favorable survival.[8] Recently, it has been suggested that the estimated glomerular filtration rate (eGFR), determined from the serum creatinine and cystatin levels in accordance with the Chronic Kidney Disease (CKD) Epidemiology Collaboration (EPI) suggestion (CKD-EPI serum creatinine-cystatin C), might independently predict for survival in a cohort of patients with symptomatic MM.[9] Serum lactate dehydrogenase (LDH) is also a variable that is inexpensive to measure and adds prognostic value to the ISS, even when the

[1]Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece
[2]Department of Clinical Therapeutics, "Alexandra" Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

Submitted: Nov 12, 2015; Revised: Feb 25, 2016; Accepted: Mar 21, 2016; Epub: Mar 29, 2016

Address for correspondence: Meletios A. Dimopoulos, MD, Department of Clinical Therapeutics, "Alexandra" Hospital, School of Medicine, National and Kapodistrian University of Athens, 80 Vas Sofias Avenue, Athens 115 28, Greece
E-mail contact: mdimop@med.uoa.gr

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.03.006

patients have received novel agent-based therapies. A high LDH level has been associated with poorer overall survival rates across all ISS groups.[10] The serum calcium level[11] and the presence of thrombocytopenia[12] and anemia[13] could also be prognostic factors.

Apart from the aforementioned clinical and laboratory indexes, considerable attention has shifted to the prognostic significance of cytogenetic abnormalities. According to the Intergroupe Francophone du Myelome (IFM) 99 trials, a poor prognostic role has been attributed to the presence of del(13), t(4;14), and del(17p), because their absence, together with β_2-microglobulin < 5.5 mg/L, has been associated with an 8-year survival rate of 75%.[14] Other studies have also highlighted the poor prognostic role of del(13) in patients with MM undergoing autologous transplantation.[15] Notably, gender might modify the prevalence of the primary genetic events in MM, with del(13q) and add(1q) found more frequently in female patients with MM and affecting the prognosis.[16] Current evidence has suggested that with the advent of bortezomib, the prognostic role of cytogenetic events might be modified.[17,18] Most recently, the revised ISS published in 2015 has encompassed the ISS, LDH level, and cytogenetic events.[19]

Thus, the present study evaluated the potential prognostic role of cytogenetic events, namely del(13q), t(4;14), del(17p), add(1q21), t(14;16), and t(11;14), and their combinations, in terms of overall survival in a cohort of patients with MM. Special attention was given to the potential independent role of cytogenetic events, cautiously accounting for the established clinical laboratory survival predictors for MM and the potential modifying role of bortezomib-based regimens.

Patients and Methods

Patient Cohort

We studied 432 newly diagnosed and previously untreated patients with symptomatic MM treated at the Department of Clinical Therapeutics, "Alexandra" Hospital, School of Medicine (Athens, Greece) from 1990 to 2013. Information about patient age at the first treatment, gender, ISS score, Eastern Cooperative Oncology Group (ECOG) PS, serum LDH level, serum calcium level, platelet count, and blood hemoglobin level were abstracted from the patients' hospital records. Renal function was assessed by the eGFR using the CKD-EPI formula. The patients were classified into the 5 CKD stages of the Kidney Disease: Improving Global Outcomes (KDIGO) classification (stage I, eGFR > 90 mL/min/1.73 m^2; stage II, 60-89 mL/min/1.73 m^2; stage III, 30-59 mL/min/1.73 m^2; stage IV, 15-29 mL/min/1.73 m^2; and stage V, < 15 mL/min/1.73 m^2 or dialysis required).

Information on ≥ 1 of the examined cytogenetic abnormalities [ie, del(13q), t(4;14), del(17p), add(1q21), t(14;16), t(11;14), and ploidy], was obtained. Fluorescence in situ hybridization (FISH) was performed in all patients. Interphase FISH was performed according to the recommendations for FISH in MM[20] on uncultured bone marrow, on either cytoplasmic immunoglobulin-enhanced cells or nuclei from purified $CD138^+$ plasma cells. Commercially available DNA probes (Abbott-VYSIS; Abbott Laboratories, Abbott Park, IL) were used for the detection of del(17p), del(13q), add(1q21), t(4;14), t(11;14), and t(14;16). All the study participants provided written informed consent. The present study adhered to the principles of the Declaration of Helsinki, and the local institutional review board approved the study.

Statistical Analysis

The primary endpoint was overall survival from the time of the first treatment. Kaplan-Meier curves were estimated for the graphic presentation of the results. The effects of del(13q), t(4;14), del(17p), add(1q21), t(14;16), and t(11;14) were examined. Univariate and multivariate Cox regression analysis was performed to evaluate the association between the cytogenetic events and overall survival. Post hoc, the combinations of cytogenetic factors that proved significant on multivariate analysis were evaluated with respect to their potential effect on overall survival (Figure 1).

All multivariate models were adjusted for age (≤ 65 years as reference; 66-79 years, and ≥ 80 years), gender (male vs. female), CKD-EPI KDIGO classification (stage I and II as reference, stage III, and stage IV and V), ISS (stage I as reference, stage II, and stage III); ECOG PS (2-4 vs. 0-1), serum LDH level (≥ 300 vs. < 300 IU/L), serum calcium level (≥ 11 vs. < 11 mg/dL), platelet count (≤ 130 vs. $> 130 \times 10^9$/L), and blood hemoglobin level (< 10 vs. ≥ 10 g/dL). In addition to the overall analysis, a subgroup analysis of patients receiving bortezomib-based regimens as primary therapy was performed. Statistical analysis was performed using STATA/SE, version 13, statistical software (StataCorp, College Station, TX).

Results

The results of the Cox regression analysis for overall survival in the cohort of patients with MM ($n = 432$), examining the effects of the traditional clinical and laboratory parameters are listed in Table 1. The median overall survival was 55.9 months. Older age, deteriorated renal function (using the CKD-EPI KDIGO classification), higher ISS score, worse ECOG PS, higher serum LDH level, higher serum calcium level, lower platelet count, and lower blood hemoglobin level were associated with poorer overall survival. However, gender did not seem to modify the patients' overall survival.

Figure 1 Flow Chart Showing the Availability of Cytogenetic Data in the Cohort of Patients With Multiple Myeloma (MM)