Original Study

Cytogenetic Impact on Lenalidomide Treatment in Relapsed/Refractory Multiple Myeloma: A Real-Life Evaluation

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Abstract

Most of the data on the efficacy of lenalidomide in the treatment of relapsed/refractory multiple myeloma comes from clinical trials. In this real-life study, we showed that although high-risk cytogenetic findings negatively affects progression-free survival and overall survival, one third of high-risk patients experienced long survival, suggesting a role for continuos therapy in this subset of patients.

Introduction: In this retrospective real-life study in relapsed/refractory multiple myeloma patients, we analyzed clinical and biologic features distinguishing patients with rapidly progressing disease while receiving lenalidomide therapy from those without progression. **Patients and Methods:** According to time of stopping lenalidomide, patients were subdivided into 3 groups: early stop (ES) (n = 23), when therapy was discontinued within 6 months; intermediate (INT) (n = 23), when therapy was stopped between 7 to 24 months; and long survival (LS) (n = 45), when therapy was maintained for more than 2 years. The median age of the whole cohort was 70 years (range, 42-85 years); 40% had an International Staging System score of 2 or 3. **Results:** High-risk cytogenetic findings, including 1q gain, was reported in 65% ES, 43% INT, and 21% LS. Overall response rate was 63%, with median progression-free survival and overall survival of 33 and 56 months, respectively. **Conclusion:** Although high-risk cytogenetic findings negatively affect progression-free survival and overall survival, 28% of cytogenetic high-risk patients experienced long survival, provided that lenalidomide therapy was not discontinued, thus pointing to the role of maintenance therapy in this subset of patients.

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Introduction

Lenalidomide is effective in the treatment of relapsed/refractory multiple myeloma (RRMM).[1] Its tumoricidal and immunomodulatory activities in multiple myeloma (MM) patients make lenalidomide particularly valuable in the setting of continuous therapy by improving the quality of response as well as prolonging the time to relapse and, in some studies, overall survival (OS). Results from a pooled analysis of data from the MM-009 and MM-010 trials[2] documented an improvement in the median OS of 38.0 months for patients treated with lenalidomide plus dexamethasone versus 31.6 months for those receiving dexamethasone and placebo ($P < .045$). In addition, this significant OS benefit was maintained despite the fact that nearly half of the patients in the control arm

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received lenalidomide at the time of disease progression or study unblinding.[2] These exciting data were mostly obtained from clinical trials and thus do not necessarily reflect real-life behavior. Similar results can be obtained through a fine optimization of lenalidomide use that allows patients to receive treatment for a long time. In this regard, it is well established that some patients are characterized by poor response with progression of disease in the first months of lenalidomide therapy, whereas others present long-term response.

This single-center study was designed to evaluate the clinical and biologic features of a series of 91 consecutive patients treated with lenalidomide/dexamethasone for RRMM according to their clinical, biologic, and cytogenetic features and therapy response.

Methods

Patients

A total of 91 patients referred to the Department of Hematology, Padova University, were identified for the current study. The majority of patients were aged over 65 years (74%), with 18 (20%) more than 75 years old. They were diagnosed with RRMM according to International Myeloma Working Group (IMWG) criteria and had undergone 1 or more lines of therapy. Sixty percent of the patients had stage 1 disease according to the International Staging System. The Cumulative Illness Rating Scale was used to evaluate the impact of comorbidities in the patient group.[3] A comorbidity index, which refers to the number of categories with a score higher than 3, was calculated for each patient and in the majority of cases (71%) was low, indicating that comorbidities were not relevant in our cohort of patients (Table 1). The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients had complete follow-up records. All response rates were determined according to the IMWG. Summary of variables for the studied sample are reported in Table 1.

Table 1 Clinical Features of Patients Under Study

Characteristic	Category	n (%)
Gender	Male	50 (55)
	Female	41 (45)
Age group	<65 years	24 (26)
	65-75 years	49 (54)
	>75 years	18 (20)
Multiple myeloma isotype	IgG	63 (69)
	IgA	14 (15)
	Light chain	14 (15)
International Staging System score	1	55 (60)
	2	21 (23)
	3	15 (17)
Diagnosis	Refractory	55 (60)
	Relapsed	36 (40)
CIRS comorbidity index	<3	65 (71)
	>3	26 (29)
No. of previous treatment lines	1	13 (14)
	2	42 (46)
	3 or more	36 (39)
Previous treatment	Thalidomide	6 (7)
	Velcade	63 (69)
	Velcade + thalidomide	19 (21)
	Other[a]	2 (2)
Previous autologous bone marrow transplantation	No	51 (56)
	Yes	40 (44)

Abbreviation: CIRS = Cumulative Illness Rating Scale.
[a]Included vincristine, Adriamycin, and dexamethasone.

Treatment

Lenalidomide was administered orally at a starting dose of 10 mg to 25 mg daily on days 1 to 21 of each 28-day cycle. The dose adaptation was performed according to the creatinine clearance level (serum creatinine level of less than 2.5 mg/100 mL). We found a normal creatinine level in approximately 50% of patients, and initial abnormal glomerular filtration rate in the remaining patients. The majority of patients (76%) received dexamethasone at a dose of 20 mg weekly; the remaining at a dose of 10 mg weekly of each 28-day cycle. The patients received treatment until disease progression or severe toxicity (grade 4). In the latter case, the status of disease was calculated at this time point. If patients experienced grade 3 or 4 adverse events, lenalidomide was interrupted until the adverse events were resolved, and treatment was restarted with the dose reduced to 15 mg per day, with further reduction at decrements of 5 mg per day. Patients with grade 3 or 4 neutropenia without other toxicity received 5 μg/kg per day subcutaneous granulocyte colony-stimulating factor. The dexamethasone dose was adjusted for adverse events at the discretion of the physician. Dexamethasone reductions were to 10 or 5 mg per day weekly.

Metaphase and Interphase Cytogenetic Analyses

Chromosome banding analysis was performed on bone marrow aspirates after short-term culture (24 hours, 48 hours, or both) in RPMI 1640 medium (Euroclone, Pero [MI], Italy) supplemented with 20% fetal calf serum (Life Technologies, Carlsbad, CA, USA). Slides were prepared by conventional methods, and G-banding was obtained by Wright stain (Sigma-Aldrich, St Louis, MO, USA). At least 25 metaphases were analyzed for each sample, and the karyotype was described according to the International System for Human Cytogenetic Nomenclature (ISCN 2009).

When possible, MM samples were purified using Miltenyi technology (anti-CD138-coated magnetic beads; Paris, France) before fluorescence in-situ hybridization (FISH) according to the manufacturer's instructions. Otherwise, FISH was performed on the same slides obtained for cytogenetic analysis as an investigation complementary to the karyotype with locus-specific probes: LSI 13(RB1)/LSI 13q34 for deletion/monosomy of chromosome 13, LSI IGH/FGFR3 for t(4;14), LSI IGH/CCND1 XT for t(11;14), LSI IGH/MAF for t(14;16), LSI p53/CEP17 for deletion 17p13 (Vysis-Abbott Molecular, Downers Grove, IL, USA) according to the manufacturer's protocol. Three hundred interphase nuclei were analyzed for each with Axioskop 2 plus probe (Zeiss, Jena, Germany) equipped with appropriate filters. The cutoff for positive values was 10% for deletion/monosomy 13 and for 17p13 deletion, and 5% for translocation dual-color, dual-fusion probes.

High-risk cytogenetic findings were defined by the presence of at least one of the following[4]: hypodiploidy, gain 1q (+1q),