Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone

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The outcome of patients with multiple myeloma is dictated primarily by cytogenetic abnormalities and proliferative capacity of plasma cells. We studied the outcome after initial therapy with lenalidomide-dexamethasone among 100 newly diagnosed patients, risk-stratified by genetic abnormalities and plasma cell labeling index. A total of 16% had high-risk multiple myeloma, defined by the presence of hypodiploidy, del(13q) by metaphase cytogenetics, del(17p), IgH translocations [t(4;14), or t(14;16)] or plasma cell labeling index more than or equal to 3%. Response rates were 81% vs 89% in the high-risk and standard-risk groups, respectively. The median progression-free survival was shorter in the high-risk group (18.5 vs 36.5 months, \( P < .001 \)), but overall survival was comparable. Because of unavailability of all tests for every patient, we separately analyzed 55 stringently classified patients, and the results were similar. In conclusion, high-risk patients achieve less durable responses with lenalidomide-dexamethasone compared with standard-risk patients; no significant differences in overall survival are apparent so far. These results need confirmation in larger, prospectively designed studies.

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Methods

After approval of the Institutional Review Board of the Mayo Clinic, we reviewed the outcome of 100 consecutive patients who received Len-Dex as initial therapy for symptomatic MM, between March 2004 and November 2007. Patients received lenalidomide (25 mg/day orally) on days 1 to 21 of a 4-week cycle in combination with either low-dose (40 mg weekly; \( n = 43 \)) or high-dose (40 mg, days 1-4, 9-12, and 17-20 of each 28-day cycle; \( n = 57 \)) oral dexamethasone.

The patients were risk-stratified into 2 groups. The high-risk group was defined by the presence of at least one of the following: hypodiploidy, monosomelic loss of chromosome 13 or its long arm by metaphase cytogenetics only, deletion of p53 (locus 17p13), immunoglobulin heavy chain (IgH) translocations [t(4;14) or t(14;16)] by fluorescence in situ hybridization (FISH) or cytogenetics, or plasma cell labeling index (PCLI) more than or equal to 3%. PCLI was performed as previously described.10 Patients without any of these features were considered standard risk. Responses were assessed by the IMWG uniform response criteria.11 Progression-free survival (PFS), time to progression (TTP), and overall survival (OS) were estimated by Kaplan-Meier method and compared by log-rank tests.

Results and discussion

The median follow-up of the entire cohort (\( N = 100 \)) was 36 months (range, 2.3-53.1 months). The baseline characteristics and laboratory findings are presented in Table 1. Sixteen (16%) patients had at least one high-risk feature identified by metaphase cytogenetics, FISH, or PCLI. Overall, 95 patients had at least one of the aforementioned test results available for risk stratification (cytogenetics, \( n = 95 \); PCLI, \( n = 89 \); FISH, \( n = 57 \)), and those without any test results were considered standard risk. The response...
to therapy was similar in the 2 groups as indicated in Table 1. The median PFS for the entire cohort was 31 months; the median OS was not reached, and the 2- and 3-year OS estimates were 93% and 83%, respectively. The median PFS was 18.5 months for the high-risk group compared with 36.5 months for the standard-risk group (n = 84, P < .001; Figure 1A). The corresponding values of the TTP were similar to the PFS, 18.5 months and 37 months, respectively (P = .001). The OS was comparable between the groups (P = .4), with median OS not reached for either group (Figure 1B). Both groups had a 2-year OS of 92%, whereas the 3-year OS was 77% and 86% for the high-risk and standard-risk groups, respectively. The PFS (or OS) of patients receiving high-dose and low-dose dexamethasone was comparable.

We repeated the analysis using a more stringent criterion by excluding the patients with insufficient pertinent information for adequate risk stratification. Fifty-five patients either had all 3 tests (metaphase cytogenetics, FISH, and PCLI) or at least one test that led to their inclusion in the high-risk category. A subgroup analysis restricted to these 55 patients demonstrated similar results (Figure 1C-D). Fifty patients underwent SCT after Len-Dex induction therapy. Because the SCT could have affected the outcome, given its lesser impact on high-risk disease, we performed a separate analysis with patients who underwent SCT before MM progression being censored on the date of SCT. The median PFS of the high-risk group was 18.5 months compared with 36.9 months for standard-risk patients (P = .002).

Because of the paucity of long-term outcome data in the high-risk population, induction regimens involving bortezomib or lenalidomide plus dexamethasone with very low early death rates12-14 have been preferentially used in patients with high-risk features. Bortezomib-based regimens may overcome the poor

Table 1. Baseline characteristics of newly diagnosed patients with multiple myeloma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (range)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (range)</td>
<td>67 (48-78)</td>
<td>63 (32-78)</td>
</tr>
<tr>
<td>ISS, N = 95</td>
<td>1.3:1</td>
<td>2:1</td>
</tr>
<tr>
<td>Stage I</td>
<td>12%</td>
<td>43%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>44%</td>
<td>47%</td>
</tr>
<tr>
<td>Stage 3</td>
<td>44%</td>
<td>10%</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>10.8 (7.9-15.6)</td>
<td>11.1 (6.0-15.6)</td>
</tr>
<tr>
<td>White blood cells, ×10^3/L</td>
<td>5.7 (3.3-8.1)</td>
<td>5.5 (2.2-5.6)</td>
</tr>
<tr>
<td>Platelets, ×10^9/L</td>
<td>214 (141-350)</td>
<td>258 (117-471)</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.5 (8.0-11)</td>
<td>9.3 (7.3-18.8)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.3 (0.3-1.7)</td>
<td>1.1 (0.7-2.4)</td>
</tr>
<tr>
<td>Lactate dehydrogenase, units/L</td>
<td>142 (118-296)</td>
<td>156 (90-317)</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>0.59 (.07-1.8)</td>
<td>0.3 (.02-7.4)</td>
</tr>
<tr>
<td>Monoclonal (M)–Spike, g/dL</td>
<td>3.5 (0.6-1.1)</td>
<td>2.9 (0.0-6.7)</td>
</tr>
</tbody>
</table>

ISS indicates international staging system; CR, complete remission; VGPR, very good partial remission; and PR, partial remission.

Figure 1. Survival analysis of patients with newly diagnosed MM who received Len-Dex as initial therapy. (A) PFS by risk stratification; median PFS is 18.5 months for high-risk versus 36.5 months for standard-risk patients (P < .001). (B) OS by risk stratification (high-risk vs standard-risk patient); median OS not reached (P = not significant).

(C) PFS of strictly categorized patients (N = 55) who either had all the 3 tests (metaphase cytogenetics, fluorescence in situ hybridization [FISH], and PCLI) or at least 1 test that led to their inclusion in the high-risk group; median PFS = 18.5 months for the high-risk group and 36.5 months for the standard-risk group (P < .001). (D) OS of strictly categorized patients (N = 55) who either had all the 3 tests (cytogenetics, FISH, and PCLI) or at least 1 test that led to their inclusion in the high-risk group; median OS not reached for either high-risk or standard-risk group.
prognostic effect of many cytogenetic abnormalities, including metaphase del(13q) and t(4;14). Outcome data on the efficacy of Len-Dex regimen in high-risk patient population are scant.

A Canadian study involving 159 relapsed/refractory MM patients demonstrated the efficacy of Len-Dex in surmounting poor prognosis conferred by t(4;14) and del(13q) by FISH. However, besides dissimilar patient cohorts (relapsed/refractory vs newly diagnosed in our study), differences exist in risk stratification of patients as del(13q) by FISH only is considered a standard-risk feature by our prognostic model but a high-risk feature in the Canadian trial. Furthermore, the possibility of selection in the high-risk relapsed/refractory t(4;14) cases surviving long enough to be enrolled in the Len-Dex expanded access program cannot be ruled out, perhaps accounting for improved PFS in the Canadian study. A subset of t(4;14) patients with β2-microglobulin less than 4 mg/L is known to have a distinct survival advantage. Possibly, a greater proportion of patients with t(4;14) in the Canadian study had β2-microglobulin of less than 4 mg/L as reflected by the low median β2-microglobulin (3.05 mg/L). In our study, the subgroup analysis of specific chromosomal abnormalities was limited by the small sample size for individual groups. Interestingly, the Canadian study is in disagreement with a recently reported French study of Len-Dex demonstrating shorter PFS and reduced OS in relapsed/refractory MM patients with FISH-detected del(13) and/or t(4;14).

Not surprisingly, in line with results of other studies, the overall response rates of high-risk patients and standard-risk patients were similar. Although the TTP and PFS of high-risk group were shorter, the absolute values are similar to those reported in patients were similar. Although the TTP and PFS of high-risk group

Furthermore, our attempt to negate the impact of SCT yielded similar results.

These preliminary results highlight the poor outcome among high-risk MM patients (a median TTP/PFS of 18-20 months in most recent studies) despite significant advances in recent years in the treatment of MM and improvement in OS. Future strategies need to target high-risk myeloma, both in terms of understanding the disease biology as well as developing targeted therapies. Only larger, prospectively designed studies with extended follow-up can more definitively assess the impact of Len-Dex therapy on patients with high-risk MM.

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Authorship


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References

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