Impact of FISH Abnormalities on Response to Lenalidomide in Patients with Multiple Myeloma

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Background

- Multiple myeloma (MM) is a heterogeneous disease with variable response to different therapeutic regimens and wide spectrum of survival.
- Much of the heterogeneity in the outcomes appear to be related to the underlying primary genetic abnormality, which in the majority of patients consist of either translocations involving the heavy chain region on chromosome 14 (IgH translocation) or trisomies of odd numbered chromosomes.
- Information regarding differences in responses and outcomes based on the specific therapies applied is lacking presently.
- Prior studies have suggested inferior outcomes with specific high risk abnormalities in the context of different therapies.

Objective

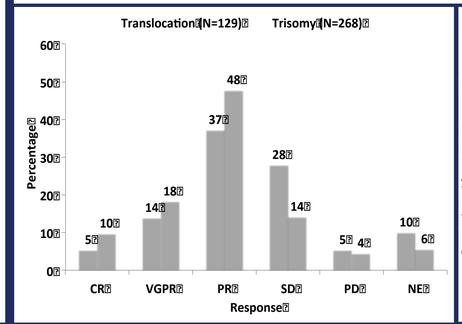
- We hypothesized that the underlying molecular subtype of myeloma determines the response to specific therapy employed and the survival outcomes after therapy.

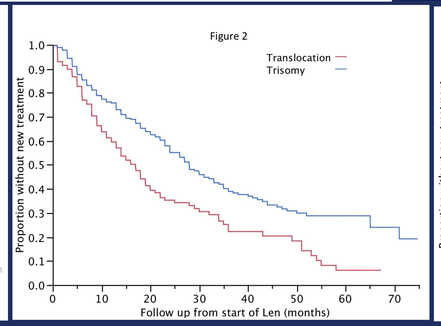
Methods and Patients

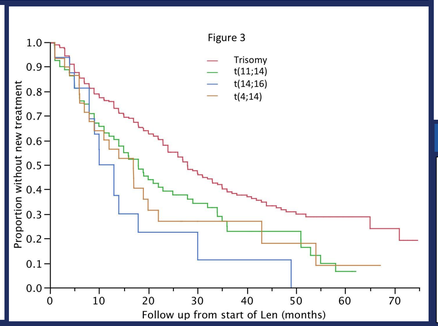
- We elected to study patients treated with Lenalidomide (Len) based regimens to examine this question, given the large proportion of patients getting Len-Dex in our practice for initial therapy of MM.
- We examined a cohort of 518 patients with available FISH results, who had been exposed to Len-based regimens.
- Medical records were reviewed and data regarding the best response and time to next therapy following treatment with Len-based regimen was obtained.
- Data from the first use of Len was collected. Len was given in with Dex with or without alkylators in combination.
- Patients who received a combination of IMiD and bortezomib as their first exposure to Len were excluded.
- Patients were grouped according to whether FISH showed a trisomy or an IgH translocation.
- Responses were measured using the IMWG uniform response criteria. Survival estimates were done using Kaplan Meier Method and curves compared using log rank test.

Results

- Median age was 62 (28-91); 190 (37%) were > 65 years
- The median estimated follow up from diagnosis was 52 months (95% CI; 50, 54); 359 patients (69%) were alive at the time of analysis.
- IgH translocation without trisomy was seen in 129 patients (30%); trisomy of one of the odd numbered chromosome was seen in 268 (62%) patients; 34(8%) had both translocations and trisomies.
- IgH translocations included t(11;14) in 92 patients (18%), t(4;14) in 45 patients (9%), and t(14;16) in 21 patients (4%)
- For the current analysis, we included only patients with either a translocation or trisomy (n=397) excluding those with neither or both of the abnormalities.
- The median time to start of Len from diagnosis was 0 months (range, 0-64). Lenalidomide based regimen was the initial therapy in X patients.
- Len-Dex was used in 458 (88%) patients, while the remaining patients received Len in combination with either cyclophosphamide or melphalan.
- A PR or better was seen in 80% of patients with trisomy compared with 63% of the patients with translocation (p<0.001); response rates were similar among the different translocation types.







- The median TTNT was 28 months among trisomy patients compared with 17 months for translocated patients (p<0.001, left figure). The median TTNT was similar across the different types of translocations (right figure).
- Among this group, 134 patients proceeded to an autologous SCT after Len induction. Among these patients, no difference was seen in terms of TTNT (29 months for patients with translocation vs. 28 months for those with trisomy (p=0.8).
- Finally, the TTNT was no different if Len was used with Dex or as part of an alkylator combination.

Figure 1: Best response to Len based therapy based on the cytogenetic type

Figure 2, 3: Time to next therapy (TTNT) following treatment with a Len based regimen based on the genetic subtype (**Fig 2**) or specific abnormalities (**Fig 3**)

Conclusions

- The current data supports the hypothesis that the underlying primary genetic abnormality can affect the response to a particular therapy.
- In this study response to Len was significantly higher in myeloma with trisomy compared with IgH translocated myeloma.
- Based on our study, newly diagnosed patients with evidence of trisomy on FISH could be considered for a Len-based regimen such as lenalidomide-low dose dexamethasone.
- Additional studies should examine if use of bortezomib in patients with IgH translocation will lead to better outcomes compared with Len based therapies.
- This would allow development of therapies directed based on genetic abnormalities and enable best outcomes with the least toxicity and cost

Disclosures

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