



Letter to Editor

Double hit/triple hit multiple myeloma: Myeloma with worse prognosis

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Sir!

Multiple myeloma (MM) accounts for 10% of all hematological cancers and in addition to the biochemical biomarkers, bone marrow findings, cytogenetic and molecular indicators have been accepted as crucial components of assessment.

Risk assessment in newly diagnosed multiple myeloma patients is the first and the most crucial determinant of treatment. With the utilization of FISH analysis as a part of routine practice, high risk Multiple Myeloma (MM) is defined as having at least one of the mutations related with poor prognosis including; t(4;14) t(14;16), t(14;20), del 17p, p53 mutation, gain 1q and del 1p. Risk stratification in hematological malignancies are of prognostic importance.

Risk stratification of MM is generally based on Fluorescence in Situ Hybridization (FISH) method. High risk MM is defined as having at least one of the mutations related with poor prognosis including; t(4;14), t(14;16), t(14;20), del 17p, p53 mutation, gain 1q and del 1p. As per Mayo clinic MM risk stratification guidelines, if two of the high risk genetic abnormalities are found, it is named as DOUBLE HIT MM and having any three is defined as TRIPLE HIT MM.¹⁻⁴

From this perspective, double or triple hit MM might be related with even poorer outcomes MM is still accepted as incurable and eventually all patients relapse. Therefore, it is important to notice which patient may bear a higher risk in

the initial diagnostic period.

1. Discussion

The heterogeneity of the clinical course of MM has been one of the major challenges, to predict the rapid progression of the disease. The prognosis has been suggested to be dependent on tumor burden (stage of the disease), patient's condition and comorbidities, access to treatment and disease biology. To identify disease biology, it is important to know bone marrow plasma cell immunophenotype and certain aberrancies, the rate and capacity of the plasma cell proliferation, the presence of plasma cells in circulation and cytogenetic abnormalities. At the time of diagnosis, it is recommended to determine specific cytogenetic abnormalities using FISH method.⁵⁻⁸

Due to the slow proliferation capacity of plasma cells in MM, FISH method rather than the metaphase cytogenetic method is regarded to be plausible for the detection of translocations in clonal cells. One of the major disadvantages of FISH method is the dependency to the quantity of bone marrow plasma cell percentage. Interphase FISH method with plasma cell enrichment by CD 138 labelling rather than examining on cultured bone marrow samples are suggested for higher detection rates of genetic abnormalities. While the genetic abnormalities in these clonal cells contribute to the nature and aggressiveness of MM, tissue microenvironment, which is the interaction and response of the surrounding bone marrow to these malignant

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cells are thought to contribute to the poor prognosis of these patients. In this perspective, some patients may harbour an ultra-high risk disease classified as double-hit or triple-hit MM. Besides FISH method, Next generation sequencing (NGS) method has been more and more popular in MM as well as in all other hematological malignancies and premalignant conditions.

2. Conclusion

Proteasome inhibitors and immunomodulatory drugs are the drugs that have changed the outcome and dramatically prolonged the survival of MM even in high risk patients. The evolution of monoclonal gammopathy of undetermined significance to overt MM with the addition of extra genetical evolution and instability step by step shows us a great example of cancer stem cell theory. Double or triple hit MM may find their place as the last ring in this theory. As double-hit or triple-hit lymphomas are accepted to need intensive treatment compared to standard risk patients, it may be attributed to MM as a concern that double hit or triple hit MM patients should also be treated more intensively. Patients with one or two high-risk abnormalities had lower overall survival than patients with no high-risk abnormality. Double Hit or Triple Hit MM should be better defined so that individualized therapy in MM can be started.

3. Source of Funding

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4. Conflict of Interest

None.

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