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NPM1, General AML

Evaluation of Minimal Residual Disease in Acute Myeloid Leukemia with NPM1 Marker

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Assessment of Minimal Residual Disease (MRD) predicts early recurrence and long-term survival in AML patients. NPM1 mutations are considered as one of the most sensitive and specific molecular markers that can be used to predict response of chemotherapy. This mutation may provide a reliable indication of MRD.

Ghandforoush N. A *et al.* retrospectively analyzed a small sample of patients (n = 11) with the NPM1 mutation at diagnosis who were followed up (median follow-up duration after chemotherapy was 11 months). Their results were published in Int J Hematol Oncol Stem Cell Res in July 2016.

Despite the small sample size the key findings were:

- The percent of NPMmut/ABL level showed a range between 132 and 757 with a median of 383.5 in samples at diagnosis.
- The median NPMmut transcript level log reduction was 3 logs and relapse occurred in 54.5% of patients (n=6)
- On the basis of MRD kinetics in 11 patients who were monitored after treatment, distinct patterns of NPM1mut transcript level reduction were observed as follows:
- Two patients showed good response to treatment with more than 5-log reduction in the NPM1mut levels. They were subjected to allo and auto-HSCT 3 and 4 months after diagnosis and in their first CR, respectively. They did not relapse during the follow-up (mean: 10.5 months).
- Four patients showed 4-log reduction in the NPM1mut levels. During follow-up, 2 of them had a gradual increase in mutant transcript levels and finally in both of them relapse occurred after 6 months. The 2 other patients showed steady decline in NPM1mut levels (one of them was undergoing allogenic transplantation) and were in complete remission at last follow-up (mean: 20.7 months).
- Two patients with 3-log reduction in mutant transcripts experienced relapse during average 9.5 months of follow-up. In one case recurrence and death occurred 2 and 3 months after allo-HSCT, respectively.
- Relapse and death occurred in 2 of the 3 patients with a 1-log reduction in NPM1mut levels (mean follow-up: 7.25 months).

This study is clearly exploratory owing to the very small sample size, as such it is difficult to draw any concrete conclusions. However, the observations suggest that levels of mutant NPM1 reduction after induction treatment can be considered important for patient outcomes. This study provides a basis to further investigate the impact of NPM1 mutations on patient outcomes.

Abstract

BACKGROUND:

Minimal residual disease (MRD) tests provide early identification of hematologic relapse and timely management of acute myeloid leukemia (AML) patients. Approximately, 50% of AML patients do not have clonal chromosomal aberrations and categorize as a cytogenetically normal acute myeloid leukemia (CN-AML). About 60% of adult CN-AML has a mutation in exon 12 of NPM1 gene. This mutation is specific for malignant clone and potentially is a good marker of MRD. In this retrospective study, we set up a quantitative test for quantifying NPM1 type A mutation and AML patients carrying this mutation at the time of diagnosis, were followed-up. Materials and Methods: We prepared plasmids containing a cDNA fragment of NPM1 and ABL genes by PCR cloning. The plasmids were used to construct standard curves. Eleven patients were analyzed using established method. Serial PB and/or BM samples (n=71) were taken in 1-3 months intervals (mean 1.5-month intervals) and median follow-up duration after chemotherapy was 11 months (5-28.5 months).

RESULTS:

In this study, we developed RNA-based RQ-PCR to quantitation of NPM1 mutation A with sensitivities of 10((-5)). The percent of NPMmut/ABL level showed a range between 132 and 757 with median of 383.5 in samples at diagnosis. The median NPMmut transcript level log reduction was 3 logs. Relapse occurred in 54.5% of patients (n=6), all cases at diagnosis demonstrated the same mutation at relapse. In patients who experienced relapse, log reduction levels of NPM1 mRNA transcript after therapy were 4 (n=2), 3 (n=2) and 1 log (n=2). Totally, NPMmut level showed less than 5 log reduction in all of them, whereas this reduction was 5-6 logs in other patients.

CONCLUSION:

Despite the limitations of this study in terms of sample size and duration of follow-up, it showed the accuracy of set up for detection of mutation and this marker has worth for following-up at different stages of disease. Because of high frequency, stability, specificity to abnormal clone and high sensitivity, NPM1 is a suitable marker for monitoring of NPMc+ AML patients.

References

1. Ghandforoush N. *A.* *et al.* Evaluation of Minimal Residual Disease in Acute Myeloid Leukemia with NPM1 Marker. Int J Hematol Oncol Stem Cell Res. 2016 Jul 1;10(3):147-52