CHROMOSOMAL ABNORMALITIES DETERMINE OUTCOME IN NPM1MUT/FLT3-ITDNEG/LOW ACUTE MYELOID LEUKEMIA

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EHA Library. Angenendt L.

Jun 16, 2019; 267368

Abstract: S1614

Type: Oral Presentation

Presentation during EHA24: On Sunday, June 16, 2019 from 08:30 - 08:45

Location: Forum Hall

Background

Nucleophosmin 1 (*NPM1*) mutations confer a favorable prognosis in acute myeloid leukemia (AML) when an internal tandem duplication (ITD) in the *fms related tyrosine kinase 3* gene (*FLT3*) with a high allelic ratio is absent (*FLT3*-ITD$^{neg/low}$). The prognostic impact is considered to be independent of the karyotype, most influentially in the most recent 2017 ELN genetic risk classification. Here we investigate the validity of this assumption.

Aims

This study investigates the prognostic impact of concomitant cytogenetic abnormalities in *NPM1*^{mut}/*FLT3*-ITD$^{neg/low}$ AML.

Methods

We analyzed the impact of karyotype on outcome in intensively treated patients with *NPM1*^{mut}/*FLT3*-ITD$^{neg/low}$ AML who were prospectively enrolled in registry databases from nine international study groups or treatment centers. *NPM1*^{wt}/*FLT3*-ITD$^{neg/low}$ AML patients with adverse cytogenetic abnormalities from the same cohorts served as comparator for adverse risk.

Results

We identified 2426 patients with *NPM1*^{mut}/*FLT3*-ITD$^{neg/low}$ AML. 2000 (82.4%) of these had a normal and 426 (17.6%) had an abnormal karyotype, including 329 (13.6%) patients with karyotype abnormalities of intermediate risk and 83 (3.4%) patients with karyotype abnormalities of adverse risk. In patients with *NPM1*^{mut}/*FLT3*-ITD$^{neg/low}$ AML, adverse cytogenetics were associated with lower complete remission (CR) rates (87.7%, 86.0%, and 66.3% for normal, aberrant intermediate, and adverse karyotype, respectively; $P < .0001$), inferior overall (5-year OS, 52.4%, 44.8%, 19.5%; $P < .0001$) and event-free survival (5-year EFS, 40.5%, 35.8%, 18.0%; $P < .0001$), and a higher cumulative incidence of relapse (5-year CIR, 43.6%, 44.2%, 51.9%; $P = .0012$). Cytogenetic risk remained independently associated with all endpoints in multivariable mixed-effects regression analyses adjusted for known clinicopathological risk factors ($P < .0001$ for all endpoints). In patients with

adverse risk chromosomal aberrations, we found no significant influence of the *NPM1* mutational status on outcome.

Conclusion

This international collaborative study reveals that cytogenetic abnormalities are important determinants of outcome in *NPM1*^{mut}/*FLT3*-ITD$^{neg/low}$ AML. Most importantly, *NPM1* mutated patients with the *FLT3*-ITD$^{neg/low}$ genotype and adverse risk cytogenetics share the same unfavorable prognosis as their *NPM1* wildtype counterparts and should be classified accordingly