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Clonal heterogeneity in differentiation response and resistance to the IDH2 Inhibitor enasidenib in acute myeloid leukemia

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Published data from a phase I/II dose escalation and expansion study (NCT01915498), which evaluated the safety and efficacy of enasidenib (AG-221), a first-in-class, oral, selective inhibitor of mutations in isocitrate dehydrogenase 2 (IDH2), in patients with mutant IDH2 relapsed or refractory (R/R) acute myeloid leukemia (AML) demonstrated that enasidenib monotherapy was well tolerated and led to an overall response rate of 40.3% by promoting differentiation.[1,2] The clonal basis of response and the clonal mechanism of acquired resistance to enasidenib is not yet understood, hence the rationale for this study published in Nature Medicine by a group of international researchers.

One-hundred and seventy-six patients with R/R AML were enrolled in this phase I/II study. The researchers specifically studied a cytogenetic and genetically representative subset of 37 patients that were enriched in enasidenib responders (n = 30).

The researchers first quantified using flow cytometry the hematopoietic stem/progenitor, precursor and mature myeloid populations in 15 patients at trial entry. Differentiation arrest in these patients resulted in 11/15 patients having abnormally expanded progenitor-like compartment and 4/15 had an abnormally expanded myeloid compartment (precursor AML). Further analysis of bone marrow samples of five patients who achieved complete remission after enasidenib therapy demonstrated that there was a near normalization of the sizes of the stem/progenitor compartments. Hence, “enasidenib rebalanced progenitor and precursor compartment sizes and restored progenitor function”.

In order to understand how enasidenib could have directly or indirectly restored differentiation, the clonal basis of differentiation in response to enasidenib was investigated in six patients. Samples from patients were analyzed at multiple time points; before and after treatment and relapse. Analysis of one patient showed that at the start of therapy, the patient had the presence of wild-type cells with three mutant clones. At CR, a majority of the hematopoietic clones did not have mutations present thus indicating that “in a minority of patients enasidenib therapy resulted in the restoration of wild-type hematopoiesis from wild-type cells”. Furthermore, in one patient, enasidenib promoted differentiation from terminal clones. In four patients, enasidenib driven differentiation was seen from terminal clones.

Regardless of a median survival of 18-21 months in patients who respond to enasidenib, most patients eventually relapse. The researchers investigated the mechanisms leading to relapse in patients by measuring the 2-HG levels in 16 patients at diagnosis and relapse. At relapse, there was no second site IDH-2 mutations and 2-HG levels remain suppressed in 14/16 patients between best response and relapse thus indicating that enasidenib is effective at inhibiting the mIDH2 enzyme. Interestingly, seven patterns of clonal evolution with the acquisition of recurrent AML-associated genetic changes were detected. Clonal evolution at relapse was associated with acquisition of IDH1 codon R132 mutations which resulted in a rise in 2HG (n = 2), deletion of chromosome 7q (n = 4), gain of function mutations in genes (FLT3, CSF3R) encoding

cytokine receptors (n = 4), and mutation in genes (GATA2, RUNX1) coding for hematopoietic transcription factors (n = 4). Clonal evolution at relapse also associated with genes not previously implicated in AML including NFKB1, DDX1, MTUS1, DHX15 and DEAF1.

In summary, "enasidenib therapy led to a clone specific differentiation response either from a terminal or ancestral clone thus leading to a near normalization of the sizes and functionality of progenitor and precursor hematopoietic compartments with an altered clonal mix". Additionally, acquired resistance to enasidenib therapy was not due to a second mutation but rather as a result of clonal evolution.

The researchers concluded by stating that their study demonstrates "how mapping of clonal structure in cell populations at different stages of differentiation can reveal the response and evolution of clones during treatment response and relapse".

References

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