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IDH1/2

The impact of 2-hydroxyglutarate levels, *IDH1/2* mutational status on the outcomes of patients with newly diagnosed acute myeloid leukemia

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Mutations in isocitrate dehydrogenase (*IDH*) 1 and 2 are found in approximately 15–25% of patients with acute myeloid leukemia (AML). 2-hydroxyglutarate (2HG), an oncometabolite of α-ketoglutarate, has been previously studied as a disease biomarker. Andrew M. Brunner from Massachusetts General Hospital, Boston, MA, USA, and colleagues conducted a study to examine 2HG as a potential biomarker of disease activity and response, the role of 2HG regarding the type and clonal burden of *IDH1/2* mutations, and whether the above factors can predict outcomes and support treatment decision-making for newly diagnosed patients with *IDH1/2* AML who received standard chemotherapy. The paper was published in *Cancer* in November 2018.

In total, 202 patients (median age = 65 years; range, 19–87), who had *IDH1/2* mutation status available, were included in this analysis. Initial treatment with '7 + 3' chemotherapy was administered in 140 cases (69%). Fifty-seven patients (28%) received HMA-based therapy, five patients received alternative induction regimens such as topotecan plus cytarabine (four patients) or intermediate dose of cytarabine (one patient). Serum, urine, and bone marrow samples were assessed to measure 2HG levels.

Key findings:

- Fifty-one (25.2%) patients harbored *IDH1/2* mutations
- There was no significant difference found in *IDH1/2*-mutated and wild-type patients regarding complete response rates, $P = 0.24$
- There was no significant difference found in *IDH1/2*-mutated and wild-type patients in overall survival, $P = 0.309$
- Elevated 2HG levels were found in patients harboring *IDH1/2* mutations in serum ($P < 0.0001$), urine ($P < 0.0001$), marrow aspirate ($P < 0.0001$), and aspirate cell pellet samples ($P < 0.0001$)
- Serum 2HG level > 534.5 ng/mL was found to be 98.8% specific for *IDH1/2* mutations
- The 2-year event-free survival and OS of IDH1/2- mutated patients receiving '7 + 3' chemotherapy were 44% and 57%, respectively
- There was no significant difference in EFS ($P = 0.40$) or OS ($P = 0.49$) between *IDH1/2*-mutated (n = 102) patients and wild-type patients (n = 38) who received '7 + 3' chemotherapy
- Day-14 serum 2HG levels at baseline significantly correlated with inferior event-free survival: HR = 6.5; $P = 0.047$
- Day-14 serum 2HG levels at baseline showed significant correlation with poor overall survival: HR = 24.5; $P = 0.019$

In summary, “among patients with IDH1/2-mutated AML, 2HG levels are highly specific for the mutational status at diagnosis, and they have prognostic relevance in patients receiving standard chemotherapy." In addition, initial 2HG levels had a significant predictive value for *IDH1/2* mutations during induction chemotherapy. This will allow to better identify early treatment strategies, moreover, early identification of mutations may help to guide patient-tailored treatment options from the outset of *IDH1/2* mutated AML. Larger trials are underway evaluating AML patients with *IDH1/2* mutations and further studying 2HG and clonal dynamics with combination therapies including mutant *IDH1/2* inhibitors (NCT02677922, NCT02632708). These clinical trials will deliver a further understanding of monitoring responses and targeting interventions in patients with AML.

References

1. Brunner A.M. *et al*. Isocitrate dehydrogenase 1 and 2 mutations, 2-hydroxyglutarate levels, and response to standard chemotherapy for patients with newly diagnosed acute myeloid leukemia. Cancer. 2018 Nov 13. DOI: 10.1002/cncr.31729. [Epub ahead of print].
