Circulating tumor dna sequencing for very early molecular evaluation of response to immune checkpoint blockade in patients with hodgkin lymphoma

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Abstract

Background

Due to its effectiveness, immune checkpoint blockade (ICB) in combination with chemotherapy has been established as a possible standard of care for previously untreated classic Hodgkin lymphoma (HL) recently. Determining whether ICB alone may be sufficient to achieve long-term remission in a subset of these patients and the development of biomarkers for their identification remains a high unmet medical need. We recently developed a technically and clinically validated circulating tumor (ct)DNA sequencing assay for genotyping and simultaneous detection of minimal residual disease (MRD) and - based on this assay - a biological classification of HL with one of the subgroups being characterized by an immune escape geno- and phenotype that might be particularly susceptible to ICB.

Objective

To assess MRD after sequential application of ICB and chemotherapy in patients with HL across biologic subgroups.

Methods

The GHSG phase II NIVAHL trial evaluated an either sequential or concomitant combination of AVD chemotherapy with the anti-PD1 antibody nivolumab (N) for patients with previously untreated, early-stage unfavorable HL. ctDNA sequencing was performed as previously described using plasma samples obtained at baseline, 7-10 days after the first infusion and at all three imaging response assessments.

Results

Samples were available from 69 (baseline), 23 (after one infusion), 30 (first restaging), 24 (second restaging) and 24 (end of treatment) patients, respectively. Strikingly, no MRD was detectable in 6/19 (31.6%) patients following just one infusion of nivolumab. Patients with a biologic subgroup characterized by an immune escape geno- and phenotype were more likely to achieve MRD negativity compared with patients with a biologic subtype characterized by a high tumor mutational burden including recurrent genetic alterations in key oncogenic pathways of HL (50% vs. 23.1% of patients). At later timepoints, assessment of MRD allowed for the detection of complete remission also in patients with remaining metabolic activity by positron emission tomography (PET), thus improving the performance of Deauville-score based PET assessment alone.

Conclusion

ctDNA-based biologic classification and early phase MRD assessment might enable the selection of HL patients with exceptional benefit from anti-PD1 ICB and reduction or omission of chemo- and/or radiotherapy in future clinical trials.

Do you have any conflicts of interest?

Yes, I have a conflict of interest.

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