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Cancer Aneuploidy May Predict Responses to Immunotherapy in Patients with Non-small Cell Lung Cancer

PHILADELPHIA – Lower levels of cancer aneuploidy were associated with more favorable outcomes after immune checkpoint inhibition in patients with non-small cell lung cancer (NSCLC), according to data presented during Week 1 of the virtual AACR Annual Meeting 2021, held April 10-15.

"Cancer aneuploidy, which is an unbalanced number of chromosomes in cancer cells, is a widespread alteration in NSCLC and is associated with altered immune signaling; however, the functional significance of cancer aneuploidy remains unclear," said presenting author João Alessi, MD, a research clinical fellow at Dana-Farber Cancer Institute. Despite the availability of predictive biomarkers, such as PD-L1 expression and tumor mutational burden, fewer than 50 percent of patients with NSCLC respond to immune checkpoint inhibition, highlighting the need for additional markers to identify patients likely to respond to the treatment, he explained.

In this study, Alessi and colleagues retrospectively analyzed the association between cancer aneuploidy and response to anti-PD1/PD-L1 immune checkpoint inhibition in patients with NSCLC. The analysis included data from 279 patients who were treated with this therapy and whose tumors underwent next-generation sequencing. Tumors were assigned an aneuploidy score, which was defined as the total number of altered chromosome arms and ranged from 0 (no altered chromosome arms) to 39 (alterations in all examined chromosome arms).

The researchers found that patients with complete or partial responses to immune checkpoint inhibition had a significantly lower aneuploidy score compared with those with stable or progressive disease (median aneuploidy score of 4 vs. 7). Patients with cancer aneuploidy scores less than or equal to 2 had significantly higher overall response rates (43.0 percent vs. 19.8 percent), significantly longer progression-free survival (6.2 vs. 2.9 months), and significantly longer overall survival (19.8 vs. 13.8 months) than patients with aneuploidy score greater than 2.

Aneuploidy score was significantly associated with progression-free and overall survival even after adjusting for other factors, such as performance status, oncogenic driver mutation, PD-L1 expression, tumor mutational burden, and line of treatment. After adjustment, patients with aneuploidy score less than or equal to 2 were 28 percent and 36 percent more likely to have improved progression-free and overall survival, respectively, compared with patients with aneuploidy score greater than 2.

Alessi and colleagues also found that tumors with low aneuploidy scores had significantly higher numbers of immune cells positive for CD8, Foxp3, and PD-1. The presence of these inflammatory markers indicates that tumors with low aneuploidy may be more immunogenic than those with higher aneuploidy levels, which could contribute to increased responses to immune checkpoint inhibition. Aneuploidy score was not associated with PD-L1 expression or tumor mutational burden, suggesting that aneuploidy score could serve as an independent predictive biomarker.

"Given the burgeoning number of recommended molecular tests for NSCLC, next-generation sequencing offers an opportunity for aneuploidy assessment," said Alessi. "Incorporating aneuploidy score in molecular testing may aid treatment decisions and clinical trial design."

A limitation of the study was that it was a retrospective analysis of cases from a single cancer center. Alessi cautioned that further data from prospective studies are needed to validate the associations the researchers observed and to determine the optimal aneuploidy score threshold for predicting responses. Sample purity and the lack of a standard method to measure aneuploidy were additional limitations. Alessi noted that samples with low purity were removed from the analysis.

The study was supported by the Dana-Farber Cancer Institute. Alessi declares no conflicts of interest.

Abstract

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Abstract Body: **Introduction:** Cancer aneuploidy, an unbalanced number of chromosomes, is associated with somatic mutation rate, expression of proliferative genes, and altered immune signaling. Whether aneuploidy impacts clinical outcomes to immune checkpoint inhibitors (ICIs) in NSCLC is unknown.

Methods: In NSCLCs which underwent targeted next-generation sequencing (NGS), we retrospectively analyzed the aneuploidy score (AS), defined as the sum of the number of altered chromosome arms, among patients treated with immune checkpoint inhibitors. An unbiased recursive partitioning (URP) algorithm was used to investigate an optimal AS cut-off with respect to objective response rate (ORR). Multiplexed immunofluorescence (mIF) to quantify CD8+, FOXP3+, PD-1+ immune cells, and PD-L1 was performed to determine differences in tumor immune cells subsets according to AS cut-off.

Results: Among 279 patients with NSCLC treated with ICIs, the median AS was 6 (range 0 to 23). The AS was significantly lower among patients with a partial response to ICI compared to those with stable or progressive disease (4 vs 7, P=0.004). An unbiased recursive partitioning analysis identified an AS of 2 as the strongest discriminator of objective response to ICI. Compared to patients with an AS >2 (N= 207, 74.2%), patients with AS ≤2 (N=72, 25.8%) had a significantly higher overall response rate (ORR 43.0% vs 19.8%, P<0.001), a significantly longer median progression free survival (mPFS 6.2 months vs 2.9 months, HR: 0.70 [95% CI: 0.52-0.94], P=0.02), and a significantly longer median overall survival (mOS 19.8 months versus 13.8 months, HR: 0.66 [95% CI: 0.47-0.94], P=0.02) to treatment with ICIs. After adjusting for other variables such as performance status, presence of oncogenic driver mutation, PD-L1 expression, tumor mutational burden, and line of treatment, AS was significantly associated with improved mPFS (HR: 0.72 [95% CI: 0.52-0.99], P=0.04) and mOS (HR: 0.64 [95% CI: 0.44-0.94], P=0.02). Among 179 NSCLCs profiled by multiplex immunofluorescence, compared to cancers with an AS >2, those with low aneuploidy (AS ≤2) had significantly higher numbers of CD8+, FOXP3+, PD-1+ immune cells, and PD-1+ CD8+ T cells, both intratumorally and when looking at the total numbers of cells within the tumor and the tumor-stroma interface. There was no significant difference in PD-L1 expression levels or tumor mutational burden on tumor cells or on immune cells according to aneuploidy score.

Conclusion: NSCLCs with low aneuploidy have a distinct immune microenvironment and more favorable outcomes to ICIs.

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