New Combination Therapy Shows Promise for Aggressive Lymphoma Resistant to Immunotherapy

Epigenetic therapy boosted immunotherapy response in refractory natural killer/T-cell lymphoma by turning cold tumors hot.

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Combining an epigenetic therapy with an anti-PD-1 antibody, which uses the body's natural response to viral infections, showed promising results in patients with relapsed or refractory natural killer/T-cell lymphoma (R/R NKTL), a rare and aggressive cancer with limited treatment options, according to a study published in Cancer Discovery, a journal of the American Association for Cancer Research (AACR).

"R/R NKTL is a rare subtype of non-Hodgkin lymphoma that currently has no standard treatment strategy," said Jing Tan, PhD, author of this study and principal investigator in the State Key Laboratory of Oncology in South China at the Sun Yat-sen University Cancer Center.

Anti-PD-1 therapy, which involves helping the immune system to better find and attack the cancer cells, has shown promise for R/R NKTL treatment, but many patients either do not respond or develop resistance, he explained.

DNA methyltransferase (DNMT) inhibitors are epigenetic modifying enzyme drugs that can activate silenced genes called endogenous retroviral elements, said Choon Kiat Ong, PhD, coauthor and principal investigator in the Lymphoma Translational Research Laboratory at the Division of Cellular and Molecular Research at the National Cancer Centre Singapore. Endogenous retroviral elements are remnants of ancient viral infections now embedded in the human genome, and when activated, put the body's immune system into high alert, a process called "viral mimicry," he explained.

"We hypothesized that DNMT inhibitors could trigger viral mimicry and change a 'cold' tumor 'hot,' thereby restoring NKTL sensitivity to anti-PD-1 therapy," said Ong.

Tan and collaborators conducted a retrospective analysis of 21 patients with R/R NKTL who initially responded to anti-PD-1 therapy but subsequently experienced disease recurrence. The researchers treated these patients with a combination of the PD-1 inhibitor sintilimab [Tyvyt; not

yet approved in the U.S.] and either decitabine or azacitidine, both DNMT inhibitors. Preclinical mouse models were also developed to study mechanisms of resistance and response.

Of the 21 patients, 10 had complete remission and four had a partial response following treatment with the combination.

The two-year overall survival rate was 50.2%. “This new therapy achieves a significantly improved median overall survival, compared to the three-month benchmark for patients whose disease has progressed after anti-PD-1 treatment, and this combination therapy can potentially be curative for a subset of patients who experience recurrence,” said Huiqiang Huang, MD, coauthor and principal investigator working alongside Tan in the same facility.

“Our study highlights the utility of DNMT inhibitors in switching on the immune response through viral mimicry,” said Huang. “This combination therapy offers a scientifically validated and immediately accessible option that could significantly improve survival for patients with R/R NKTL,” he added.

Preclinical data showed that DNMT inhibitors reversed immune resistance by demethylating (activating) endogenous retroviral elements. Tan and collaborators showed that this activation caused an immune response through a specific mechanism called the type 1 interferon signaling pathway, attracting the CD8-positive T cells into the tumor, making it vulnerable to attack.

This finding is consistent with previous studies on other cancer types suggesting that viral mimicry response presents a promising strategy to enhance the effectiveness of immunotherapy delivered to tumors, said Tan.

A limitation of this study is its retrospective nature and small sample size, which may introduce selection bias, limiting the applicability of this study’s findings to a wider population. Another limitation is the rarity of NKTL and the retrospective design constraining the researchers’ ability to obtain sufficient tumor tissue for comprehensive profiling and analysis. Further, although the preclinical model used in the study demonstrated that the acquired resistance to anti-PD-1 treatment was associated with the typical features of “cold” tumors, the exact tumor microenvironment characteristics in NKTL patients were not investigated in this study.

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