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Combining epigenetic therapies with immunotherapies likely to improve cancer patient outcomes

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Recent data suggest that epigenetic therapies are likely to provide additional clinical benefit to cancer patients when rationally combined with immunotherapeutic drugs, according to a review published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

"The term epigenetics refers to the study of cellular changes in gene expression that are heritably transmitted during cell replication," said Michele Maio, MD, PhD, chair of medical oncology and immunotherapy, Ospedale Santa Maria alle Scotte, Istituto Toscano Tumori, in Siena, Italy. "Epigenetic modifications do not involve structural alterations of the DNA sequence, as in the case of genetic mutations. Instead, they are chemical modifications of the DNA structure at specific sites that lead to the 'hypermethylation' or 'hypomethylation' of specific DNA elements that regulate gene expression.

"Cancer was the first human disease in which epigenetic modifications were found to play an important role in development and progression," explained Maio.

Maio said that his team recently provided comprehensive evidence demonstrating that epigenetic changes play a major role in downregulating or shutting off the expression of certain cell-surface

molecules that play a crucial role in the efficient recognition and elimination of cancer cells by the immune system. As a result, cancer cells become "invisible" to the immune system, which cannot eliminate them from the body. "Based on experimental evidence from our studies, we expect that epigenetic drugs could be efficiently utilized to restore the expression of these molecules, thus rendering cancer cells again 'visible' to the immune system to effectively eliminate them," Maio said.

In addition, epigenetic drugs can also act by lowering or eliminating specific subsets of immune cells such as myeloid-derived suppressor cells, which have been shown to facilitate tumor growth, Maio explained.

Maio and colleagues delineated in this review article evidence from preclinical studies that provides the rationale behind combining epigenetic therapies with immunotherapies such as interleukin-2 therapy, adoptive T-cell transfer, and immune checkpoint inhibitors, among others.

"The data we generated in a mouse model demonstrated that combining epigenetic drugs, such as the DNA methyltransferase inhibitors (DNMTi) 5-aza-2?-deoxycytidine and guadecitabine, with immunomodulating antibodies that target CTLA-4 or the PD-1/PDL-1 immune checkpoint improves the therapeutic efficacy of each drug utilized alone. Based on this experimental evidence, we have now designed a phase Ib clinical trial in which guadecitabine and the anti-CTLA-4 immunomodulating monoclonal antibody ipilimumab will be given in sequence as first-line or second-line therapy to metastatic melanoma patients; this study is sponsored by the NIBIT Foundation and partially supported by Astex Pharmaceuticals," Maio added.

The review article also provides a comprehensive overview of all ongoing clinical trials that are evaluating combinations of epigenetic drugs and immunotherapy against many cancer types, including

leukemias, metastatic melanoma, metastatic kidney cancer, peripheral neuroectodermal tumors, non-small cell lung cancer, and metastatic colorectal cancer.

"The major and well-known side effect of DNMTi is myelotoxicity, which poses limits to their dosage and length of administration, and needs to be carefully monitored in the course of treatment," Maio cautioned. "Along this line, combination regimens with these epigenetic drugs have to be carefully reasoned and evaluated for potential additive myelotoxicity," he added.

"Like the tango, which takes two and in perfect syntony, the most successful results with cancer immunotherapies will require a perfect interaction between patients' immune systems and their cancer cells. In light of their powerful immunomodulating potential, epigenetic drugs are seemingly the best 'partner drugs' to emerging immunotherapies to achieve this perfect interaction, and will most likely provide additional clinical benefit to cancer patients treated with state-of-the-art immunotherapeutic drugs," Maio said.

Provided by American Association for Cancer Research

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