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Novel therapy holds promise of remission in relapsed patients with diffuse large B-cell lymphoma

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A phase 2 clinical trial of a novel therapy for patients who have experienced a relapse of diffuse large B-cell lymphoma (DLBCL) resulted in extended remission, averaging 14.5 months, and longer than three years in exceptional cases. The drug, which targets histone-modifying enzymes (HME), was shown to be effective against a particular genetic mutation. The trial was initiated, designed, and coordinated by Dr. Sarit Assouline, a hematologist oncologist at the Segal Cancer Centre at the Jewish General Hospital and clinician-scientist at the Lady Davis Institute. The results were published in *Blood*.

"DLBCL is one of the more common forms of lymphoma and is highly aggressive," pointed out Dr. Assouline, Associate Professor of Medicine and Oncology at McGill University. "Following relapse, there are no effective standards of treatment and life expectancy averages six months. Our challenge is to identify new biomarkers and target specific mutations in order to improve the prognosis. While many clinical trials simply report on how patients respond to a therapy, we devised this study to reveal the mechanisms on which the therapy works in order to understand which patients would benefit."

As many as 40% of patients with diffuse large B-cell lymphoma cannot be cured with standard chemoimmunotherapy or combinations of existing treatments and stem cell transplantation. Consequently, novel approaches that delve deeper into the molecular structure of their disease

are needed. Since most DLBCL tumors contain mutations in histone-modifying enzymes, drugs known as histone deacetylase inhibitors suggested a potential pathway to significantly improve patient outcomes. Participants in the trial were given panobinostat orally in 30 mg doses three times per week.

Sophisticated genomic analyses of the mutations presented in each individual patient's tumor revealed which patients were most likely to respond, as well as distinguishing those who would not. Overall, 28% of the patients in the trial experienced a positive response to the treatment. A mutation in the gene MEF2B was found to be significantly associated with this effect (approximately 11% of patients with DLBCL have this mutation). Moreover, the patients who responded remained in remission upon terminating the therapy. At the same time, increased levels of circulating tumor DNA (ctDNA) observed in plasma samples were strongly associated with a failure to respond.

This study revealed that panobinostat seemed to impact a variety of proteins, suggesting that collecting biopsies and blood samples for analysis at intervals during treatment is a useful means for monitoring how a cancer evolves over time. This reinforces the importance of precision medicine in cancer.

A commentary by Dr. Mark Roschewski of the National Cancer Institute that accompanied the paper in Blood drew attention to "the comprehensive set of molecular predictive biomarkers used in this study." He went on to commend Dr. Assouline and her collaborators "for conducting a clinical trial that incorporates informative translational studies, and hence provides a far more nuanced result than response rates alone."

The trial included 42 patients at four Canadian sites, including the Segal Cancer Centre at the Jewish General Hospital in Montreal, between

December 2010 and December 2013.

"This trial has generated considerable data regarding methodology for processing samples from a clinical study, the genetic mutations associated with DLBCL and how they evolve over time, on ctDNA, and mechanisms of resistance to histone deacetylase inhibitors," said Dr. Assouline. "Our success is attributable to the tremendous synergy between clinical and research facilities at the JGH and Segal Cancer Centre. Having all the facilities and access to collaborators with different expertise, including the Molecular Pathology Centre, is what enables us to make the most of clinical and translational opportunities."

More information: S. E. Assouline et al. Phase 2 study of panobinostat with or without rituximab in relapsed diffuse large B-cell lymphoma, *Blood* (2016). DOI: 10.1182/blood-2016-02-699520

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