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622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

A Novel Patient-Derived Xenograft Model IO-FIVE for Drug Discovery and Precision Medicine in Lymphoma and Leukemia Patients

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Lymphoma and leukemia have been the top two hematopoietic cancers in US, leading to more than 40,000 deaths each year. Although the 5-year relative survival rates have been improved up to 60%, there is still a lot of patients showed not response to standard therapy.

Patient-Derived Xenograft model (PDX model), as the classical mouse xenograft tumor model that best represents the genetic information characteristics of human tumors, can be used to predict the therapeutic effect, and develop individualized treatment for patients. Its greatest advantage is that the model retains the microenvironment of the original tumor cells, inherits all the molecular biological properties of the primary tumor, and preserves the heterogeneity of the tumor. However, due to the factors that the loss of tumor heterogeneity in hematopoietic cancers after *ex vivo* clonal expansion and selection, and this *in vitro* assay based system could not fully reflect the host response to the drugs, including a range of novel immunotherapeutic agents such as PD-1 monoclonal antibody, CD38 monoclonal antibody, etc. With the increasing clinical use of oncology immunological agents, recently we are developing a new assay, named IO-FIVE (Immuno-Oncology drugs Fast In Vivo Efficacy test) for research and therapy, by retaining an appropriate proportion of tumor-infiltrating immune cells (and stromal cells) mixed with tumor cells when digesting clinical tumor samples or patient-derived xenografts-preserved tumor samples into cell suspensions, and then injecting them into the specialized IO-FIVE device, a modified microencapsulation and hollow fiber culture system (OncoVee® MiniPDX), which is implanted subcutaneously into mice and administered systematically for immuno-drug susceptibility testing to screen for immuno-drugs or combinations suitable for individual treatment.

The IO-FIVE testing cycle takes only 14 days and is performed using Celltiter Glo before and after the injection of cell suspensions into the specialized device. Celltiter Glo, flow cytometry and Omics (RNA-seq, DNA-seq) are used to measure the viability of total cell subpopulations, the relative ratio of tumor cells to immune cells and the alteration of cellular transcription levels in the device, in order to further explore the sensitivity of tumor tissues to the immunotherapeutic drugs and the potential molecular mechanism for the responders and non-responders.

Immune regulatory CD38 antibody Daratumumab has been tested in more than 40 acute myeloid leukemia (AML) cases, with its overall *in vivo* efficacy around 25%, which is consistent with previous research. It is interesting to uncover novel pathways for drug discovery and clinic treatment since CD38 is well expressed in most AML patients, but at least half of those CD38^{+} AML patients are not sensitive or resistant to Daratumumab monotherapy. Expression of CD38 on AML is not enough to distinguish the responder vs non-responder of Daratumumab. IO-FIVE could potentially be a companion diagnosis on AML for the patient stratification of Daratumumab. PD1 antibody Sintilimab has been tested in all the patients (12 lymphoma, 52 leukemia), and the only two laboratory PD1-Ab non-responsive T cell lymphoma patients have been showed to be clinically non-responders as well. Immunotherapy and chemical or targeted therapy combination could enhance tumor killing ability and disease control.

We will use the IO-FIVE data to further compare it with its source of real-world clinical patients to obtain more evidence-based evidence that can predict individualized treatment with immunotherapy.

Disclosures No relevant conflicts of interest to declare.

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