PRECISION ONCOLOGY NEWS

Combining Lymphoma Molecular Profiles, Microenvironment Signatures May Improve Prognosis

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NEW YORK – A research collaboration between biomedical software startup BostonGene and Weill Cornell Medicine has found that the tumor microenvironment influences the prognosis of patients with diffuse large B-cell lymphoma (DLBCL), suggesting that genomics alone may not provide a complete picture of a patient's disease trajectory.

Their results, presented earlier this month at the American Society of Hematology annual meeting, could be useful for designing more precise diagnostics and clinical trials for patients and improving understanding of why some cancer patients respond to targeted treatments and immunotherapy while others don't.

"The treatment for DLBCL has not changed for the past 20 years, and it's based on chemo-immunotherapy," said Leandro Cerchietti, a cancer researcher at Weill Cornell Medicine and the first author on the study. Although some patients have done well on that treatment, "there still remains a high proportion of patients who either will not respond, or they will relapse after the treatment," he said. "There is also a proportion of patients who have been overtreated by this approach."

Cerchietti noted that there is a need for precision oncology approaches in this setting, and that this may be achievable through more granular characterization of lymphoma cells and their environment.

In the past few years, researchers have profiled the genomes of lymphomas, defined mutations that confer good and bad prognoses, and found several clinically actionable mutations.

But according to Cerchietti, "the mutations do not explain the full spectrum of the disease."

The non-lymphoma cells lingering in the tumor's microenvironment, for example, can modify the effect of the mutations, he said. The microenvironment includes surrounding blood vessels, immune cells, fibroblasts, signaling molecules, and the extracellular matrix that encapsulate the cancerous cells. Although gene alterations driving a tumor provide information about cancer cell aggressiveness, non-malignant cells of the tumor microenvironment have the potential to promote malignant growth by supporting immune evasion and enabling the development of new blood vessels.

BostonGene and Weill Cornell researchers wanted to explore how the tumor environment and tumor mutations work together to promote malignancy. By drawing on more than 3,000 DLBCL samples from 13 datasets, including a new cohort of 127 patients seen at Weill Cornell, the researchers identified transcriptomic signatures of cells and pathways in the lymphoma microenvironment. More than 560 patient samples had information on genetic mutations available, as did 22 patients from the new cohort who had whole-exome sequencing on matched tumor and normal samples done.

The researchers then applied density-based clustering to identify four lymphoma microenvironment signatures that provided prognostic information beyond what could be gleaned from just lymphoma cell transcriptomes and mutations. Two of the signatures, named "immunosuppressive" and "mesenchymal," were associated with making tumor mutations behave better, and the other two, called "anti-tumor immunity" and "depleted," were associated with making mutations behave worse.

When patients have a tumor mutation associated with poor prognosis in a good tumor microenvironment, that mutation may not be that bad, they showed. Conversely, when patients have a tumor mutation that usually indicates a good prognosis but it is in a bad microenvironment, that mutation can be detrimental.

For example, double-hit (DH) lymphomas are well-known subgroups that harbor both BCL2 and MYC gene translocations. Considering the genetics alone, this subgroup is usually associated with a bad prognosis. However, when DH lymphomas exhibit a microenvironment subtype with a good prognosis, research by Cerchietti and colleagues showed, the prognosis of these DH lymphoma patients is usually improved.

"We classified the tumors, we considered new categories that were not considered before to increase the precision of the diagnosis," said Cerchietti. "It also offers the possibility of doing more precise clinical trials now that we have this information available for the patients."

BostonGene is planning a clinical trial with different treatment arms based on molecular profiling of the tumor and its microenvironment. A BostonGene spokesperson mentioned as an example that a subtype of DLBCL called activated B cell with a "depleted" microenvironment tends to have the most aggressive lymphomas with frequent genome hypermethylation. This type of lymphoma could benefit from the treatment with hypomethylating drugs such as azacytidine and decitabine.

Cerchietti said he sees the relationship between tumor mutations and microenvironment as an opportunity to examine current gaps in knowledge about why some drugs work well in some cancer patients but not others. "For example, checkpoint inhibitors that work really well in solid tumors don't work as well in lymphoma and we don't understand why," he said. "If we incorporate the microenvironment information, we can identify a small group of these [lymphoma] patients that would be more likely to respond to this type of treatment."

In addition, Cerchietti wants to investigate whether the different types of mutation and microenvironment combinations present areas of vulnerability that can be targeted with either existing, repurposed microenvironment-targeting agents or new molecules in preclinical studies of lymphoma.

The newly gathered data about tumor microenvironments is based on BostonGene's efforts to advance the so-called 'molecular functional portrait' (MF Portrait) of the tumor, according to Nava Almog, senior director of clinical genomics at BostonGene.

The MF Portrait is a digital reconstruction of the patient’s tumor. It visualizes the tumor microenvironment composition, tumor genetics, and activity of tumor-associated pathways for an individual patient. The patented technology can be used to assess the immune fitness and to better understand whether the tumor microenvironment is susceptible to targeted drugs or immunotherapy.

In doing so, BostonGene hopes to give physicians a better estimate of drug combinations that likely work best for a patient, and help them select patients for clinical trials. The company is pursuing collaborations with cancer centers around the US, Almog said.

"As we look into the future and gain additional information from the clinical trials and all the investigational drugs that are being tested, our hope is that comprehensive genomic tests will become more prevalent and more common in the clinic," said Almog. "We need that comprehensive analysis of the genomics of the patient — not only the tumor cells, but the microenvironment as well."