Transcriptomic Algorithm Shows Ability to Predict Progression-Free Survival in Cancer Patients

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NEW YORK – Researchers within the Worldwide Innovative Networking (WIN) Consortium are pushing ahead with research to try to show that a transcriptomic algorithm can more precisely predict the extent to which cancer patients might benefit from targeted treatments or immunotherapy compared to genomic biomarkers.

In a paper published in NPJ Precision Oncology this week, researchers co-led by Vladimir Lazar, WIN's chief scientific and operating officer, described the development of a prototype "digital display precision predictor," or DDPP, which after further prospective validation, could provide insights into not just whether patients might respond to certain treatments, which is what current companion tests assessing genomic biomarkers assess, but also estimate the extent of their outcomes on these drugs.

WIN is an effort that brings together physician-scientists from cancer centers, drugmakers, and technology companies around the world to advance precision cancer research. A few years ago, WIN researchers conducted one of the first trials, called WINTHER, that used transcriptomics to prospectively match patients to drugs. That study didn't reach its primary endpoint, but it showed that transcriptomics can match patients to drugs when DNA sequencing cannot. It also was instrumental in the development of the DDPP, which Lazar presented as a novel biomarker concept in precision oncology.

Currently, oncologists hoping to identify personalized treatment options for their patients typically test their tumors for specific genomic aberrations using a variety of methods including immunohistochemistry, fluorescence in situ hybridization, PCR, and next-generations sequencing. And while testing for overexpression of certain genes, such as HER2, is standard of care in some tumor types, such as breast and stomach cancers, currently, oncologists are not fully sequencing the RNA in tumor and normal cells to gain a comprehensive picture of how gene expression may be harnessed to direct cancer treatment.

When patients come to oncologists for the first time suspecting cancer, Lazar said, the top questions on their minds are: Do they have cancer? Is there a treatment?

And will they die of their disease? In his view, current biomarker testing methods oncologists are using to identify treatment options for patients aren't very precise.

Although DNA biomarker testing can tell you whether or not a patient is likely to respond to treatment, using these tests it is impossible to gauge the extent of a patient's response. Two patients with the same EGFR mutation driving their lung cancers may both initially respond to an EGFR inhibitor, but one patient may experience recurrence much sooner than the other.
"The major difference between DDPP and currently used technologies is that [DDPP] doesn't say 'yes' or 'no' in terms of treatment response but predicts the duration of the progression-free survival," Lazar explained. For example, "We're not saying whether patients will or won't response to everolimus [Novartis' Afinitor], but we can predict whether or not they will progress on therapy after six months, 12 months, 24 months or more. This is totally different."

In fact, in the previously reported WINTHER trial, one patient treated with the mTOR inhibitor everolimus lived without cancer progression for more than five years, but had no genomic tumor alterations, for example, in the PI2K/AKT/mTOR pathway that might explain the exceptional response. In comparison, patients with much shorter progression-free survival with gastrointestinal tract neuroendocrine tumors did have mutations in this pathway but didn't respond all that well, likely due to co-occurring resistance alterations.

To address the shortcomings of DNA biomarkers to fully explain the differences in responses seen in WINTHER, Lazar and colleagues described in the NPJ Precision Oncology paper DDPP, a transcriptomics-based algorithm that can be attuned to any drug under consideration for a patient. They demonstrated this by creating a predictive algorithm for patients likely to benefit from evorolimus using data from the WINTHER trial. To develop the algorithm, researchers first sifted through the literature and identified a list of genes associated with treatment response.

In the case of everolimus, the researchers identified 17 genes in the MTOR pathway that bind to everolimus. They then characterized the differential expression of each of these genes in the tumor and normal samples of six patients in the WINTHER trial who received everolimus and correlated this differential expression with their progression-free survival on the drug.

Lazar and colleagues ranked the individual genes in order of significance in terms of their association with progression-free survival and built a predictor by adding the genes one by one to the algorithm and assessing its ability to predict progression-free survival until adding genes no longer improved the DDPP's predictive abilities. The iteration of the predictor that performed optimally in being able to predict progression-free survival in the six WINTHER patients included eight genes: AKT2, TSC1, FKB-12, TSC2, RPTOR, RHEB, PIK3CA, and PIK3CB.

"The higher the relative expression of these key genes in tumor tissue, the longer the progression-free survival is under treatment with everolimus," Lazar's team wrote in the paper.

To further test their approach, Lazar and colleagues ran another analysis where they developed predictive algorithms using five out of the six patients who received everolimus in WINTHER, and then tested the algorithms' ability to predict progression-free survival in the patient left out. Each time there was a significant concordance between the predicted and real progression-free survival of the patients left out. However, every iteration of the predictor included different subsets of genes, which suggested to the authors that when a small number of patients is used to generate the DDPP, it may be unstable.

Lazar and colleagues did this same experiment, generating a DDPP and evaluating its ability to predict progression-free survival in patients who received the tyrosine kinase inhibitor axitinib (Pfizer's Inlyta), the MEK inhibitor trametinib (Novartis' Mekinist), the EGFR inhibitor afatinib (Boehringer Ingelheim's Gilotrif), FGFR inhibitors, and immunotherapy, and reported similar findings.

Notably, since only a minority of patients experience enduring benefit with checkpoint inhibitors, there is significant interest in strategies to predict response with more precision than available biomarkers, such as PD-L1 expression and tumor mutation burden. In this study, Lazar developed a six-gene DDPP using data from three patients who received various PD-1 inhibitors in WINTHER and painted a tantalizing picture of the insights that can be gleaned using a transcriptomics algorithm.

They used the six-gene DDPP "in silico" to model the progression-free survival that could have been experienced by 82 patients in WINTHER if they had received a PD-1 inhibitor. The algorithm predicted that nearly 60 percent of patients would have progression-free survival of six months or less on immunotherapy, with the majority living less than three months without progression. Twenty-five patients, on the other hand, would live longer than that without progression, according to DDPP predictions, and 20 percent within this group would be progression free for more than two years.

The ability of Lazar's team to generate predictors for specific drugs was limited since only a few patients received the same treatment within WINTHER. Based on these experiments, however, the researchers showed that a DDPP predictor can be developed using data from as few as three patients. However, using statistical modeling they also showed that the DDPP starts to "become very robust" once you exceed 10 patients, Lazar said.

While promising, he acknowledged that this paper is only an initial demonstration of the DDPP concept and that it will need to be prospectively validated in a larger

cohort of patients. His group has already started validating the DDPP and so far has data on 20 patients, which shows that the predictor becomes more precise and stabilizes with more patients. The group is in discussions about publishing this data.

In the current precision oncology paradigm, commercializing such a predictor may have its challenges, since the algorithm requires assessing transcriptomics in tumor and normal samples.
"Since that's still not employed, that may be a limitation," Lazar acknowledged. "But a counterpoint is that there is a benefit to patients" in terms of being able to potentially identify with greater accuracy the treatments from which they will benefit most.

Another challenge with DDPP is that transcriptomics analysis is "problematic" and "not reliable" when done on paraffin-embedded tissue blocks, Lazar said, and should be done on fresh, frozen samples. The use of fresh, frozen tissue is also currently not standard practice when it comes to biomarker analysis.

"Today the standard of care in almost all the countries is to have paraffin biopsies and tumoronly [biomarker] analysis, usually via sequencing or IHC," Lazar said, noting that whenever introducing new concepts, one must weigh the relative benefit and risk to the patient.

In the WiNTHER trial, his team previously showed that there is no added co-morbidity with additional sampling of normal tissue and patients are willing to provide it. At one time tumor tissue collection for biomarker analysis was also unusual in drug trials, Lazar reminded, and it took trials like BATTLE and others to incorporate the practice for it to take hold. Trials like
WINTHER are trying to encourage the same when it comes to tumor/normal sampling, he said.

The willingness of risk-averse drugmakers to embrace a new concept like DDPP in the companion diagnostic realm is another consideration. Pharmaceutical companies are quite comfortable at this point relying on low-cost and widely available technologies like IHC for companion diagnostics that will identify the patients who will receive their drugs on a global scale. According to Lazar, the fact that DDPP can predict the duration of progression-free survival to their drugs, not just are they likely to respond, has caught the attention of drugmakers that have partnered with WIN and are familiar with its work in this regard.

Ultimately, he proposed that stakeholders in the field need to consider if the current biomarker methods in precision oncology are truly precise. "Or are there new possibilities?" Lazar asked.
"It's interesting as an intellectual exercise to see a new prototype. Whether this will be implemented or not, only the future and further validation can say."