Precision Monitoring by Next-Generation Sequencing in Lymphoma: Circulating Tumor DNA as a New Biomarker

August 15, 2016 | Oncology Journal [1], Hematologic Malignancies Year in Review 2016 [2], Hematologic Malignancies [3], Leukemia & Lymphoma [4]
By Leo I. Gordon, MD [5]

It is clear that as our understanding of both aggressive and indolent lymphomas improves, the goals of treatment change and the bar for success is set higher.

In this review, Drs. Melani and Roschewski discuss the current state of molecular-based prediction of outcomes and monitoring of patients with lymphoma before, during, and after treatment.[1] They outline novel techniques based on a better understanding of the biology of lymphoma and on the availability of new technology that allows deeper investigation of minimal residual disease (MRD), as well as identification of relevant mutations that can be detected in the peripheral blood. This approach has the potential to change the paradigm for the management of patients with lymphomas and ultimately to improve outcomes. In aggressive lymphomas that we consider curable, measurement of circulating tumor DNA (ctDNA) in blood (“liquid biopsy”) may be used to detect minimal residual disease (MRD) and thus allow for alternate therapy; measurement of ctDNA also may alter the approach for indolent lymphomas—by allowing “selective maintenance” in patients who exhibit MRD recurrence before disease is detectable by physical examination or imaging.

It is clear that as our understanding of both aggressive and indolent lymphomas improves, the goals of treatment change and the bar for success is set higher. Numerous studies have tried to identify biomarkers that will allow for more successful outcomes and predict treatment failure and early relapse. In diffuse large B-cell lymphoma (DLBCL), most of the biomarkers to date have been clinical, relying either on patient characteristics, such as age and performance status, or on tumor characteristics, such as serum lactate dehydrogenase level and number of extranodal sites. These biomarkers informed the original International Prognostic Index (IPI),[2] and subsequent iterations of the IPI have resulted in fine-tuning.[3-6] Similarly, prognostic indices in mantle cell lymphoma[7-10] and in chronic lymphocytic leukemia[11] have evolved as predictors of outcome and guides to clinical trial interpretation. In follicular lymphoma, the Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI 2 scores have emerged and provided prognostic information,[12-14] and in classical Hodgkin lymphoma, the International Prognostic Score and its evolution in the last decade have allowed us to better understand and predict the clinical course in this heterogeneous disease.[15-17] Other biomarkers, which are based upon molecular profiles at the time of diagnosis, also exist for classical Hodgkin lymphoma.[18-20]

It has recently been recognized that perhaps more important than assessing the initial clinical or biologic features in a cohort of patients is assessment of the response to our best treatment in each individual patient. It was with that aim in mind that the concept of interim imaging techniques began to gain a foothold. Recent studies in classical Hodgkin lymphoma have identified the interim positron emission tomography (PET) scan as a new biomarker, since it turns out to be a major predictor of response. Recent data suggest that PET findings may serve as a signal to change chemotherapy regimens or to include or eliminate alternate therapeutic modalities such as radiation.[21,22] Similar studies have now been completed in DLBCL.[23]

As our technology has evolved, we are presented with the prospect of increasingly sensitive and possibly more accurate and predictive tools and models for managing patients with lymphoma and other malignancies. The concept of using ctDNA levels to monitor a malignancy is not new, and the utility of this approach has been discussed and reviewed in the literature, albeit mostly in solid tumors.[24-26] However, in lymphoid tumors, we are now able to take advantage of our understanding of lymphoid biology, so the ability to identify the variable, diversity, and joining (VDJ) regions of immunoglobulin receptors has provided a very sensitive and specific method for detection of ctDNA in peripheral blood. This has come about because our ability to combine universal polymerase chain reaction primers with next-generation sequencing (NGS) has made it possible to detect both ctDNA and tumor-specific mutations (eg,
c-MYC, CARD11, and MYD88) in DLBCL.[27] Work by Kurtz,[28] Alizadeh,[29] and Hohaus[30,31] has suggested that the detection of ctDNA with NGS-based assays can serve as our newest and possibly our most reliable biomarker. It is imperative, however, that this approach be compared against the existing clinical and biologic parameters upon which we have relied for decades.

The precision and the noninvasive quantitative nature of the techniques described by Melani and Roschewski, and their ability to detect clonotypic evolution in lymphoma, make them appealing for broad clinical use. This technology holds great promise for improving outcomes by making it possible to design treatment strategies using a rational and scientifically based approach.

Financial Disclosure: The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.


References:


Source URL:
http://www.cancernetwork.com/oncology-journal/precision-monitoring-next-generation-sequencing-lymphoma-circulating-tumor-dna-new-biomarker

Links:
[1] http://www.cancernetwork.com/oncology-journal
[5] http://www.cancernetwork.com/authors/leo-i-gordon-md