ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Burkitt Lymphoma: Analysis of the Genome

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H&O What is Burkitt lymphoma (BL), and how is it currently treated?

SD BL is a form of lymphoma that is one of the fastest growing cancers known. It was discovered almost 50 years ago by the British missionary surgeon Dennis P. Burkitt, after whom it is named. BL is rare, with approximately 2,000 new cases diagnosed every year. Children are more commonly affected than adults. HIV increases the risk of developing BL by more than tenfold. BL can be treated with intensive chemotherapy regimens that usually require the patient to stay in the hospital while receiving treatment.

H&O What have been some of the difficulties in distinguishing a diagnosis of BL from a diagnosis of diffuse large B-cell lymphoma (DLBCL)?

SD BL must be considered in the context of other lymphomas. BL can be confused with DLBCL, which is also the most common form of lymphoma in adults. However, distinguishing between the 2 entities is critically important, as there are major differences in the treatment for each disease. When treating BL, one typically employs intensive chemotherapy regimens; something that penetrates the blood-brain barrier is necessary because the tumors tend to spread to the central nervous system. Radiation tends to be avoided in these tumors, because they spread very early on. Making the distinction between BL and DLBCL is important but not always easy. The 2 diseases have considerable overlap in their morphology, immunophenotype, and known genetic profile. The defining feature of BL is the presence of genetic translocations involving the c-Myc gene. However, the same translocation can also occur in approximately 10% of DLBCL cases. Thus, each of the different criteria used to distinguish between these 2 diseases have uncertainty built into them, which can result in an uncertain or erroneous diagnosis, posing major difficulties for the treating physicians.

H&O What are some highlights from your study presented at the 2011 American Society of Hematology (ASH) conference on whole genome and exome sequencing in BL?

SD The first question we sought to answer was what are the genetic changes in BL beyond the well-known c-Myc translocations? In order to address that, we sequenced a BL genome, as well as a whole genome from a patient with DLBCL. The differences could not have been more striking. DLBCL is a very complex disease that has many different subtypes and hundreds of genetic mutations, including those that affect gene-regulatory regions and gene-encoding regions. The picture was very different for BL, however. Beyond the c-Myc translocation, we only identified a few dozen genetic mutations that affect gene-encoding or gene-regulatory regions. This finding indicates that BL is a genetically simpler tumor in many ways, which might be one reason why it is curable with multi-agent chemotherapy, something that is often not the case with other lymphomas or other cancers.

Ultimately, it is difficult to know the degree to which a single whole genome (or even a few whole genomes) is representative of the disease as a whole. We were interested in discovering the role of other genetic mutations that might play a collaborative role with the c-Myc translocation to give the full phenotype of BL. Whole genome sequencing covers all of the DNA in the genome. However, only about 1% of the genome encodes protein-coding genes. To better understand the mutations that directly affect the protein-coding genes, we performed exome sequencing, which allows the selective sequencing of these protein-coding genes in a larger number of BL cases. We performed exome sequencing in an additional 45 tumors. We also sequenced 95 DLBCL tumors. Once again, we found that BL had fewer genes mutated than the average case of DLBCL. We also found that there were 2 groups of genes that were frequently mutated in BL when compared with DLBCL, one of which involved tyrosine kinases. This group of genes is important because there are immediate treatments available that are driven by tyrosine kinases. For example, patients with chronic myelogenous leukemia (CML) are now being routinely treated with the tyrosine kinase inhibitor (TKI) imatinib (Gleevec, Novartis). Many other TKIs that target this group of genes are clinically available or under development. What we found is that a number of tyrosine kinase genes, including PDGFRA and RET, were recurrently mutated in patients with BL.

H&O What are the implications of these findings?

SD Until this point, the role of tyrosine kinases in lymphomas had not been fully established; our study is an early demonstration of the role of these oncogenes in lymphomas, and especially in BL. These data suggest the potential application of TKIs in patients who have mutations in those genes. We are exploring this notion in preclinical models. Further, BL has traditionally been regarded as a model disease. Our genetic data show that it is a good disease to try and model because it has fewer abnormalities. As we try to model cancers in mice and by using other methods, it is not always clear how closely these mouse tumors resemble their human counterparts. By fully defining the genetics of the tumor, we can then go back and see if a mouse tumor exhibits strong similarities to the human counterpart, or if there are only 1 or 2 genes in common. Our study not only provides the basis for examining the degree to which these mouse tumors resemble their human counterparts, but it also offers the opportunity to develop new models for this disease. If BL can be successfully modeled with the use of animal models and other methods, that might be a starting point for trying to model other kinds of more complex lymphomas and cancers.

H&O Where should we focus our efforts for the future?

SD Future efforts need to identify better diagnostic methods and better treatments for patients with BL. If BL is diagnosed and treated correctly, the vast majority of patients will have good outcomes, especially children. Our data suggest that assaying individual genetic alterations might have a role in distinguishing BL from DLBCL. Our study data also provide potential clues as to what other treatments may be effective alternatives, such as TKIs. The treatment regimens for BL have remained largely unchanged for decades. The vast majority of relapsed patients tend to die from their disease. Our work, along with other ongoing investigations, will hopefully demonstrate a role for new agents, such as TKIs and PI3 kinase inhibitors, that can be used to improve outcomes in patients with BL.

Suggested Readings

Love CL, Jima D, Zhang J, et al. Whole genome and exome sequencing reveals the genetic landscape of Burkitt lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118: Abstract 433.

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Salaverria I, Zettl A, Beà S, et al. Chromosomal alterations detected by comparative genomic hybridization in subgroups of gene expression-defined Burkitt's lymphoma. *Haematologica.* 2008;93:1327-1334.