Microbiomarkers with big impact in CLL

Comment on Ferrajoli et al, page 1891

Microbiomarkers with big impact in CLL

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In this issue of Blood, Ferrajoli et al examined the microRNA (miRNA) miR-155 as a biomarker for chronic lymphocytic leukemia (CLL).1 Increased expression of cellular and plasma miR-155 was observed in patients with CLL and correlated with poor survival and therapeutic response, suggesting that plasma-based noncoding RNA biomarkers may one day be a reality.

B-cell CLL is the most common type of leukemia in adults and accounts for approximately one-third of all leukemias in the United States. CLL is a heterogeneous disease that stems from a clonal proliferation of CD5-positive B lymphocytes accumulating in the blood, bone marrow, lymph nodes, and to some extent, spleen and liver. CLL stems from a combination of genetic (chromosomal abnormalities, gene mutations) as well as epigenetic (altered microRNA expression, DNA methylation) modifications.

A major goal of CLL research is to more completely understand the molecular basis of the disease and to have predictors available for the response to treatment.

Monoclonal B-cell lymphocytosis (MBL) is a disorder of hyperproliferative B cells with molecular features that are similar to CLL. Individuals who are diagnosed with MBL have a much lower neoplastic B-cell count compared with those with CLL. Although 1% to 2% of patients with MBL will develop CLL requiring treatment,2 a direct progression of MBL to CLL is controversial.3

For years, researchers have focused on alterations to DNA and protein as evidence of CLL progression. A number of studies, including one published in this issue of Blood,1 suggest that small, noncoding miRNA may offer clues to the etiology and prognosis of this disease. Ferrajoli et al, in George Calin’s laboratory, examined the expression of the miRNA miR-155 in large discovery and validation cohorts of patients with CLL and MBL. miR-155 has previously been shown to be highly expressed in patients with CLL,4,5 and transgenic mice overexpressing miR-155 develop a B cell-type of leukemia.6 However a link between miR-155 and CLL prognosis has been missing until now.

miR-155 expression was higher in MBL, CLL, and CLL poor responders. Approximately 1% to 2% of patients with MBL will develop CLL; however, a direct correlation between MBL and CLL is controversial. Ferrajoli et al report that cellular miR-155 expression increased from B cells to MBL and CLL. Microvesicles secreted from both MBL and CLL also contained miR-155 in increasing amounts. Patients with lower cellular miR-155 expression responded to standard therapies better than those patients with high miR-155 levels. Professional illustration by Alice Y. Chen.

Increased miR-155 expression in MBL, CLL, and CLL poor responders.Approximately 1% to 2% of patients with MBL will develop CLL; however, a direct correlation between MBL and CLL is controversial. Ferrajoli et al report that cellular miR-155 expression increased from B cells to MBL and CLL. Microvesicles secreted from both MBL and CLL also contained miR-155 in increasing amounts. Patients with lower cellular miR-155 expression responded to standard therapies better than those patients with high miR-155 levels. Professional illustration by Alice Y. Chen.
In this issue of Blood, Nazi and colleagues have demonstrated that patients with immune thrombocytopenia (ITP) who receive rituximab display impaired responses to immunization with pneumococcal and Haemophilus influenzae type b (Hib) vaccines. Although similar observations have been reported in patients with other disorders who have received rituximab, this is the first study to examine this issue in patients with ITP.1

Rituximab is an effective therapy for ITP, with an overall response rate of ~60%; importantly, however, retrospective studies demonstrate that >20% of patients with ITP treated with rituximab achieve a long-term remission.3 Although the positioning of rituximab in the overall scheme of ITP therapy is a matter of debate, these response rates have led to wide acceptance of rituximab as a key component of ITP therapy that is often used prior to thrombopoietic agents, splenectomy, or other interventions.

Splenectomy offers the best chance for long-term remission of ITP, although its use has decreased over the last decade as more effective ITP therapies have become available. It is well appreciated that splenectomy is associated with an increased risk of infection, including overwhelming sepsis caused by encapsulated organisms such as pneumococcus; recent studies suggest the potential for additional long-term complications.4 The association of the asplenic state with infectious risk and the diminished response to vaccination following splenectomy has led to incorporation of recommendations for presplenectomy vaccination for pneumococcus, Hib, and meningococcus into ITP guidelines.5,6

What has not been as widely appreciated is the fact that treatment with rituximab may also inhibit responses to vaccination and that this effect may persist for 6 to 12 months; this observation has particularly important implications for patients with ITP who fail to respond to rituximab and are then referred for splenectomy. Even if such individuals receive vaccination prior to splenectomy, the study by Nazi and colleagues demonstrates that their response is likely to be significantly impaired.1 In this study, only 3 of 14 patients who received rituximab in a randomized clinical trial, vs 4 of 6 patients from the same trial who received placebo, achieved a fourfold increase in anti-pneumococcal antibodies (P = .12). Likewise, only 4 of 14 rituximab-treated patients vs 5 of 6 placebo-treated patients demonstrated a fourfold increase in anti-Hib antibodies (P < .05). The numbers of patients included in this report are small, and this is a notable weakness. However, the significance of these findings is supported by the fact that fewer rituximab-treated patients demonstrated Hib killing in a functional assay.

Why do rituximab-treated patients demonstrate an impaired response to vaccines? The explanation is likely more complex than a simple reduction in circulating and splenic CD20-positive B cells. Genetic analysis of platelet autoantibodies from patients with ITP suggests that these arise through a T-cell–dependent, antigen-driven process.7 The central role of T cells in the immunopathogenesis of ITP has been increasingly appreciated, reflecting the importance of B-cell–T-cell interactions in the generation of the humoral and cellular immune responses to platelets and megakaryocytes (see figure). Clinical correlates include the observations that the degree of B-cell depletion, particularly in the spleen,8 does not correlate directly with the response to rituximab, and that the use of rituximab leads to alterations in the T-cell compartment including restoration of regulatory T-cell number and suppressive

Comment on Nazi et al, page 1946

Better late than never?

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In this issue of Blood, Nazi and colleagues have demonstrated that patients with immune thrombocytopenia (ITP) who receive rituximab display impaired responses to immunization with pneumococcal and Haemophilus influenzae type b (Hib) vaccines. Although similar observations have been reported in patients with other disorders who have received rituximab, this is the first study to examine this issue in patients with ITP.1

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REFERENCES
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