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The White House crusade against ... MGUS?

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Cancer Group.¹¹ Thus, the clinician faced with a patient with DS and ALL has difficult choices. Intensive chemotherapy is likely to cause life-endangering toxicity but is also required for cure, especially if the leukemia lacks the ETV6-RUNX1 translocation or hyperdiploidy. However, there may be a light at the end of this tricky maze. The activation of the CRLF2-JAK-STAT signaling pathway in the majority of DS-ALLs suggests a therapeutic potential for JAK inhibitors. If confirmed in clinical trials, this therapy will target the unique biological properties of ALLs in children with DS.

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chain (immunoglobulin G versus others), and the presence of an abnormal free light chain ratio. Based upon these criteria, there are high-risk MGUS patients whose risk of progression is on the order of 58% at 5 years, and low-risk MGUS patients whose risk of progression is 5% at more than 20 years. Although there are recent studies that suggest that MGUS almost always precedes the diagnosis of myeloma,^{8,9} they are based on patients who have myeloma retrospectively demonstrating the presence of a preexisting monoclonal protein. But is the reverse true? Closely evaluating the 2 papers that suggest that MGUS and myeloma are linked, it is notable that they used banked serum samples, such that all that can easily be determined is the presence or absence of a monoclonal protein. One cannot tell whether these patients had preexisting indolent myeloma or MGUS from these samples, and while one may accept that all myeloma patients have preceding MGUS, do all MGUS patients develop myeloma?

It is clear that MGUS can occur for many different reasons, and not all of them guarantee a future myeloma diagnosis. Patients with low-risk MGUS can also have concomitant autoimmune or chronic viral illnesses that result in the production of a small clonal protein that has little or no chance of clinical sequelae, and among the group with the highest incidence, those older than age 80, it is also likely that many patients will die of other causes. So does a higher risk of MGUS mean a higher risk of myeloma? Although the higher relative risk for developing MGUS is associated with obesity in the current article, other papers evaluating the risk for developing myeloma with obesity are much less clear with only weak or no significant correlations.¹⁰⁻¹² In the discussion, Landgren et al seem to imply that MGUS-ogenesis is synonymous with myelomagenesis as they suggest that factors known to sustain growth of the malignant plasma cell clone such as interleukin 6 (IL6) and insulin-like growth factor-1 (IGF-1) are overexpressed in obese patients and thus may be related to the pathology of MGUS, yet the role of these cytokines in tumor cell initiation is much less established. We know IL6 and IGF-1 are local cytokines that are secreted by either the marrow microenvironment or by plasma cells themselves, used to sustain the viability of a malignant clone. In vitro work suggests that myeloma plasma cells can be induced to proliferation and enhanced to survive

CLINICAL TRIALS

Comment on Landgren et al, page 1056

The White House crusade against ... MGUS?

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From the White House, the First Lady is leading a well-publicized campaign against childhood obesity that has the potential to impact not only the health of children, but also one of the most frequent hematologic disorders of the elderly, MGUS. In this issue of *Blood*, Landgren and colleagues suggest that in addition to race and age, obesity also appears to be associated with a significantly increased risk for the development of MGUS.¹

It is well known that the incidence of myeloma and monoclonal gammopathy of undetermined significance (MGUS) are 2- to 3-fold higher among blacks, and that prevalence of MGUS can be as high as 3% among those older than age 70,² but does the risk of MGUS and subsequent myeloma now represent yet another reason to say no to dessert?

The presence of a paraprotein with less than 10% plasma cells and the absence of end-organ damage characterize MGUS, carrying with it an aggregate risk of progression to myeloma or other B-cell disorders of 1% per year.² The preexisting diagnosis of MGUS is

associated with a higher risk of thrombosis,^{3,4} osteoporosis, hip fracture,⁵ and neurologic disorders⁶ compared with age-matched non-MGUS controls. But are all MGUS patients the same? Is the risk of progression to malignancy equal among all patients, or are there "benign" and "malignant" MGUS patients? Studies from Kyle and others have identified a stratification model for MGUS that identifies groups of patients with high risk of transformation versus patients with low risk of transformation to a malignant B-cell disorder.⁷ This can be identified predominately by the magnitude of the m-protein, type of heavy

when these cytokines are present,¹³ but do we know that IL6 and IGF-1 can have an impact before establishment of the malignant clone? Do these cytokines play a role in the initial development of MGUS that is destined to become myeloma, or are they most important in sustaining a malignant clone once established?

Much of the data evaluating the risk factors for developing MGUS focus on a heterogeneous condition, and treat it as homogeneous. This equates developing MGUS with myelomagenesis, and therefore developing MGUS is considered a harbinger of doom. However, not all patients with MGUS will develop myeloma. The correct association is not between obesity and myelomagenesis, but rather between obesity and the development of MGUS, of whom those with low-risk disease are less likely to develop cancer in their lifetime. This observation is quite different from race and age, where we clearly know that the risk of developing MGUS and myeloma is higher among blacks and those with more advanced age. What we know for now is that not all clonal plasma cell disorders are created equally, and that while obesity is linked with MGUS development, pathophysiologically the link between MGUS, myeloma, and obesity is less clear. Until we have more molecular tools to stratify and identify groups of MGUS and myeloma patients to better identify risk of progression and outcomes, clinical and basic laboratory criteria will have to suffice. Although there are clearly other reasons to be healthy and active, increased risk of myeloma as a consequence of obesity has yet to be definitively proven.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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SzS is the leukemic variant of the most common subtype of cutaneous T-cell lymphoma (CTCL), mycosis fungoides, and constitutes 2.5% of CTCL. It is characterized by generalized erythroderma, lymphadenopathy, and presence of 5% or more of CD4⁺ malignant T cells with cerebriform nuclei (Sezary cells). Although common genetic aberrations and defects in cytokine response and immune regulation have been identified, the molecular biology of the disease has not been well established.²

miRNA are small noncoding RNAs of approximately 22 nucleotides that target mRNAs and function as posttranslational regulators. Generally, miRNA binds to the 3' untranslated region of target mRNA via complementary binding. Binding typically leads to either translational repression or mRNA degradation. miRNA can be located on introns or exons of the coding (host gene) or noncoding transcriptional unit.³

Aberrant expression of miRNA has been described in different cancers.⁴ Global reduction in miRNA biogenesis is tumorigenic,⁵ and may be due to deletion of DICER1, a key protein involved in miRNA biogenesis and a haploinsufficient tumor suppressor gene.⁶ miRNAs are also located in genomic loci commonly aberrant in cancers and may be deregulated as a result of gain or loss of genomic loci.⁷ One miRNA may affect multiple targets and have wide ranging impact on gene and protein expression. Although their impact on an individual target may be subtle, the combined effect on a synergistic network of genes may have significant consequence. They have been shown to be responsible for mediating some of the downstream effect of important oncogenes and tumor suppressor genes such as MYC and p53. Overall, the body of evidence suggests miRNA are important to tumor biology.

Ballabio and colleagues identify a single miRNA, miR-223, that could distinguish SzS from healthy controls and mycosis fungoides with 90% accuracy, suggesting that this may be a useful diagnostic marker. While exciting, how this performs in relation to previously defined gene expression signatures will need to be formally addressed. Whether miR-223 can be used to identify cases currently difficult to diagnose will be a critical test of its clinical utility. The process by which this diagnostic biomarker was identified highlights the difficulty in validating predictive signatures. The attrition from the initial 10 discriminating

● ● ● LYMPHOID NEOPLASIA

Comment on Ballabio et al, page 1105

“Micro”-managing the MiRNome in SzS

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In this issue of *Blood*, Ballabio and colleagues performed microRNA (miRNA) profiling in Sezary syndrome (SzS) and identified that miR-233 can distinguish T cells from patients with SzS from healthy controls and from patients with mycosis fungoides.¹ In addition, they identified that down-regulation of miR-342 may play a role in the pathogenesis of SzS through inhibition of apoptosis. The investigators also identified a novel mechanism of regulation of miR-342 via binding of miR-199a* to the host gene of miR-342, *EVL*.