20 to 40 nM is able to largely overcome the inhibitory impact of a 2.5- to 5.0-μM concentration of EGCG. These considerations argue against the possibility that even high levels of EGCG ingestion would impact upon the clinical efficacy of bortezomib.

Nonetheless, these data serve as an always timely reminder for healthcare providers of the importance of eliciting a complete history from patients and their families, including concomitant medications and over-the-counter supplements. The risks of such drug interactions are very real, whether they involve bortezomib and EGCG, bortezomib and vitamin C, cyclophosphamide and curcumin, or any of the other myriad possibilities. Moreover, they highlight the need for additional and careful studies along the lines of Golden et al, using physiologically relevant model systems to evaluate such possible interactions. Finally, they remind us of the words “moderation in all things” attributed to the Roman playwright Publius Terentius Afer, which should especially apply to any supplements used in the setting of chemotherapy.

Acknowledgments: D. J. K. acknowledges support from the American Cancer Society (PF-07-112-01-01-CDD 01), R. Z. O., a Leukemia & Lymphoma Society Scholar in Clinical Research, acknowledges support from the Leukemia & Lymphoma Society (6096-07), and the National Cancer Institute (R01 CA110227).

Conflict-of-interest disclosure: The authors declare no competing financial interests.

References


Acute myeloid leukemia (AML) is a clinically and genetically heterogeneous disease that accounts for 20% and 70% of acute leukemia in children and adults, respectively. Currently, cytogenetic analysis at diagnosis allows for stratification of AML cases into a favorable group [t(8;21), inv(16) and t(15;17)], an unfavorable group [t(6;9), abn(3q), -7/7, -5/del(5q), -5/del(5q)], and an intermediate group (normal cytogenetics or other cytogenetic abnormalities). For the favorable and unfavorable groups, risk-dependent treatment decisions, such as whether to consolidate with hematopoietic stem cell transplantation (HSCT) in first remission, have become part of standard practice. Data upon which to base such decisions have been lacking in the intermediate-risk group, however, and 60% to 70% of cases of adult and childhood AML fall into this group.

This situation has changed in recent years with the discovery of a number of molecular abnormalities that are found primarily in the intermediate-risk group and are undetectable by standard cytogenetics. Perhaps the most significant of these is the FLT3/ITD mutation, which occurs in about 10% of cases of intermediate-risk adult AML and is associated with unfavorable prognosis. A recent candidate for inclusion in this list of mutations is WT1, which occurs in about 10% of cases of intermediate-risk adult AML and is associated with unfavorable prognosis. This article by Hollink et al is the first to fully characterize WT1 mutations in childhood AML.

A major strength of this study is the use of complementary techniques to thoroughly analyze WT1 at the genomic and transcript levels. Thirty-five of 298 cases (12%) harbored WT1 mutations, most of which were frameshift insertions in exon 7. In about half of the cases, biallelic WT1 involvement could be demonstrated, due either to mutations of both alleles or to loss of heterozygosity (LOH). In cases with only one mutation, expression of both the mutant and wild-type alleles at the RNA level was confirmed, but the authors were unfortunately not able to assess expression at the protein level. Thus, the important question as to whether the wild-type protein is expressed and functional in these cases remains unanswered. This study was able to demonstrate the stability of WT1 mutations in paired diagnostic and relapse samples, making a strong case that these mutations are a primary leukemogenic event. Moreover, WT1 mutations were occasionally gained at relapse and may therefore represent a marker of disease progression.

Another major strength of this study is its comprehensive clinical and prognostic analysis. Like NPM1 and FLT3/ITD mutations, WT1 mutations are almost never seen in patients younger than 3 years at diagnosis, suggesting either a prolonged latency or an age-related resistance to the initial acquisition of these lesions. Remarkably, WT1 and NPM1 mutations are mutually exclusive and are both

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Adding WT1 to childhood AML alphabet soup

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In this issue of Blood, Hollink and colleagues establish WT1 mutations as a worthy addition to a growing list of molecular abnormalities that promise to improve the biologic understanding and treatment of intermediate-risk AML.
strongly associated with FLT3/ITD mutations. It is tempting to speculate that these cases are linked by a common underlying mutation that predisposes to DNA replication errors. What “unlinks” WT1 and NPM1 are their different prognostic influences. This study makes it clear that WT1 mutations are associated with unfavorable outcomes in childhood AML, as shown in the figure. Another important difference between WT1 and NPM1 mutations is that WT1 mutations retain prognostic significance in the presence of FLT3/ITD. While the favorable influence of NPM1 mutations appears to be “trumped” by FLT3/ITD, this study suggests that the unfavorable influence of FLT3/ITD may be “trumped” by wild-type WT1, since the outcome for FLT3/ITD+ patients that lacked WT1 mutations was not significantly worse than for patients with wild-type FLT3.

What this study lacks is evidence supporting a causative link between WT1 mutations and the comparatively poor response to therapy. Of particular interest would be evidence at a functional cellular level that WT1 mutational status is associated with parameters that might predict for poor clinical outcome, such as in vitro chemoresistance or differences in apoptotic responses to DNA damage. Such findings might pave the way for WT1 mutations to serve not only as prognostic markers but as potential molecular targets for novel antileukemic therapies.

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

REFERENCES

Itchy mast cells in MPNs

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In this issue of Blood, Ishii and colleagues investigate the role of mast cells in the pathogenesis of pruritus in patients with MPNs.

The BCR–ABL–negative myeloproliferative neoplasms (MPNs) of polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are characterized by a predisposition to thrombosis and hemorrhage, risk of blastic transformation, and premature death. In addition to these serious consequences, myeloproliferative disorder patients suffer variable constitutional symptoms, such as fatigue, bone pain, night sweats, and pruritus. Data gathered from 1179 MPN patients reported that 81% suffer from pruritus, and this symptom was present in 72%, 84%, and 85% of ET, PMF, and PV patients, respectively. The intensity of the pruritus can be severe, frequently exacerbated by water (ie, aquagenic pruritus), and has led some patients to discontinue bathing or to commit suicide in intractable cases. Therapy of MPN pruritus has been empiric, with antihistamines sometimes providing relief. Additionally, the use of selective serotonin reuptake inhibitors has been helpful, and has suggested that platelets (the repository for serotonin in the blood) may have a role in MPN pruritus.

The pathogenesis of constitutional symptoms and particularly pruritus in MPN remains uncertain, despite recent insights into some aspects of molecular pathogenesis with identification of mutations that affect the JAK–STAT pathway including the JAK2V617F, mutations in the 12th exon of JAK2, and mutations in cMPL. Increased JAK2 allele burden has been associated with a greater burden of pruritus among PV patients, although the exact mechanism for this association has remained uncertain, with speculation focusing on increased peripheral blood levels of cytokines. Additionally, investigators have investigated the various subsets of leukocytes that might be increased or activated in MPN patients. An association between the JAK2 mutation in basophils from PV patients, basophil activation, and degranulation with disease-associated pruritus was presented at the 2008 American Society of Hematology annual meeting. Further work defining the role of basophils in the pathogenesis of MPN pruritus is ongoing.

Mast cells contain a variety of mediators of the inflammatory response (ie, histamine, tryptase, prostaglandins, and leukotrienes) that can generate pruritus. Ishii et al isolate peripheral blood mast cells as well as generating mast cells from CD34+ cells of MPN patients suffering from pruritus, while not on cytoreductive therapy. In their article in this issue of Blood, they make several salient observations. The first is that mast cells arising from MPN patients were functionally different from normal control mast cells in that they release greater levels of pruritogenic factors. Second, they observe that among patients with the most severe pruritus, (1) more mast cells are generated from CD34+ cells, (2) their mast cells are less prone to apoptosis, and (3) they
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