Bortezomib and EGCG: no green tea for you?

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In this issue of Blood, Golden and colleagues report findings that indicate patients undergoing bortezomib-containing chemotherapy should avoid consuming green tea products.

Since the first description of its clinical activity against multiple myeloma and mantle cell lymphoma, the proteasome inhibitor bortezomib has become a standard of care for patients with these diseases in the relapsed/refractory setting. Modulation of proteasome function has also become an established approach to overcome chemoresistance and achieve chemosensitization in patients with relapsed/refractory and newly diagnosed myeloma, making bortezomib a crucial part of our chemotherapeutic armamentarium. Importantly, Golden et al have found that polyphenolic components of green tea, including (-)-Epigallocatechin gallate (EGCG), antagonized bortezomib in preclinical in vitro and in vivo model systems. EGCG inhibited the antiproliferative effects of bortezomib on myeloma cell lines; prevented bortezomib from inhibiting the proteasome, inducing caspase-7 cleavage and activating the unfolded protein response; and protected xenografts from the proapoptotic effects of this and other peptidylboronate inhibitors, but not of nonboronate proteasome inhibitors. Presumably, this occurred as a result of a direct interaction leading to formation of a covalent cyclic boronate between EGCG and bortezomib (see figure), which was then no longer able to bind to the N-terminal threonine active site of the chymotrypsin-like proteasome moiety.

EGCG is only one of many polyphenols found in green tea that are classified as flavonoids, with others including epigallocatechin and epicatechin, both of which were found to inhibit bortezomib as well, although with less potency. If all compounds containing 1,2-diol groups were to have a similar activity, then black tea, which also has a number of important polyphenolic constituents including theaflavins and thearubigins, could inhibit bortezomib as well. Other compounds in this class would include myricetin and quercetin, the latter of which has already been found to bind and inhibit bortezomib. Quercetin is another flavonoid that can be found at appreciable concentrations in foods, such as capers, leafy green vegetables, red onions, red grapes, red apples, and a number of berries, among other sources. Interestingly, epinephrine, norepinephrine, and dopamine, all of which are derived from catechol, bear 1,2-diols, and boronates can also be bound by 1,3-diols based on resorcinol. This by no means exhaustive list clearly indicates that green tea may represent only the beginning of this story rather than its end.

Do these findings support a recommendation to patients that they avoid the use of green and black teas and flavonoid-containing foods, such as those described above, including chocolate? At least in the case of green tea, EGCG concentrations of 2.5 μM or higher were needed to see inhibition of bortezomib’s activity, which were well above the maximal concentrations detected in one phase 1 trial that studied this agent’s pharmacokinetics. While such levels were achieved in a follow-up trial, this required that patients ingest, preferably in a fasting state, large doses of Polyphenon E. This decaffeinated green tea catechin extract contained about 60% EGCG, which represents a much greater content of this polyphenol than that found in brewed green tea. Also of note, pharmacokinetic studies of bortezomib after a standard dose of 1.3 mg/m² have revealed plasma concentrations up to 187.03 ng/mL, or greater than 450 nM. In contrast, Golden et al show that bortezomib at
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,10 cyclophosphamide and curcumin,10 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.

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Comment on Hollink et al, page 5951

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.

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), abnl(3q), -7/ del(7q), -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/negative (FLT3/ITD), since it identifies a group of patients that not only is at high risk of relapse1 but may also benefit from novel agents that target FLT3 signaling.2 Other important abnormalities include mutations in NPM13 and CEBPA,4 each of which has been shown to identify a group of patients with a more favorable prognosis. A more 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.5

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 leuke-

mogenic 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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