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EDITORIAL

Commentary on Perrone *et al.*: 'Vitamin C: not for breakfast anymore…if you have myeloma'

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In the September issue of *Leukemia*, Dr Perrone *et al.*[1] describe the effect of clinically relevant vitamin C concentrations on the *in vivo* activity of bortezomib. Their findings are consistent with earlier work suggesting that vitamin C, owing to its vicinal diol group, directly inactivates bortezomib by forming a tight but reversible complex which prevents binding to the chymotryptic site within the proteasome, and possibly attenuates the drug's permeation across cellular membranes (Figure 1).[2] This observation, coupled with the recent findings of Golden *et al.*[3] that green tea constituents also interfere with the efficacy of bortezomib, raise a number of important clinical issues as we move forward with small molecule-based therapy in cancer.

Given the extensive knowledge available on ligands and macromolecular targets, is there a mechanism by which we can predict and prevent this and other types of antagonistic interactions?

Pharmacophore models in drug discovery have traditionally been used to identify compounds with activities against a known and desired receptor. Application to off-target effects (including binding to other non-biological structures) and prediction of direct and indirect competitor targets have lagged. Use of 2-D and 3-D molecular descriptors of both ligand and receptor characteristics can provide some prediction of potential ligands, for intended and unintended targets.[4] In this regard, the knowledge of chemistry of ligand properties has an important role. Expansion of informatics modelling techniques can enhance *in vivo* evaluation and explanation of unexpected early treatment failures.[5] Hybrid methods, combining chemical informatics with systems and structural biology offer new potential for mapping diverse adverse events during early stage trials or in larger population studies,[6] but at this time their widespread use is limited. Institutional initiatives assisting the release of de-identified electronic patient data into public research databases are sorely needed if we are to accelerate such discoveries.

How much supplemental vitamin C is too much?

Studies in hospitalized stem cell transplant patients have shown that ascorbic acid and dehydroascorbic acid concentrations can increase to the levels seen in Dr Perrone's evaluation following initiation of chemotherapy and radiation, albeit with great variability.[7] As baseline and on-treatment measurements of ascorbic acid and metabolites have not been performed in patients receiving bortezomib, it is difficult to quantify the potential clinical impact of vitamin C daily doses from 250 mg to 1 g. From Dr Perrone's work it appears that ingestion of 250 mg of vitamin C has the potential to abrogate the effect of bortezomib. Thus, the safest approach for clinical application of this important work is to suggest to patients that they should not ingest supplemental vitamin C on the days of bortezomib dosing. Similar suggestions could also be extended to tea products and herbal supplements containing flavonoids, which often contain aryl vicinal diols.

What effect should these publications have on the interpretation of ongoing and previous clinical trials?

Vitamin C use by historical clinical trial participants receiving bortezomib was likely frequent and underreported, leading to

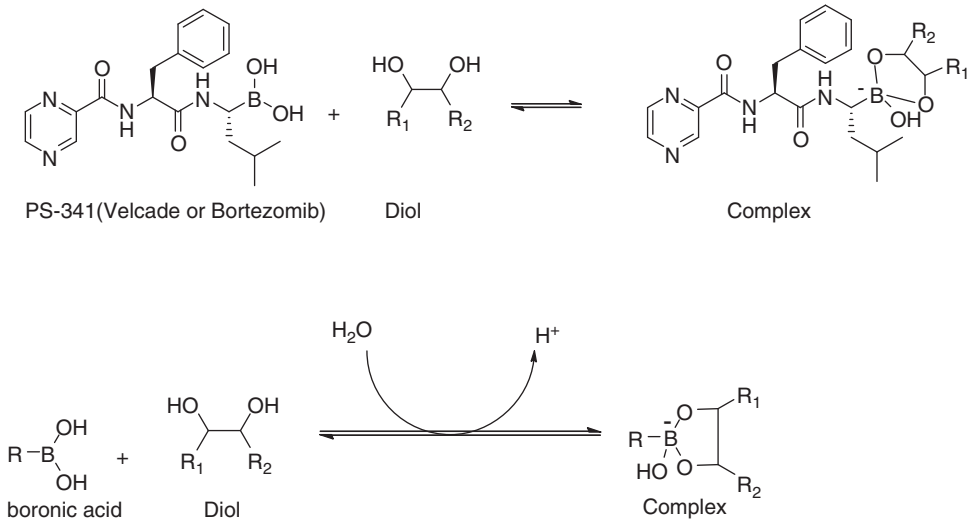

Figure 1 A diagram for potential binding between bortezomib or boronic acids and compounds with a vicinal diol group.

potential underestimation of the benefit for bortezomib-based therapy. However, the combination of bortezomib, prescribed vitamin C and melphalan without corticosteroids has been evaluated in phase II trials,[8] with disease outcomes in untreated patients that appear to be inferior to bortezomib, melphalan and prednisone. So although we have no direct comparison of regimens with and without vitamin C in an equivalent population, the work of Perrone *et al.* combined with what clinical trial information we do have should lead us to, at least, exercise caution during bortezomib treatment.

What do we tell patients about the use of vitamin C and other antioxidants historically viewed as harmless adjuncts to cancer treatment? Is this a real problem?

The potential practice implications of this work on bortezomib and antioxidant antagonism cannot be overstated, as 77% of patients report using vitamins or herbs concurrently with conventional anticancer treatment.[9] The use of vitamin C and other antioxidants has many variables: (1) use may be sporadic, (2) there may be variable dosing and (3) its use may occur in combination with other antioxidants or potentially antagonistic herbal compounds. Boronic acids are known to bind to compounds with the diol functional group through the formation of a tight but reversible complex[10] (Figure 1). Given that bortezomib is a dipeptidyl boronic acid, it is plausible to speculate that any agents that possess a vicinal diol group may chemically interact with bortezomib to attenuate its anticancer activity. In fact, some natural products or antioxidants such as luteolin, ellagic acid, flavonoids, protocatechuic acid, rosmarinic acid, phenethyl caffeate and catechin from vegetables, fruits or herbs have one or more vicinal diol groups. Thus these agents may have the potential to chemically interact with bortezomib and antagonize its activity.

In the ongoing 'friend or foe?' discussion of antioxidants and cancer, it is clear that there is much work to be done to easily and rapidly identify potential antagonistic interactions between our prescribed anticancer therapies, and a whole host of over the counter remedies that patients take based on little objective data. For the time being, it is reasonable to suggest to patients that there are potentially negative interactions between proven anticancer therapies and 'complementary' therapies. Until we, as researchers and clinicians, have a clear understanding of the potential interactions or lack thereof, we should caution our patients to limit their use to maximize their benefit from treatment.

Conflict of interest

SL received research support from Millennium and is a consultant for Millennium, Celgene, Bristol-Myers Squibb, and Novartis. Other authors have nothing to disclose.

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