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A phase 1 Bayesian dose selection study of bortezomib and sunitinib in patients with refractory solid tumor malignancies

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Background: This phase 1 trial utilising a Bayesian continual reassessment method evaluated bortezomib and sunitinib to determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLT), and recommended doses of the combination.

Methods: Patients with advanced solid organ malignancies were enrolled and received bortezomib weekly with sunitinib daily for 4 weeks, every 6 weeks. Initial doses were sunitinib 25 mg and bortezomib 1 mg m⁻². Cohort size and dose level estimation was performed utilising the Escalation with Overdose Control (EWOC) adaptive method. Seven dose levels were evaluated; initially, sunitinib was increased to a goal dose of 50 mg with fixed bortezomib, then bortezomib was increased. Efficacy assessment occurred after each cycle using RECIST criteria.

Results: Thirty patients were evaluable. During sunitinib escalation, DLTs of grade 4 thrombocytopenia (14%) and neutropenia (6%) at sunitinib 50 mg and bortezomib 1.3 mg m⁻² were seen. Subsequent experience showed tolerability and activity for sunitinib 37.5 mg and bortezomib 1.9 mg m⁻². Common grade 3/4 toxicities were neutropenia, thrombocytopenia, hypertension, and diarrhoea. The recommended doses for further study are bortezomib 1.9 mg m⁻² and sunitinib 37.5 mg. Four partial responses were seen. Stable disease >6 months was noted in an additional six patients.

Conclusion: Bortezomib and sunitinib are well tolerated and have anticancer activity, particularly in thyroid cancer. A phase 2 study of this combination in thyroid cancer patients is planned.

The development of receptor- and protein complex-targeted anticancer agents has improved disease outcomes with favourable tolerability profiles. While monotherapy with these drugs has had success in cancers with historically poor outcomes (e.g., gastrointestinal stromal tumours and renal cell carcinoma), single agent responses in other solid tumour malignancies have been limited (Barrios et al, 2010; Gallagher et al, 2010). Combinations with conventional DNA-damaging agents have also generally failed to show improvement over cytotoxics alone (Socinski et al, 2010). Alternative approaches inhibiting multiple interacting and interdependent pathways, vertically and horizontally, with two or more molecularly targeted therapies holds greater potential for improved outcomes.

Sunitinib is an oral, small-molecule inhibitor of multiple receptors (platelet-derived growth factor, vascular endothelial growth factor, and others). In addition to known activity in RCC and GIST, sunitinib is efficacious in refractory differentiated and medullary thyroid cancers. Bortezomib is a first-in-class reversible...
inhibitor of the 26S proteasome, which leads to apoptosis through multiple mechanisms. It is approved by the US Food and Drug Administration (FDA) for the treatment of multiple myeloma and relapsed mantle cell lymphoma. To date, single agent response rates in heavily pretreated patients with solid tumour malignancies have been low; however, combination strategies with conventional chemotherapy and molecularly targeted agents have activity and are tolerable (Fanucchi et al, 2006; Dees et al, 2008; Dudek et al, 2009).

Based on complementary antiangiogenic activity (Williams et al, 2003; Ebos et al, 2007) and an expected synergy between the two compounds (Wright 2010), we conducted a phase 1 evaluation of sunitinib and bortezomib in patients with refractory solid tumours (NCT00720148). The primary objective was to establish the safety and determine the maximum tolerated doses (MTD) of bortezomib and sunitinib in combination. Secondary objectives were to define toxicities and obtain preliminary information on the anticancer activity of the regimen.

Methods

Patients with confirmed solid organ malignancies refractory to standard therapy, or for whom no standard therapy existed, and measurable disease by RECIST criteria (version 1.0) were eligible. Other eligibility criteria included age ≥ 18 years; Eastern Cooperative Group (ECOG) performance status ≤ 2; adequate bone marrow reserve, renal and hepatic function. Patients were excluded if they had prior radiation to bone marrow reserve, renal and hepatic function. Patients were fixed at 1 mg m



Toxicity Criteria for Adverse Events (CTCAE), version 4; and/or WHO grades of 2 or less were used prior to dose reduction or discontinuation. Bortezomib was dose-reduced by one level for neuropathy. Patients were deemed evaluable for DLT if they completed ≥ 75% of the first cycle.

Tumour assessments were done at baseline and the end of each cycle, and responses were classified using RECIST criteria. The initial dose level was sunitinib 25 mg and bortezomib 1.0 mg m

Dose escalation was conducted in two stages; initially bortezomib was fixed whereas sunitinib was escalated to its MTD. Specifically, each patient received 1.0 mg m

During this stage, the parameter \( x \) was increased, after each successive patient, in increments of 0.05 from an initial value of 0.4 to a terminal value of 0.5. At the end of the second stage of the trial, an MTD was estimated using data from the second stage as the median of the posterior distribution of the MTD of bortezomib given that sunitinib was = 37.5 mg.

RESULTS

Thirty-seven patients consented, of whom 31 received at least one dose of the study drug and 30 were evaluable for the primary endpoint. Demographic data are presented in Table 2. The seven ineligible patients had rapidly progressive disease and did not complete cycle 1. Because enrolment occurred real time as patients were referred, the majority of experience was with the sunitinib 50 mg dose level and bortezomib 1 or 1.3 mg m

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Cycle 1 adverse event data is summarised in Table 3. DLTs were seen at dose level four (sunitinib 50 mg and bortezomib 1.3 mg m

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Following cycle 1, the most common treatment-emergent adverse events were thrombocytopenia, diarrhoea, mucositis, and fatigue. Two patients developed varicella zoster infections at dose level three, prompting the institution of acyclovir prophylaxis in subsequent subjects. One patient at dose level three who developed grade 3 hypertension in cycle 1 (subsequently controlled on lisinopril), went on to develop grade 2 proteinuria (3239 mg over 24 h), which spontaneously resolved.

The median number of cycles delivered was 3 (range 1–12), for a median time on study of 18 weeks (range 6–72). Four patients achieved partial response by RECIST criteria, two at dose level three (medullary thyroid cancer and squamous cell cancer of the

Table 1. Cohort enrolment

| Dose Level | Sunitinib (mg) | Bortezomib (mg m\(^{-2}\)) | Patients consented/ evaluable |
|------------|----------------|-----------------------------|-------------------------------|
| 1          | 25             | 1                           | 4/2                           |
| 2          | 37.5           | 1                           | 5/2                           |
| 3          | 50             | 1                           | 13/12                         |
| 4          | 50             | 1.3                         | 8/7                           |
| 5          | 37.5           | 1.3                         | 3/3                           |
| 6          | 37.5           | 1.6                         | 1/1                           |
| 7          | 37.5           | 1.9                         | 3/3                           |

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nasopharynx), and one each at dose levels four (Hurthle cell thyroid) and seven (papillary thyroid cancer). Stable disease lasting 4–6 months was noted in an additional six subjects, specifically in patients with papillary (two) and medullary (one) thyroid cancers, pancreatic neuroendocrine tumour, melanoma, and pleomorphic sarcoma. Taken together, the clinical benefit rate was 30%. At the conclusion of dose escalation and after considering the overall toxicity profile, the recommended phase 2 doses of the combination using EWOC were sunitinib 37.5 mg PO daily and bortezomib 1.9 mg m$^{-2}$/C0 IV weekly, each given 4 weeks of 6.

**DISCUSSION**

Anticancer drug development has evolved to include combinations of targeted agents without traditional cytotoxic partners. Although multitargeted receptor tyrosine kinase inhibitors such as sunitinib have advanced therapy in the single agent setting, the goal of further tumour burden reduction and clinically meaningful prolongation of disease control is likely going to require multiple agents to achieve. The combination of bortezomib and sunitinib is a rational one, as proteasome inhibition impairs cycle progression and proliferation, activates apoptosis, and inhibits angiogenesis and metastasis (Boccadoro et al, 2005). Additionally, bortezomib-induced inhibition of the NFκB pathway is augmented in the presence of sunitinib, suggesting at least additive if not synergistic activity in combination (Sorolla et al, 2012). Furthermore, sunitinib sensitises cancer cells to bortezomib-induced apoptosis (Yeramian et al, 2012). These preclinical data, along with favourable toxicity profiles, support the combination evaluated.

The addition of bortezomib to sunitinib was well tolerated and demonstrated meaningful anticancer activity in a number of solid tumours. We observed intolerable haematologic toxicity with sunitinib 50 mg and bortezomib 1.3 mg m$^{-2}$/C0, leading to escalation of bortezomib at a lower dose of sunitinib to gain further insight into the relative contribution of each agent to haematologic toxicity. The adaptive Bayesian design allowed accrual to both the known safest and most effective dose during the trial, as well as informed decision-making for subsequent evaluation. When compared with different up-and-down schemes, including ‘3+3’ designs, EWOC assigns fewer patients to either subtherapeutic or toxic dose levels, treats more patients at optimal dose levels and estimates the MTD with smaller average bias and mean squared error (Babb et al, 1998).

We preferentially enrolled patients with thyroid cancers, due to the previously reported activity of sunitinib (Carr et al, 2010). Both the radiographic and biochemical activity noted in thyroid cancer in our trial compares favourably to prior data with single agent sunitinib. The sunitinib dose selected here is slightly lower than prior experiences; however, improved long-term tolerability in combination with bortezomib formed the basis of the recommendation. Subsequent evaluation of the combination in thyroid cancer is warranted.

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DISCLAIMER

The authors take full responsibility for the scope, direction, and content of the manuscript and have approved the submitted manuscript.

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