Dose-ranging study of metronomic oral vinorelbine in patients with advanced refractory cancer.

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Source

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Abstract

AIM:

To determine the safe dose range and pharmacokinetics of metronomic oral vinorelbine and obtain preliminary data on biomarkers and efficacy in patients with advanced cancer.

METHODS:

Successive cohorts of patients received escalated doses of oral vinorelbine given thrice a week until disease progression, unacceptable toxicity (UT), or consent withdrawal. UT was any grade 4 toxicity, or grade 2 or 3 toxicity that would result to longer than 2-week break during the first 2 months of treatment. Blood samples were collected for pharmacokinetics and quantification of angiogenesis regulatory proteins.

RESULTS:

Sixty-two patients (median age, 60 years) enrolled at six dose levels from 20 to 70 mg and received treatment for median 12.25 weeks (range, 2-216+). Unacceptable toxicity occurred in two of six patients treated at 60 mg (leucopenia grade 4 and epistaxis grade 2) and in one at 70 mg (leucopenia grade 2). The upper metronomic dose was 50 mg. Objective antitumor response documented in eight cases and 32% of patients experienced disease stability for minimum 6 months. Three responders (renal cancer, medullary thyroid carcinoma, and Kaposi sarcoma) received nonstop treatment for over 3 years without overt toxicity. Low pretreatment levels of circulating interleukin-8, vascular endothelial growth factor, and basic fibroblast growth factor were found predictors of efficacy. Steady-state concentrations of vinorelbine and its active metabolite ranged from 0.5 to 1.5 ng/mL.

CONCLUSIONS:

Metronomic administration of oral vinorelbine is feasible at doses up to 50 mg thrice a week and can yield sustainable antitumor activity without overt toxicity, probably through antiangiogenic mechanism. Further clinical investigation is warranted.