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Dose selection trial of metronomic oral vinorelbine monotherapy in patients with metastatic cancer: a hellenic cooperative oncology group clinical translational study.

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Abstract

BACKGROUND:

Metronomic chemotherapy is considered an anti-angiogenic therapy that involves chronic administration of low-dose chemotherapy at regular short intervals. We investigated the optimal metronomic dose of oral vinorelbine when given as monotherapy in patients with metastatic cancer.

METHODS:

Patients with recurrent metastatic breast (BC), prostate (PC) or non-small cell lung cancer (NSCLC) and adequate organ functions were randomly assigned to 30, 40 or 50 mg vinorelbine, taken orally three times a week. Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or maximum 24 months. Primary endpoint was time-to-treatment failure (TTF) and secondary were progression-free survival (PFS), toxicity, changes in blood concentrations of angiogenesis-associated biomarkers and pharmacokinetics.

RESULTS:

Seventy-three patients were enrolled. Four-month TTF rate did not differ between the three arms: 25.9% (11.1%-46.2% 95% Confidence Interval), 33.3% (15.6%-55.3%) and 18.2% (5.2%-40.3%) for the 30 mg, 40 mg and 50 mg arms (p-value = 0.56). Objective response was seen in 2 patients with NSCLC (treated at 30 and 50 mg respectively), one with BC (at 40 m g) and one with PC (at 50 mg) and lasted from 4 to 100 weeks, with maximum response duration achieved at 50 mg. Adverse events were mild and negligible and did not differ between the three arms. Blood levels of vinorelbine reached steady state from the second week of treatment and mean values for the 30, 40 and 50 mg were respectively 1.8 ng/ml (SD 1.10), 2.2 ng/ml (SD 1.87) and 2.6 ng/ml (SD 0.69). Low pre-treatment blood concentrations of FGF2 and IL8 predicted favorable response to therapy (p values 0.02 and 0.006, respectively), while high levels of TEK gene transcript predicted treatment resistance.

CONCLUSIONS:

Considering the antitumor activity and response duration, the negligible toxicity of the highest dose investigated and the lack of drug accumulation over time, we suggest that 50 mg given three times a week is the optimal dose for metronomic oral vinorelbine. Further investigation of metronomic oral vinorelbine (MOVIN) at this dose is warranted in combination with conventional chemotherapy regimens and targeted therapies.Trial registration: Clinicaltrials.gov NCT00278070.