Vinorelbine metronomic chemotherapy for advanced tumor patients: observational study.

E.Pezzolo[1-2], L.Bertolaso[1], A.Bononi[3], Y.Modena[3], D.Menon[3], C.Barile[3], G.Crepaldi[3], F.Pasini[3], P.Giusti[2], A.Gaspardo[4], D.Caruso[4], M.Gusella[1-3].

1 Laboratory of Pharmacology and Molecular Biology, Trecenta S.Luca Hospital, Dept. of Oncology, Azienda ULSS 18 – Rovigo.
2 Dept. of Pharmaceutical Sciences – Section of Pharmacology- University of Padova.
[3] Oncology Unit, Rovigo Hospital, Dept. of Oncology, Azienda ULSS 18 – Rovigo.
[4] Laboratorio di Biochimica e Biologia Molecolare del Metabolismo, Dip. di Scienze Farmacologiche e Biomolecolari - Università degli Studi di Milano

Background:
Metronomic chemotherapy (MC) is a recently introduced method for administration of anticancer drugs that consists in fractionated, frequent and long term administration of single drug doses without suspension until disease progression or intolerable toxicity.
MC acts as a cytostatic treatment aimed to overcome drug resistance contrasting tumor regrowth that may arise between chemotherapy cycles.
Vinorelbine is used in a metronomic setting. It can be administered for long period time, according to clinical benefit and tolerability. Approved dose is 50 mg 3times/week, but lower doses and different schedules are also used, according to medical judgement. Little is known about pharmacokinets on early and long lasting administration.
The aim of this study was to evaluate vinorelbine pharmacokinetics with metronomic scheme and related it to main clinical end points.
Material and methods:
Patients affected by advanced cancers treated with oral vinorelbine as palliative care were the study population.
Inclusion criteria were: PS 0-2, life expectation > 3months, good hepatic and kidney functionality, suitable blood count (Hb>10g/L;GB>3.5x109/L;neutrophils>1.5x109/L, PTL>150x109/L).
Vinorelbine was administered as monotherapy, 20mg or 30mg per os, every other day until disease progression or toxicity onset. Some patients taking the standard dose of 50 mg 3times/week were also analyzed for comparison.
Patients were monitored every week during the first 30 days and then monthly. Together with clinical visit, peripheral blood samples were collected for haematological tests and pharmacokinetic analysis. The clinical benefit was determined according to the duration of prescription (cut-off : 90 days), because it is usually associated to disease stability or symptom relief.
Blood samples were stored at -20°C until processing. Vinorelbine and its active metabolite 4-O-deacetylvinorelbine (DAC-vinorelbine) blood concentrations were determined through acetonitrile-based liquid/liquid extraction followed by LC/MS-MS.
Results:
149 patients, 53 female and 96 male, mean age 73 years old (range 29-93) were enrolled. They were affected by lung (n=53), prostate (n=20), breast (n=27) and other (n=49) cancers. Vinorelbine was prescribed for a mean time of 4,7 month (range 0-36,9).
Pharmacokinetic analysis was performed on the most significant series, constituted by 53 patients with lung cancer (adenocarcinomas and squamous cell cancers). Drug and metabolite blood levels progressively increased after the first doses and reached stationary levels after one month; thereafter, they remained stable for long time. Mean blood concentrations of vinorelbine and 4-O-deacetylvinorelbine were 1,9±1,89 ng/mL and 3,2±3,70 ng/mL, respectively. They were not significantly different from blood levels in younger patients treated with 50 mg 3times/week. In addition, no significant difference was found according to vinorelbine doses (20 vs 30 mg) both in drug blood levels and clinical tolerability or benefit.
Higher vinorelbine levels and age were associated to toxicity. Two patients, 72 and 64 years old, experienced severe haematological toxicity after 21 and 45 days of treatment with 30mg vinorelbine and stopped therapy; vinorelbine blood concentrations were 6,3ng/mL and 21,3ng/mL, respectively.
Two patients, 80 and 73 years old, experienced toxicity after 90 days and 127 days with 30mg vinorelbine treatment, presenting drug blood concentrations of 2,9ng/mL and 5,2ng/mL, respectively. After side effect recovery, their treatment was restarted with dose reduction to 20 mg. Vinorelbine blood levels lowered to 0,6 and 1,4 ng/ml and treatment continued for 2 years and 7 months, respectively, showing clinical benefit and good tolerability.
Conclusions:
These early findings show that metronomic vinorelbine pharmacokinetic analysis is feasible and may have a clinical utility in optimising outcomes and reduce toxicity.