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Letter to the Editor

Vincristine and Bleomycin do not Interfere with Infusional Plasma Levels of Methotrexate

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VINCA alkaloids have been shown to increase intracellular accumulation of methotrexate (MTX) *in vitro* [1–5] while bleomycin (BLM) produced a slight decrease [3]. In animal systems a synergism between vincristine (VCR) and MTX [3] has also been described. These data suggested that it would be interesting to check whether plasma levels of MTX are modified by VCR and BLM in cancer patients.

A pilot study was conducted in four patients under a multidrug protocol including BLM, MTX and VCR, to verify the effect of VCR and BLM on infusional plasma levels of MTX. Three of the four patients, aged from 52 to 70 years, with advanced pelvic tumors (gynecological and colon), previously treated with TCT and chemotherapy, received a 6-hr i.v. infusion of 100 mg/m^2 MTX. VCR, 1 mg/m^2 i.v. and BLM 15 mg/m^2/day, infused i.v. for 72 hr, were administered every 28 days. The fourth patient was given only VCR and MTX. All patients had normal hematological, hepatic and renal function before each treatment cycle.

Seven plasma samples were collected at intervals during MTX infusion (from 15 to 360 min) and MTX plasma concentrations were determined by fluorimetry [6]. This was done for a total of 17 cycles of MTX infusions.

The infusion curve was calculated according to the Dost formula for one compartment. The steady state concentration (C_{ss}) and ab-

Table 1

Schedule	Patient No.	Cycle No.	AUC (μg/ml × min)	k_{abs} (min^{-1})	C_{ss} (μg/ml)
A. BLM + VCR + MTX	1	I	558	0.0052	3
		IV	567	—	—
		VII	1843	0.011	7
	2	I	864	0.005	4.6
	3	I	444	0.0035	3
		VI	1825	0.0079	8
B. BLM + VCR $\xrightarrow[48\,hr]{24\,hr}$ MTX	1	II	1168	0.014	4.1
		III	1365	0.014	5
		V	913	0.048	5
		VI	886	—	—
	2	II	1068	0.0062	5
C. BLM + MTX $\xrightarrow{24\,hr}$ VCR	3	II	559	0.0056	2.5
		III	624	0.0038	3.8
D. VCR + MTX	4	I	1071	0.005	5.5
		II	1567	0.0045	9
E. VCR $\xrightarrow{24\,hr}$ MTX	4	III	1189	0.0058	6
VCR $\xrightarrow{48\,hr}$ MTX		IV	1762	0.0067	6

For abbreviations, see text.

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sorbance constant (k_{abs}) were also calculated. The area under the curve of the MTX plasma levels over time (AUC) for each course of treatment was calculated by the trapezoid method.

At Schedule A in the table the above parameters are set out for MTX during infusion in three patients receiving BLM + VCR + MTX concomitantly. Patients 1 and 2, under schedule B, received MTX 24 and 48 hr after the other two drugs. In schedule C, where VCR was given 24 hr after BLM + MTX, the direct effect of BLM on MTX was tested. The direct interaction of VCR and MTX in the simultaneous D schedule or delayed regimen E was investigated in patient 4 who was given only MTX + VCR.

As the parameters reported were all in the same range of values, the study was discontinued since the changes in plasma MTX levels induced by the two other drugs tested were smaller than the variability anyway encountered in these levels. In addition, the intraindividual variability found, despite the accuracy of the infusion pump used, merits further investigation.

In conclusion, the effect of VCR and BLM on cellular uptake of MTX, evaluated at plasma level, can be considered only limited, whereas at cell level it is much more important, as shown by the authors mentioned. The scant information on the slight inhibitory effect of BLM on cellular uptake of MTX [3] cannot, however, be confirmed by this approach. Studies of cell pharmacodynamics and pharmacokinetics are thus necessary in any attempt to make chemotherapy more effective.

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