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Short Communications

Experimental in vivo Cross-resistance of Vinca Alkaloid Drugs

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Summary. In human therapy, an absence of cross-resistance has been observed between vincristine and vindesine in patients receiving polychemotherapy whilst, in our experimental in vivo studies, such a cross-resistance has been found between Vinca alkaloids. Further studies are required to explain this discrepancy.

Introduction

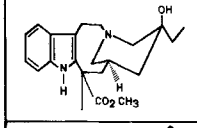
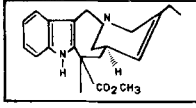
Cross-resistance between compounds of different groups having various mechanisms of action, such as anthracyclines, actinomycin D and Vinca alkaloids, has long been observed (11,12). At the other end of the scale, cross-resistance has not been found between compounds of the same family, namely vincristine and vindesine when under clinical study (1,3,4,5,6,15,16,17,18,19,20).

Using a strain of P388 mouse leukemia resistant to vincristine, it appeared to us interesting to carry out an experimental study to confirm or question the clinicians' findings. Thus we decided to examine not only the activities of vincristine (VCR) and vindesine (VDS), but also those of vinblastine (VLB) and navelbine (NAV).

Materials and Methods

Compounds (Figure 1)

Vinca alkaloid derivatives

Catharanthine moiety	Drug	Vindoline moiety		
		R1	R2	R3
	Vincristine (VCR)	-CHO	$-CO_2CH_3$	$-O-CO-CH_3$
	Vinblastine (VLB)	$-CH_3$	$-CO_2CH_3$	$-O-CO-CH_3$
	Vindesine desacetyl amide Vinblastine (VDS)	$-CH_3$	$-CONH_2$	-OH
	Navelbine 5'-Nor-anhydro Vinblastine (NAV)	$-CH_3$	$-CO_2CH_3$	$-O-CO-CH_3$

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Vincristine, vinblastine and vindesine, in the form of sulphate, were purchased from Eli Lilly Laboratories. Navelbine (5'-noranhydrovinblastine), in tartrate form, is a semi-synthetic compound prepared by P. Potier's group (13,14). Solutions of these water soluble compounds were prepared extemporaneously and the dosages are expressed in active form.

P 388 leukemia

We used the P 388 strain of leukemia, highly sensitive to vincristine and a sub-line of P 388 leukemia resistant to vincristine (P 388/VCR), which we obtained by courtesy of Dr A.E. Bogden (Laboratory of Experimental Oncology, Mason Research Institute, Worcester, Mass.). The tumour (P 388 or P 388/VCR), maintained in DBA/2 Ola mice, was grafted IP (10^6 cells) at day 0 into B6-D2 F1/Ola mice. We took 8 mice for each treatment group and 16 as controls, which only received the solvent (distilled water).

Treatments, by IP route, took place on days 1, 5, and 9. Two doses were used for each compound:

- the optimal active dose on P 388 leukemia (established during previous trials), for VCR and VLB: 1.0 mg/kg IP, and for VDS: 3.0 mg/kg IP or for NAV: 10.0 mg/kg IP
- and half the optimal dose.

For VDS or VCR (treatments on d. 1, 5, and 9), the chosen doses were in agreement with those used by others but, for VLB, in our experimental conditions, the doses were not so high (2).

Expression of activity

$$\text{Increase of life span (I.L.S.)} = \frac{\text{Median survival time treated group}}{\text{Median survival time control group}} \times 100$$

Statistical analysis of the results: Wilcoxon's non-parametric test.

Results

The results obtained are given in Table 1. Vindesine was found to give the best results on

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Table 1. Activity of Vinca alkaloids on P 388 and P 388/VCR leukemia

Drug	mg/kg IP	P 388			P 388/VCR			
		I.L.S. T/C x 100	p (a)	N° alive d 30 (b1)	N° alive d 100 (b2)	I.L.S. T/C x 100	p (a)	N° alive d 30 (b1)
Vincristine (VCR)	1.0	283	0.001	7/8	1/8	103	NS (d)	0/8
	0.5	203	0.001	4/8	1/8	103	NS (d)	0/8
Vinblastine (VLB)	1.0	196	0.001	3/8	2/8	130	0.001	0/8
	0.5	157	0.001	0/8	0/8	123	0.01	0/8
Vindesine (VDS)	3.0	∞ (c)	0.001	7/8	4/8	116	NS (d)	0/8
	1.5	∞ (c)	0.001	7/8	5/8	113	NS (d)	0/8
Navelbine (NAV)	10.0	196	0.001	4/8	2/8	123	0.001	0/8
	5.0	166	0.001	0/8	0/8	120	0.01	0/8

(a) p: statistical analysis in comparison with controls (Wilcoxon's non-parametric test)
(b) = long survivors on day 30 (b1) and on day 100 (b2)
(c) = ∞ : when in a treated group 50% or more of the animals are cured
(d) = NS = not significant ($p > 0.05$)

P 388 sensitive leukemia, the activities of the three other alkaloids also being good. There are no survivors at d. 30 in the P 388/VCR leukemia group, whilst there are many survivors at d. 30, and even some survivors at d. 100, in the P 388 sensitive leukemia group: it is clear that a cross-resistance exists with P 388/VCR leukemia. However, the statistical analysis suggests degrees in this cross-resistance which seems less marked in the case of vinblastine or navelbine.

Discussion

With P 388/VCR leukemia, we observed - in our experimental conditions - a cross-resistance between the four alkaloids used, namely between VCR and VDS. These data confirm the assertion of Barnett et al. (2): VDS does not increase the survival time of mice bearing the P 388/VCR strain of leukemia.

These results appear to be in contradiction with the clinical observations previously mentioned. However, it should be noted that the clinical situation is much more complex than in the laboratory: polychemotherapies are administered according to various protocols and, due to lack of remission, one alkaloid will be introduced following another. If a favourable therapeutic response is observed, does one have the right to say, in these complex cases, that the two alkaloids do not present a cross-resistance?

This assessment is even more open to criticism than the favourable responses which are only observed in certain percentages of patients during the reinduction with the second alkaloids, VDS or VCR (1,4,6,16).

It should be noted that the experimental and clinical results with other groups of compounds, such as the anthracyclines, have also shown a similar discrepancy.

In addition, we should draw attention to the in vitro results of Hill (7,8) when the VCR/resistant and VDS/resistant cell lines [L5178 Y cells] did not show a clear cross-resistance to these two drugs. However, it is difficult to confirm that a resistant cell line induced in vitro represents a true in vivo model (it is known that differences of behaviour exist in vivo and in vitro, for example the stability of resistance).

This study shows up the difficulty in solving the problems presented by the resistance of antitumour drugs. It could be suggested that, contrary to the complex situation in human tumours, the malignant cell population is uniform (clonogenic) in the experimental tumours (for example, P 388/VCR); this may explain why, in experimental conditions, a clear resistance is observed whilst, in the clinic, sensitivity is seen to vary. Another hypothesis may be proposed: the metabolism of drugs (here of Vinca alkaloids) differs in animals and Man.

Pharmacokinetic studies at the cell level [drug retention resulting from drug uptake and drug efflux (9,10)] could perhaps be of aid in solving the problems posed by the difference in results obtained with VCR and VDS in the laboratory (in vivo or in vitro) and in the clinic (polychemotherapy).

These results again call into question the predictability of the usual experimental tumour chemotherapy techniques as applied to the therapeutic activity of drugs in the clinic.

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