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Antitumor activity study of Vinflunine against a human small cell lung tumor xenografted in *Nude* rats.

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Abstract

Vinflunine (VFL) is a novel fluorinated vinca-alkaloid derivative which has shown antitumor activity in experimental *Nude* mouse models. In order to develop an assay to test VFL in combination with other chemotherapeutic agents, we have studied the antitumor activity and the tolerance to VFL administered as 4 weekly IV injections (q7dx4) to *Nude* rats bearing subcutaneous (SC) NCI-H69 human lung tumors. The maximal tolerated dose of VFL was between 6.0 and 8.0 mg/kg/injection (inj). We observed lethality only in *Nude* rats treated with VFL at 8.0 mg/kg/inj, with no significant mean body weight changes after VFL at doses of 1.5 to 6.0 mg/kg/inj. VFL produced a low cumulative hematotoxicity at doses of 6 and 8 mg/kg/inj. The duration of leucopenia was only 3 days and the white blood cell count returned to normal levels after the first three VFL injections of 6 mg/kg/inj. However, the nadir induced by the fourth injection was longer and could be explained by a relative sparing of the immature compartment. The red blood cell count was affected by VFL treatment in a dose-dependent manner and returned to normal levels after each VFL injection of either 1.5, 3.0 or 6.0 mg /kg, but not from 8.0 mg /kg. The platelet number was not affected by VFL treatment. The mean doubling time of SC tumors was significantly longer after VFL injections of 4.0 and 6.0 mg/kg than after vehicle injections (5.8 *vs* 15.1 and 14.2 days, respectively). The %T/C parameters provided evidence of significant antitumor activity for VFL at doses of 4.0 and 6.0 mg/kg/inj. compared to control groups (%T/C of 42 and 36%, respectively).VFL is a well-tolerated drug which displays significant antitumor activity against NCI-H69 tumors xenografted onto *Nude* rats, which is a promising model for testing combinations of other chemotherapeutic drugs with VFL, as well as its Pharmacokinetic /Pharmacodynamic relationships.

Introduction

➢ Vinflunine (VFL) is a novel fluorinated vinorelbine derivative obtained by reaction in superacid media (20',20'-dichloro-3',4'-dihydrovinorelbine), which has shown markedly superior antitumor activity in comparison with vinorelbine (VRL), in various experimental animal models,

➢ VFL, new vinca-alkaloid, is currently in phase II clinical trial,

➢ VFL has shown high activity against NCI-H69 tumors xenografted in *Nude* mice following the treatment schedule Q7DX4 (2):

Summary table of antitumor activity parameters of VFL on the growth of SC NCI-H69 tumors xenografted in *Nude* mice (2):

VFL dose (mg base/kg/inj.)	Adm. route	MBWC (%)	Optimal T/C%	SGD	No. CR (%)
20.0	IP	Gain	36	0.2	0
40.0	IP	-8.7	6	3.7	20

CR: Complete response

➢ The *Nude* rat is particularly adapted to study the rationale of a new treatment strategy. It's decisive advantage is size, which facilitates multiple and repetitive sampling (blood, urine, faeces…..), and affords various injection routes for both cells and compounds.

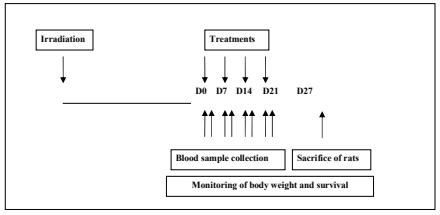
➢ In order to test the combination of VFL with other chemotherapeutic agents, we have evaluated vinflunine against NCI-H69 tumors xenografted in *Nude* rats.

Methodology

- **Test substance : Vinflunine (VFL)**
- **Tumor implant : NCI-H69**
- **Animals : *Nude* rats (Harlan SD Inc., Indianapolis)**

DETERMINATION OF THE MTD OF VFL IN IRRADIATED *NUDE* RATS:

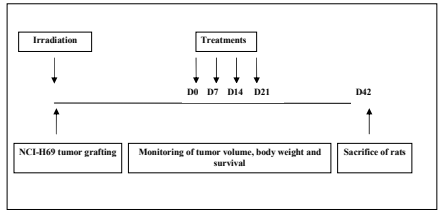
❖Whole body irradiation of *Nude* rats at 7.0 Gray with a γ source (Co^{60}).
❖Treatment schedule :
➢Treatment start (D0) 25 days after irradiation.
➢4 weekly IV injections of VFL at 1.5, 3.0, 6.0 and 8.0 mg base/kg/inj. (D0, D7, D14 and D21, Q7DX4, 3 rats/group).
➢Blood sample collection by the tail vein at D0, D3, D7, D10, D14, D17, D21 and D24.
➢Blood cell count (white blood cells [(WBC], red blood cells [RBC] and platelets [PLT]) with a Sysmex counter (Merck, Germany).
➢Monitoring of body weight and survival twice a week.
➢Sacrifice and autopsy of rats at D27.



ANTITUMOR ACTIVITY OF VFL ON THE GROWTH OF SC NCI-H69 TUMORS XENOGRAFTED IN *NUDE* RATS

•Whole body irradiation of *Nude* rats at 7.0 Gray with a γ source (Co^{60}),
•Grafting of NCI-H69 tumour implants in the right flank of rats.
❖Treatment schedule :
➢Treatment start (D0) 25 days after irradiation when the mean tumor volumes reached 160 mm^3.
➢Randomisation of rats.
➢4 weekly IV injections of VFL at 2.0, 4.0 and 6.0 mg base/kg/inj. (at D0, D7, D14 and D21, Q7DX4, 10 rats/group).
➢Monitoring of tumor size, body weight and survival twice a week.
➢Sacrifice and autopsy of rats at D42.

The *in vivo* experiments were performed following the United Kingdom Guidelines for the Welfare of Animals in experimental neoplasia (1).



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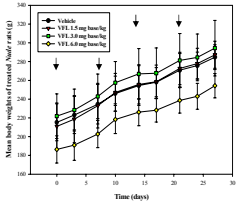
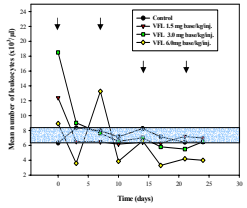
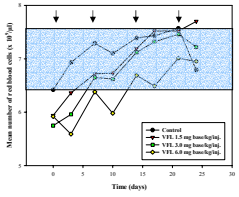
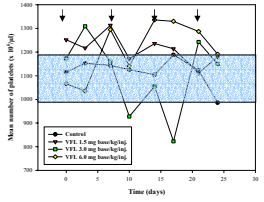
2. Hill B.T. *et al.*, Superior *in vivo* experimental antitumor activity of vinflunine, relative to vinorelbine, in a panel of human tumour xenografts, Eur. J. Cancer, 35: 512-520, 1999.

RESULTS: Tolerance study of VFL on irradiated *Nude* rats.





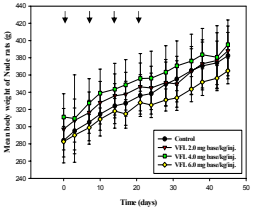


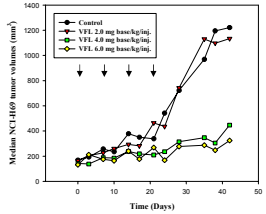


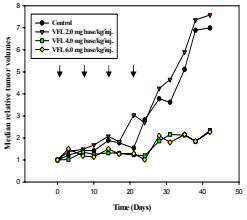
Test substance	Adm. route	Period of treatment	Dose/inj. (mg base/kg)	Survival rate at D52 (%)	MBWC ± SD D0-D21 (g)	MBWC D0-D21 (%)
NaCl 0.9%	IV	D0-D21	0.0	100	+ 55.43 ± 4.68	+ 25.94 ± 3.80
VFL	IV	D0-D21	1.5	100	+ 61.70 ± 8.23	+ 29.78 ± 6.97
VFL	IV	D0-D21	3.0	100	+ 59.40 ± 5.31	+ 26.82 ± 1.21
VFL	IV	D0-D21	6.0	100	+ 52.30 ± 6.68	+ 28.23 ± 4.68
VFL	IV	D0-D21	8.0	0	NA	NA

MBWC: Mean body weight change (between D0-D21)

RESULTS: Antitumor activity study of VFL in irradiated *Nude* rats bearing SC NCI-H69 tumors.







Adm. route	Period of treatment	Dose/inj. (mg base/kg)	MBWC ± SD D0-D24 (g)	MBWC ± SD D0-D24 (%)	DT ± SD (Days)	Optimal T/C% at D42	SGD	No. PR (%)
IV	D0-D21	0.0	+ 55.5 ± 13.6	+ 20.0 ± 5.8	5.8 ± 0.9	NA	-	0
IV	D0-D21	2.0	+ 47.8 ± 8.6	+ 16.2 ± 3.3	7.25 ± 2.2	93	0.3	0
IV	D0-D21	4.0	+ 45.1 ± 8.6	+ 14.5 ± 2.4	15.1 ± 5.9	36	1.6	20
IV	D0-D21	6.0	+ 42.6 ± 7.9	+ 15.2 ± 3.2	14.2 ± 5.1	26	1.5	29

PR: Partial response when the tumor volume was lower than 32 mm^3 at D42

Conclusions

➢ VFL was well tolerated by irradiated *Nude* rats after 4 repeated weekly IV injections.
➢ VFL displayed a significant antitumor activity on the growth of human SC lung carcinoma tumors (NCI-H69) xenografted in irradiated *Nude* rats as well as in *Nude* mice,
➢ The *Nude* rat is more sensitive than *Nude* mice to the toxic effects of anticancer agents,
➢ NCI-H69 tumor xenografted in *Nude* rat is a promising model to test further chemotherapeutic combinations of VFL.

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