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Phase II Trial of TCNU and Vindesine in Patients with Adenocarcinoma of the Lung

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VINDESINE (VDS) is among the most active single agents in adenocarcinoma of the lung (ACL) with a response rate of 20–25% [1]. In two phase I studies of TCNU (1-(2-chloroethyl)-3-[2-(dimethylaminosulfonyl)ethyl]-1-nitrosourea), a newer water soluble nitrosourea, impressive activity was observed [2, 3]; a subsequent phase II trial showed modest activity [4].

A phase II study of vindesine and TCNU has been carried out in patients with adenocarcinoma of the lung. Patient characteristics are shown in Table 1. Entry criteria were: non-resectable ACL (WHO), no previous chemotherapy or radiotherapy, measurable or evaluable disease, performance status ≤3 (ECOG scale), age ≤75 years, no previous or concurrent malignancies, no active uncontrolled infection, adequate haematological parameters, normal liver and renal function. Informed consent was obtained and the trial was approved by the regional ethical committee.

The dose for TCNU was 110 mg/m^2 p.o. every 4 weeks, and for vindesine 3 mg/m^2 i.v. for 8 weeks, then bi-weekly. Chemotherapy was postponed in the absence of full haematological recovery (i.e. WBC $<2{\cdot}5 \times 10^9$/l or platelets $<100 \times 10^9$/l), at the time of scheduled retreatment. Doses were adjusted according to the nadir values of WBC and platelets, and also according to neurotoxicity in the case of VDS. Treatment was discontinued where there was progressive disease after the first course. The duration of response was measured from the date the response was first observed, to the date of disease progression [5]. Patients were considered evaluable if they had received at least one treatment cycle. Patients with early death (death within 4 weeks) were considered as non-responders.

Table 1. Patient characteristics, response and survival

Total No. patients	64	
Not eligible	8	
Median age in years (range)	58 (38–73)	
Sex F/M	35/21	
Performance status (ECOG)		
PS 0–1	38 (68%)	
PS 2–3	18 (32%)	
Partial remission	11 patients	(20%)
Respone duration (range)	14 weeks	(2–49)
Median survival (range)	28 weeks	(0.5–86)

The response status of the 56 eligible patients is shown in Table 1. Toxicity was considerable, with dose reduction needed in 71% of the evaluable patients, either due to neurotoxicity (62%) or haematological toxicity (37%). Fifty-two per cent of the patients obtained WHO grade III and IV haematological toxicity. One death from sepsis was observed (WBC 0.2×10^9/l, platelets 21×10^9/l).

The response rate of 20% was comparable to either drug given alone. The doses employed in combination were lower than those used in single agent studies; however, it appears not to be possible to increase drug doses because the toxicity encountered was considerable. Treatment with TCNU and VDS in the present dose and schedule can not be recommended in patients with ACL.

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Phase II Trial of High Dose Recombinant Gamma-interferon in Advanced Hepatocellular Carcinoma

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THERE have been a few reported clinical trials of IFN-γ in human malignancies [1–3]. The results of low-dose IFN-γ for hepatocellular carcinoma (HCC) have been disappointing to date [4]. In a preliminary report from Japan [5], however, the tumour volume doubling time was reported to be prolonged in two of

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Table 1. Patient characteristics and response

	No. of patients
Male/female	13/2
Median age (range)	59.6 (37–77)
Liver cirrhosis	11
Ascites	4
HBsAg positive	0
Prior chemotherapy	
No	15
Yes	0
Performance status	
0–1	13
2	2
3	0
Eligible	14
Ineligible	1
Complete response	0
Partial response	0
Stable disease	9
Progressive disease	5

*Table 2. Adverse effects**

	No. of patients
Patients evaluable for toxicity	14
Flu-like symptoms	12
Pyrexia	12
Anorexia	7
Nausea and vomiting	4
Headache	3
Sore throat	1
Arrhythmia†	1
Leukopenia	0
Thrombocytopenia	0
Hepatotoxicity‡	8
Proteinuria†	1

*Adverse effects more severe than grade 3 are listed.
†Adverse effects of grade 3.
‡Transaminase levels before treatment were not always normal, so only patients whose values a week after treatment were elevated higher than grade 2 and/or 200 IU/l are listed.

seven HCC cases after treatment with low-dose INF-γ, although there was no responder. The aim of this study was to evaluate whether or not the antineoplastic activity against HCC could be enhanced by higher doses of IFN-γ and to assess its toxic effects.

All patients with non-resectable HCC were eligible for the trial if they had a measurable lesion, a life expectancy of at least 6 weeks and performance status better than 3 by World Health Organization (WHO) guidelines [6]. No patient had previous chemotherapy or radiotherapy. Nine patients had histologically verified HCC, in six patients the diagnosis was based on computed tomography, ultrasonography and hepatic angiography. All patients gave written informed consent. A dose of $1.6–2.4 \times 10^7$ units of IFN-γ (Kyowa Hakko Corp., Tokyo, Japan) was administered intravenously over 1 h for 5 consecutive days every 2 weeks. The tumour size was measured every 4 weeks by ultrasonography and/or computed tomography. Antitumour effect and toxicity were evaluated by WHO guidelines. An antipyretic agent was given to all patients for fever, before the administration of IFN-γ.

Patient characteristics and the antitumour effects of IFN-γ are shown in Table 1. There were no responders among our 14 evaluable patients. All the toxic effects were mild and transient (Table 2).

These results indicate that while a high dose IFN-γ treatment is tolerable, it has no favourable effect in patients with advanced HCC, at least by the regimen employed in this study.

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