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Clinical Trial Summary

A Phase II Trial of TCNU in Patients with Squamous, Adeno and Large Cell Carcinoma of the Lung

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INTRODUCTION

SQUAMOUS CELL CARCINOMA, adenocarcinoma and large cell carcinoma constitute about 75% of all histologic types of lung cancer, and the response rates for all types are low. For this reason careful clinical screening of new, hopefully more active, agents deserves high priority.

TCNU (1-(2-chloroethyl)-3-[2-(dimethylaminosulfonyl) ethyl]-1-nitrosourea) is a newly developed water-soluble nitrosourea [1]. In experimental murine tumours TCNU exhibits activity similar to or better than other nitrosoureas, and in two clinical phase I trials of patients with primary bronchogenic carcinoma, impressive clinical activity was observed [2, 3]. The present study was undertaken to extend the phase I experience and to further characterize the toxicity profile of TCNU.

MATERIALS AND METHODS

A total of 109 patients were included in the study: 61 at the Finsen Institute, 22 at Herlev Hosptial, 16 at Bispedbjerg Hospital and 10 at Western General Hospital. Patient characteristics are given in Table 1. Entry criteria included: histologically proven incurable NSCCL (histopathological classification according to WHO criteria) [4], no previous chemotherapy, measurable/evaluable disease, performance status < 3 (WHO scale), age < 75 years, no previous or concurrent malignancies and no active uncontrolled infection. Pretherapeutic values of haemoglobin (> 6.5 mmol/l), white blood cell counts ($> 3.0 \times 10^9$/l) and platelets ($> 100 \times 10^9$/l) were required as were normal liver and renal function tests, unless the abnormal values were shown to be directly related to the underlying disease. Informed consent was obtained from the patient, according to the Helsinki declaration.

TCNU was supplied by the LEO Company, Helsingborg, Sweden, as tablets (10, 25 and 50 mg) and was given at a starting dose of 130 mg/m^2 p.o. with retreatment given every 4 weeks in Copenhagen and every 5 weeks in Edinburgh. Chemotherapy was postponed if there was no full haemotologic recovery (i.e. WBC $< 2.5 \times 10^9$/l and platelets $> 100 \times 10^9$/l), at the time of scheduled treatment. Doses were adjusted according to the lowest value of WBC and platelets.

Treatment with TCNU was discontinued when there was clear evidence of progressive disease (WHO criteria), after the first course whereas no change (NC) or remission (PR or CR) indicated continuation of therapy until disease progression. WHO criteria was also applied in the evaluation of toxicity.

Patients were considered evaluable if they had received at least one treatment cycle with TCNU. Early death patients (death during first course without severe toxicity) were considered to be non-responders.

Twenty patients (18%) were found to be ineligible, which leaves 89 fully evaluable patients

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Table 1. Pretreatment characteristics

	Histological subclassification					
	WHO I	WHO III	WHO IV	Mix.	Unclass.	Total
No. of evaluable* patients	15	49	21	2	2	89
Age in years						
median	65	57	56	—	—	60
range	41–72	43–74	33–69	37–62	63–73	33–74
Sex						
male	9	24	17	1	2	53
female	6	25	4	1	—	36
WHO performance status						
0	2	12	5	1	1	21
1	7	22	10	—	1	40
2	6	14	5	1	—	26
3	—	1	1		—	2

*Evaluable for response and survival.

Table 2. Objective tumour response

	Histological subclassification					
	WHO I	WHO III	WHO IV	Mix.	Unclass.	Total
No. of evaluable* patients	15	49	21	2	2	89
Response						
complete remission	—	1	—	—	1	2
partial remission	—	6	—	—	—	6
no change	3	13	8	1	1	26
progressive disease	10	23	11	1	—	45
early death	2	6	2	—	—	10
Duration of response (weeks)						
		8			47+	
		8				
		21				
		25				
		28				
		38				
		56+				
Survival (weeks)						
median	27+	18	20	—	—	21
range	3–42	1–80+	3–38	—	—	1–80+

*Evaluable for response and survival.

for response, although only 79 patients could be evaluated for toxicity since 10 were classified as early death.

RESULTS

Of the 89 evaluable patients, seven with adenocarcinoma and one with unclassified NSCCL responded to TCNU in the form of two complete and six partial remissions (Table 2) yielding a response rate (CR + PR) for bronchogenic adenocarcinoma of 14%. The duration of response ranged from 8 to 56 weeks (median 27 weeks). Of the responders, one patient had performance status (PS) 0, four had PS 1, two had PS 2 and one patient PS 3, reflecting the overall study population.

The 79 patients evaluable for toxicity received a total of 273 courses of TCNU ranging from one to 11 courses each (Table 3). Of the 194 retreatments, 158 (81%) were administrated within the recommended 4–5 weeks, 16 (8%) were delayed by 2

Table 3. Number of courses received and feasibility of the recommended dose and schedule of TCNU

	Histological subclassification					
	WHO I	WHO III	WHO IV	Mix.	Unclass.	Total
No. of evaluable* patients	13	43	19	2	2	79
No. of courses						
1	2	6	1	—	—	9
2	3	12	3	2	1	21
3	5	6	8	—	—	19
4	2	4	3	—	—	9
5	—	6	3	—	—	9
6	1	4	1	—	—	6
7	—	2	—	—	1	3
8	—	2	—	—	—	2
9	—	—	—	—	—	—
10	—	—	—	—	—	—
11	—	1	—	—	—	1
$\sum_{1}^{11}$ No. of courses	37	159	64	4	9	273
Delay of retreatment (weeks)						
0	16	74	30	1	2	123
1	4	18	11	—	2	35
2	2	10	3	—	1	16
3	2	7	—	1	1	11
4	—	2	1	—	1	4
5–7	—	5	—	—	—	5
$\frac{\text{Cumulative dose/m}^2}{130\ \text{mg/m}^2 \times \text{No. of courses}} \times 100\%$						
Median	100	100	100	—	—	100
Range	73–117	70–146	91–135	100–100	86–100	70–146

*Evaluable for toxicity: eligible patients — early death.

weeks and 11 (6%) by 3 weeks. Eighty per cent of the patients were able to receive the scheduled doses without reductions.

Thrombocytopenia — especially cumulative — was the most significant toxic effect (Table 4). There were no drug-related deaths. Twenty-four patients (30%) achieved a nadir of thromobocytes $< 25 \times 10^9$/l (WHO grade 4) necessitating platelet transfusions. Cumulative thrombocytopenia occurred after three to eight courses. Leucocytopenia WHO grade 4 (WBC $< 1.0 \times 10^9$/l) was observed in two patients.

The majority of the patients (77%) experienced nausea and vomiting WHO grade 1–4 with seven patients (9%) suffering from intractable vomiting, despite antiemetics administered before TCNU (Table 4).

Other toxic effects included diarrhoea and stomatitis (one patient each) and also pain in the tumor area. Reversible hepatoxicity was observed in three patients consisting of increases in se-ASAT, se-alkaline phosphatases and se-bilirubin.

DISCUSSION

The activity of TCNU as single agent has been evaluated in this clinical phase II trial in patients with 'non-small cell' lung cancer. All 89 previously untreated patients were ambulatory and had good performance status as 61% had PS 0 or 1. With two complete and six partial remissions the overall response rate was 9%. The response rate according to histological subclassification was 0% for squamous cell carcinoma (WHO I), 14% for adenocarcinoma (WHO III) and 0% for large cell carcinoma of the lung (WHO IV).

In general TCNU was tolerated to an acceptable degree in the dose and schedule tested. Of the 79 evaluable patients, 80% were able to receive the

Table 4. Haematologic nadir values and nausea/vomiting during all course (WHO gradings)

	Histological subclassification					
	WHO I	WHO III	WHO IV	Mix.	Unclass.	Total
No. of evaluable* patients	13	43	19	2	2	79
Thrombocytes WHO grade						
0	3	9	7	1	1	21
1	—	2	1	—	—	3
2	4	6	1	—	—	11
3	3	12	3	1	1	20
4	3	14	7	—	—	24
Leucocytes WHO grade						
0	3	18	9	1	—	31
1	2	7	4	—	2	15
2	4	10	3	1	—	18
3	4	7	2	—	—	13
4	—	1	1	—	—	2
Nausea/vomiting WHO grade						
0	2	5	1	1	—	9
1	5	12	4	—	1	22
2	1	8	7	—	—	16
3	3	11	1	1	—	16
4	—	2	5	—	—	7
†	2	5	1	—	1	9

*Evaluable for toxicity: eligible patients — early death.
†Not reported.

scheduled doses without reductions and 81% of the prescribed retreatments were given within 4–5 weeks. The dose-limiting factor was delayed haemotologic toxicity especially thrombocytopenia as 30% of the patients achieved WHO grade 4.

Compared with the effects of single agents previously tested in phase II trials in patients with advanced NSCCL the results are not encouraging. The highest median response rates of 20–25% are reported for iphosphamide, cisplatin and VP-16 in squamous cell carcinoma, and for vindesine, iphosphamide and cisplatin in adenocarcinoma [5, 6].

As stressed by Hansen and Rørth [7], initial reports of high response rates are frequently followed by reports of much lower rates when the studies are performed in a stricter fashion within cooperative groups. In this study performed by the same two groups who carried out the phase I studies, we can only conclude that the lower responses seen in large cell in the phase II study merely reflect the importance of not making premature assumptions about activity seen in the relatively small number of patients entered into phase I trials.

The activity of TCNU in adenocarcinoma of the lung reported here confirms that this drug had modest activity of the same order as that of other commonly used cytostatic agents mentioned above.

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