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A Phase II Study of Neocarzinostatin (NSC 157365) in Malignant Hepatoma

An Eastern Cooperative Oncology Group Pilot Study

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Summary. *Thirty evaluable patients with histologically confirmed primary liver cancer (PLC) were treated with neocarzinostatin (NCS). All patients had measurable disease and an Eastern Cooperative Oncology Group (ECOG) performance status of 1, 2, or 3. NCS 2250 units/m² was given daily for 5 days, repeated at 28-day intervals. Hemopoietic suppression was the major side effect. In 23 of 30 patients (13 with leukopenia and 19 with thrombocytopenia), this toxic effect was documented. Other toxic effects included nausea, vomiting, allergic-type reaction, and elevation of NPN. Partial response, with a median duration of 12.7 weeks (range 4–37 weeks) was observed in seven patients. In nine patients the response was classified as no change, and in 14 patients there was progressive disease. NCS has some therapeutic activity in patients with PLC.*

Introduction

Neocarzinostatin (NSC 157365, NCS) is an acidic polypeptide antibiotic isolated from *Streptomyces carzinostaticus* var. F41 [4, 5]. NCS is composed of 109 L amino acids [9]. The mechanism of action of NCS appears to be inhibition of thymidine incorporation into DNA [10], the principle cytocidal effects being in the G_2 phase [11].

NCS is the first antitumor protein of defined structure being used in cancer chemotherapy. The drug disappears rapidly from the serum and is excreted immunochemically intact in the urine, the primary mode of excretion being glomerular filtration [1].

On the basis of its activity against experimental animal tumors, clinical trials were performed in Japan. In the Japanese trials, five of eight patients with hepatoma had subjective response to treatment with NCS [6]. At the Sidney Farber Cancer Institute partial response was reported in three of three patients with hepatoma [3].

Various types of toxic manifestations have been documented in clinical phase I studies [3, 7, 8]. Acute reactions have included chills, fever, rigor, hypertension, and mental confusion. Nausea and vomiting, though often seen, were not dose-limiting. Myelosuppression was usually dose-limiting. Leukopenia and/or thrombocytopenia were somewhat unpredictable and often prolonged. Other side effects were occasional anaphylaxis, and hepatic and renal dysfunction.

Only minor advances have been made in the treatment of hepatoma in man [2], so that the early results with NCS [3] served as additional motivation for the present study.

The aim of the present study was to do a phase II trial of NCS in patients with primary liver cancer (PLC) so as to assess the possible value of the agent for later incorporation into a phase III clinical trial.

Materials and Methods

Patients with histologically confirmed PLC beyond hope of surgical cure were considered eligible for this study if they had a measurable area of known malignant disease to serve as an objective indicator of response to treatment. Hepatomegaly was utilized in all patients, as in this series the liver (known to contain carcinoma) was always more than 5 cm below the xiphoid process or the costal margin on quiet respiration. Patients who had undergone surgery with resection or anastomosis within the previous 3 weeks were excluded, and the eligibility criteria further included absence of an active infectious process, leukopenia ($< 4{,}000/mm^3$), thrombocytopenia ($< 100{,}000/mm^3$), and renal disease (creatinine > 1.5 mg% or BUN > 30 mg).

At the start of treatment the following examinations were performed: Studies obtained prior to initial therapy consisted of HGB, WBC, platelet count, differential count, urinalysis, BUN or creatinine, bilirubin, alkaline phosphatase, SGOT, serum protein electrophoresis, prothrombin time, α-fetoprotein, and carcinoembryonic antigen (CEA). HGB, WBC, and platelet count were repeated at weekly

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Table 1. Phase II study: Neocarzinostatin in primary liver cancer

No. of cycles of treatment	1	2	3	4	5	6	7
No. of patients	16	6	5	1	0	1	1

intervals, BUN or creatinine and bilirubin 2 weeks after initiation of each course, and the remaining studies every 4 weeks. Height and weight, symptomatic status and performance status were assessed on the first day of therapy.

Thirty-one patients were entered on study. The last patient entered the study recently and is therefore not yet evaluable and has not been included for analysis. Of the 30 evaluable patients, 22 were black South Africans, two white South Africans and six white North Americans. There was one child (a white American aged 3 years, 9 months). The age range of the other 29 patients was 21–75 (median age 42). There were 26 males and four females. Ten patients had an ECOG performance status of 1, ten an ECOG performance status of 2, and ten an ECOG performance status of 3 at the start of treatment (ECOG performance status: 0, normal activity; 1, symptoms but ambulatory; 2, in bed < 50% of time; 3, in bed > 50% of time; 4, 100% bedridden). Fifteen of the 30 patients had jaundice at the start of treatment and eight had ascites. Eight patients had lung metastases, one had confirmed peritoneal metastases, and one had bone metastases.

Two patients had mixed cholangiocellular and hepatocellular carcinoma. The remaining 28 patients had hepatocellular carcinoma. In eight patients concomitant cirrhosis was documented and one patient had concomitant siderosis. In 12 South African patients the diagnosis of chronic Budd-Chiari syndrome [12] was based on the findings of centrilobular fibrosis in which numerous vascular channels occurred. The adjacent liver sinusoids were congested. Inflammatory cell infiltration was minimal. Although patients were assigned to this category purely on the basis of the histological appearance at liver biopsy, this was confirmed at necropsy (2), inferior venogram (8), or both (2).

Among the 24 South African patients at the start of treatment, 16 had elevated α-fetoprotein and 11 had positive HB_sAg.

The dose of NCS was 2,250 units/m^2/d IV daily for 5 days, repeated if the hemogram allowed at 28-day intervals. In all but two of the patients who received several courses it was possible to give the cycle every 28 days. In one patient the first cycle was delayed for 42 days due to a rapid fall in leukocytes (this patient's WBC dropped from 11,600 to 4,000). In a second patient the third cycle only was delayed, due to a nadir of 2,200. Dose modification to 75% of the planned dose was necessary in four patients because of hemopoietic toxicity after the first course. The agent was infused (in the dark to prevent light destruction of the drug) in 150 ml D5W over 30 min. Diphenhydramine 25 mg was given 30 min before the administration of NCS. The dose range among the 29 adult patients was 11,250–120,000 units (median 20,000). The number of treatment cycles is shown in Table 1.

Results

Toxic Effects

Hemopoietic toxicity ascribed to NCS was documented in 23 patients. Thirteen developed leukopenia and 19 thrombocytopenia. Leukopenia lasted up to 6 weeks and thrombocytopenia up to 11 weeks (see Table 2).

Table 2. Neocarzinostatin in primary liver cancer: Hemopoietic toxicity[a] among 30 patients

Leukopenia
- Grade I: 5
- Grade II: 4
- Grade III: 4
- Total: 13

Median time to nadir 5 weeks (2–15)
Median duration 2 weeks (1–6)
- Median lowest WBC: 4.8 (10^3)
- Median lowest neutrophil: 3.8 (10^3)

Thrombocytopenia
- Grade I: 2
- Grade II: 7
- Grade III: 8
- Grade IV: 2
- Total: 19

Median time to nadir 8 weeks (2–23)
Median duration 4 weeks (1–11)
- Median lowest thrombocyte: 84 (10^3)

Total no. of patients with hemopoietic toxicity: 23

[a] Toxicity key

	0	1	2	3	4
Leukopenia	≧4.5	3.0–<4.5	2.0–<3.0	1.0–<2.0	<1.0
Thrombocytopenia	≧130	90–<130	50–<90	25–<50	<25

Table 3. Neocarzinostatin in primary liver cancer: Other side effects[a]

A. Gastrointestinal

Nausea and vomiting
- Grade I: 4
- Grade II: 0
- Grade III: 2

Diarrhea: 1
Total: 7

B. Allergic type reaction

Fever: 1
Flushing: 1
Myalgia: 1 (required removal from study)
Total: 3

C. Renal

Elevated NPN: 1
Flame bleeding kidneys: 1
Total: 2

[a] Toxicity key

	0	1	2	3
Nausea + vomiting	None	Nausea	Controllable	Intractable
Diarrhea	None	No dehydration	Dehydration	Grossly bloody

Other side effects included nausea and vomiting, diarrhea, allergic type reactions and renal toxicity (see Table 3). Renal toxicity was only seen in two patients, one of whom developed an elevated NPN and while in the second patient's case flame bleedings were seen in the kidneys at autopsy, although renal toxicity had not been suspected during life.

Therapeutic Effect

There were seven patients who met the criteria for partial response. Hepatomegaly was the measurable lesion in all seven patients. None had extrahepatic metastases. There had to be a reduction of the sum of liver measurements below each costal margin at the midclavicular line and xiphoid process by at least 30%. This response had to be of at least 4 weeks' duration. For partial regressions there could be no significant deterioration in weight, symptoms, or performance status. None of the patients with measurable lung metastases met the criteria for partial response, which required a reduction by at least 50% of the product of the largest perpendicular diameters of the most clearly measurable mass lesion with no increase in any other indicator lesion, and the absence of new areas of malignant disease. Partial response lasted from 4–37 weeks, with a median duration of 12.7 weeks. In five of these seven patients there was also an improvement in performance status, while in the remaining two the performance status remained stable during the period of partial response. Of the seven patients, six had elevated alkaline phosphatase at the start of treatment, and five of these showed a decrease in alkaline phosphatase; one of three with elevated bilirubin showed a decrease in bilirubin; and two of three with decreased serum albumin showed an increase in serum albumin.

Nine patients were considered to have either stable disease or to have shown improvement less than the minimum criteria for partial response. Among the patients with stable disease, one patient showed a decrease in the liver and bone lesions, and a further two patients showed a decrease in the liver measurements. The longest duration of stable disease was 26 weeks.

In 14 patients there was progressive disease despite treatment.

Survival Times

The median survival times for all patients from the start of treatment with NCS was 6 weeks (range 1–42 weeks). The median survival time of the seven patients showing partial response was 17 weeks (range 9.5–42.6 weeks).

Of the six USA patients, all had received prior chemotherapy; none of the South African patients had received prior chemotherapy. The median survival time of the 20 South African black patients was 5 weeks (range 1–41 weeks). In a previous study, USA patients had a median survival of 14 weeks and South African black patients had a median survival of 6.2 weeks. Patients treated with oral 5-fluorouracil had a median survival of 6.7 weeks, while South African black patients had a median survival of 3.1 weeks [2]. As in previous studies, the survival time correlates with performance status at the start of treatment. In this study, patients with a performance status of 1 at the start of treatment had a median survival time of 12.9 weeks, while those with a performance status of 2–3 had a median survival time of only 5.4 weeks.

Discussion and Conclusion

In this pilot study a definite therapeutic effect of NCS in primary liver cancer has been demonstrated, with seven of 30 patients achieving a partial response status. The median duration of the partial response was 12.7 weeks. The median survival time of the seven responders was 17 weeks. Of the seven responders, two had a performance status of 1 at the start of treatment. The median survival time of patients with a performance status of 2 or 3 the median survival time was 5.4 weeks. As in previous studies, the survival time was clearly related to performance status at the start of treatment. The results of this phase II study are adequate motivation to include NCS in a phase III prospective randomized trial. Such a phase III study, comparing NCS with adriamycin in patients with primary liver cancer, is planned by the Eastern Cooperative Oncology Group.

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