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Short communication

Phase II clinical trial of high-dose recombinant human tumor necrosis factor

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Summary. Based on a phase I study in 1986, 22 patients have been entered in a phase II study of high-dose human tumor necrosis factor (rH-TNF) since May 1987. Of these patients, 18 are evaluable at present, 2 are still under investigation, and 2 have dropped out. All had advanced stages of cancer (9 soft-tissue sarcomas, 3 melanomas, 5 hypernephromas) and inclusion in the study was ethically acceptable (informed consent). The daily dose of rH-TNF was 15×10^5 units/m^2, escalated to 21×10^5 units/m^2 (683–956 μg/m^2 every week; range 1–6 cycles). Additional prophylactic ketoprofen administration was carried out. Of the 18 evaluable patients, 4 responsed with no change (2/4, clinical improvement) and 14 showed progressive disease. The main toxicities observed were hypotension (decrease in systolic blood pressure, 21–60 Torr), leukocytosis, increases in ALAT/ASAT (WHO grade 0–4), fever (WHO grade 1–2), chills (mild to moderate), neurotoxicity (WHO grade 0–2), and nausea/vomiting (WHO grade 0–3).

Introduction

A phase I and pharmacokinetic study of human tumor necrosis factor (rH-TNF) was carried out in this institute between February 1986 and February 1987, including 15 patients [4, 5]. In accordance with other reports [2], acute toxicities in the form of fever, chills, tachycardia, hypertension, peripheral cyanosis, nausea and vomiting, headache, chest tightness, low back pain, diarrhea, and shortness of breath were seen but were not dose-limiting or dose-related. The dose-limiting toxicity was hypotension that occurred after the end of the drug infusion, neurotoxicity, and hepatotoxicity. There was no mortality or long-term morbidity. On the basis of the data in this study, the recommended starting dose for phase II studies of the single dose is 15×10^5 units/m^2 (683 μg/m^2). This dose is definitely higher than those used in other, comparable studies [2, 3].

Patients, methods and results

We report a phase II trial of rH-TNF in patients with biopsy-proven, prognostically unfavorable cancer (Table 1) not amenable to other treatment or in whom other treatment had proven to be ineffective. All patients had evaluable disease.

Table 1. Patient characteristics

Characteristic	Patients (*n*)
Entered	22
Evaluable for toxicity	21
Evaluable for response	18
Dropped out (toxicity)	2
Still under investigation	2
Median age in years (range)	44.7 (24–67)
Median Karnofsky performance status (range)	70% (60–100%)
Men/Women	11/11
Extent/histology of disease	22
Advanced	
Soft-tissue sarcoma	9
Hypernephroma	5
Melanoma	3
SCLC	1
Ovarian cancer	1
Gastric cancer	1
Pancreatic cancer	1
Testicular cancer	1
Prior treatment:	
None	13
Chemotherapy	4
First-line	1
Salvage	1
Radiotherapy	1
Combined	3

The drug was supplied by the Asahi Chemical Industry Company Limited, Tokyo, Japan, in vials containing 5×10^5 units; it was >99% pure after purification and contained no detectable endotoxin or DNA. The specific activity of the material was 2.2×10^6 units/mg.

The i.v. dose of rH-TNF was 15×10^5 units/m^2, escalated to 21×10^5 units/m^2 (683–956 μg/m^2), injected over 30–60 min with dextran and dopamine in water at 8- to 12-day intervals. According to our information, this dose is significantly higher than those used in other, comparable rH-TNF phase II studies. Patients were pretreated with ketoprofen. All patients were hospitalized under intensive-care conditions from the day before treatment until at least 6 days after treatment. A median of 3.3 courses (range 1–6) of rH-TNF were given (3 patients were given 6 courses).

No complete or partial responses were observed in the 18 evaluable patients treated in this study; 4 showed no progression during treatment (3 soft-tissue sarcomas and 1 melanoma; progression 3, 4, 4, and 13 weeks after the end of treatment, respectively) and 14 had disease progression during treatment. Acute hypotension (decrease in systolic blood pressure: 21–40 Torr, 10 patients; 41–60 Torr, 9 patients; >60 Torr, 2 patients), increases in ALAT (WHO grade III + IV, 6 patients) and ASAT (WHO grade III + IV, 10 patients), fever (WHO grade II, 19 patients), chills (mild/moderate, 17 patients; severe, 2 patients), nausea and vomiting (WHO grade II + III, 15 patients), and neurotoxicity (WHO grade I + II, 18 patients) were the most common toxic effects seen.

Discussion

We could not demonstrate any therapeutic value for rH-TNF at this dose and schedule among extensively pretreated patients with prognostically unfavorable cancer of diverse histologies. Nevertheless, the achievement of disease-stability and clinical improvement in four patients indicates that the role of TNF remains to be defined. Over the coming few years we will learn much more about the biology of TNF as well as how to apply this knowledge to a clinical setting. Many important questions concerning the optimal mode of administration of rH-TNF, especially the dose level, schedule, and duration of treatment, remain unanswered.

Early preparations of TNF were scarce, of variable purity and potency, and prohibitively expensive. The cloning of the TNF gene and the application of recombinant DNA technology to the production of biological molecules has enabled the manufacture of highly pure forms of human TNF. Sufficient quantities of rH-TNF are now available, enabling properly conducted clinical trials to answer the questions posed above.

The future role of rH-TNF as an anticancer agent may lie in combination chemotherapy with other types of biological response modifiers or conventional cytotoxic drugs. Furthermore, simple single-drug rH-TNF regimens following other approaches of scheduling (e.g. continuous infusion) should be investigated.

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