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Phase II study of NK313 in malignant lymphomas: an NK313 Malignant Lymphoma Study Group trial

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Summary. Liblomycin (NK313) is a bleomycin analog that has proved to be associated with less pulmonary toxicity and with more potent antitumor activity than bleomycin in animal tumors. In a phase I study, pulmonary toxicity was not observed, whereas myelosuppression was the dose-limiting factor. The maximum tolerated dose was 140 mg/m^2 given once a week for 4 weeks. In the present phase II study, patients with malignant lymphomas received liblomycin at 80 or 100 mg/m^2 by intravenous infusion over 15 min once a week for 4 weeks. A total of 39 patients were entered, and 31 [4 with Hodgkin's disease (HD) and 27 with non-Hodgkin's lymphoma (NHL)] were evaluable. The median age of the patients was 52 years (range, 22–74 years), and their performance status ranged from 0 to 3. In all, 28 of the patients had a history of intensive anticancer chemotherapy. Responses were evaluated according to WHO criteria. We obtained 1 complete remission and 9 partial remissions (PRs), for an overall response rate of 37%, in the 27 patients with NHL, whereas 1 PR was achieved in the 4 patients with HD. In all, 9 PRs (32.1%) were obtained in patients who had been exposed to prior chemotherapy, including 4 PRs (33.3%) in 12 patients who had previously been treated with bleomycin. Myelosuppression and nausea and vomiting were the major toxicities, which occurred in about 50% of the patients, and myelosuppression was severe in two patients treated at a dose of 100 mg/m^2. We concluded that liblomycin demonstrated significant antitumor activity against malignant lymphomas.

Introduction

Bleomycin is one of the most effective chemotherapeutic agents against malignant lymphomas, testicular tumor, skin cancer, cervical cancer, and head and neck cancer. As it is not accompanied by a myelosuppressive effect, bleomycin has been a useful agent in combination chemotherapy. However, pulmonary toxicity is the major dose-limiting factor for its clinical application in long-term chemotherapy. In 1981, after an intensive search for an analog of reduced pulmonary toxicity but with a broader antitumor spectrum, peplomycin was developed as such an agent. The clinical efficacy of peplomycin has since been extended to include prostatic cancer [4]. However, the agent retains its pulmonary toxicity, which is again dose-limiting.

Liblomycin has a bulky lipophilic group at the end of the terminal amine, which is introduced by reductive *N*-alkylation of biosynthetic bleomycin [7]. Liblomycin has been found to have activity superior to that of peplomycin in HeLa S_3, L1210 mouse leukemia, P388 mouse leukemia, Ehrlich carcinoma, and rat ascites hepatoma AH66F [7]. Takahashi et al. [7] reported that the pulmonary toxicity of liblomycin was milder than that of peplomycin or bleomycin. In a phase I study, no pulmonary toxicity was observed, whereas myelosuppression was found to be a dose-limiting factor [1].

This paper reports the results of a phase II study of liblomycin conducted by the Malignant Lymphoma Study Group in patients with malignant lymphomas that relapsed or were refractory to previous chemotherapy.

Patients and methods

All of the patients entered in the present study had histologically proven malignant lymphomas. The eligibility criteria included a performance status of $\leqq 3$ (WHO), an expected survival of at least 2 months, the presence of measurable lesions and of disease resistant to conventional chemotherapy, evidence of disease progression during the preceding 2 months, no exposure to chemotherapy or radiotherapy over the preceding period of at least 4 weeks, a WBC of $\geqq 3.0 \times 10^3/\mu l$, a platelet count

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Table 1. Clinical features of the 31 evaluable patients

Characteristics	Number of patients receiving		
	80 mg/m²	100 mg/m²	Total
Sex (M/F)	13/6	6/6	19/12
Median age (range)	56 (22–74) years	49 (26–72) years	52 (22–74) years
Clinical stage:			
I	1		1
II	1	1	2
III	4	4	8
IV	13	7	20
Symptom status (A/B)	14/5	5/7	19/12
Histology:			
Hodgkin's disease	2	2	4
Non-Hodgkin's lymphoma:			
FSC	3	1	4
FM	2	1	3
FL	1	0	1
DSC	5	2	7
DM	1	2	3
DL	5	2	7
IBL	0	2	2
PS:			
0	3	4	7
1	9	6	15
2	2	2	4
3	5	0	5
	19	12	31

FSC, Follicular, predominantly small-cleaved-cell; FM, follicular, mixed small-cleaved- and large-cell; FL, follicular, predominantly large-cell; DSC, diffuse, small-cleaved-cell; DM, diffuse, mixed small- and large-cell; DL, diffuse, large-cell; IBL, large-cell, immunoblastic; PS, performance status

of $\geqq 75 \times 10^3/\mu l$, a serum creatinine level of $\leqq 2.0$ mg/dl, and a serum bilirubin value of $\leqq 2.0$ mg/dl. Patients who were in the leukemic phase or showed a symptomatic involvement of the central nervous system were excluded. In the first study, liblomycin was given at a dose of 100 mg/m² dissolved in 100 ml saline by intravenous infusion over 15 min once a week for 4 weeks. In the second study, it was given at a dose of 80 mg/m². The drug was supplied by Nippon Kayaku Co. Ltd. (Tokyo, Japan).

Responses were evaluated according to the criterion described by Miller et al. [5]. A complete remission (CR) was defined as the resolution of all evidence of disease; a partial remission (PR), as a decrease of >50% in the two largest perpendicular diameters of each tumor mass; a minor response (MR), as an objective decrease ranging from $\geqq 25\%$ to <50% in the two largest perpendicular diameters of each tumor mass. The responses were to persist for >1 month. The grades of toxicities were defined according to WHO criteria [8].

Results

A total of 39 patients with malignant lymphomas, of whom 17 were given a dose of 100 mg/m² liblomycin and 22 were given 80 mg/m², were entered the study. Of the 39 patients, 5 were ineligible owing to the following protocol violations: 3 received liblomycin within <1 week of prior chemotherapy and 2 received chemotherapy in combination with other anitumor agents. These patients were excluded from analyses of response and side effects.

Of the 34 eligible patients, 3 were inevaluable for response but evaluable for side effects for the following reasons: 2 patients refused further administration of liblomycin due to vomiting after receiving only one treatment with liblomycin, and 1 patient refused further therapy after developing a chill following only one infusion of liblomycin. The clinical characteristics of the 31 patients who were evaluable for response are summarized in Table 1. They included 12 women and 19 men ranging in age from 22 to 74 years (median, 52 years). The median performance status was 1 (range, 0–3). In all, 12 of the 31 patients had B symptoms, and 64.5% of the patients had advanced disease (stage IV).

The results of treatment are summarized in Table 2. The overall response rate was 35.5% for malignant lymphomas. We obtained 1 PR (25.0%) in the 4 patients with HD, whereas 1 CR and 9 PRs were achieved in the 27 patients with NHL, for an overall response rate of 37%. Of the 20 patients with clinical stage IV disease, 5 showed a PR, the response rate being 25%. Of the 12 patients with B symptoms, 3 (25%) responded with a PR, whereas 42.1% of the 19 patients with A symptoms showed a response, including 1 CR. In all, 19 of the patients received liblomycin at a dose of 80 mg/m², and 6 achieved a PR. In the 12 patients treated at 100 mg/m², 1 CR and 4 PRs were observed. Among the 28 patients who had a history of several intensive anticancer chemotherapy regimens, 12 patients who had received bleomycin and 16 who had no prior history of bleomycin treatment attained response rates of 33.3% and 31.3%, respectively. In 11 patients who

Table 2. Results of treatment

	Number of patients	CR	PR	MR	NC	PD	Response rate (CR+PR)
Histology:							
Hodgkin's disease	4		1		1	2	25.0%
Non-Hodgkin's lymphoma	27	1	9	5	5	7	37.0%
Low grade	8	1	3	3		1	50.0%
Intermediate grade	17		5	2	4	6	29.4%
High grade	2		1		1		50.0%
Clinical stage:							
I	1		1				100%
II	2		1		1		50.0%
III	8	1	3	1		3	50.0%
IV	20		5	4	5	6	25.0%
Symptom status:							
A	19	1	7	4	3	4	42.1%
B	12		3	1	3	5	25.0%
Dose of liblomycin:							
80 mg/m^2	19		6	4	3	6	31.6%
100 mg/m^2	12	1	4	1	3	3	41.7%
Prior chemotherapy:							
None	3	1	1			1	66.7%
With bleomycin	12		4	1	2	5	33.3%
Without bleomycin	16		5	4	4	3	31.3%
	31	1	10	5	6	9	35.5%

achieved a PR or CR, decreases of 50% in the tumor mass were observed at a median of 14 days (range, 3–28 days) after the first administration of liblomycin. The duration of responses extended from 4 to 13 weeks.

Leukopenia was documented in 47% of the 34 evaluable patients. Decreases in WBCs to grade 1 (3.0–3.9 $\times$ 10^3/μl) were seen in 8 patients (23.5%); decreases to grade 2 (2.0–2.9 $\times$ 10^3/μl), in 8 (23.5%); decreases to grade 3 (1.0–1.9 $\times$ 10^3/μl), in 3 (8.8%); and decreases to grade 4 (<1.0 $\times$ 10^3/μl), in 3 (8.8%). Granulocytopenia was observed in 11 of 27 evaluable patients ($\geqq$2.0 $\times$ 10^3/μl before the first administration of liblomycin). Decreases in granulocyte counts to grade 1 (1.5–1.9 $\times$ 10^3/μl) were seen in 2 patients (7.4%); decreases to grade 2 (1.0–1.4 $\times$ 10^3/μl), in 3 (11.1%); decreases to grade 3 (0.5–0.9 $\times$ 10^3/μl), in 3 (11.1%); and decreases to grade 4 (<0.5 $\times$ 10^3/μl), in 3 (11.1%). Thrombocytopenia manifested as platelet counts ranging between 7.5 $\times$ 10^4 and 9.9 $\times$ 10^4/μl (grade 1) in 5 patients (14.7%), between 5.0 $\times$ 10^4 and 7.4 $\times$ 10^4/μl (grade 2) in 2 (5.9%), between 2.5 $\times$ 10^4 and 4.9 $\times$ 10^4/μl (grade 3) in 6 (11.8%), and <2.5 $\times$ 10^4/μl (grade 4) in 2 (5.9%). Decreases in hemoglobin (Hb) were observed in 11 of 20 evaluable patients ($\geqq$11.0 g/dl before the first administration of liblomycin). Decreases to grade 1 (9.5–10.9 g/dl) were seen in 3 patients (15%); decreases to grade 2 (8.0–9.4 g/dl), in 5 (25%); and decreases to grade 3 (6.5–7.9 g/dl), in 3 (15%).

The median time to nadir values as measured from the final administration of liblomycin for WBCs, platelets, and Hb was 9 days (range, 0–54 days), 16 days (range, 3–58 days), and 7 days (range, 0–35 days), respectively. The median time for recovery from nadir values as determined for WBCs, platelets and Hb was 17 days (range, 7–32 days), 16 days (range, 7–42 days), and 9 days (range, 2–28 days), respectively. In two patients treated at a dose of 100 mg/m^2, prolonged myelosuppression was observed, and lymphoma was not detected in the marrow of these patients.

The nonhematologic toxicities encountered are listed in Table 3. Nausea and vomiting occurred in 18 (52.9%) of the 34 patients. In all, 4 of these patients required treatment for nausea and vomiting: 3 were given antiemetics and 1 received antiemetics and hydration. Fever occurred on the day of drug administration in 13 patients (38.2%), and only 1 patient was observed to run a fever higher than 40° C; in almost all cases the fever resolved on the following day. Malaise was experienced by 29.4% of the patients. In all, 28 patients were evaluable for alopecia because 6 patients had no hair at the start of the present study due to prior chemotherapy, and hair loss occurred in 12 patients (42.9%). Increases in serum GOT and GPT values were observed in 8 (23.5%) and 7 (20.6%) patients, respectively, and these subsequently recovered to normal levels. Reductions in arterial oxygen pressure (PaO_2) to <70 mmHg occurred in 3 patients (13.6%), and reductions in ($\%D_{LCO2}$) the percentage of CO_2-diffusing capacity were observed in 6 of 11 patients who accomplished the examination of diffusing capacity. However, symptoms such as shortness of breath, respiratory distress, or changes in chest X-rays were not observed. Moreover, 6 of 15 patients who died of malignant lymphomas within 6 months after the end of this study were autopsied and no pulmonary fibrosis was observed.

Table 3. Nonhematologic toxicities of liblomycin

	Number of patients		Grade		Frequency (%)
	For evaluation	With side effects	3	4	
Nausea/vomiting	34	18	4		52.9
Malaise	34	10	2		29.4
Fever	34	13	1		38.2
Hair loss	28	12			42.9
Stomatitis	34	3			8.8
Chill	34	1			2.9
Phlebitis	34	1			2.9
Increases in:					
BUN	34	2			5.9
SGOT	34	8			23.5
SGPT	34	7			20.6
Decreases in:					
PaO_2	22	3			13.6
$\%D_LCO_2$	11	6			54.5

Discussion

Bleomycin has significant antitumor activity against epidermoid carcinomas of the head and neck, uterine cervix, and esophagus. It is also active in both NHL and HD. In spite of the terminal, refractory character of malignancies in the majority of patients thus far studied, definite responses have been reported in 30%–85% of patients [6]. As bleomycin is not myelosuppressive, a number of combination regimens include this drug for the treatment of malignant lymphomas. However, the avoidance of pulmonary toxicity requires that bleomycin be given on intermittent administration schedules and at low doses such as those used in Adriamycin/bleomycin/vincristine/dexamethasone (ABVD) [2] or methotrexate/Adriamycin/cyclophosphamide/vincristine/prednisone-bleomycin (MACOP-B) [3] combinations. Pulmonary toxicity, however, limits the chronic use of bleomycin and, consequently, its potential as a maintenance agent. Liblomycin is a bleomycin analog that has proved in animals to be associated with less pulmonary toxicity and with more potent antitumor activity than bleomycin [7].

In the present study, liblomycin given at a dose of 100 mg/m^2 was effective in treating patients with NHL, although it caused severe and persistent myelosuppression in two patients. At a dose of 80 mg/m^2, liblomycin was observed to cause moderate myelosuppression. The phase I study of liblomycin reported by Ariyoshi et al. [1] was perfomed in patients with solid tumors. In that trial, the dose-limiting factor was myelosuppression and the maximum tolerated dose was 140 mg/m^2 daily, whereas in the present study, a dose of 100 mg/m^2 daily seemed to be the maximum tolerated dose in patients with malignant lymphoma who had previously received several intensive chemotherapy regimens. As in the phase I study, the dose-limiting toxicity of liblomycin was myelosuppression.

Although the dose-limiting factor for the use of bleomycin is pulmonary toxicity, this side effect developed in only 13.6% of our series of 34 patients who were treated with liblomycin. Therefore the incidence and severity of the pulmonary toxicity encountered during liblomycin therapy were judged to be lower than those resulting from bleomycin treatment.

The role of liblomycin in the treatment of advanced NHL (clinical stage IV) is not clear. However, in NHL patients with low-grade histology, early-stage disease (clinical stages I, II and III), or a no-symptom status, liblomycin was therapeutically effective. The response rates observed in patients with a history of bleomycin treatment were similar to those obtained in patients who had not previously received the drug. Liblomycin proved to be active against malignant lymphomas.

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