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Treatment of acute leukemia and malignant lymphoma with (2''R)-4'-O-tetrahydropyranyladriamycin

Ryuzo Ohno, Kiyoji Kimura, Ichita Amaki, Masami Hirano, Akira Hoshino, Yasushi Ikeda, Ikuro Kimura, Masahide Kobayashi, Kiyoshi Konno, Hisashi Majima, Toru Masaoka, Harumitsu Mizuno, Makoto Ogawa, Masao Oguro, Tatuo Saito, Masanori Shimoyama, Shigeru Shirakawa, Yuzuru Sugawara, Fumimaro Takaku, Hideo Yamada, Kazumasa Yamada, Kaoru Yamagata, Yutaka Yoshida, Satoshi Yoshikawa, Akira Wakui, and the THP Study Group on Hematological Malignancy

Summary. Eighty-four previously treated adult patients with acute leukemia and malignant lymphoma were treated with (2''*R*)-4'-*O*-tetrahydropyranyladriamycin (THP). THP (10–55 mg/m^2) was administered by i.v. bolus injection daily for acute leukemia, and according to three different schedules for malignant lymphoma: daily, weekly or once every 3–4 weeks. Complete and partial remission (CR and PR) were achieved by 1 (5%) and 3 of 19 patients with acute myelogenous leukemia and by 2 (13%) and 3 of 15 patients with acute lymphoblastic leukemia, respectively. All CRs were in the groups receiving 25 mg/m^2 THP daily. CR and PR were achieved by 6 (14%) and 8 of 42 patients with non-Hodgkin lymphoma (NHL) and by 4 (50%) and 2 of 8 patients with Hodgkin's disease (HD), respectively. No particular sensitivity was found among the subtypes of NHL and HD. Response (CR + PR) was noted in 10 (40%) of 25 patients treated every 3–4 weeks, in 1 (17%) of 6 treated weekly, and in 9 (47%) of 19 treated daily. The major side effects were myelosuppression and gastrointestinal toxicities. Alopecia was observed in only 10 (12%) patients. ECG abnormalities were observed in 7 (10%) patients, all of whom had previously been treated with other anthracyclines. No severe cardiotoxicity was observed.

Introduction

Adriamycin (ADM) is one of the most effective chemotherapeutic agent in the treatment of malignant tumors such as acute leukemia, malignant lymphoma, breast cancer, and lung cancer [1, 2, 4, 6, 8, 30]. In spite of its strong antitumor efficacy, the long-term use of ADM has been limited by the development of severe dose-dependent cardiomyopathy [6, 7]. Thus, a great deal of effort has been made to develop new anthracyclines that have weaker cardiotoxicity but possess antitumor activity similar or superior to that of ADM [7]. Recently, (2''*R*)-4'-*O*-tetrahydropyranyladriamycin (THP) was synthesized by Umezawa et al. [27], and reported to be superior to ADM in its activity against L1210 leukemia and other tumors in mice [26, 27], and to show the weakest cardiotoxicity among 9 anthracyclines tested in golden hamsters [9].

Offprint requests to: Ryuzo Ohno, First Department of Internal Medicine, Nagoya University School of Medicine, 65 Tsurumai-cho, Showaku, Nagoya, Japan 466

Clinical studies of THP were initiated from 1982, and in phase I studies, the dose-limiting toxicity was found to be myelosuppression and the maximal tolerated dose for a single i.v. injection was estimated to be 54–66 mg/m^2 [15, 21, 29]. Cardiotoxicity and alopecia were infrequently seen. Phase II studies reported its antitumor efficacy on acute leukemia, malignant lymphoma, head and neck cancer, breast cancer, ovarian cancer and cervical cancer [11, 22, 28]. Cardiotoxicity has been reported in only a few cases.

In this paper, we report the result of a multi-institutional cooperative study of THP on previously treated acute leukemia and malignant lymphoma. THP was found effective in these tumors with minimal cardiotoxicity.

Patients and methods

Eighty-four previously treated patients with acute leukemia and malignant lymphoma were treated with THP at 21 major universities and cancer center hospitals in Japan. The characteristics of patients were listed in Table 1. There were 54 male and 30 female patients. The ages of those with acute leukemia ranged from 15 to 66 years with a median of 33, and the age range was 16–82, with a median of 51 years, among those with malignant lymphoma. Among 34 patients with acute leukemia, 14 were refractory to conventional chemotherapy and 20 were relapsed cases. There were 19 acute myelogenous leukemia (AML) (14 myeloblastic, 3 promyelocytic, 1 myelomonocytic and 1 monocytic), and 15 acute lymphoblastic leukemia (ALL). Among 50 patients with malignant lymphoma, 15 were refractory to conventional chemotherapy and 35 were relapsed cases after conventional chemotherapy and/or radiotherapy. Thirty-two (94.1%) patients with acute leukemia had received anthracyclines in their previous treatments. Of the patients with malignant lymphoma, 25 had received chemotherapy alone as their previous treatments, 22 patients chemotherapy and radiotherapy, and 3 patients radiotherapy alone. In all, 29 (61.7%) of the 47 patients previously treated with chemotherapy had received anthracyclines.

THP was supplied by Meiji Seika Kaisha, Ltd, Tokyo, and Sanraku Co., Ltd, Tokyo, in vials containing 20 mg THP and 180 mg lactose, and was administered daily for acute leukemia, and by three different schedules for malignant lymphoma: daily, weekly or once every 3 to 4 weeks. In daily schedules, THP was usually given for 5 days, but,

Table 1. Patient characteristics

	Acute leukemia	Malignant lymphoma
No. of cases	34	50
Sex: male/female	20/14	34/16
Age range (median)	15–66 (33)	16–82 (51)
Type		
Acute myelogenous leukemia	19	
Acute lymphoblastic leukemia	15	
Non-Hodgkin lymphoma		42
Nodular		6
Diffuse		36
Hodgkin's disease		8
Previously treated with		
Chemotherapy alone	34	25
Chemo- + radiotherapy	0	22
(Anthracyclines)	(32)	(29)
Radiotherapy alone	0	3

in some cases the treatment period was modified according to the responses and the next courses were started when peripheral blood counts recovered. The doses ranged from 10 to 55 mg/m^2, and the drug was given by i.v. bolus injection. When responses were obtained, the drug was usually maintained in the same schedule as induction therapy. Toxicity was evaluated by blood counts, liver and renal function tests, urinalysis and electrocardiogram (ECG), and was graded by the toxicity criteria of WHO-EORTC-NCI [19].

Response for acute leukemia was evaluated by the following criteria. Complete remission (CR) was considered established when the proportion of blasts in bone marrow became less than 5% with normal levels of granuloid and erythroid series and with normal levels of peripheral leukocytes and platelets. Partial remission (PR) was defined when the proportion of blasts in bone marrow became less than 50% of the pretreatment value with some recovery of normal granuloid and erythroid series, and of normal peripheral leukocytes and platelets, but did not fulfill the CR criteria. Response for malignant lymphoma was evaluated by the following criteria. CR was considered established when measurable tumors had completely disappeared. PR was defined when there was more than 50% decrease of measurable tumors (longest diameter × shortest diameter).

Table 2. Result of THP therapy an acute leukemia and malignant lymphoma

Disease	No. of cases	Response (%)		
		CR	PR	CR + PR
AML	19	1 (5.3)	3 (15.8)	4 (21.1)
ALL	15	2 (13.3)	3 (20.0)	5 (33.3)
HD	8	4 (50.0)	2 (25.0)	6 (75.0)
NHL	42	6 (14.3)	8 (19.0)	14 (33.3)
nodular	6	1 (16.7)	1 (16.7)	2 (33.3)
diffuse	36	5 (13.9)	7 (19.4)	12 (33.3)

Results

Among 19 patients with AML, 1 (5.3%) achieved CR and 3 (15.8%) PR. Among 15 patients with ALL, 2 (13.3%) achieved CR and 3 (20%) PR (Table 2). Among 20 relapsed cases, 3 achieved CR and 4 PR. Among 14 refractory cases, 2 (1 AML, 1 ALL) achieved PR. CR was reached at 20, 28 and 48 days after the start of treatment and lasted for 90, 81+ and 180 days, respectively. PR was reached at 9–34 days with a median of 23 days after the start of treatment and lasted for 14–33 days with a median of 25 days. Among 32 patients who had been previously treated with ADM, daunorubicin (DNR) and/or aclacinomycin (ACM), 3 patients (9.4%) achieved CR and 5 (15.6%) PR (Table 3). Seven of the 8 responders had responded to the previous anthracyclines. In 6 patients who had not responded to anthracyclines in their previous treatments, no response to THP was observed. All CRs were in the groups which received 25 mg/m^2 of THP daily, although PR was obtained in other groups which received lower daily doses (Table 4). The treatment period was 3 days in 3 cases, 5 days in 28 cases, 7 days in 1, 8 days in 1, and 10 days in 1. CR was reached after 3 courses of 3-day treatment in 1 case, after 1 course of 3-day treatment in 1, and after 1 course of 5-day treatment in 1.

Among 42 patients with non-Hodgkin lymphoma (NHL), 6 (14.3%) achieved CR and 8 (19%) PR. Among 8 patients with Hodgkin's disease (HD), 4 achieved CR and 2 PR (Table 2). Among 35 relapsed cases, 7 (20%) achieved CR and 8 (22.9%) PR. Among 15 refractory cases, 3 (20%) achieved CR and 2 (13.3%) PR. CR was reached at 10–135 days (median 40 days) after the start of treatment and lasted for 28–360+ days, with a median of 112 days. PR was

Table 3. Response according to previous anthracycline treatment

Disease	With anthracyclines				Without anthracyclines			
	No. of cases	CR	PR	CR + PR	No. of cases	CR	PR	CR + PR
AML	18	1	3	4	1	0	0	0
ALL	14	2	2	4	1	0	1	1
Total	32	3 (9.4%)	5 (15.6%)	8 (25%)	2	0	1 (50%)	1 (50%)
NHL	26	4	4	8	13	1	3	4
HD	3	2	0	2	5	2	2	4
Total	29	6 (20.7%)	4 (13.8%)	10 (34.5%)	18	3 (16.7%)	5 (27.8%)	8 (44.4%)

Table 4. Response according to dosage and schedule

Dose (mg/m^2)	Schedule	No. of cases	Response		
			CR	PR	CR + PR (%)
Acute leukemia					
10	daily	6	0	3	3 (50%)
15	daily	8	0	0	0
20	daily	13	0	2	2 (15.4%)
25	daily	5	3	0	3 (60%)
30–35	daily	2	0	1	1 (50%)
Malignant lymphoma					
10	daily	13	0	6	6 (46.2%)
20	daily	5	3	0	3 (60%)
40	daily	1	0	0	0
10–20	weekly	4	1	0	1 (25%)
25–40	weekly	2	0	0	0
20–25	q3–4 weeks	2	0	0	0
30	q3–4 weeks	4	0	1	1 (25%)
35	q3–4 weeks	6	3	1	4 (66.7%)
40	q3–4 weeks	7	0	2	2 (28.6%)
45	q3–4 weeks	5	2	0	2 (40%)
55	q4 weeks	1	1	0	1 (100%)

Table 5. Toxicity of THP

Toxicity	No. of cases (%)	Toxicity	No. of cases (%)
Anorexia	44 (52.4)	Leukopenia*	
Nausea	21 (25%)	$<3000/\mu l$	38 (76%)
Vomiting	16 (19%)	<2000	28 (56%)
Stomatitis	21 (25%)	<1000	16 (32%)
Malaise	24 (28.6%)	Decrease of Hb*	
Alopecia	10 (11.9%)	<9.5 g/dl	14 (28%)
Phlebitis	3 (3.6%)	<8.0	8 (16%)
Diarrhea	9 (10.7%)	<6.5	4 (8%)
Elevation of		Thrombocytopenia*	
GOT/GPT	5 (6%)	$<75\times10^3/\mu l$	16 (32%)
BUN	3 (3.6%)	$<50\times10^3$	11 (22%)
ECG change	7/67 (10.4%)	$<25\times10^3$	4 (8%)

* Myelosuppression was evaluated only in patients with malignant lymphoma

reached at 3–35 days (median 16 days) after the start of treatment and lasted for 28–90 days, with a median of 36 days. Both nodular and diffuse types of NHL responded to THP. No particular sensitivity was found among subtypes of nodular and diffuse NHL. No particular sensitivity was either found among the subtypes of HD. Among 29 patients who had been previously treated with anthracyclines, 6 (20.7%) achieved CR and 4 (13.8%) PR (Table 3). Seven of the 10 responders had responded to the previous anthracyclines. In 6 patients who had not responded to anthracyclines in their previous treatment, no response to THP was observed. CR was obtained in all 3 treatment groups which received the drug once every 3–4 weeks, once a week or daily. Responses (CR + PR) were noted in 10 (40%) of 25 patients treated every 3–4 weeks, in 1 (16.7%) of 6 treated weekly, and 9 (47.4%) of 19 treated daily (Table 4). In the daily schedule, the treatment period was 4 days in 2 cases and 5 days in 17, and CR was obtained after one course in 2 cases and after three courses in 1. In the every 3- to 4-week schedule, CR was obtained after one dose in 1 case, after two doses in 4 cases, and after three doses in 1 case. In the weekly schedule 1 CR was obtained after 19 doses.

Major side effect was myelosuppression (Table 5). Leukopenia (less than $3000/\mu l$) was observed in 38 (76%) of 50 patients with malignant lymphoma, 16 of whom showed a decrease of less than $1000/\mu l$. With all three treatment schedules, nadir was reached around 2 weeks after the start of therapy, and the counts recovered to the pretreatment values 2–3 weeks afterwards. Anemia (Hb less than 9.5 g/dl) was noted in 14 (28%) patients, 4 of whom showed a decrease in Hb to less than 6.5 g/dl. Thrombocytopenia (less than $75000/\mu l$) was seen in 16 (32%) patients, 4 of whom showed a decrease to less than $25000/\mu l$.

Anorexia was observed in 44 (52.4%) of 84 patients studied. Nausea was noted in 25%, vomiting in 19% and diarrhea in 10.7%. Stomatitis was seen in 25%, and phlebitis and vascular pain along the vein at injection sites was noted in 3 cases and 1 case, respectively. Alopecia was observed in 10 (11.9%). The grade of alopecia by WHO-EORTC-NCI criteria was 1 in 5 patients, 2 in 4 patients and 3 in 1 patient. Palpitations and dyspnea were complained of in 2 cases each. Liver and renal dysfunction probably related to THP was reported in 5 and 3 cases, respectively. Abnormality of ECG was observed in 7 (10.4%) patients, all of whom had previously been treated with anthracyclines (110–827 mg/m^2 ADM, DNR and/or ACM). ECG abnormality consisted of low voltage in 2 cases, flattening or inversion of the T-wave in 2, premature ventricular contraction in 2, sinus tachycardia in 2, ST depression in one and mitral P in 1 (Table 6).

Discussion

In animal experiments, THP showed equal or superior activity against L1210 leukemia, P388 leukemia, Lewis lung carcinoma, B16 melanoma and colon carcinoma 38 than ADM [26, 27]. THP was shown to be taken up by tumor

Table 6. Abnormal ECG findings during THP therapy

Disease	Age/sex	ECG abnormality	Anthracycline (mg/m²)					Sequelae
			ADM	DNR	ACM	THP	Total	
AML	32/M	low voltage	0	827	0	80	907	Reversible
AML	61/M	T-flat. or inv.	81	257	145	101	584	Reversible
ALL	46/F	T-flat. or inv.	232	0	0	103	335	Irreversible
AML	50/M	PVC	0	470	268	128	866	Irreversible
HD	16/M	low voltage	178	0	0	36	214	Reversible
NHL	44/F	PVC sinus tachycardia	168	0	0	35	203	Not well followed up[a]
AML	55/F	sinus tachycardia ST depression Mitral P	0	110	0	200	310	Not well followed up[a]

[a] Died of progressive disease 1 week after the onset of abnormal ECG

cells much faster than ADM in vitro [13]. In ADM-resistant tumor cell lines, THP was taken up much more quickly than ADM and its intracellular concentration became higher than ADM [14]. The effulux of THP from the ADM-resistant cells is smaller than that of ADM, and THP showed stronger cytostatic activity on ADM-resistant cells than ADM [14]. These findings suggest that THP may be more effective than ADM, working on ADM-resistant tumors and having no cross resistance to ADM. In the present study, however, patients with acute leukemia and malignant lymphoma refractory to ADM, DNR and/or ACM did not respond to THP. Among the patients who had previously been treated with anthracyclines, those who responded to THP were mostly the patients who had responded to the previous anthracyclines. Thus, patients who had tumors sensitive to already available anthracyclines tended to respond to THP. In patients with tumors refractory to conventional anthracyclines, this new analogue showed little response. Therefore, the advantage of this drug over ADM seems to reside in its lower toxicity, and especially in probably weaker cardiotoxicity, and milder alopecia.

THP was reported to show the weakest cardiotoxicity and skin toxicity of nine anthracyclines including ADM, DNR and ACM, in golden hamsters [9]. In clinical pharmacokinetic studies, THP showed a shorter plasma half-life and a higher tissue concentration than ADM [16]. Comparative studies on pharmacokinetics of ADM and THP in the same subjects revealed a similar result; THP was more quickly transferred into tissues and the metabolism rate of THP was faster than that of ADM [20]. These properties of THP are considered to contribute to the weaker toxicity of THP than of ADM. In the present study, the major toxicities of THP were myelosuppression and gastrointestinal toxicities. Cardiotoxicity judged by ECG was noted only in 7 (10.4%) patients, all of whom had previously been treated with other anthracyclines. No congestive heart failure was reported among these patients. This should perhaps have been expected, since the heart failure in patients treated with anthracyclines is usually observed when their total cumulative dose exceeds a certain dose; 550 mg/m^2 in the case of ADM [6, 7]. In the present study, the maximum total dose of THP did not exceed 350 mg/m^2. No abnormality of ECG was seen in 23 patients who had not received anthracyclines in their prior therapy. There have been other studies on patients with solid tumor in which THP has not led to severe cardiotoxicity [22]. However, severe cardiotoxicity may occur if the cumulative dose of this drug exceeds a certain limit. In phase II studies, including ours, the cumulative dose might not have exceeded the limit. Nevertheless, the cardiotoxicity of THP is probably lower than that of ADM, since ECG changes were observed in 33% of patients treated with ADM in its phase I and early phase II studies [4].

Alopecia is not a life-threatening toxicity, but causes cancer patients a considerable mental suffering, especially female patients. Alopecia is seen in almost all patients who receive ADM and DNR [6]. A new anthracycline analogue is regarded as superior to its parent compound if this side effect is attenuated [7]. In the present study this side effect was noted in only 12% of patients.

The clinical effect of THP as a single agent on acute leukemia and malignant lymphoma was not dramatic. In the phase II studies in the late 1960s and early 1970s, ADM as a single agent produced 7%–33% CR and 0–17% PR in AML, 0–67% CR and 0–28% PR in ALL, and 0–13% CR and 29%–44% PR in malignant lymphoma [1, 2, 4, 6, 8, 30]. DNR produced 15%–55% CR and 10%–17% PR in AML, and 25%–33% CR and 3%–33% PR in ALL [3, 5, 10, 17, 25]. In the present study, THP produced 5% CR and 16% PR in AML, 13% CR and 20% PR in ALL, and 20% CR and 20% PR in malignant lymphoma. Although the response rate of these tumors to THP was less than that to ADM and DNR, this should have been expected, since in the phase II studies of ADM and DNR a considerable proportion of cases were previously untreated and most of the previously treated patients had received no anthracyclines. In the present study of THP in previously treated patients, nearly all patients with acute leukemia and more than half the patients with malignant lymphoma had previously been treated with anthracyclines.

The antitumor effect of THP was comparable to that of ACM, a new anthracycline with reportedly weak cardiotoxicity, which has recently been developed in Japan and introduced onto the market. ACM produced 18%–43% CR and 0–13% PR in AML, and 0–33% CR and 0–33% PR in ALL [12, 18, 23, 24].

Since cardiotoxicity occured less frequently, and the alopecia far less frequently in patients treated with THP than in those treated with ADM and DNR, THP seems to

be a useful drug for acute leukemia and malignant lymphoma. Further studies in combination with other antitumor agents are warranted.

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