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(2"-*R*)-4'-*o*-Tetrahydropyranyladriamycin, a new anthracycline derivative; its effectiveness in lymphoid malignancies

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Summary. Thirty-eight patients with adult acute lymphoblastic leukemia (ALL) or non-Hodgkin's lymphoma (NHL) were treated intravenously with (2"-*R*)-4'-*o*-Tetrahydropyranyladriamycin (THP) at a dose of 10 mg/m^2 for 5 consecutive days. Seven complete and 15 partial responses were observed in 35 evaluable patients (overall response rate, 62.8%). Both antitumor activity and antitumor spectrum were similar to those for doxorubicin. Since the patients who had had chemotherapy previously, including other kinds of anthracycline, responded rather poorly to THP, cross-resistance between THP and other anthracyclines may be present. Leukopenia and thrombocytopenia were dose-limiting factors. Nausea and vomiting episodes were mild, and epilation was also minimal. Although the observation period was short and a cumulative dose was not large enough to evaluate cardiotoxicity, there were no abnormal EKG changes or clinical signs of cardiotoxicity in this study. THP is a potent antitumor agent in the treatment of lymphoid malignancies.

Introduction

(2"*R*)-4'-*o*-Tetrahydropyranyladriamycin (THP; Fig. 1) is one of the anthracycline derivatives and is experimentally known to have the least cardiotoxicity among the anthracycline analogs [2, 3, 14]. The phase I clinical study [6, 9] showed that a dose-limiting factor is leukopenia. Nausea and vomiting episodes were mild and epilation minimal. No abnormal EKG changes or clinical signs of cardiotoxicity have been seen so far. A response to THP was observed in patients with malignant lymphomas, ovarian cancer, and cancer of the uterus. The phase II clinical study by the THP study group [4, 10] showed that THP is effective against various hematological malignancies, and we independently experienced its significant effects on recurrent non-Hodgkin's lymphomas (NHL) or adult acute lymphoblastic leukemia (ALL) after initial treatment with other kinds of anthracycline [11]. Therefore, the purpose of this study was to confirm the antitumor activity of THP on lymphoid malignancies and to estimate whether cross-resistance between THP and other kinds of anthracycline is present or not.

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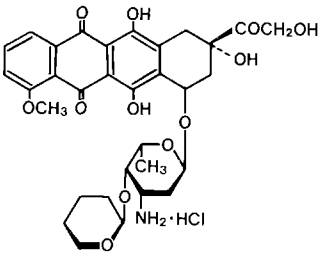
Chemical structure of THP



Molecular formula : $C_{32}H_{37}NO_{12} \cdot HCl$
Molecular weight : 664.10

Fig. 1. Chemical structure of THP

Patients and methods

This is a retrospective analysis of the patients who were treated with THP alone between June 1982 and April 1984. The criteria for eligible patients were as follows: an established diagnosis of NHL or ALL, any measurable disease, single primary disease, good performance status (PS) 0–3 and PS 0–4 in ALL cases, and no functional impairment of the liver or kidneys. The patient characteristics are summarized in Table 1. Six patients with ALL and 32 patients with NHL were included in this study. Of the 6 patients with ALL, 5 had the L2 subtype and 1 of L1 subtype [3]. In the 32 patients with NHL, the disease was confirmed histologically and then categorized according to the Japanese LSG classification; this classification is similar to that of the Working Formulation of the National Cancer Institute [7, 12]. The Ann Arbor staging system was employed. Of the 9 patients with NHL in stage IV, 3 patients were in the leukemic stage, 4 had bone-marrow involvement, 1 hepatic involvement, and 1 pleural fluid. The patients who had suffered relapses or had refractory disease were entered into this study by the end of 1982, but as of January 1983 all of the patients who satisfied the criteria described were first treated with THP alone. Consequently, 16 previously untreated patients were included in this study. Twenty-two patients had had treatment previously, and 17 of those were given the other kinds of anthracycline. The anthracyclines administered during previous treatment were: doxorubicin, with a dose of 60–390 mg (median, 100 mg)

Table 1. Patient characteristics

Number of patients	38
Years of age median (range)	52 (21–77)
Male/female ratio	22 : 16
ALL[a] (L1/L2)	6 (1/5)
NHL	32
Histology[c]	
Diffuse large	12
Diffuse mixed	6
Diffuse medium	6
Follicular medium	5
Lymphoblastic	2
Burkitt	1
Stage[b]	
II	12
III	11
IV	9
Previous treatment	
Chemotherapy including Anthracyclines	17
Chemotherapy without Anthracyclines	2
Radiotherapy	3
No Treatment	16

[a] FAB classification [9]
[b] Ann Arbor staging system
[c] LSG classification [10, 11]

in 13 patients; aclarubicin, with a dose of 140–620 mg (median, 200 mg) in 5 patients; daunorubicin at a dose of 400 mg in 1 patient.

THP was supplied by Sanraku Company in a powdered form and was dissolved in 250 ml of 5% glucose solution. THP was given alone intravenously for 1 h. THP was given on days 1–5 (10 mg/m^2) but 3 of the patients received THP for 7 days (on days 1–7). Administration of THP (THP therapy) was repeated every 3 weeks, and the clinical response was evaluated after two courses. In NHL, the WHO criteria of tumor response was employed [15]: complete response (CR) indicated the disappearance of all clinical, radiological, and biochemical evidence of lymphoma for at least 4 weeks; partial response (PR) indicated more than 50% regression of the measurable disease. Response in ALL was defined as follows: CR meant less than 5% leukemic cells with recovery of normal hematopoiesis and PR between 5% and 25% of leukemic cells with considerable recovery of hematopoiesis.

In 27 patients, more than two courses of THP therapy were administered. Only one course was given in 11 patients, including 6 whose tumor did not regress at all (no change), 2 with progressive disease, and 3 who died of hyperuricemic nephropathy. In these patients, the cumulative THP dose did not reach 100 mg, and the observation period was shorter than 4 weeks. Twenty-one patients received two courses, followed by multidrug combination chemotherapy and/or radiotherapy. The cumulative dose was 110–160 mg and the observation period shorter than 8 weeks. Six patients were treated with more than three courses and the cumulative dose amounted to 280 mg on average (range of 205–510 mg); the observation period ranged from 12 to 30 weeks.

Results

Three patients with NHL could not be evaluated because they died early during THP therapy. Of the 35 evaluable patients, the overall response rate was 66.7% in ALL and 62.1% in NHL (Table 2). In NHL, the response rate was similar in each histological group and disease stage (Table 3), but CR was achieved only in the group showing diffuse histology and stage II or III. The duration of the response was evaluated in 6 patients who received more than three courses of THP therapy (Table 4). Three patients maintained a CR status for 25, 12, and 11 weeks, respectively, and PR status lasted for 12, 10, and 6 weeks, respectively, in the remaining 3 patients. In other 16 patients in whom CR or PR was achieved, multidrug combination chemotherapy and/or radiotherapy was administered after 4-week observation of their status.

The WHO criteria were used to evaluate the acute toxicity induced by THP in the 38 patients (Table 5). Stomatitis greater than grade 3 was observed in 2 patients who had had intensive chemotherapy previously and who suffered from severe leukopenia. The leukopenia and thrombocytopenia nadir was 700/μl and 19,000/μl and was observed on days 13 and 15, respectively; the patients recovered 3 weeks later. Severe leukopenia and/or severe thrombocytopenia were seen in patients with ALL or NHL in the leukemic stage or patients who had had previous chemotherapy. An infection episode developed in 4 patients: minor pharyngitis in 1, moderate urinary tract infection in 2, and septicemia in 1. All were treated with antibiotics and recovered.

An elevation in the level of blood urea nitrogen or serum creatinine was seen in 4 patients. In 3 hyperuricemic nephropathy, induced by rapid and massive tumor lysis, was associated. All 3 patients had a rapidly growing tumor burden. Two of them died of acute renal failure on days 7 and 11, respectively. The remaining 1 recovered temporarily from severe renal failure and urinary tract infection, but died of general deterioration on day 12. No anaphylactoid reaction or phlebitis was seen during THP therapy, and no abnormal EKG changes or clinical signs of cardiotoxicity were observed. In addition, there was no sign of abnormal liver function data as a result of THP administration, nor was pulmonary toxicity or neurotoxicity clinically detected. Inadvertent extravasation was also not observed in this study.

Table 2. Overall response rate

Number of patients	38
Evaluable	35
ALL	4/6 (66.7%)
CR	2
PR	2
NR	2
NHL[a]	18/29 (62.1%)
CR	5
PR	13
NC	9
PD	2
Total	22/35 (62.8%)

[a] WHO criteria

Table 3. Response rate in NHL

	No. of evaluation	CR	PR	Response rate
Histology				
Lymphoblastic and Burkitt	3	0	2	66.7%
Diffuse	21	5	8	61.9%
Follicular	5	0	3	60.0%
Stage				
II	12	2	4	50.0%
III	10	3	4	79.0%
IV	7	0	5	71.4%
Previous treatment				
Chemotherapy, including anthracyclines,	12	1	4	41.7%
chemotherapy without anthracyclines,	1	0	1	100.0%
radiotherapy,	3	0	2	66.7%
and no treatment	13	4	6	76.9%

Table 4. Duration of response

Patient	Status	Duration (weeks)	No. of course	Cumulative dose (mg)	Comments
1. ALL	CR	11	3	205	BMT[a] followed
2. ALL	PR	12	3	240	Exacerbated
3. ALL	PR	6	3	210	Exacerbated
4. NHL	CR	25	4	300	RA[b] followed
5. NHL	CR	12	4	340	Relapse
6. NHL	PR	10	7	510	Exacerbated

[a] BMT, Allogeneic bone marrow transplantation
[b] RA, radiotherapy

Table 5. Acute toxicity

Toxicity	WHO grade				> Grade 3
	1	2	3	4	
Nausea/vomiting	7	3	1	0	2.6%
Stomatitis	9	5	2	0	5.3%
Alopecia	5	0	0	0	0%
Leukopenia	1	10	7	13	52.6%
Thrombocytopenia	0	1	5	8	34.2%
Anemia	9	8	7	5	31.6%
BUN/creatinine	1	1	1	1	5.3%

Discussion

In 1979, Umezawa et al. [14] found baumycins in the culture filtrates of a daunomycin-producing strain. Baumycin A1, one of the baumycin compounds, exhibited stronger antitumor activity on L-1210 than adriamycin or daunomycin. The yield of baumycin A1 was very small, and baumycin derivatives were synthesized. 4'-*O*-Tetrahydropyranyladriamycin was one of the baumycin derivatives that exhibited greater activity and lesser toxicity in experimental animals [2, 13]. The phase I clinical study of THP was performed by Ogawa et al. [9] in 1982. The starting dose of THP was 3 mg/m^2, and then the dose was escalated gradually to 54 mg/m^2. The dose-limiting factor was leukopenia. The estimated maximum tolerance dose (MTD) was 54 mg/m^2, and the recommended dose schedule for the phase II study was 40 mg/m^2 every 3 weeks. In the phase I clinical study by Majima [6] MTD was estimated to be 66.6 mg/m^2 as a single dose, and the recommended administration schedule was 50 mg/m^2 every 3 weeks. The multicenter cooperative THP group study started in April 1982, and a dose schedule of 40 mg/m^2 every 3 weeks was used for solid tumors. Meanwhile, in the early part of phase II of this study, a remarkable antitumor effect on adult ALL was observed when using 10–20 mg/m^2 for a consecutive 3–5 days [4]. We also experienced independently that a remarkable response was obtained in the 8 patients with relapsed or refractory NHL when administering 10 mg/m^2 for a consecutive 5 days. The results obtained were outstanding: CR in 1 and PR in 4; in 2 other patients who died of hyperuricemic nephropathy, complete tumor necrosis was disclosed by autopsy. Our experience was striking enough to use THP in first-line chemotherapy on adult ALL or NHL. From the beginning of 1983, we have used THP for patients without previous treatment. We treated the patients first with two courses of THP therapy and, if favorable responses were seen, THP-based multidrug combination chemotherapy (VEP-THP therapy) followed thereafter.

This study demonstrated the remarkable antitumor effects of THP in patients with lymphoid malignancies. The overall response rate was 62.8% (66.7% in ALL and 62.1%

in NHL) in the 35 evaluable patients with adult ALL or NHL, and the high response rate is comparable to that of doxorubicin [1, 8]. The response rate was similar in each stage or histology group, but CR was observed only in patients with intermediate-grade histology results and who had stage II or III disease. These data suggest that the antitumor spectrum of THP is close to that of doxorubicin. The response rate (41.7% vs 76.5%) seemed to be lower in patients who had undergone chemotherapy previously, including anthracyclines, than in those who had not received anthracyclines, than in those who had not received anthracyclines, but the number was so small that the difference was not statistically significant ($P=1.95$, $0.2>P>0.1$). There could be a cross-resistance among THP and other anthracycline analogues, although it may not be complete.

Major dose-limiting factors are leukopenia and thrombocytopenia. Leukopenia and thrombocytopenia were severe in the patients who were treated previously with intensive chemotherapy, but were rarely seen in patients without previous chemotherapy. Unexpected hyperuricemic nephropathy was associated in 3 patients, 2 of whom died of acute renal failure. It should be kept in mind that rapid and massive tumor lysis can take place in patients with a rapidly growing tumor if a fractionated small dose is administered. An oral dose of allopurinol with hydration of more than 2500 ml/day is recommended to prevent hyperuricemic nephropathy in patients with rapidly growing, bulky tumors. No abnormal EKG changes were seen in any of the patients as a result of THP, but the cumulative dose of THP was not large enough and the observation period not long enough to evaluate chronic toxicity. A longer period of observation and a subclinical investigation for cardiotoxicity are needed. Gastrointestinal toxicity was mild and alopecia minimal.

The administration schedule of THP used in this study is rather unique; bolus i. v. administration of a greater dose is the usual regimen for anthracyclines. The dose schedule we used in this study is theoretically dependent on experimental data by Kunimoto et al. [5]. They disclosed that THP can be incorporated into intracellular compartments 170 times as fast as doxorubicin. Remarkable tumor cell reduction was observed in patients with ALL who were treated with this dose schedule in the early phase II study of THP study group [4]. Besides these data, we measured the THP level in the fraction of serum, tumor cells, and red blood cells in 2 patients with ALL or NHL in the leukemic stage [11]. The THP level was extremely higher in the fraction of tumor cells than in the serum or red blood cells, and a remarkable reduction in tumor cells was obtained in both patients. It is quite conceivable that the intracellular level of THP can be sufficiently high by the administration of a fractionated low dose. It is also considered that this modality of administration is helpful in reducing toxicity. However, further reseach is needed to determine the best modality of THP administration.

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