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Treatment of leukemia and myelodysplastic syndromes with orally administered N^4-palmitoyl-l-β-D-arabinofuranosylcytosine

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Summary. N^4-Palmitoyl-1-β-D-arabinofuranosylcytosine (PLAC) was administered PO to 76 patients with acute leukemia, myelodysplastic syndromes (MDSs), and myeloproliferative disorders (MPDs). Of 20 patients with acute myelogenous leukemia, 2 achieved complete remission, and the only patient with acute lymphoblastic leukemia achieved partial remission. Remission was reached with PLAC 100–300 mg/day 25–66 days after the start of therapy. Among 22 patients with MDS, 1 patient achieved a good response and 8 achieved partial response. Responses were reached with PLAC 50–200 mg/day 7–153 days (median, 33 days) after the start of therapy. Improvement of polycythemia was observed in all 5 patients with polycythemia vera, and reduction of thrombocytosis was observed in 5 out of 6 patients with essential thrombocythemia and myelofibrosis. An antileukemia effect was noted in 1 of 5 with chronic myelogenous leukemia. Major side effects were gastrointestinal toxicities and myelosupression. In spite of the disadvantages, such as unpredictable absorption and a lower response rate to acute leukemia compared with its parent compound, this antileukemia Ara-C analogue that is administrable PO will be useful in the treatment of MDSs and MPDs, which do not necessarily require admission to hospital, and in the treatment of acute leukemia of the aged, a condition for which intensive chemotherapy is not appropriate.

Introduction

1-β-D-Arabinofuranosylcytosine (Ara-C) is one of the most effective drugs for the treatment of acute myelogenous leukemia (AML) [4, 8]. Since Ara-C is rapidly deaminated to an inactive metabolite in vivo, a great deal of effort has been devoted to converting Ara-C into a compound which resists cytidine deaminase or is slowly metabolized to Ara-C. Recently, a series of N^4-acyl-1-β-D-arabinofuranosylcytosines were synthesized, and N^4-behenoyl-1-β-D-arabinofuranosylcytosine (BHAC) and N^4-palmitoyl-1-β-D-arabinofuranosylcytosine (PLAC) were found to possess strong antitumor activities against a wide variety of experimental tumors [1, 2, 5]. Both drugs exhibited their activities regardless of the treatment schedules, mainly because of their resistance to cytidine deaminase.

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BHAC has been introduced clinically and been shown to be effective for AML [6, 11] and it is now commercially available in Japan. PLAC has been shown to exert its effect by both parenteral and oral administrations. Phase I clinical and pharmacokinetic study of PLAC by single or 5-consecutive-day administration PO revealed dose-dependent plasma levels of PLAC, and showed the dose-limiting toxicity to be gastrointestinal in these schedules [7]. We describe here the results of a multi-institutional study of PLAC for acute leukemia, myelodysplastic syndromes (MDSs) and myeloproliferative disorders (MPDs).

Patients and methods

Seventy-six patients with acute leukemia, MDSs, and MPDs, who were treated at 14 hospitals belonging to the Tokai Blood Cancer Study Group, were entered in this study. There were 26 with acute myelogenous leukemia (AML); 1 with acute lymphoblastic leukemia (ALL); 1 with adult T cell leukemia; 5 with chronic myelogenous leukemia (CML); 6 with polycythemia vera (PV); 5 with essential thrombocythemia (ET); 1 with myelofibrosis (MF), 6 with blastic crisis of CML (CML-BC); 2 with blastic crisis of PV (PV-BC); 1 with blast crisis of MF (MF-BC); and 22 with MDSs. For AML and ALL, in which it is well established that multidrug combination chemotherapy produces high rates of complete remission, only patients who were refractory to conventional chemotherapies were entered. Previously untreated patients aged 60 years or over, however, were allowed to be entered with informed consent. For other diseases for which there are no established therapies with definite therapeutic benefit, both previously treated and previously untreated patients were entered.

PLAC, which was supplied by Asahi Chemical Industry Co. Ltd in capsules containing 50, 100, or 200 mg PLAC, was given PO before meals once or twice a day until myelosuppression or side effects made its continuation difficult, or until treatment had been given for at least 4 weeks with no clinical effect. The starting daily doses were 50 mg in 2 patients; 100 mg in 24; 150 mg in 8; 200 mg in 22; 250 mg in 2; 300 mg in 12; 350 mg in 1; 600 mg in 1; 750 mg in 1; 800 mg in 2; and 1200 mg in 1. The daily doses were reduced by approximately 50%–100% if gastrointestinal (GI) toxicities such as nausea and vomiting appeared.

Table 1. Response criteria for myelodysplastic syndromes

Category			Points
1) Blasts in bone marrow:	Pretreatment	Post-treatment	
	>10%	<3%	25
	>10%	Less than 1/2	15
	5%–10%	<3%	20
	5%–10%	Less than 1/2	10
2) Hemoglobin:	Increase of 3 g/dl or more		25
	Increase of 1.5 g/dl to 3 g/dl		15
Blood transfusion:	Less than a half of previous month		10[a]
3) Neutrophils:	Increase of 1000/mm³ or more		25
	Increase of 500 to 1000/mm³		15
4) Platelets:	Increase of 8×10^4/mm³ or more		25
	Increase of $4 \times$ to 8×10^4/mm³		15
No requirement of platelet transfusion			10[a]

Up to 24 points: Minor response (MR)
25–49 points: Partial response (PR)
50–: Good response (GR)
75– plus blasts in marrow less than 5%: Complete remission (CR)

If proportion of blasts in marrow is not evaluable, multiply the sum of the other three categories by 100/75. The response should sustain for at least 4 weeks in GR and CR and at least 2 weeks in PR

[a] Count only when there is no aforementioned increase

Table 2. Characteristics of patients

Entered	76
Unevaluable	9
Evaluable	67
Male/female	42/25
Age: Range (median)	18–83 (59)
AML	20
ALL	1
ATL	1
CML-BC	4
PV-BC	2
MF-BC	1
MDS	22
CML	5
PV	5
ET	5
MF	1

Table 3. Treatment of acute leukemia and blast crisis of myeloproliferative disorders with PLAC

Type	No. of cases	Response (duration, weeks)		
		CR	PR	Failure
AML	20	2 (86,5)	0	18
ALL	1	0	1 (4)	0
ATL	1	0	0	1
CML-BC	4	0	0	4
PC-BC	2	0	0	2
MF-BC	1	0	0	1
Total	29	2 (6.9%)	1 (3.4%)	26 (89.7%)

Response for acute leukemia was evaluated by the standard criteria [3]. Complete remission (CR) was considered to be established when the proportion of blasts in bone marrow became less than 5% with normal levels of granuloid and erythroid series and normal levels of peripheral leukocytes and platelets. Response for MDSs was evaluated according to the criteria described in Table 1. Response was assessed by percentage of blasts in bone marrow, hemoglobin level, neutrophil counts, and platelet counts. If bone marrows were unevaluable because of dry-tap marrow or because the pretreatment blasts were less than 5%, the total points in the other three categories were multiplied by 100/75. Complete remission (CR) was recorded if the total points came to 75 or more with less than 5% blasts in the bone marrow; good response (GR) if the points came to 50 or more; partial response (PR) if 25–49 points were scored; and minor response (MR) if there was a score of 10–24. The response should be sustained for at least 4 weeks for CR and GR and at least 2 weeks for PR and MR.

Results

Among 76 patients treated by oral PLAC, 6 patients were excluded from the evaluation of response because the administration period of PLAC was 14 days or less, mainly because of side effects such as nausea and vomiting. One patient with CML-BC was also excluded because PLAC was discontinued due to the elevation of GOT and GPT on day 16, although a certain response was observed at this point. Two further patients were excluded because of concomitant use of other antitumor drugs. Thus, 67 patients were evaluable for response (Table 2).

Among 29 evaluable patients with acute leukemia and blastic crisis of MPD, 20 had been previously treated and 9 were previously untreated. CR was obtained in a previously untreated 83-year-old woman with an FAB classification of M1 and a previously treated 68-year-old woman with M5 (Table 3). CR was reached 56 days after the start of therapy in the former patient, who had been given PLAC 600 mg/day as a starting dose, which was reduced because of GI toxicities to 400 mg/day on day 8 and to 200 mg/day on day 13 and after. CR was reached 66 days after the start of therapy in the other, whose starting dose was 150 mg/day, which was reduced because of GI toxicities to 100 mg/day on day 17 and after. The remission lasted for 86 weeks in the former and only 5 weeks in the latter. One ALL showed PR 38 days after the start of therapy with PLAC 300 mg/day, which lasted for 4 weeks.

Among 22 evaluable patients with MDSs (20 previously untreated and 2 previously treated), 1 achieved a good response and 8 partial responses. No response was noted in either of 2 patients with refractory anemia (RA) (blasts in bone marrow less than 5%). Responses were observed in 4 of 7 patients with refractory anemia with excess of blasts (RAEB) (blasts 5%–20%); 2 out of 4 with RAEB in transformation (RAEB-T) (blasts 20%–30%); and in 3 out of 8 with RAEB in blastic crisis (RAEB-BC) (blasts 30%–40%). The overall response rate was 40.9% (Table 4). Responses were noted in both the patients who received of PLAC 50 mg/day; 6 out of 10 patients who received 100 mg/day; 1 out of 3 who received 150 mg/day; 1 out of 6 who received 200 mg/day; and none in the one patient who re-

Table 4. Treatment of myelodysplastic syndromes with PLAC

Type	No. of cases	Response (duration, weeks)			
		Good	Partial	Minor	Failure
RA	2	0	0	1	1
RAEB	7	1 (16)	3 (10, 6, 3)	0	3
RAEB-T	5	0	2 (9, 3)	3	0
RAEB-BC	8	0	3 (6, 3, 3)	2	3
Total	22	1 (4.5%)	8 (36.4%)	6 (27.2%)	7 (31.8%)

Table 5. Side effects of PLAC treatment

Total evaluated	76
Nausea	28 (36.8%)
Anorexia	21 (27.6%)
Vomiting	12 (15.8%)
Diarrhea	4 (5.3%)
Constipation	2 (2.6%)
Epigastralgia	2 (2.6%)
Leukopenia [a]	41 (53.9%)
Anemia [b]	39 (51.3%)
Thrombocytopenia [a]	49 (64.5%)
Elevation of GOT/GPT	19 (25.0%)

[a] More than 25% reduction against pretreatment values
[b] More than $50 \times 10^4/mm^3$ reduction against pretreatment values

ceived 300 mg/day. The response was reached at 7–153 days (median 33 days) after the initiation of therapy, and lasted for 3–16 weeks (median 6 weeks).

Among five patients with CML, and antileukemia effect was observed in one. Improvement of polycythemia was observed in all five with PV. Among five patients with ET and one with MF, improvement of thrombocythemia was observed in five: more than 50% reduction in two and 25%–50% reduction in three.

Major side effects (Table 5) were gastrointestinal toxicities, which made the continuation of PLAC difficult in six patients for longer than 14 days. Nausea was observed in 37% of 76 patients evaluable for side effects, anorexia in 28%, vomiting in 16%, diarrhea in 5%, and epigastralgia in 3%. Myelosuppression was observed commonly. Leukopenia was noted in 54%, anemia in 51% and thrombocytopenia in 65% of the evaluable patients. Anemia was mostly macrocytic in nature. Mild elevations of GOT and GPT were noted in 25%, although direct correlation with PLAC was not clear. GI toxicities were not entirely dose-dependent in all patients. However, they were apparently dose-dependent in individual patients, because they became milder when the daily dose of PLAC was reduced.

Discussion

Although Ara-C is one of the most effective drugs for the treatment of AML, it is rapidly deaminated to an inactive metabolite in vivo. Therefore, a great deal of effort has been devoted to converting Ara-C into a compound which resists cytidine deaminase or is slowly metabolized to Ara-C. PLAC is one of the newly synthesized Ara-C analogues, which exhibits a strong antitumor activity against a wide variety of experimental tumors regardless of the treatment schedules, mainly because of its resistance to cytidine deaminase. Since PLAC exerts its antitumor activity by both parenteral and oral administration, it has been introduced clinically as an oral form. A phase I study revealed that the dose-limiting toxicity was gastrointestinal. The pharmacokinetic study showed a dose-dependent plasma level of PLAC, which is detectable for as long as 6 h with a peak level at 3 h after oral administration [7].

The present study revealed that orally administered PLAC had definite effects on leukemia, producing CR in 7% of patients with acute leukemia and responses in 41% of those with MDSs. The CR rate in acute leukemia, however, was apparently inferior to that of Ara-C [4, 8] or BHAC [6], which produced CR in around 30% of the subjects in their phase II studies for AML. Therefore, PLAC may not be a drug of choice for the remission induction therapy for acute leukemia, except in aged patients who are unable to tolerate conventional remission induction regimens. PLAC had a considerable effect on MDS, however; these are a group of acquired bone marrow disorders characterized by progressive impairment in the maturation of hematopoietic cells. Their eventual evolution into acute leukemia suggests that they are early stages of leukemia. Efforts to treat these disorders have been largely unsuccessful, and there are no standard treatments for them. Several investigators, however, have recently reported beneficial effects of low-dose Ara-C on MDS following continuous IV infusion of SC injections every 12 h [9, 10]. Orally administered PLAC may give an effect equivalent to that of low-dose Ara-C. Since most patients with MDSs do not require hospitalization until acute transformation, an oral form of an Ara-C analogue may have an advantage over a parenteral form of Ara-C or of its analogue, which necessitates hospitalization of patients. PLAC will also be useful as a drug for maintenance chemotherapy in acute leukemia while patients are in outpatient clinics.

The effect of PLAC in MDSs was observed when it was given at a dosage of 50–200 mg/day for 7–153 days. Long-term continuous use of PLAC, however, would not be advisable, because of the development of macrocytic anemia. Therefore, for fairly slowly progressive diseases like MDSs PLAC may be valuable if it is given at starting doses of 50–200 mg/day for around 4–5 weeks and then resumed after an interval of 2–3 weeks.

A disadvantage of oral forms of drugs is the unpredictable absorption in any individual patient. Although the pharmacokinetic study of PLAC showed a dose-dependent plasma level in the phase I trial [7], actual absorption apparently varied in individual patients, since 16% of the patients vomited after the oral intake of PLAC and 5% had diarrhea in the present study. In spite of this disadvantage, PLAC will be useful in the treatment of certain types of malignancy, since this drug is the first orally administrable Ara-C analogue that has shown a definite clinical effect.

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