Phase I and pharmacokinetic study of oral fludarabine phosphate in relapsed indolent B-cell non-Hodgkin’s lymphoma

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Background: The primary objective of this study was to investigate the tolerability, efficacy and pharmacokinetic profile of oral fludarabine phosphate in relapsed patients with indolent B-cell non-Hodgkin’s lymphoma (B-NHL).

Patients and methods: Patients received fludarabine phosphate orally for 5 days, for a total of one to three cycles. Tolerability was assessed using the National Cancer Institute Common Toxicity Criteria. Efficacy was assessed using the International Workshop Criteria for NHL. Pharmacokinetic samples were taken on day 1 and day 5 of the first treatment cycle.

Results: Twelve patients were enrolled. One patient at 40 mg/m²/day developed grade 4 hyperuricemia. At 50 mg/m²/day, one patient developed grade 3 febrile neutropenia and grade 4 leukopenia, and another patient showed lasting grade 4 neutropenia. Most common toxicities included grade 3 or 4 lymphopenia (83%), leukopenia (50%) and neutropenia (50%). All the toxicities were reversible. The overall response rate was 67%. The AUC₀–2₄ values on day 5 indicated a dose-dependent increase in systemically available 2-fluoro-arabinofuranosyl-adenine (2F-ara-A).

Conclusions: Oral fludarabine phosphate is safe and effective for relapsed patients with indolent B-NHL. The dose of 40 mg/m²/day is recommended for a following pivotal phase II study.

Key words: fludarabine phosphate, indolent B-cell non-Hodgkin’s lymphoma, oral, pharmacokinetic

introduction

Fludarabine phosphate, an adenine nucleoside analog, is an antimetabolite with antitumor effect attributable to its inhibitory effect on DNA and RNA synthesis. A large number of studies in patients with relapsed indolent B-cell non-Hodgkin’s lymphoma (B-NHL) using the intravenous (i.v.) fludarabine phosphate have been conducted and high response rates have been reported [1–3]. In addition, i.v. fludarabine phosphate-based combination regimens for patients with indolent B-NHL have been reported with remarkable response rates, more than 90% in several studies [4, 5]. However, 5-day i.v. administration is inconvenient in the outpatient setting.

In the development of oral formulation, pharmacokinetics was investigated in Caucasian patients with B-cell chronic lymphocytic leukemia (B-CLL) and indolent B-NHL. The bioavailability of 2-fluoro-arabinofuranosyl-adenine (2F-ara-A), a plasma metabolite of oral fludarabine phosphate, was confirmed to be about 60% of that of i.v. fludarabine phosphate [6]. A once daily repeated oral dose of 40 mg/m² fludarabine phosphate would lead to a similar systemic exposure to the recommended i.v. dose of 25 mg/m²/day. In recent years, oral fludarabine phosphate has become available outside Japan for the treatment of patients with B-CLL.

In Japan, no standard therapy for indolent B-NHL has been established, nor has oral formulation been developed. Oral fludarabine phosphate is expected to be an important treatment option for indolent B-NHL for its efficacy and convenience in the outpatient setting. Thus, clinical development of oral fludarabine phosphate for indolent B-NHL is planned. This study was designed to investigate tolerability, antitumor effect and the pharmacokinetic profile of oral fludarabine phosphate in relapsed indolent B-NHL patients.

patients and methods

Patients with indolent B-NHL and who satisfied the following criteria were included: (1) histologically confirmed indolent B-NHL, including small lymphocytic, lymphoplasmacytic, follicular, marginal zone, and mantle cell
lymphoma according to the World Health Organization (WHO) classification; (2) relapsed after or refractory prior to chemotherapy; (3) without influence of prior therapy; (4) predicted life-expectancy of at least 12 weeks; (5) 20–74 years old; (6) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; (7) adequate organ functions.

Patients who met any of the following criteria were excluded: (1) active infections; (2) serious complications, gastrointestinal symptoms or bleeding tendency; (3) positive for hepatitis B virus surface antigen, hepatitis C virus antibody or human immunodeficiency virus antibody; (4) serious central nervous system symptoms; (5) fever ≥38°C; (6) interstitial pneumonia or pulmonary fibrosis; (7) active concurrent cancers; (8) autoimmune hemolytic anemia; (9) granulocyte colony-stimulating factor (G-CSF) or transfusion within 2 weeks before registration; (10) allergies to purine nucleoside analogues; (11) prior therapy with i.v. fludarabine phosphate, pentostatin or cladribine; (12) pregnancy or potential pregnancy; (13) no agreement to practice contraception.

Each patient signed an informed consent form. This study was approved by the institutional review board of each institution.

**treatments**

Oral fludarabine phosphate was supplied by Nihon Schering K.K. (Osaka, Japan) as a film-coated tablet containing 10 mg of fludarabine phosphate. Patients received fludarabine phosphate orally once daily for 5 consecutive days every 4 weeks. A maximum of three cycles of treatment was allowed. Three cohorts (30, 40 and 50 mg/m2/day dosage groups) were set in this study and the administration was started at 30 mg/m2/day with the dose escalation method. The sample sizes planned were three patients for 30 mg/m2/day cohort, six for 40 mg/m2/day cohort and three for 50 mg/m2/day cohort. In the 30 and 50 mg/m2/day cohorts, if the critical toxicity was observed in one of the three patients during the first treatment cycle, three additional patients were to be added to the same cohort. If none of the three or one of the six patients developed critical toxicity during the first treatment cycle, the dosage was escalated to the next cohort. If the same critical toxicity was observed in at least two of the three or six patients, the dose-escalation was halted and no additional patients were registered. The dosage was designated as the maximum tolerated dose (MTD). The final decision of dose escalation for each step was made by obtaining approval of the Independent Data and Safety Monitoring Committee.

**safety**

Physical examinations and laboratory tests were performed every week throughout the study period. If abnormalities, of which a relationship to the investigational drug could not be excluded, persisted at the end of the study period, follow-up tests were conducted until they recovered.

Critical toxicities in the present study, according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, were defined as follows: (1) grade 4 neutropenia lasting at least 1 week accompanied by ≥38°C fever; (2) grade 4 thrombocytopenia or a bleeding tendency requiring platelet transfusion; (3) other grade 4 hematologic toxicity; (4) grade ≥3 non-hematologic toxicity.

**efficacy**

The lesions were measured by computed tomography imaging before initiation of the treatment and at the 4th week of each cycle. Antitumor effect was assessed according to the International Workshop Criteria for NHL [7]. The antitumor effect by patient and the overall response rate by cohort were evaluated.

**pharmacokinetics**

The pharmacokinetics of 2F-ara-A were assessed in the first treatment cycle. Blood samples were taken before the start of administration and at 30 min, 1, 2, 10 and 24 h after the administration on days 1 and 5 of the treatment.

Since this study was conducted using an oral formulation only, the bioavailability of oral fludarabine phosphate was estimated by comparing the mean AUC₀–₂₄h obtained on day 5 of the treatment in this study to that of i.v. fludarabine phosphate in the Japanese phase I study for patients with CLL [8].

**results**

Twelve patients, 10 with follicular lymphoma and two with mantle cell lymphoma, were enrolled. All patients were treated with oral fludarabine phosphate and were assessed for safety, efficacy and pharmacokinetics. The median age was 57 years (range 50–68) and the median number of prior regimens was two (range 1–11). They received 30, 40 or 50 mg/m²/day for 5 consecutive days every 4 weeks, for a total of one to three cycles (three patients for 30 mg/m²/day; six patients for 40 mg/m²/day; three patients for 50 mg/m²/day). Table 1 lists the demographic characteristics of each cohort.

**safety**

As for critical toxicity, grade 4 hyperuricemia was observed in one patient of the 40 mg/m²/day cohort from day 5 to 7, and grade 4 leukopenia and grade 4 neutropenia lasting at least 1 week accompanied by ≥38°C fever was observed in one patient in the 50 mg/m²/day cohort from day 12 to 22 and from day 10 to 22, respectively.

The numbers of patients who developed any toxicity are shown in Table 2. In total, grade ≥3 toxicities observed in this study were lymphopenia in 10 patients (83%), leukopenia in six patients (50%), neutropenia in six patients (50%), including one patient who developed febrile neutropenia and hyperuricemia in one patient (8%).

**Table 1. Patient characteristics**

<table>
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<tr>
<th>Dose (mg/m²)</th>
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<td>10</td>
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</table>
efficacy

The overall response rates at the end of the first treatment cycle were 33%, 50% and 67% in the 30, 40 and 50 mg/m²/day cohorts, respectively. The treatment was continued in five patients who fulfilled the requirements for the continuation of the subsequent treatment cycle, and the antitumor effect was enhanced in four of the five patients. The remaining one patient showed no change. The overall response rate at the end of last treatment cycle was 33%, 67% and 100% in the 30, 40 and 50 mg/m²/day cohorts, respectively.

In all the 12 patients treated with oral fludarabine phosphate, the overall response rate for follicular lymphoma (10 patients) was 60% and 80% at the end of the first and last treatment cycle, respectively. For the two patients with mantle cell lymphoma, antitumor effect was not evident in this study.

pharmacokinetics

The pharmacokinetics of 2F-ara-A were assessed in the first treatment cycle.

The time to the maximum plasma concentration (T\text{max}) of 2F-ara-A on days 1 and 5 was within 1–2 h after administration at any dosage, except for one patient who showed T\text{max} of 6 h. Thus, in most cases, oral fludarabine phosphate was absorbed promptly from the gastrointestinal tract and the absorption rate was independent of the dosage. In addition, a dose independent elimination for 2F-ara-A was suggested, because the elimination patterns obtained at the three dosages were almost in parallel during the period from 6 to 10 h after administration (Figure 1). The apparent bioavailability values at 30, 40 and 50 mg/m²/day of oral fludarabine phosphate were estimated to be 78%, 58% and 56%, respectively.

discussion

The tolerability, antitumor effect and pharmacokinetics of oral fludarabine phosphate were assessed in relapsed patients with indolent B-NHL.

Grade 3 or 4 toxicities observed in this study were lymphopenia, neutropenia, leukopenia and hyperuricemia. The incidence and the grade of toxicities appeared to increase with the dosage escalation.

In the 50 mg/m²/day cohort, critical toxicity was seen in only one patient, but another patient developed grade 4 neutropenia and grade 3 leukopenia which responded to G-CSF. This case might have had the critical toxicity range if G-CSF had not been given. Therefore, this case was regarded as equivalent to a case of ‘critical toxicity’. As a result, the dosage of 50 mg/m²/day was considered equivalent to the MTD on the basis of the emergence of the critical toxicity and hematologic toxicity.

The antitumor effect was observed in half of the patients after the first treatment cycle, suggesting that the antitumor effect developed from the early phase. The response rate increased with the escalation of dosage and the number of treatment cycles.

Table 2. Common adverse drug reactions

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3</td>
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<tr>
<td>NCI-CTC grade</td>
<td>1 2 3 4</td>
<td>1 2 3 4</td>
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</table>

**Hematologic toxicities**

- Leukopenia: 1 1 1 2 3 1 1 1
- Lymphopenia: 2 2
- Neutropenia: 1 1 3 2 1 2
- Anemia: 1 3 1
- Thrombocytopenia: 1 1 1 1

**Non-hematologic toxicities**

- ALT: 1 2 1 1
- AST: 1 1 1 1
- ALP: 1 1 1
- Bilirubin: 1 1
- Hyperuricemia: 1 1
- Fatigue: 1 1 1
- Constipation: 2
- Nausea: 1 1
- Stomatitis: 1 1
- Sensory neuropathy: 1 1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Figure 1. Mean plasma concentration-time profiles of 2F-ara-A after once daily oral administration of 30 (●, n = 3), 40 (□, n = 6) and 50 mg/m² (▲, n = 3) of fludarabine phosphate to indolent B-NHL patients for 5 days (A, day 1; B, day 5).
The overall response rate in 10 patients with follicular lymphoma was 80% at the end of the last treatment cycle. Higher response rates were also reported from some clinical studies using i.v. fludarabine phosphate, although the dosage was different [1–3]. On the other hand, the number of patients with mantle cell lymphoma was only two and the antitumor effect was not evident in these patients. Since the response rate in patients with mantle cell lymphoma was reported to be more than 30% in other clinical studies [9–11], further investigation is needed to assess the effect.

The AUC\(_{0–24h}\) values obtained from the plasma 2F-ara-A concentrations were within the distribution range of the data obtained from the Caucasian patients, although the values at 30 and 40 mg/m\(^2\)/day cohorts were similar in this study. In Caucasian patients with B-CLL or indolent B-NHL who received a single administration of oral fludarabine phosphate in a dose range from 22 to 64 mg/m\(^2\), AUC\(_{0–24h}\) of 2F-ara-A on day 1 increased dose-dependently [6, 12]. These results indicated that there was no ethnic difference between Japanese and Caucasians, and AUC\(_{0–24h}\) increased in proportion to dosage.

The apparent bioavailability values were similar to the values determined from the previous crossover studies in cancer patients in Europe (56%–58%) [6].

There were inter-individual variations in these pharmacokinetic parameters. This phenomenon is not specific to fludarabine phosphate but has been observed with all nucleoside analogs. However, the variations did not appear great considering its formulation, but the extent of the inter-individual variations was similar to that observed previously in the pharmacokinetic parameters after infusion of i.v. fludarabine phosphate [8].

Based on these findings, the recommended dose for the phase II study was concluded to be 40 mg/m\(^2\)/day. To further confirm the efficacy and toxicity profiles for patients with indolent B-NHL, a pivotal phase II study using the dose of 40 mg/m\(^2\)/day is to be conducted.

**references**