Pharmacological Analysis of Etoposide in Elderly Patients with Lung Cancer

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ABSTRACT

To analyze the pharmacological characteristics of etoposide in elderly patients, we conducted a Phase I trial of a 14-day administration of oral etoposide on 12 chemotherapy-naive patients, ages 75 years or older, with lung cancer. The pharmacological profiles of etoposide in elderly patients were compared with those of younger patients in our previous studies (H. Minami et al., J. Clin. Oncol., 11: 1602–1608, 1993; H. Minami et al., J. Clin. Oncol., 13: 191–199, 1995; Y. Ando et al., Jpn. J. Cancer Res., 87: 200–205, 1996). The sigmoid Emax model and logistic regression model were used for pharmacodynamic analysis. The maximum tolerated dose for elderly patients was 75 mg/body/day. The apparent oral clearance in elderly patients was 37 times that in younger patients (44 ± 12 ml/min), which was not different from that in younger patients (44 ± 12 ml/min). The area under the concentration-versus-time curve of etoposide over the treatment period (total AUC) that produced a 50% decrease in absolute neutrophil counts was significantly different between elderly and younger patients, 14.3 ± 2.5 and 21.6 ± 2.7 mg-min/ml, respectively (P = 0.048). The incidence of grade 3 or 4 neutropenia at total AUC of 30 mg-min/ml (corresponding to a plasma concentration of 1.5 mg/ml for 14 days) was 81% in elderly patients but only 48% in younger patients. Although there was no pharmacokinetic difference between elderly and younger patients, equivalent exposure to etoposide resulted in severer myelosuppression in elderly patients. These findings suggest that prolonged etoposide administration with plasma concentration maintained at 1–2 μg/ml may cause severe myelotoxicity in elderly patients.

INTRODUCTION

Etoposide is a semi-synthetic derivative of podophytoxin and is efficacious against small cell lung cancer, malignant lymphoma, leukemia, and probably non-small cell lung cancer (1, 2). Etoposide works through a reversible interaction with topoisomerase II (3, 4), and its efficacy has been shown to be cell cycle-dependent (5) and related to the duration of drug exposure in vitro (6–8). Clinical studies have demonstrated that etoposide has a schedule-dependent effect (9, 10), and that five consecutive daily infusions of divided doses were more effective than a 24-h infusion of the same total dose. More prolonged administration of etoposide was also extensively studied (11, 12). Some investigators have suggested that a plasma etoposide concentration of 2–3 μg/ml may be associated with hematological toxicity, whereas a 1–2 μg/ml may be associated with antitumor activity (10, 13–15).

In a previous study (16), we showed that a thrice daily dose (25-mg capsule) of etoposide could achieve a stable plasma concentration, with the mean concentration of etoposide ranging from 0.5 to 2.0 μg/ml. However, it is well known that elderly patients have an increased risk in both the frequency and the severity of adverse reactions to anticancer drugs (17, 18). Such adverse reactions are often related to changes in drug disposition that result from age-related changes in body composition and organ-system functions and to an age-related decline in plasma albumin concentration (19–21). Another explanation for the increase in adverse drug reactions in elderly patients is a greater pharmacodynamic response to drug exposure (20). Thus far, there have been only a few studies focusing on the exposure-effect relationship of anticancer drugs in elderly patients (22). The retrospective analysis of our trials of continuous infusion of etoposide found that the percentage decrease in absolute neutrophil counts became severer in proportion to age despite the absence of a correlation between age and AUC3 of etoposide; all three of the patients, ages 75 years or more, experienced more than an 80% decrease in absolute neutrophil counts, although such a small number of patients prevented any detailed analysis of the effect of aging on hematological toxicities (23, 24).

In the present study, we performed a Phase I trial of a 14-day administration of oral etoposide on 12 chemotherapy-naive patients, ages 75 years or older, with lung cancer to see whether multiple dosing with oral etoposide would achieve desirable plasma etoposide concentrations in elderly patients.

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3 The abbreviations used are: AUC, area under the plasma concentration-versus-time curve; E_{AUC50} total AUC that produced half of the maximal effect.
and to clarify the differences in the pharmacokinetic and/or pharmacodynamic profiles of etoposide between elderly and younger patients.

**PATIENTS AND METHODS**

**Patients and Treatment in Phase I Trial.** The eligibility criteria for our Phase I trial were as follows: (a) WHO performance status ≤ 2; (b) estimated life expectancy ≥ 8 weeks; (c) leucocyte count ≥ 3500/μl; (d) platelet count ≥ 100 × 10^3/μl; (e) serum creatinine level ≤ 2.0 mg/dl; and (f) serum bilirubin level ≤ 2.0 mg/dl. Pretreatment evaluation included a complete history and a physical examination as well as the following laboratory tests: (a) complete blood cell counts; (b) differential smear; (c) serum electrolytes; (d) total protein; (e) albumin; (f) total bilirubin; (g) aspartate aminotransferase; (h) alanine aminotransferase; (i) alkaline phosphatase; (j) lactate dehydrogenase; (k) creatinine; (l) urea nitrogen; (m) creatinine clearance; and (n) urinalysis. During the study, a complete blood cell count with differential smear was obtained two to three times per week, and the other laboratory tests were repeated weekly. Toxicities were reported using the Japan Clinical Oncology Group grading system (25). At level 1 in the Phase I study, the etoposide dose was set at 50 mg/body/day, and a 25-mg capsule (Nippon Kayaku Co., Tokyo) was administered twice daily at 7:00 a.m. and 7:00 p.m.. At level 2, the etoposide dose was increased to 75 mg/body/day, and a 25-mg capsule was administered thrice daily at 7:00 a.m., 1:00 p.m., and 7:00 p.m.. This time schedule of etoposide administration was the same as that in our previous study (16). Etoposide was discontinued if the leucocyte count decreased to less than 2000/μl, if the platelet count decreased to less than 75 × 10^3/μl, or if there was a grade 2 or greater nonhematological toxicity other than alopecia or emesis. At least three patients were to be entered at each dose level; and, when any of them developed hematological toxicities reaching grade 3 or nonhematological toxicities other than alopecia and nausea reaching grade 2, three additional patients were to be entered. The maximum tolerated dose was defined as the dose level producing any of the following: (a) a grade 3 or greater nonhematological toxicity other than alopecia or emesis; (b) grade 2 or greater nonhematological toxicities reaching grade 2 in two-thirds or more of the patients; or (c) grade 4 hematological toxicities in one-third or more of the patients. This Phase I study was approved by the ethical committee of the Nagoya University School of Medicine, and written informed consent was obtained from all of the patients.

**Pharmacokinetic Analysis.** Blood sampling was performed on days 3 and 10 in the first cycle of chemotherapy. At dose level 1, heparinized blood samples were obtained at 7:00 a.m., 7:30 a.m., 8:00 a.m., 9:00 a.m., 10:00 a.m., 1:00 p.m., and 7:00 p.m. corresponding, respectively, to before and 0.5, 1, 2, 3, 6, and 12 h after administration; and at dose level 2, blood samples were drawn at 1:00 p.m., 3:00 p.m., 4:00 p.m., and 7:00 p.m., which were before and 0.5, 1, 2, 3, and 6 h after administration, respectively. Plasma was immediately separated by centrifugation and frozen at −20°C until analysis. The etoposide concentration was determined by high-performance liquid chromatography (26). The detection limit of the assay was less than 0.02 μg/ml. The intra- and interassay coefficients of variation were less than 3 and 10%, respectively.

The mean concentration of etoposide was calculated by AUC divided by sampling hours as follows: (a) dividing AUC from 7:00 a.m. to 7:00 p.m. by 12 h at level 1; and (b) dividing AUC from 1:00 p.m. to 7:00 p.m. by 6 h at level 2. The apparent oral clearance of etoposide was calculated as follows, and compared with that obtained from 16 younger patients who had been treated with 75 mg/body/day of oral etoposide for inoperable lung cancer previously in our hospital (16):

**Apparent oral clearance**

\[
\text{dose (mg/day)} \times 24 \text{ (hours)}
\]

\[
= \frac{\text{mean concentration of etoposide} \times 24 \text{ (hours)}}{\text{number of days etoposide was administered}}
\]

where AUC\(_{\text{day 3}}\) or AUC\(_{\text{day 10}}\) was calculated as follows:

\[
\text{AUC}_{\text{day 3}} \text{ or AUC}_{\text{day 10}} = \frac{\text{mean concentration of etoposide} \times 24 \text{ (hours)}}{2}
\]

In our previous study of oral etoposide, total AUC was calculated in the same way. When etoposide was administered i.v. in our previous study, total AUC was calculated by the trapezoidal method with extrapolation to infinity (23). The pharmacodynamic analysis was focused on neutropenia because this toxicity became dose-limiting in the present study. The relationship between total AUC and the percentage decrease in absolute neutrophil counts was analyzed using a sigmoid Emax model. E\(_{\text{AUC50}}\) of elderly patients was compared with that of younger patients using a z statistic for normal distribution. The effect of age as a continuous variable on pharmacodynamics was analyzed using a stepwise logistic regression model; other factors such as total AUC, total AUC of unbound etoposide, gender, performance status (0, 1, 2), serum albumin (g/dl), total bilirubin (mg/dl), neutrophil count before chemotherapy (per μl), and
types of treatment were also evaluated. The unbound fraction of etoposide was estimated from serum albumin and total bilirubin concentration (28).

RESULTS

Toxicities and Responses in Phase I Trial.

Patient characteristics were different in age, gender and histology between the current and previous studies (Table 1).

At dose level 1 (50 mg/body/day), one patient experienced grade 3 thrombocytopenia, and an additional three patients were entered (Table 2). Because two of the six patients suffered grade 3 neutropenia, the dose was then increased. At dose level 2 (75 mg/body/day), one of the first three patients experienced grade 4 neutropenia, and an additional three patients were entered. Among these, one patient experienced grade 4 neutropenia on day 11 and was taken off etoposide but died of pneumonia on day 19. Another patient at this dose level developed fever associated with grade 4 neutropenia and received i.v. antibiotics. We decided that the maximum tolerated dose in this trial was 75 mg/body/day because three patients experienced grade 4 neutropenia including one toxic death at that level. We observed no dose-limiting nonhematological toxicities (Table 3). Overall, 38 courses of chemotherapy were administered (1–8 courses; median, 2 in each patient). The median nadir neutrophil count for all of the courses was 1360/μl (range, 0–3040). There was no evidence of cumulative hematological toxicities. In five patients with small cell lung cancer, one complete response and three partial responses were observed; the mean concentration of etoposide in responders ranged from 0.6 to 1.4 μg/ml. No response was observed in seven patients with non-small cell lung cancer.

Pharmacokinetics. All of the patients were treated as inpatients and took all of the capsules at the planned time. The plasma concentration versus time curve during the dosing interval is shown in Fig. 1. The apparent oral clearance in 12 elderly patients in this study was 37 ± 10 (mean ± SD) ml/min, which was not different from that in 16 younger patients treated with 75 mg/body/day of oral etoposide (44 ± 12 ml/min; P = 0.200 by Mann-Whitney test; Ref. 16). There was no difference in the mean concentration of etoposide in responders ranged from 0.6 to 1.4 μg/ml.

| Table 1 | Demographic characteristics of patients entered in the present Phase I study and our previous studies of long-term administration of infusional or oral etoposide |
|---|---|---|
| Characteristics | Phase I study | Previous studies |
| | Age ≥75 | Age ≥75 | Age <75 |
| Age Median | 79 | 77 | 64 |
| Range | 75–84 | 76–85 | 47–73 |
| Body surface area (m²) Median | 1.48 | 1.36 | 1.42 |
| Range | 1.28–1.57 | 1.32–1.68 | 1.27–1.70 |
| Gender Male | 12 | 5 | 13 |
| Female | 0 | 1 | 10 |
| Performance status 0 | 3 | 0 | 4 |
| 1 | 6 | 4 | 14 |
| 2 | 3 | 2 | 5 |
| Albumin (g/dl) Median | 3.8 | 3.5 | 4.0 |
| Range | 2.9–4.5 | 3.0–4.3 | 3.1–4.7 |
| Histology Small cell lung cancer | 5 | 0 | 0 |
| Non-small cell lung cancer | 7 | 6 | 23 |
| Previous treatment Surgery + irradiation | 1 | 0 | 0 |
| None | 11 | 6 | 23 |

| Table 2 | Hematological toxicity in elderly patients* in the first cycle of Phase I trial of oral etoposide |
|---|---|---|---|---|---|
| Etoposide dose (mg/body/day) | Leukocytopenia | Neutropenia | Thrombocytopenia | Anemia |
| | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 |
| 50 | 0 | 0 | 2 | 0 | 1 | 0 | 0 |
| 75 | 1 | 1 | 0 | 3 | 0 | 0 | 3 |

* n = 6.
the previous study. The resultant EAUC_{50} (13.4 mg/min/ml) was the same as that for female patients (34.0 ± 8.1 mg/min/ml). Similarly, the percentage decreases in absolute neutrophil counts for male and female patients were 72 ± 24% and 71 ± 24%, respectively. Estimated E_AUC_{50} ± SD of elderly patients was 14.3 ± 2.5 mg/min/ml and significantly lower than that of younger patients (21.6 ± 2.7 mg/min/ml; P = 0.048; Fig. 2). Because the inclusion of the 6 elderly patients from the previous studies might have led to some bias, we conducted a further analysis using the 12 patients without the 6 patients from the previous study. The resultant E_AUC_{50} (13.4 ± 2.4 mg/min/ml, mean ± SD) remained significantly lower than that of the younger patients (P = 0.023). In a stepwise logistic regression analysis, total AUC was significantly correlated with the incidence of grade 3 or 4 neutropenia (P < 0.001), and there was a trend toward a greater risk of neutropenia as a patient got older (P = 0.066). In elderly patients, a more rapid increase in the plasma concentration of etoposide to keep the plasma concentration at 1.5 μg/ml, the estimated incidence was 81% in elderly patients in contrast to only 48% in younger patients (Fig. 3).

When total AUC of unbound etoposide was calculated by multiplying the total AUC by the unbound fraction, it failed to improve correlation coefficients of sigmoid Emax models in either elderly (r = 0.55) or younger patients (r = 0.33) and was not selected in a stepwise logistic regression in any of the 41 patients.

**DISCUSSION**

Our results showed that elderly patients had pharmacokinetics for long-term administration of oral etoposide similar to younger patients but showed greater pharmacodynamic sensitivity. Although the results of our study should be interpreted carefully because the elder and younger patients were evaluated in separate studies, the study conducted by Fujiwara et al. (29) also supported our conclusion, which showed that there was no meaningful pharmacokinetic difference for etoposide between elderly (ages 75 years or older) and younger patients.

The narrow therapeutic range of cytotoxic anticancer drugs makes dose optimization for individual patients necessary, and chemotherapy in elderly patients can be considered as a good example of the need for this optimization. However, the pharmacological characteristics of anticancer agents in elderly patients, which should be a basis for dose optimization in the population, have rarely been investigated (30). In the present study, the mean concentration of etoposide in elderly patients was within the range observed in younger patients treated with 75 mg/body/day of oral etoposide (0.5–2.0 μg/ml; Ref. 16), and 8 of 12 elderly patients had a mean concentration between 1 and 2 μg/ml, which was considered to be “therapeutic range.” However, an equivalent exposure to etoposide brought severe myelosuppression in elderly patients as demonstrated by a pharmacodynamic analysis using a sigmoid Emax model and a logistic model. This suggests that prolonged administration of etoposide to maintain a plasma etoposide concentration of 1 to 2 μg/ml would pose a toxic risk for elderly patients.

High toxicities were observed in elderly patients in many studies of chemotherapy. In a retrospective review of the data from nonprotocol settings and clinical trials, the attenuation of chemotherapy by dose reduction or omission occurred more frequently in elderly patients (31, 32), which suggested that aging and its consequences indeed influenced chemotherapy dose delivery. Our study demonstrated that, for patients ages 75 years or older, a thrice daily dose of 25 mg etoposide for 14 days was toxic but caused minimal toxicity in younger patients (16). This was explained by the pharmacodynamic alterations in elderly patients rather than by any change in pharmacokinetics related to aging. The greater sensitivity of hematopoietic cells to...
anticancer drugs may be responsible for severer neutropenia in elderly patients (33, 34).

Previous investigators (35, 36) have demonstrated the importance of unbound etoposide as a pharmacokinetic parameter to delineate the exposure-effect relationship. We do not believe that a greater fraction of unbound etoposide can explain the greater sensitivity in the elderly patients in our study because the estimated unbound fraction was not correlated with age ($r = 0.23$), and the total AUC of unbound etoposide did not improve the predictability of neutropenia. Reasons for the poor relationship between the total AUC of unbound etoposide and neutropenia may lie in the narrow range of total bilirubin (0.2–1.5 mg/dl) and greater age compared with the study reported by Stewart et al. (28), which included patients (ages 37–72 years; median, 61) with hyperbilirubinemia and excluded elderly patients. Additional studies should continue to scrutinize the importance of unbound etoposide.

Recently, two randomized trials of the palliative treatment of unfit patients with small cell lung cancer demonstrated that oral etoposide was inferior to i.v. combination chemotherapy (37, 38). In addition to a small disadvantage in survival, oral etoposide was associated with increased hematological toxicity. In these studies, a total of 1000 mg of etoposide was administered over a period of 5–10 days, which was a standard dose of oral etoposide and might have been overdosing for unfit patients. In the present study, we showed that increased hematological toxicity in elderly patients was brought on by an altered exposure-effect relationship rather than by any change in the pharmacokinetics of etoposide. Our pharmacological analysis did not justify a dose reduction to alleviate hematological toxicity in elderly patients because that would involve decreased exposure to etoposide and an additional reduction in antitumor activity. These findings argue against the long-term administration of oral etoposide in elderly patients.

Despite the relatively small number of patients, the present study could detect a 27% difference in the apparent oral clearance with a statistical power of 80% when compared with that of the 16 younger patients. Therefore, we consider that the present study could detect a clinically important difference in pharmacokinetics.

We conclude that the exposure-effect relationship of etoposide in elderly patients is different from that in younger patients, whereas the pharmacokinetics of long-term administration of oral etoposide is not. Additional studies of the difference in exposure-effect relationship should include biological studies of the mechanism of this difference.

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