UFT Plus Cisplatin in Advanced Non-Small-Cell Lung Cancer: Interim Analysis of 67 Patients

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A single-institution phase II study indicated that combination chemotherapy using UFT (tegafur and uracil) plus cisplatin (Platinol) in patients with non-small-cell lung cancer was active with less host toxicity than other cisplatin-

Introduction

In a single-institution phase II trial, combination chemotherapy with oral UFT (tegafur and uracil) plus cisplatin (Platinol) for treatment of inoperable advanced non-small-cell lung cancer was reported to produce an objective response rate of 35%.[1] In addition to this response rate, which is comparable with that of other active cisplatin-based regimens,[2] the incidence of adverse events with this regimen was extremely low. For instance, it was reported that grades 3 and 4 hematologic toxicities such as leukopenia and thrombocytopenia occurred in only 6% of the patients, and there were no grade 3 or 4 nonhematologic toxicities.[1] These observations suggest that UFT plus cisplatin is an active regimen with less host toxicity than some alternative regimens. Therefore, the Japan UFT Lung Cancer Study Group conducted a multi-institutional phase II trial to determine the efficacy and toxicity of oral UFT plus cisplatin in patients with advanced non-small-cell lung cancer.

Patients and Methods

Patients eligible for this study had either cytologically or histologically confirmed non-small-cell lung cancer; measurable lesions; stage IIIB or IV disease; no previous therapy; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2; expected survival of more than 3 months; age younger than 79 years; adequate hematologic function (leukocyte count was ≥ 4,000/µL and platelet count was ≥ 100,000/µL), hepatic function (bilirubin level ≤ 1.5 mg/dL and aspartate aminotransferase and alanine aminotransferase was ≤ 2 times the upper limit of normal), and renal function (normal creatinine concentration and creatinine clearance ≥ 60 mL/min); no evidence of severe heart or pulmonary disease; and no active concomitant malignant disease. Staging was performed according to the international staging system,[3] and informed consent was required from all patients.

UFT 400 mg/m², in the form of 100-mg capsules, was administered orally from days 1 to 14. The daily dose of UFT was rounded up or down to the nearest 100 mg, divided into two doses, and given before meals. If the capsule dose could not be divided equally, the higher dose was administered in the morning and the lower dose in the evening. In practice, most patients received 600 mg UFT per day. Cisplatin 80 mg/m² was administered as a 90-minute infusion on day 8, at which time patients also received hydration of at least 2,500 mL. The treatment was repeated every 3 or 4 weeks, with at least two cycles given unless unequivocal disease progression or unacceptable toxicity was observed.

A complete blood cell count and blood chemistry were performed once a week after treatment began and a chest x-ray was performed periodically, and patients were evaluated for response based on the standard World Health Organization criteria.[4] Toxicities were assessed using common toxicity criteria.[5]

Since promising and clinically uninteresting response rates obtained by this treatment would be 30% and 20%, respectively, a sample size of 110 patients was required, with an alpha error of 0.05 and a power of 0.8. Overall survival was estimated using the Kaplan-Meier method, with the confidence interval calculated using the methods of Simon.[6]
Results

The number of patients planned for this trial was 110. Between April 1995 and May 1996, 67 patients were enrolled. All 67 were considered eligible for an interim analysis performed in October 1996. As shown in Table 1, the patient population included 46 men and 21 women, with a mean age of 64 years and a median Eastern Cooperative Oncology Group performance status of 1. The predominant histology, identified in 41 patients (61%), was adenocarcinoma; 21 patients (31%) had stage IIIb disease, and 46 (69%) had stage IV.

Patients received between one and five cycles of treatment (18 patients, one cycle; 31 patients, two cycles; 9 patients, three cycles; 6 patients, four cycles; and 3 patients, five cycles). Four patients did not receive cisplatin in the first cycle and discontinued the trial. These 4 patients were excluded from the response evaluation but were included in the analysis of toxicities and survival. Among 63 patients evaluable for response, there was an overall response rate of 30% (95% confidence interval, 19% to 41%), with 1 complete response, and 18 partial responses. No change was defined for 34 patients, of whom 4 experienced a minor response. Ten patients had progressive disease. In comparison with the total population group, the 19 patients with a major response were classified as follows: 11 (55% of 20) had stage IIIb disease, and 8 (19% of 43) had stage IV; 10 (56% of 18) had squamous cell carcinomas, and 9 (22% of 41) had adenocarcinomas. With a median follow-up duration of 44 weeks, the median survival time was 32 weeks, and the 1-year survival was 25%.

The toxicities observed for all 67 patients during the entire treatment period are listed in Table 2. Leukopenia of grade 3 was observed in only 1 patient. There was no grade 3 or greater thrombocytopenia. In terms of nonhematologic toxicities, 6 patients demonstrated grade 3 or 4 vomiting and 16 patients had grade 2 vomiting. Nevertheless, 96% of the projected dose of UFT could be administered. A transient abnormality in liver function was observed in a few patients. No other severe toxicities, including cardiac and pulmonary toxicities, were observed. There were also no treatment-related deaths.

Future Plan

This interim analysis indicates that a combination chemotherapy using oral UFT and cisplatin in patients with advanced non-small-cell lung cancer has activity comparable with that of other cisplatin-based combination therapies. In addition, the incidence of adverse events has been extremely low, supporting results of the previous phase II study. Enrollment in this multi-institutional phase II trial was due to be finished by March 1997. If the final results are similar to those of this interim analysis, a prospective randomized comparison of oral UFT plus cisplatin versus an existing cisplatin-based regimen is warranted.

References:


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