Efficacy and safety of amrubicin hydrochloride for the treatment of relapsed small cell lung cancer (SCLC): Clinical data and presentation of results

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ABSTRACT

Regarding overall survival of refractory Small-cell lung cancer (SCLC) patients, long-term survival is quite uncommon, with less than 25% of patients with limited-stage, and 1-2 % of patients with extensive-stage disease remaining alive at 5 years. Recent clinical studies demonstrated the promising efficacy of amrubicin for patients with relapsed SCLC, and this review presents the results of clinical studies showing the efficacy and safety of amrubicin for the treatment of relapsed SCLC. Amrubicin is a completely synthetic anthracycline agent with a similar structure to doxorubicin, in which the hydroxyl group at position 9 is replaced by an amino group in amrubicin to enhance efficacy. It is converted to an active metabolite, amrubicinol, which is 5-54 times more active than amrubicine. Amrubicine and amrubicinol are inhibitors of DNA topoisomerase II, developing their cytotoxic effects by stabilizing a topoisomerase II-mediated cleavable complex. Toxicities of amrubicin are similar to that of doxorubicin, however, amrubicin shows almost no cardiotoxicity. Amrubicin was administered intravenously at a dose of 35-40 mg/m^2 on days 1 to 3 every 3 weeks. The response rate was 34-52% and the median survival times were 8.1-12.0 months. Common adverse events were hematologic toxicities, including neutropenia, leucopenia, anemia, thrombocytopenia, and febrile neutropenia. Non-hematologic adverse events included grade 3-4 anorexia, asthenia, hyponatremia and nausea. The results of the studies which demonstrated the efficacy of monotherapy for relapsed SCLC involved mainly Japanese patients. Therefore, it is necessary to conduct clinical studies more in non-Japanese patients to confirm the amrubicin efficacy.

Key words: amrubicin, amrubicinol, small-cell lung cancer, relapse

INTRODUCTION

Small-cell lung cancer (SCLC) accounts for approximately 15% of all lung cancer cases, with two thirds of patients presenting with extensive disease (ED). Without treatment, tumor progression in patients with SCLC is rapid, with a poor prognosis. Meanwhile, it shows a high response rate to chemotherapy and radiotherapy, except in a low percent of patients. Treatment options for relapsed SCLC patients remains limited. A randomized trial demonstrated that single-agent topotecan was at least as efficacious as the three-drug combination of cyclophosphamide, doxorubicin, and vincristin (CAV) for the treatment of patients with sensitive relapsed cases (1). Response rates and median survival times were 24%, and 25.0 weeks for topotecan, and 18% and 24.7 weeks for CAV, respectively. In previously untreated ED-SCLC, amrubicin yielded an extremely high response rate of 79% and a median survival time (MST) of 11 months, which was comparable to the results of platinum (2, 3). Recently, clinical studies demonstrated the efficacy of amrubicin for patients with relapsed SCLC. This review presents the results of clinical studies showing the efficacy and safety of amrubicin for the treatment of relapsed SCLC.

STRUCTURE AND CHARACTERISTICS

Amrubicin hydrochloride is a completely synthetic anthracycline agent with a similar structure to doxorubicin, in which the hydroxyl group at position 9 is replaced by an amino group in amrubicin to enhance efficacy (Figure 1). Amrubicin is converted to an active metabolite, amrubicinol, which is 5-54 times more active than amrubicine, through reduction of its C-13 ketone group to a hydroxyl group by carbonyl reductase

(4). Other enzymes metabolizing amrubicin and amrubicinol are NADPH-dependent P450 reductase and NAD[P]H-dependent quinone oxidereductase. Doxorubicin, amrubicine and amrubicinol are inhibitors of DNA topoisomerase II, developing their cytotoxic effects by stabilizing a topoisomerase II-mediated cleavable complex (5). Additionally, they are more or less only one-tenth as potent as doxorubicin in producing DNA intercalation.

PRECLINICAL STUDIES

Antitumor activities and toxicological aspects were firstly reported by Morisada et al. They evaluated in six murine experimental tumor systems and nine human tumor-nude mouse systems, and anti-tumor activities of amrubicin were superior to adriamycin (ADR) against human tumor xenografts, and almost equal against murine experimental tumors (6). They also evaluated toxicities in mice after a bolus intravenous injection. The acute toxic signs were body weight decrease, ataxia, hair loss, and myelosuppression and these toxicities were qualitatively comparable to those induced by ADR. The maximum tolerated dose (MTD) for such administration was estimated to be 25 mg/kg in 4 mouse strains, and it has anticancer activity against human lung cancer xenografts in vivo (7).

Cardiomyopathy is burdensome toxicity for anthracyclines. Suzuki et al evaluated the degree of cardiotoxicity of amrubicin compared with that of ADR in rabbits (8). Drugs were intravenously administered 3 times a week for 8 weeks. In the electrocardiogram study, prolongation of QTc interval and ST-T change were observed in rabbits administered amrubicin and ADR. Morphological studies showed that myocardial tissue damage in animals administered amrubicin was comparable to that in

the negative controls. Considering the results of antitumor efficacy studies comparing with ADR, they concluded the cardiotoxicity of amrubicin was very slight.

RELAPSED SCLC

Regarding overall survival of refractory SCLC patients, long-term survival is quite uncommon, with less than 25% of patients with limited-stage, and 1-2 % of patients with extensive-stage disease remaining alive at 5 years. A phase II study was conducted in patients with relapsed disease who had previously received one or two regimens, including at least one regimen of platinum-based chemotherapy (9) (Table 1). Sixty patients were enrolled in this multicenter trial. Sixteen and 44 patients, respectively, in refractory groups, in which the disease progressed within 60 days after the final dose of previous chemotherapy, and in sensitive groups, in which complete response (CR) or partial response (PR) was observed with previous chemotherapy and the disease then progressed or relapsed at least 60 days after the final dose of previous chemotherapy were eligible for the study, and were assessable for toxicity, response, and survival. Amrubicin was administered intravenously at a dose of 40 mg/m^2 on days 1 to 3 every 3 weeks. The response rate was 52% [95% CI: 38-65%]. There were no differences in the response rate between 50% [95% CI: 25-75%] for refractory disease and 52% [95% CI: 37-68%] for sensitive disease. The median survival times were 10.3 months in the refractory group and 11.6 months in the sensitive group, respectively ($p=0.0974$; log rank test). Common adverse events were hematologic toxicities, including grade 3-4 neutropenia (83%), leucopenia (70%), anemia (33%), thrombocytopenia (20%), and febrile neutropenia (5%). Non-hematologic adverse events included grade 3-4 anorexia (15%), asthenia (15%), hyponatremia (8%) and

nausea (5%).

Another phase II study of amrubicin in patients with previously treated SCLC was conducted by Kaira et al. (10) (Table 2). Twenty-nine patients with relapsed SCLC who had previously received platinum-based chemotherapy were enrolled in the trial of 10 patients with sensitive relapse and 19 patients with refractory relapse. Amrubicin was administered intravenously at a dose of 35 mg/m^2 on day 1 to 3 every 3 weeks. The response rate was 44.8% (95% CI: 26-64%): 60% for sensitive cases and 37% for refractory cases. No significant difference in the response rate was observed between sensitive cases and relapsed cases (p=0.233; log rank test). The median progression-free survival and median survival times were 4.0 months (sensitive relapse, 4.0 months; refractory relapse, 4.0 months) and 12.0 months (sensitive relapse, 12.0 months; refractory relapse, 11.0 months). There were no differenced in median progression-free survivals and median survival time between sensitive relapse and refractory relapse. Grade 3 or 4 neutropenia and febrile neutropenia were observed in 42% and 3%. Non-hematological toxicity more than grade 3 was not observed. The results of this study show the efficacy of monotherapy for relapsed SCLC; however, this study involved only Japanese patients, it is therefore necessary to conduct clinical studies in non-Japanese patients to confirm the efficacy.

A randomized phase II trial of amrubivin versus topotecan as second-line treatment for sensitive ED-SCLC was therefore conducted (11) (Table 3). Seventy-six patients who had previously received platinum-based first-line chemotherapy were enrolled. All were sensitive cases, in which CR or PR had been observed with the previous chemotherapy and the disease had then progressed or relapsed at least 90 days after the final dose. Patients were randomized at a 2:1 ratio to receive either amrubicin

or topotecan. Amrubicin was administered intravenously at a dose of 40 mg/m^2 on day 1 to 3 every 3 weeks. Topotecan was administered intravenously at a dose of 1.5 mg/m^2 on day 1 to 5 every 3 weeks. The response rate of amrubicin was 34% [95% CI: 22-48%], and topotecan was 4% [95% CI: 1-19%]. There was a trend toward a longer progression-free survival time in the amrubicin group (4.6 months, 95% CI: 64-187) than in the topotecan group (3.5 months, 95% CI: 75-177). This study showed that amrubicin is active in non-Japanese patients and is well tolerated, with myelotoxicity being the main dose-limiting toxicity. Sugawara et al. conducted a randomized phase II trial comparing amrubicin with topotecan in not only sensitive relapse but refractory cases (12) (Table 4). Sensitive cases were defined as CR or PR being achieved with the previous chemotherapy after which the disease progressed or relapsed at least 90 days after the final dose. Fifty-nine patients were randomized at a 1:1 ratio to receive either amrubicin or topotecan. Amrubicin was administered intravenously at a dose of 40 mg/m^2 on day 1 to 3 every 3 weeks. Topotecan was administered intravenously at a dose of 1.0 mg/m^2 on day 1 to 5 every 3 weeks. The response rate of amrubicin was 38% [95% CI: 60-92%], and topotecan was 13% [95% CI: 4-31%]. In sensitive relapsed cases, the response rate of amrubicin was 53% [95% CI: 28-77%], and topotecan was 21% [95% CI: 6-46%]. In refractory relapsed cases, the response rate of amrubicin was 17% [95% CI: 2-48%], and topotecan was 0% [95% CI: 0-28%]. The median progression-free survival with amrubicin was 3.5 months, and topotecan was 2.2 months. The median overall survival with amrubicin was 8.1 months, and topotecan was 8.4 months. There was no difference in the frequency of hematological toxicity more than grade 3 between amrubicin and topotecan. These studies showed that amrubicin monotherapy is an encouraging regimen for second-line treatment of SCLC.

CONCLUSION

Clinical studies of the novel anticancer agent amrubicin have increased quickly, and there are high expectations for this agent in trials to improve the outcome for relapsed SCLC patients. Amrubicin is an active agent for the treatment of relapsed SCLC, but because it is strongly myelotoxic, particular care should be taken.

AUTHORS' DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors declared no potential conflicts of interest.

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FIGURE LEGENDS

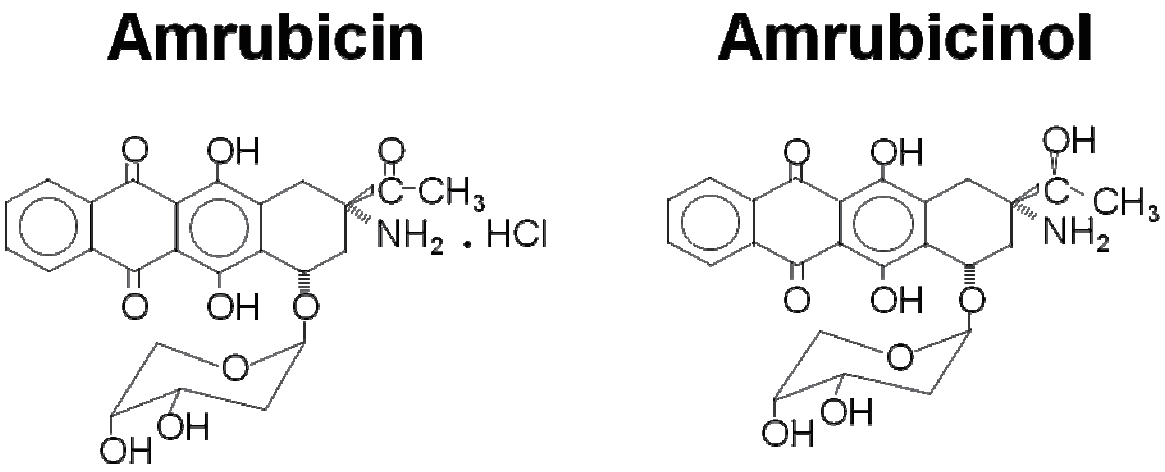

Figure 1.

Chemical structure of amrubicin and amrubicinol

Table 1 Phase II trial of amrubicin for treatment of refractory or relapsed small cell lung cancer (Thoracic Oncology Research Group Study 0301)

	Sensitive case	Refractory case	Total
No. of patients	44	16	60
CR	1	1	2
PR	22	7	2
SD	10	2	12
PD	11	6	17
Response rate (95% CI)	52% (37–68%)	50% (25–75%)	52% (38–65%)
Progression-free survival (95% CI)	4.2 months (10.0–15.8)	2.9 months (1.4–4.6)	3.9 months (3.4–4.6)
Median survival time (95% CI)	11.6 months (10.0–15.8)	10.3 months (4.8–∞)	11.0 months (10.0–13.2)
1-yr survival (95% CI)	45.5% (29.9–59.8)	40.3% (15.1–64.6)	44.1% (30.6–56.8)

Table 2 Phase II trial of amrubicin for treatment of relapsed small cell lung cancer

	Sensitive case	Refractory case	Total
No. of patients	10	19	29
Response rate (95% CI)	60%	37%	45% (26–64%)
Progression-free survival	4.0 months	4.0 months	4.0 months
Median survival time	12.0 months	11.0 months	12.0 months

Table 3 Randomized phase II trial of amrubicin vs topotecan for treatment of sensitive relapsed small cell lung cancer

	Amrubicin	Topotecan	p. value
No. of patients	50	26	
Overall response rate (95% CI)	34% (22.4–47.8%)	4% (0.7–18.9%)	< 0.004
CR (95% CI)	8% (3.2–18.8%)	0%	
PR (95% CI)	26% (15.9–39.6)	4% (0.7–18.9%)	
SD (95% CI)	32% (20.8–45.8%)	46% (28.8–64.5%)	
PD (95% CI)	24% (14.3–37.4%)	23% (11.0–42.1%)	
Median progression-free survival (95% CI)	138 days (64–187)	106 days (75–177)	

Table 4 Randomized phase II trial comparing amrubicin with topotecan in patients with sensitive and refractory relapsed small cell lung cancer

	Amrubicin	Topotecan	p. value
No. of patients	29	30	
Overall response rate (95% CI)	38% (21–58%)	13% (2–31%)	= 0.039
ORR* in sensitive cases (95% CI)	53% (28–77%)	21% (6–46%)	= 0.082
ORR in refractory cases (95% CI)	67% (35–90%)	18% (2–52%)	= 0.478
Median progression-free survival	3.5 months	2.2 months	= 0.16
Overall survival	8.1 months	8.4 months	= 0.17

* Overall response rate