Amrubicin for the Treatment of Small Cell Lung Cancer: Does Effectiveness Cross the Pacific?

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Abstract: Amrubicin is a synthetic 9-aminoanthracycline that has significant antitumor activity in Japanese patients with extensive stage small cell lung cancer (SCLC). Clinical trials ongoing in the United States and Europe will determine whether amrubicin will be effective in other ethnic groups (whites) or whether this will be an example of geographic and/or genetic variation. Genetic polymorphisms in the UGT1A1 gene have been identified as one of the causes of the increased diarrhea seen in white patients treated with irinotecan when compared with Japanese patients. Nicotinamide adenine dinucleotide phosphate, reduced form–quinone oxidoreductase (NQO1) is an enzyme that participates in the metabolism of amrubicin and polymorphisms of the enzyme, known to occur in the Asian population, might explain the effectiveness of the drug in Japanese patients with small cell lung cancer. Studies to evaluate the drug in US and European patients with extensive stage small cell lung cancer are ongoing. Levels of NQO1 will also be determined in these studies.

Key Words: Amrubicin, Small cell, Extensive stage.

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Small cell lung cancer (SCLC) accounts for approximately 13% of new cases of lung cancer diagnosed in the United States.1 Sixty percent to 70% of patients with SCLC present with extensive-stage SCLC (i.e., metastatic disease), whereas 30% to 40% of patients have limited-stage SCLC, defined as disease confined to one hemithorax with or without regional lymph nodes (hilar or mediastinal), with or without ipsilateral supraclavicular lymph node involvement, and without ipsilateral pleural effusions.2

SCLC is a rapidly proliferating tumor that responds both to chemotherapy and radiation therapy. Unfortunately, although limited-stage SCLC is potentially curable with combined modality therapy (i.e., 15%–25% 5-year survival rate), extensive stage, despite treatment with chemotherapy, has a poor long-term survival rate, with almost all such patients dead within 2 years from initial diagnosis.3

Despite the introduction of effective chemotherapeutic drugs in the treatment of untreated SCLC patients in the 1990s (i.e., paclitaxel, docetaxel, topotecan, irinotecan, vinorelbine, gemcitabine), there has been no significant improvement in the survival of patients with SCLC (Table 1).4–11

There is a need for new and effective agents to treat patients with SCLC. One such new agent may be amrubicin, a drug that has been studied in Japan and is now approved for both SCLC and non-small cell lung cancer (NSCLC). Amrubicin is being evaluated in the United States and Europe in the treatment of patients with SCLC.

AMRUBICIN

Amrubicin (Figure 1) was discovered and developed by Sumitomo Pharmaceuticals in Japan.12 It is a synthetic 9-aminoanthracycline with potent antitumor activity against various human tumor xenografts.13

Amrubicin is metabolized to the active metabolite amrubcinol, which has five to 200 times higher growth inhibitory activity against human tumor cell lines in vitro compared with doxorubicin. The in vitro growth inhibitor activity of amrubcinol was comparable with or higher than that of doxorubicin. In human xenograft models, antitumor effects on administration of amrubicin were highly correlated with the intratumor concentration of amrubcinol. In this regard, amrubicin is distinct from other anthracyclines for which metabolites have equal or decreased cytotoxic activity relative to the parent compounds. In human xenograft models, amrubicin exhibited antitumor effects comparable with or superior to those of doxorubicin, when both were administered at their maximum tolerated dose.

Anthracyclines have been reported to have diverse molecular effects (e.g., DNA intercalation, inhibition of topoisomerase II, and stabilization of topoisomerase II cleavable complexes). Amrubcin demonstrates decreased DNA intercalation compared with doxorubicin. The decreased DNA interaction appears to influence the intracellular distribution because amrubcin and amrubcinol showed only 20% distribution into the nucleus of P388 cells compared with the 80% nuclear distribution observed with doxorubicin. The cell growth inhibitory effects of amrubcin and amrubcinol appear to be primarily related to inhibition of topoisomerase II.14

The primary metabolite (amrubcinol) in rats and dogs is a product of reduction by cytoplasmic carbonyl reductase at
the C-13 carbonyl group. Other enzymes participating in the metabolism of amrubicin and amrubicinol were nicotinamide adenine dinucleotide phosphate, reduced form (NADPH)–P450 reductase and nicotinamide adenine dinucleotide [phosphate] (NAD[P]H)-quinone oxidoreductase. Twelve additional metabolites were detected in vivo and in vitro. These included four aglycone metabolites, two amrubicinol glucuronides, deaminated amrubicin, and five highly polar unknowns. In vitro cell growth inhibitory activity of the minor metabolites was substantially lower than that of amrubicinol. Excretion of amrubicin and its metabolites is primarily hepatobiliary. Enterohepatic recycling was demonstrated in rats.

Single-dose studies were conducted in mice, rats, and dogs, and repeated-dose evaluations were conducted for dosing periods up to 6 months in rats and dogs. Additional repeated-dose studies were conducted in rabbits and dogs to evaluate the cardiotoxicity potential of amrubicin compared with that of doxorubicin.

Based on acute intravenous dose toxicity studies, the lethal dose to 50% of animals was estimated to be 42 mg/kg in mice, 14 mg/kg in rats, and 4 mg/kg in dogs. The primary target organs of amrubicin toxicity were similar across species. Histopathologic lesions were found in tissues with relatively rapid cellular turnover, i.e., hematopoietic and lymphatic systems, the digestive tract, the reproductive systems, and hair follicles and were similar across species. In an acute mouse study, a low incidence of kidney toxicity was also observed.

Clinical manifestations of toxicity observed on acute and repeated administration of amrubicin in rats and dogs were dose related and reversible including fecal changes (mucoid or bloody feces/diarrhea), body weight decreases, decreased food consumption, decreased activity, and alopecia. Similar findings were observed at doses of doxorubicin approximately one half those of amrubicin.

Results from the amrubicin toxicology program show that hematologic parameters are the most important parameters to monitor in clinical studies. In addition, studies in rabbits and dogs determined that amrubicin did not induce cardiomyopathy nor exacerbate doxorubicin-induced cardiomyopathy. Amrubicin demonstrated reproductive and developmental toxicity in rabbits and rats. It also was shown to be mutagenic.

Clinical development of amrubicin was initiated in December 1986. It was approved for use in Japan for the treatment of NSCLC and SCLC in April 2002.

The maximum tolerated dose of amrubicin was determined to be 130 mg/m² in a single-dose schedule, 25 mg/m²/day (125 mg/m² in total) in daily doses for 5 days, and 50 mg/m²/day (150 mg/m² in total) for 3 days. The dose-limiting toxicity was myelosuppression (neutropenia/thrombocytopenia and anemia). Leukopenia and neutropenia developed in >80% of the patients who received amrubicin. The incidence and severity were affected by previous treatment, target lesion, and administration dose. Decreased hemoglobin level (71%) and thrombocytopenia (35%) also developed at relatively high frequency.

The plasma pharmacokinetics of amrubicin in cancer patients are characterized by low total clearance (22% of total
liver blood flow) and a moderate volume of distribution (1.4 times total body water). Amrubicin plasma concentrations followed a biphasic pattern with peak concentrations observed immediately after dosing followed by $\alpha$ and $\beta$ half-lives ($t_{1/2}$) of 0.06 ± 0.01 and 2.0 ± 0.3 hours, respectively. Concentrations of amrubicin in red blood cells (RBCs) were similar to those observed in plasma. Amrubicin plasma and red blood cell pharmacokinetic parameters were linear over a 10- to 130-mg/m² dose range as evidenced by dose proportional increases in the area under the curve (AUC) and dose-independent $t_{1/2}$. Amrubicin concentrations in plasma and RBCs and $t_{1/2}$ values after three and five consecutive daily doses were similar to those observed after the first dose, suggesting that amrubicin pharmacokinetic parameters were not altered on repeated administration (amrubicin hydrochloride investigator’s brochure [IND 22,883], 2005).

Peak plasma concentrations of the active metabolite amrubicinol were observed from immediately after dosing to 1 hour after dosing. Plasma concentrations of amrubicinol were low compared with amrubicin plasma concentrations, and the average plasma amrubicinol $t_{1/2}$ was 15 ± 8 hours. The plasma amrubicinol AUC was approximately 10-fold lower than the amrubicin plasma AUC. Concentrations of amrubicinol were higher in RBCs as compared with plasma. Amrubicinol AUCs ranged from 2.5-fold to 57.9-fold higher in RBCs compared with plasma; however, the $t_{1/2}$ of amrubicinol in RBCs was 14 ± 3 hours and thus was similar to the plasma value. Because amrubicinol distributes into RBCs to a greater extent than amrubicin, the concentrations of amrubicinol and amrubicin in RBCs were similar. The AUC of amrubicinol in RBCs was approximately twofold lower than the amrubicin RBC AUC (amrubicin hydrochloride investigator’s brochure [IND 22,883], 2005).

Amrubicin plasma and RBC AUCs increased in proportion to amrubicin dose and $t_{1/2}$ was independent of dose, suggesting linear PK. Upon repeated daily amrubicin administration, amrubicin accumulation was observed in plasma and RBCs. On day 3, the amrubicin plasma AUC was 1.2-fold to 6-fold higher than day 1 values; the RBC AUC was 1.2-fold to 1.7-fold higher than day 1 values. After 5 consecutive daily doses, plasma and RBC amrubicin AUCs were 1.2-fold to 2.0-fold higher than day 1 values (amrubicin hydrochloride investigator’s brochure [IND 22,883], 2005).

Urinary excretion of amrubicin and amrubicinol after administration of amrubicin accounted for 2.7% to 19.6% of the dose. The amount of excreted amrubicinol was approximately 10-fold greater than excreted amrubicin (amrubicin hydrochloride investigator’s brochure [IND 22,883], 2005).

The intravenous administration of amrubicin at a dose of 45 mg/m²/day for three consecutive days at 3-week intervals is the approved schedule used in Japan.

**AMRUBICIN AS FIRST-LINE THERAPY**

In the first phase II study of amrubicin in previously untreated patients with extensive-stage SCLC, an overall response rate of 78.8% was reported18 (Table 2). Thirty-five patients were entered in the study of which 33 were eligible.

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**TABLE 2. Summary of Studies with Amrubicin in the Treatment of Extensive-Stage Small Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy Regimen</th>
<th>Dose of Drugs</th>
<th>No. of Patients</th>
<th>Response, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>mana et al.18</td>
<td>Cyclophosphamide, doxorubicin, vincristine, etoposide</td>
<td>d 1–3q 3 wk</td>
<td>35 (33)</td>
<td>15.2</td>
</tr>
<tr>
<td>Yamamoto et al.19</td>
<td>Amrubicin 45 mg/m²</td>
<td>d 1–3q 3 wk</td>
<td>44 (44)</td>
<td>9.7</td>
</tr>
<tr>
<td>Shibayama et al.21</td>
<td>Amrubicin 45 mg/m²</td>
<td>d 1–3q 3 wk</td>
<td>26 (26)</td>
<td>18.5</td>
</tr>
<tr>
<td>Hasegawa et al.22</td>
<td>Amrubicin 30–40 mg/m²</td>
<td>d 1–3q 3 wk</td>
<td>35 (33)</td>
<td>15.2</td>
</tr>
<tr>
<td>Onoda et al.23</td>
<td>Amrubicin 30–40 mg/m²</td>
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<td>44 (44)</td>
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<td>18.5</td>
</tr>
<tr>
<td>Okuda et al.25</td>
<td>Amrubicin 30–40 mg/m²</td>
<td>d 1–3q 3 wk</td>
<td>60 (60)</td>
<td>60</td>
</tr>
<tr>
<td>Yamamoto et al.19</td>
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</tr>
</tbody>
</table>

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*Two-year survival rate. Sen, sensitive disease; Ref, refractory disease.
The median age of the eligible patients was 66 years (range, 42–78), 29 were male and Eastern Cooperative Oncology Group performance statuses (PSs) were PS 0–5, PS 1–2, PS 2–2. Amrubicin was administered by intravenous injection of 45 mg/m²/day for three consecutive days every 3 weeks. The median number of courses of therapy was four (range, one to six). Of the 33 eligible patients, five had a complete response (15.2%) and 21 patients had a partial response (63.6%), for an overall response rate of 78.8%. The median survival was 11.3 months (range, 2–21+). The 1- and 2-year overall survival rates were 46.9% and 23.1%, respectively. The major toxicity was myelosuppression. Grade 3 and 4 leukopenia and neutropenia was 39% and 39% and 12% and 39%, respectively. Nonhematologic toxicity of grade 3 and higher was not observed except for anorexia (9.1%) and alopecia (3%). Cardiac toxicity was not observed.

**AMRUBICIN IN MEDICALLY UNFIT OR HEAVILY PRETREATED PATIENTS**

Amrubicin monotherapy was also tested in patients with SCLC who were unable to tolerate combination chemotherapy because of old age, poor PS, or other contraindications or patients who had previously undergone two or more regimens of chemotherapy.20 Twenty-one patients were treated with amrubicin given on days 1, 2, and 3 every 3 weeks. Amrubicin was administered at 40 mg/m² (or 35 mg/m² for six patients in consideration of their general health). Seven patients were chemoanaive. The overall response rate was 71% (five of seven patients) in chemoanaive patients and 14% (two of 14) in patients with previous chemotherapy. Median survival time was 9.4 months (95% confidence interval: 7.7–14.1) and 6 months (95% confidence interval: 2.6–8.6), respectively. Hematologic toxicity was common and relatively mild. Therefore, amrubicin monotherapy could be considered for patients with SCLC who are unfit for combination chemotherapy.

**AMRUBICIN PLUS CISPLATIN**

In a phase I/II study, amrubicin and cisplatin in previously untreated patients with extensive-stage SCLC were studied.20 Amrubicin (40–45 mg/m²/day) on days 1 to 3 and cisplatin 60 mg/m²) on day 1 were administered intravenously every 3 weeks to patients with a good PS. Four and three patients received the amrubicin dose of 40 (level 1) and 45 mg/m²/day (level 2), respectively. The maximum tolerated dose was determined to be the 45 mg/m²/day of amrubicin plus cisplatin 60 mg/m², whereas the recommended phase II dose was the lower dose of amrubicin plus cisplatin. No dose-limiting toxicities were observed during the first course of level 1, whereas at level 2, grade 4 febrile neutropenia occurred in two patients. An additional 37 patients were entered in the study. A total of 41 patients were a treated at the recommended phase II dose. The response rate was 87.8% (10% complete response). The median survival time and 1-year survival rate were 13.6 months and 56.1%, respectively. Grade 3/4 neutropenia and leukopenia occurred on 95.1% and 65.9% of patients, respectively. Grade 3 thrombocytopenia occurred in 24% of patients, and grade 3/4 hyponatremia was present in 22% of patients.

**AMRUBICIN PLUS TOPOTECAN**

A phase I study of amrubicin and topotecan in patients who were either chemotherapy naïve or relapsed with extensive-stage SCLC was conducted.21 Topotecan was administered on days 1 to 5, and amrubicin was administered on days 3 to 5. Cycles were to be repeated every 4 weeks. Nine patients (four chemoanaive, five relapsed [three patients with sensitive disease, two patients with refractory disease]) were treated. The dose-limiting toxicity was neutropenia, febrile neutropenia, and thrombocytopenia. The maximum tolerated dose for topotecan was 0.75 mg/m² and 40 mg/m² for amrubicin. Six patients (67%) had a partial response to the therapy (four of five [80%] relapsed patients and two of four [50%] chemoanaive patients). The median time to progression was 4 months.

**AMRUBICIN AS SECOND-LINE THERAPY**

In a phase II study conducted in previously treated patients with SCLC, amrubicin 40 mg/m²/day intravenously was administered for three consecutive days every 3 weeks.22 Twenty-six patients (nine sensitive-disease, 17 refractory-disease patients), 22 men, four women; median age, 62.5 years (range, 43–78) received a median number of three cycles of therapy. The response rate was 46.2% (55.6% sensitive disease, 41.2% refractory disease). The median survival time was 9.4 months (11.0 months for sensitive disease, 5.7 months for refractory disease). Grade 4 leukopenia and neutropenia occurred in 42.3% and 73.1% of patients, respectively. Grade 3 or 4 thrombocytopenia occurred in 50% of patients.

The Japanese Thoracic Oncology Research Group conducted a phase II study of amrubicin for the treatment of previously treated SCLC.23 It is the largest study evaluating this drug in this patient population. Patients were eligible for the study if they had measurable disease and an Eastern Cooperative Oncology Group PS of 0–2, were previously treated with at least one platinum-based chemotherapy regimen, and either had refractory disease (failed first-line treatment <60 days from discontinuing treatment) or sensitive disease (progressed ≥60 days after discontinuing treatment).

Amrubicin 40 mg/m²/day was administered as a 5-minute intravenous injection for three consecutive days every 3 weeks.23 Sixty patients (16 with refractory disease and 44 with sensitive disease) were entered in the study. The median number of cycles given was four (range, one to eight). The overall response rates were 52% (1.9% complete response) in the sensitive-disease group and 50% (2% complete response) in the refractory-disease group of patients. The overall and 1-year survival rate in the sensitive-disease group were 11.6 months and 45.5%, respectively, whereas in the refractory-disease group, they were 10.3 months and 40.3%, respectively. The major toxicity was hematologic. Grade 3/4 toxicities occurred as follows: neutropenia, 83.3%; leukopenia, 70.0%; anemia, 33.3%; thrombocytopenia, 20%; an-
orexia, 15%; and asthenia, 15%. Nonhematologic toxicity was relatively mild. No cardiac toxicity was observed.

**DISCUSSION**

The only drug approved for second-line treatment of SCLC in the United States is topotecan (Hycamtin). The U.S. Food and Drug Administration approved it on November 30, 1998. In part, their decision was based on the results of a phase III multicenter study of SCLC patients who relapsed >60 days after completion of first-line chemotherapy and then were randomized to receive either topotecan or cyclophosphamide, doxorubicin, and vincristine (CAV). The patient population was considered as having SCLC sensitive disease. The response rate to topotecan-treated patients was 24.3% compared with 18.3% for the patients receiving CAV \( (p = 0.285) \). The median survival was 25.0 weeks for the topotecan-treated patients and 24.7 weeks for the CAV-treated patients \( (p = 0.795) \). There was greater symptom improvement (shortness of breath, anorexia, hoarseness, and fatigue) and less toxicity associated with topotecan treatment compared with CAV treatment.

In an earlier phase II study, SCLC patients were stratified as having refractory or sensitive disease and given topotecan as second-line therapy. In the study, patients with refractory disease were defined as patients who relapsed <90 days after first-line chemotherapy for the treatment of SCLC. Patients with sensitive disease was defined as SCLC patients who relapsed >90 days after completion of initial chemotherapy. In sensitive-disease SCLC patients, the response rate was 37.8%, whereas in refractory-disease patients, it was 6.4%. The median survival for all patients was 5.4 months, and for sensitive-disease patients, it was 6.9 months.

Although studies have shown that topotecan is effective as a second-line treatment of SCLC patients, especially those who have chemosensitive disease, it has not had a significant impact on the survival of such patients. New therapies are needed to inhibit distant metastasis and thereby improve survival rates of SCLC patients.

Is amrubicin one of these new therapies? In Japan, as a single agent and in combination with other agents, it appears to be effective in treating extensive-stage SCLC patients especially as second-line therapy. However, thus far, the studies reported of its effectiveness are small and there has been no phase III study to evaluate its effectiveness compared with standard treatments.

In addition, can its effectiveness in treating Japanese patients with extensive-stage SCLC be reproduced in Western patients with the disease? If not, will this be another situation of possible geographic and/or ethnic variation in the effectiveness of the same treatment given to patients with geographic and ethnic differences.

The most striking example of the above has been seen in both the activity and toxicity of the tyrosine kinase inhibitor gefitinib in the treatment of NSCLC patients in Japan and the United States. Japanese patients had a higher response rate (28%) and longer median survival (12 months) compared with U.S. patients who had a response rate of 10% and median survival of 6 to 7 months receiving gefitinib. In addition, 2% of Japanese patients developed interstitial lung disease associated with gefitinib administration, whereas no U.S. patients developed the toxicity.

Does geographic and/or ethnic variation apply to the effectiveness of irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive-stage SCLC? In a Japanese phase III study, the median survival 12.8 months for SCLC patients treated with irinotecan/cisplatin compared with 9.4 months \( (p = 0.002) \) for the patients treated with etoposide/cisplatin. The survival rate at 2 years was 19.5% for the patients treated with irinotecan/cisplatin and 5.2% for the patients treated with etoposide/cisplatin.

In a U.S. phase III study comparing irinotecan/cisplatin with etoposide/cisplatin in SCLC patients, there was no improvement in survival in the patients receiving irinotecan/cisplatin. The median survival was 9.3 months versus 10.2 months \( (p = 0.74) \). In this study, the patients appeared to have more advanced disease compared with the patients in the Japanese study. In addition, a different dose and schedule of irinotecan/cisplatin was used in the U.S. study.

There is an ongoing Southwest Oncology Group study comparing irinotecan/cisplatin with etoposide/cisplatin using the same dose and schedule as in the Japanese study to treat patients with extensive-stage SCLC.

Why are there these differences between the Japanese patients and U.S. patients? Is it geographic variations in treatment? In the former study, this may be operative because of health care economics, the influence of regulatory agencies, and physician biases. In addition, in both the former and latter studies, another explanation could be biologic differences between Japanese and U.S. patients in regard to pharmacogenomic aspects of drug metabolism or differences in tumor susceptibility affecting efficacy and toxicity.

What genetic variations might explain the effectiveness of amrubicin in Japanese patients with SCLC? It is known that polymorphisms of NQ01 subunits affect doxorubicin efflux transporters, thereby increasing the risk of anthracycline-induced cardiotoxicity. In addition, NQ01 detoxifies quinones derived from the oxidation of phenolic metabolites of benzene. Individuals homozygous for the 609C-T polymorphisms (T/T genotype) have an increased risk of benzene poisoning. In cells with the T/T genotype, NQ01 was not detected. The prevalence of the T/T genotype was highest in the Asian populations. NAD(P)H-quinone oxidoreductase is an enzyme that participates in the metabolism of amrubicin and amrubinol. Will polymorphisms of NAD(P)H oxidase possibly explain the effectiveness of amrubicin in treating Japanese patients?

Because amrubicin appears to be the most effective single agent to treat SCLC, at least in Japan, and has not yet been tested outside Japan, it is necessary to confirm its effectiveness in U.S. patients with SCLC. Recently, a randomized phase II trial comparing amrubicin with topotecan as second-line treatment in patients with extensive-stage SCLC sensitive to first-line chemotherapy has been initiated sponsored by Cabrellis Pharmaceuticals Corporation, San Diego, CA. A phase II single-arm study will evaluate the effectiveness of the drug in patients refractory to first-line
chemotherapy and a randomized phase II study of amrubicin versus cisplatin and etoposide will evaluate the activity of amrubicin in European patients in first-line SCLC.

REFERENCES


