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 Untied 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 (NQ01) 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 NQ01 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]

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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 amrubicinol, 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 amrubicinol 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 amrubicinol. 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 IIα cleavable complexes). Amrubicin demonstrates decreased DNA intercalation compared with doxorubicin. The decreased DNA interaction appears to influence the intracellular distribution because amrubicin and amrubicinol 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 amrubicin and amrubicinol appear to be primarily related to inhibition of topoisomerase II.[14] Compared with doxorubicin, amrubicin, and amrubicinol display stronger topoisomerase II–dependent cleavage most probably due to the increased stability of the complex formed by the drug, DNA, and the enzyme.

The primary metabolite (amrubicinol) in rats and dogs is a product of reduction by cytoplasmic carbonyl reductase at

TABLE 1. Drugs for Previously Untreated Patients with Extensive-Stage Small Cell Lung Cancer

Agent	Patients (assessable)	Response Rate (%)	Median Survival (mo)
Paclitaxel[4]	36 (32)	34	9.9
Paclitaxel[5]	43 (37)	41 (68%)[a]	6.6
Docetaxel[6]	47 (43)	23	9
Topotecan[7]	48 (48)	39	9
Irinotecan[8]	16 (15)	47	6.8
Irinotecan[9]	8 (8)	50	NR
Vinorelbine[10]	30 (27)	27	NR
Gemcitabine[11]	29 (26)	27	12

[a] Ten additional regressions of assessable disease for an overall major response rate of 68%.

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.

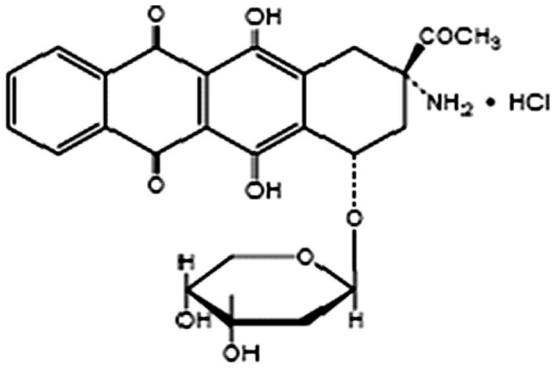
Clinical manifestations of toxicity observed on acute and repeated administration of amrubicin in rats and dogs were dose related and reversible including fecal changes (mucoid or bloody feces/diarrhea), body weight decreases, decreased food consumption, decreased activity, and alopecia. Similar findings 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.[15,16] 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/m^2 in a single-dose schedule,[17] 25 mg/m^2/day (125 mg/m^2 in total) in daily doses for 5 days, and 50 mg/m^2/day (150 mg/m^2 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



Chemical name: (7S,9S)-9-acetyl-9-amino-7-[(2-deoxy-β-D-erythro-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione hydrochloride

Molecular Weight: 519.93

FIGURE 1. Structure of amrubicin. Chemical name: (7S,9S)-9-acetyl-9-amino-7-[(2-deoxy-β-D-erythro-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione hydrochloride. Molecular weight: 519.93.