Risk Factors for Predicting Severe Neutropenia Induced by Amrubicin in Patients with Advanced Lung Cancer

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Key Words

Lung cancer · Amrubicin · Neutropenia · Risk factors for complications · Dose · Hematocrit

Abstract

Background: Neutropenia is one of the most frequent and dose-limiting toxicities in amrubicin (AMR) therapy. However, the predictive factors for the development of severe neutropenia in AMR therapy remain unknown. **Methods:** The subjects were 61 advanced lung cancer patients treated with AMR monotherapy. All data were retrospectively collected from the electronic medical record system. A stepwise logistic regression analysis was performed to identify risk factors for grade 3–4 neutropenia. **Results:** Of a total 61 patients, 50 were male and 11 were female. The median dose of AMR was 35.0 mg/m². The incidence of grade 3–4 neutropenia during the first course was 62%. In multivariate analysis, female gender (OR = 6.68; 95% CI 1.01–134.15; *p* = 0.049), higher AMR doses (40 mg/m² or more) (OR = 5.98; 95% CI 1.77–23.74; *p* = 0.003), and lower hematocrit values (OR = 2.04 per 5% decrease; 95% CI 1.04–4.38; *p* = 0.036) were significantly associ-

ated with severe neutropenia induced by AMR. **Conclusion:** The present results suggest that female gender, higher doses of AMR, and lower baseline hematocrit values are predictive factors associated with severe neutropenia induced by AMR in patients with advanced lung cancer. Patients who have these predictive factors should be monitored carefully and considered for early granulocyte colony-stimulating factor support.

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Introduction

Amrubicin (AMR), an anthracycline, has been widely used in the treatment of small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) in Japan. AMR is mainly metabolized to amrubicinol (AMR-OH) by carbonyl reductase, and both compounds have an inhibitory effect on DNA topoisomerase II [1]. The in vitro cytotoxic activity of AMR-OH is approximately 10–100 times more potent than that of AMR [2]. AMR and AMR-OH are inactivated mainly by NAD(P)H (quinone oxide re-

ductase and NADPH P-450 reductase) [3]. Then, metabolites are excreted thorough bile. In AMR monotherapy, AMR is administered at a dose of 35–45 mg/m²/day on 3 consecutive days every 3–4 weeks. In phase II trials of second- or third-line AMR monotherapy for the treatment of SCLC, the response rates and the overall survival were 21–53% and 6–12 months, respectively [4–11]. In the treatment of NSCLC, the response rates of AMR monotherapy were 12–28% [11–14].

Neutropenia is one of the most frequent and serious toxicities in cancer chemotherapy for patients with lung cancer [15, 16]. Especially, neutropenia is a dose-limiting toxicity in AMR monotherapy. In contrast, nonhematologic toxicities are generally mild. In phase II studies, the incidences of grade 3–4 neutropenia and febrile neutropenia were 39–97 and 5–41%, respectively. Severe neutropenia often induces intolerable and fatal infection. In fact, it has been reported that some patients treated with AMR died from serious neutropenic infection in phase II studies [6, 8]. In addition, neutropenic complications need antimicrobial treatment [17] and result in high health care costs [18]. Therefore, it is important to clarify the risk factors for severe neutropenia.

It has been reported that the pharmacokinetic parameters of AMR or AMR-OH are significantly associated with severe neutropenia [19–21]. However, the predictive factors for severe neutropenia in AMR therapy are unknown. Since AMR-OH is highly distributed in blood cells [22–24], blood cell counts or hematocrit values may influence the plasma concentration of AMR-OH [25]. Therefore, we investigated the predictive factors, including baseline blood cell counts and hematocrit values, for severe neutropenia in AMR monotherapy in patients with advanced lung cancer.

Patients and Methods

Patients

This retrospective study was conducted in accordance with the Declaration of Helsinki and its amendments, and the protocol was approved by the Ethics Committee of Kyushu University Graduate School and Faculty of Medicine (approval No. 23-122 of the institutional review board). The subjects were 61 patients who received AMR monotherapy for lung cancer at the Department of Respiratory Medicine, Kyushu University Hospital, from February 2003 to June 2011. Patients who received prophylactic treatment with granulocyte colony-stimulating factor (G-CSF) were excluded. One patient with a G-CSF-producing large cell carcinoma was also excluded because the neutrophil count was extremely high before AMR treatment.

Treatment and Data Collection

AMR was dissolved in normal saline and administered intravenously in a 5-min infusion on days 1–3 every 3–4 weeks. For second- or later-line treatment of SCLC or NSCLC with AMR, the administered dose of AMR was generally 35–40 mg/m², with dose reduction based on the judgment of the attending physician. The physical examinations and laboratory tests, including blood chemistry and complete blood cell counts, were performed before treatment and at least once a week during the first course. The use of G-CSF was permitted as a therapeutic intervention for neutropenia but not for prophylaxis. Other medications for underlying diseases, complications, and pain control were allowed. To investigate the association with severe neutropenia in the first course, febrile neutropenia, infections, G-CSF treatment, AMR dose reduction due to severe neutropenia or blood transfusions were also monitored in all courses. The percentage decrease in the neutrophil count was calculated as follows:

$$\% \text{ decrease in neutrophil count} = 100 \times \frac{\text{baseline neutrophil count} - \text{nadir neutrophil count}}{\text{baseline neutrophil count}}.$$

All data were retrospectively collected from an electronic medical record system. Neutropenia in the first course was graded according to the Common Terminology Criteria for Adverse Events version 4.0.

Statistical Analyses

The variables included for statistical analysis were as follows: age, gender, type of disease (SCLC or NSCLC), body surface area (BSA), body mass index (BMI), ECOG performance status (PS), number of prior chemotherapy regimens (1 or 2–4), doses of AMR, total protein, albumin, serum creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), white blood cell (WBC) count, neutrophil count, red blood cell (RBC) count, hemoglobin, hematocrit, and platelet count.

The data on patient characteristics were analyzed using the χ^2 test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables, respectively. Factors of $p < 0.25$ in univariate analyses were evaluated as potential covariates in a stepwise multivariate logistic regression with forward selection. The correlation between baseline hematocrit values and the percentage decrease in the neutrophil count was investigated using Pearson's correlation coefficient test. Data were analyzed using JMP 9.0.0.2 (SAS Institute Inc., Cary, N.C., USA), and $p < 0.05$ was considered statistically significant.

Results

Patient Characteristics

Data for 61 lung cancer patients who underwent AMR monotherapy from February 2003 to June 2011 were analyzed. Patient baseline characteristics and biochemical parameters are summarized in tables 1 and 2, respective-

ly. Fifty patients had SCLC, and 11 patients had NSCLC. Fifty patients were men, and 11 were women. Fifty-one patients had good PS (0 or 1), and 21 patients had previously received more than one regimen. The median dose of AMR was 35.0 mg/m². The median BSA (1.46 vs. 1.64, $p = 0.001$), the baseline hemoglobin levels (9.8 vs. 11.4, $p = 0.009$), and the hematocrit values (31.1 vs. 34.6%, $p = 0.033$) in females were significantly lower than those in males. The baseline mean corpuscular volume values were within 80.7 and 107.5 fl. There were 52 patients with normocytic anemia and 9 patients with macrocytic anemia.

AMR-Induced Neutropenia

The incidences of all grades and grade 3–4 neutropenia during the first course were 82% (50/61) and 62% (38/61), respectively. The incidences of blood transfusions in all courses were significantly higher in patients with grade 3–4 neutropenia in the first course (table 3). Among the patients in this study, 41 out of 61 patients were administered G-CSF (median 6 days; range 2–11 days). The median starting day of G-CSF treatment was day 12 (range, days 4–22). The number of patients who required G-CSF treatment or AMR dose reduction in the subsequent course due to myelosuppression was also significantly higher in patients with grade 3–4 neutropenia. G-CSF was administered in 17 of 38 patients after neutrophil counts decreased to less than 1,000/mm³. The incidence of severe neutropenia in the first course was significantly higher in the female gender (91 vs. 56%, $p = 0.040$) and in patients administered higher doses of AMR (79 vs. 47%, $p = 0.016$; table 4). The baseline hematocrit values were significantly lower in patients with grade 3–4 neutropenia (median 32.8 vs. 35.8%, $p = 0.021$; table 4). A statistically significant ($p = 0.048$) weak negative correlation ($r = -0.254$) was observed between the baseline hematocrit values and percentage decrease in neutrophil count.

Multivariate Analysis

To investigate the variables associated with grade 3–4 neutropenia, we carried out a stepwise logistic regression with forward selection. As hemoglobin was strongly correlated with hematocrit ($r = 0.96$), only the hematocrit value was selected for multivariate analysis. As a result, the significant predictors of grade 3–4 neutropenia were female gender (OR = 6.68; 95% CI 1.01–134.15; $p = 0.049$; table 5), higher AMR dose (OR = 5.98; 95% CI 1.77–23.74; $p = 0.003$), and lower hematocrit values (OR = 2.04 per 5% decrease; 95% CI 1.04–4.38, $p = 0.036$).

Table 1. Baseline patient characteristics

Characteristics	
Age, years	67 (38–87)
Gender	
Male	50 (82)
Female	11 (18)
Type of disease	
SCLC	50 (82)
NSCLC	11 (18)
BSA, m ²	1.58 (1.25–2.24)
BMI	21.3 (15.4–30.4)
ECOG PS	
0–1	51 (84)
2–3	10 (16)
Prior chemotherapy	
1	40 (66)
2–4	21 (34)
AMR dose	
30 mg/m ²	4 (7)
35 mg/m ²	28 (46)
40 mg/m ²	27 (44)
45 mg/m ²	2 (3)

Values are presented as medians (range) or n (%).

Table 2. Baseline patient biochemical parameters

Characteristics	
Total bilirubin, mg/dl	0.5 (0.2–1.8)
AST, IU/l	21 (12–130)
ALT, IU/l	16 (4–114)
WBC count, $\times 10^3/\text{mm}^3$	5.39 (2.17–13.11)
Neutrophil count, $\times 10^3/\text{mm}^3$	3.50 (0.97–7.28)
RBC count, $\times 10^6/\text{mm}^3$	3.71 (2.44–5.12)
Hemoglobin, g/dl	11.1 (7.1–16.2)
Hematocrit, %	33.8 (22.4–43.6)
MCV, fl	93.7 (80.7–107.5)
PLT count, $\times 10^4/\text{mm}^3$	23.0 (11.3–71.4)

Values are presented as medians (range).
MCV = Mean corpuscular volume; PLT = platelet.

Impact of AMR Dosage and Hematocrit or Hemoglobin on the Incidence of Severe Neutropenia

Figure 1a shows the influence of baseline hematocrit values and the dose of AMR on the incidence of severe neutropenia. In figure 1, the threshold value was 34%, which was the median value among patients in this study. In patients with higher hematocrit values, the incidences

Table 3. Relationship between grade 3–4 neutropenia in the first course and neutropenic events in all courses

Outcomes	Grade 2 or less (n = 23)	Grade 3–4 (n = 38)	p value
G-CSF treatment	8 (34.8)	34 (89.5)	<0.001
Febrile neutropenia	3 (13.0)	10 (26.3)	0.184
Infection without neutropenia	5 (21.7)	5 (13.2)	0.890
AMR dose reduction	0	12 (31.6)	0.002
Blood transfusions	0	6 (15.8)	0.049

Values are presented as numbers (%).

Table 4. Univariate analysis for grade 3–4 neutropenia

Characteristics	Grade 2 or less (n = 23)	Grade 3–4 (n = 38)	p value
Age, years	70 (48–77)	66 (38–87)	0.602
Gender			
Male	22	28	0.040
Female	1	10	
Type of disease			
SCLC	17	33	0.303
NSCLC	6	5	
ECOG PS			
0–1	21	30	0.294
2–3	2	8	
Prior chemotherapy			
1	17	23	0.406
2–4	6	15	
AMR dose			
30–35 mg/m ²	17	15	0.016
40–45 mg/m ²	6	23	
Total bilirubin, mg/dl	0.5 (0.3–1.8)	0.5 (0.2–1.1)	0.775
AST, IU/l	21 (12–97)	22 (12–130)	0.541
ALT, IU/l	14 (7–114)	17 (4–69)	0.794
WBC count, × 10 ³ /mm ³	5.26 (3.55–13.11)	5.42 (2.17–11.69)	0.572
Neutrophil count × 10 ³ /mm ³	3.43 (1.68–6.09)	3.69 (0.97–7.28)	0.841
RBC count, × 10 ⁶ /mm ³	3.83 (2.81–5.12)	3.64 (2.44–4.53)	0.113
Hemoglobin, g/dl	11.4 (8.9–16.2)	10.9 (7.1–14.0)	0.058
Hematocrit, %	35.8 (28.7–43.6)	32.8 (22.4–42.5)	0.021
PLT count, × 10 ⁴ /mm ³	25.1 (11.7–71.4)	21.7 (11.3–43.1)	0.261

Values are presented as medians (range) or numbers.
PLT = Platelet.

of grade 3–4 neutropenia were 26.7 and 66.7% in patients treated with ≤ 35 and ≥ 40 mg/m² of AMR, respectively. In the lower hematocrit value groups, however, the incidences were 64.7 and 92.9% in patients administered lower and higher doses of AMR. Similarly, in patients with

Table 5. Multivariate analysis for grade 3–4 neutropenia

Variable	OR	95% CI	p value
Female gender	6.68	1.01–134.15	0.049
Higher AMR dose (≥ 40 mg/m ²)	5.98	1.77–23.74	0.003
Lower hematocrit values	2.04 per 5% decrease	1.04–4.38	0.036

lower hemoglobin values, the incidences of grade 3–4 neutropenia were 56.3 and 91.7% in patients treated with ≤ 35 and ≥ 40 mg/m² of AMR, respectively (fig. 1b). These incidences were higher than those in patients with higher hemoglobin values.

Discussion

The early onset of severe neutropenia requires dose reduction or a delay in treatment, leading to chemotherapy discontinuation [26, 27]. Additionally, the current AMR therapy for advanced lung cancer is mainly aimed at disease palliation, and thus avoidance of life-threatening ADEs is necessary. In fact, the incidences of febrile neutropenia, AMR dose reduction, and blood transfusion were higher in patients who experienced grade 3–4 neutropenia in the first course (table 3). Therefore, identifying risk factors predicting severe neutropenia induced by AMR is important. Since high incidences of febrile neutropenia induced by AMR therapy have been reported, the physicians paid much attention to the decrease in neutrophil counts and started G-CSF administration in 17 of 38 patients after neutrophil counts decreased less than 1,000/mm³. It appears that the relationship between lower baseline hematocrit values and the incidence of grade 4 neutropenia was masked by this early G-CSF support. Therefore, we decided to investigate the predictive factors associated with grade 3–4 (<1,000 and ≥ 500 /mm³) rather than grade 4 (<500/mm³) neutropenia in the present study. In this study, the incidence of grade 3–4 neutropenia was 62% (38/61), which was a little lower than that in previous phase II studies (median 78%; range 39–97%) [4–14]. Multivariate logistic analysis revealed that higher doses of AMR, female gender, and lower baseline hematocrit values were significant predictors of grade 3–4 neutropenia in patients with lung cancer treated with AMR monotherapy. This dose-dependent increase in the incidence of severe neutropenia is consistent with previous clinical

Fig. 1. Combination effects of baseline hematocrit (a) or hemoglobin (b) values and AMR dose on the incidence of grade 3–4 neutropenia. * $p < 0.05$, ** $p < 0.01$ compared with patients administered lower doses of AMR and with higher hematocrit or hemoglobin values. The threshold values were the median of baseline hematocrit and hemoglobin among patients in this study.

studies [28–30]. However, female gender and lower baseline hematocrit values as predictors of severe neutropenia are new findings.

Although only 2 papers have reported the incidence of neutropenia between genders, Makino et al. [31] reported that AMR-induced grade 4 neutropenia was observed in 4 of 4 (100%) women and 9 of 17 (53%) men, respectively. In another study of 5 patients (1 woman and 4 men) with neuroendocrine carcinoma of the gastrointestinal tract treated with AMR monotherapy, the incidences of grade 4 neutropenia in females and males were 100 and 25%, respectively [32]. The results of this study support these differences in the incidences of grade 4 neutropenia between males and females. The lower baseline hematocrit value in females may lead to higher incidences of severe neutropenia.

In patients with lower (<34%) hematocrit values, the incidences of grade 3–4 neutropenia were 65 and 93% in patients treated with ≤35 and ≥40 mg/m² of AMR, respectively (fig. 1a). In the higher hematocrit value groups, however, the incidences were 27 and 67% in patients administered lower and higher doses of AMR, respectively (fig. 1a). Similarly, in patients with 11 g/dl or lower hemoglobin values, the incidences of severe neutropenia were 56 and 92% in patients treated with lower and higher doses of AMR, respectively (fig. 1b). Although the hemoglobin values were not shown in this study, they might also be a useful index for clinicians. These results suggest that

clinicians should monitor not only the absolute blood cell counts but also the hematocrit values of patients before AMR therapy. In addition, patients who have risk factors should be monitored carefully and considered for early G-CSF support.

The cytotoxic activity of AMR-OH is higher than that of AMR [2]. In mouse experiments, Noguchi et al. [22] reported that AMR-OH was highly distributed from plasma into blood cells and its concentration in blood cells was higher than that in plasma. In patients with lung cancer, the AUC of AMR-OH in blood cells was 6.6 ± 6.7 times (mean $\pm$ SD) higher than that in plasma [23, 24]. Matsunaga et al. [20] reported a significant relationship between the grade of leukopenia and the AUC of AMR-OH in plasma in patients with lung cancer. Kimura et al. [21] also revealed a significant relationship between the plasma concentration of AMR-OH and the toxicity grades of neutropenia. However, Makino et al. [31] reported that there was no significant relationship between baseline factors or pharmacokinetic parameters and severe neutropenia in a multivariate analysis. The reasons for these results were that the sample size was too small or that the hematocrit value may not have been included as a predictive factor in their study. Among drugs which are highly distributed in erythrocytes, the hematocrit value influences the plasma concentration of the drugs [25]. Therefore, we speculate that the lower blood cell volume leads to a decrease in the distribution volume of

AMR-OH in patients with lower baseline hematocrit values. In these patients, the plasma concentration of AMR-OH may be increased, which seems to be related to the higher incidence of severe neutropenia.

This study was not a prospective design, and it did not detect blood concentrations of AMR or AMR-OH. The results of the present study should be confirmed in a large-sized prospective study that analyzes the AMR-OH pharmacokinetic parameters not only in plasma but also in blood cells.

In conclusion, the present report indicates for the first time that lower baseline hematocrit values and female gender, as well as higher doses of AMR, are significantly associated with severe neutropenia induced by AMR in patients with advanced lung cancer. Patients who have these risk factors should be monitored carefully and considered for early G-CSF support.

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