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Amrubicin at a lower-dose with routine prophylactic use of granulocyte-colony stimulating factor for relapsed small-cell lung cancer

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ABSTRACT

Background: Recent reports have suggested the efficacy of amrubicin (AMR) for relapsed small-cell lung cancer (SCLC). However, doses of AMR in these reports were 40 mg/m^2 or 45 mg/m^2, and severe and frequent myelosuppression were observed. Such side effects are occasionally intolerable, as serious myelosuppression may induce fatal infections. To overcome this clinical problem, we investigated whether 35 mg/m^2 of AMR administration with routine prophylactic use of granulocyte-colony stimulating factor (G-CSF) can reduce myelosuppression, while maintaining efficacy.

Methods: Between July 2003 and November 2008, 30 relapsed SCLC patients receiving 35 mg/m^2/day of AMR were evaluated. Amrubicin was administered on days 1–3 every 3 or 4 weeks. Routine prophylactic use of G-CSF was performed beginning on day 8 and continuing for at least 5 consecutive days or until neutrophils recovered to the normal level.

Results: The median number of treatment cycles was four (range 1–9). No complete responses and 13 partial responses were observed, with response rates of: overall 43% (95% confidence interval [CI]: 26–63%); sensitive cases 33% (95% CI: 10–65%); and refractory cases 50% (95% CI: 26–74%) ($p = 0.4651$). The disease control rate (partial response and stable disease) was 80% (95% CI: 61–92%). The progression-free survival times were: overall 4.2 months (95% CI: 3.2–5.2 months); sensitive cases 4.7 months (95% CI: 2.6–5.4 months); and refractory cases 3.5 months (95% CI: 2.6–5.2 months) ($p = 0.7124$). The median OS times were: overall 9.6 months (95% CI: 7.2–12.5 months); sensitive cases 8.4 months (95% CI: 4.6–13.4 months); and refractory cases 11.0 months (95% CI: 6.5–12.6 months) ($p = 0.9315$). The 1-year survival rate was 33%. Regarding grade 3/4 hematological toxicities: leukopenia (47%); neutropenia (50%); anemia (30%); and thrombocytopenia (33%) were observed. Febrile neutropenia occurred in three patients (10%). Transfusions of red blood cells and platelets were performed for eight (27%) and one (3%) patients, respectively. Treatment-related deaths and grade 3/4 non-hematological toxicities were not observed at all.

Conclusions: Considering both safety and efficacy, AMR at a dose of 35 mg/m^2 with routine prophylactic use of G-CSF may be more desirable for the treatment of relapsed SCLC in clinical practice.

1. Introduction

Lung cancer is the leading cause of death from malignant diseases in many countries. Small-cell lung cancer (SCLC) is a lung cancer subtype strongly associated with smoking and accounts for approximately 15% of all lung cancer cases [1]. SCLC is the most aggressive subtype of lung cancers, and most cases already have distant metastases when diagnosis is confirmed [2]. Thus, systemic chemotherapy is indicated for most cases of SCLC, and cisplatin plus etoposide is established as the first-line of effective chemotherapy.

Despite the high initial response to first-line chemotherapy, the majority of SCLC patients experience disease relapse and treatment resistance with a high risk of brain metastases, even in limited disease (LD) patients [3]. Second-line chemotherapy is therefore important to salvage such patients, and some agents have been developed for relapsed SCLC patients. [4–11]. Of these agents, topotecan (TPT) has been recommended by clinical practice guidelines [12] and is considered the standard regimen of second-line chemotherapy for relapsed SCLC in western countries. However, the efficacy of TPT seems insufficient in refractory relapsed patients.

Recent reports suggest that amrubicin (AMR) has efficacy comparable to TPT for relapsed SCLC, with a similar or better response rate (RR), progression-free survival (PFS), and overall survival (OS) [13–17]. Moreover, the efficacy of AMR has been suggested as

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superior to that of TPT for refractory relapsed patients. However, AMR was administered in these reports at doses of 40 mg/m^2 or 45 mg/m^2, which caused severe and frequent myelosuppression. Such side effects are occasionally intolerable, as serious myelosuppression may induce fatal opportunistic infections. To overcome this clinical problem, we reduced AMR dosage to 35 mg/m^2.

Febrile neutropenia is also a frequently observed side effect of AMR treatment for SCLC. According to American Society of Clinical Oncology (ASCO) guidelines, prophylactic use of granulocyte-colony stimulating factor (G-CSF) is indicated if febrile neutropenia is likely to occur in more than 20% of cases [18]. Considering the incidence of febrile neutropenia, severe and frequent myelosuppression, and fatal adverse events, treatment with AMR is similar to other chemotherapy regimens, which exhibit more than a 20% incidence of febrile neutropenia. We therefore regarded AMR therapy for relapsed SCLC to indicate prophylactic use of G-CSF. To reduce febrile neutropenia, we adopted routine prophylactic use of G-CSF with AMR at 35 mg/m^2 in our clinical practice.

The aim of this study is to investigate whether the combination of lower-dose AMR and prophylactic use of G-CSF can reduce myelosuppression while maintaining efficacy in the treatment of relapsed SCLC patients.

2. Patients and methods

2.1. Patient enrollment

Between July 2003 and November 2008, 30 relapsed SCLC patients receiving 35 mg/m^2 of AMR as second, third, and fourth-line treatment in our institution were retrospectively evaluated. Written informed consents were obtained from all patients.

2.2. Treatment methods

Amrubicin was administered intravenously at a dose of 35 mg/m^2/day on days 1–3 every 3 or 4 weeks and was injected to patients after dissolving in 20 ml of normal saline. We performed routine prophylactic use of G-CSF beginning on day 8 and continuing for at least 5 consecutive days or until neutrophils recovered to the normal level. In the absence of evidence of disease progression, we continued administration of up to four cycles of AMR. Continuation of therapy beyond four cycles was at the discretion of the physicians in charge. If side effects including myelosuppression were severe, the dose of AMR was reduced from 35 mg/m^2 to 30 mg/m^2.

2.3. Evaluation of efficacy and toxicity

Baseline evaluations including medical history, physical examinations, and laboratory tests were performed. Evaluation of treatment response by computed tomography scan was repeated every 4–8 weeks. Patient response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. In our study, refractory relapse was defined as disease progression during chemotherapy, or relapse less than 90 days after the initial chemotherapy. Sensitive relapse was defined as relapse more than 90 days after the previous chemotherapy. Before AMR administration, and during disease progression or relapse, patients were assessed with a complete medical history, physical examination, chest radiography, computed tomography of the chest and abdomen, magnetic resonance imaging of the head, a bone scintiscan, and/or positron emission tomography. Adverse events were graded according to the National Cancer Institute, Common Terminology Criteria for Adverse Events, Version 3.0.

2.4. Statistical analysis

Overall survival was measured from the start of AMR treatment to the date of death. Progression-free survival was measured from the start of AMR treatment to the date of documented disease progression or death. Median OS, 1-year survival rate, and PFS were calculated using the Kaplan–Meier method. Progression-free survival times between sensitive and refractory relapse patients were compared using the log-rank test. Response rates among demographic factor groups were compared using Fisher's exact test or Spearman's rank correlation. *P*-values of less than 0.05 were considered statistically significant. Statistical analysis was performed using JMP 7 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Between July 2003 and November 2008, 30 relapsed SCLC patients received AMR monotherapy at 35 mg/m^2 as salvage chemotherapy in our institutions. Table 1 exhibits patient characteristics. The median patient age was 65 (range 47–75). Most patients were male (20 of 30, 67%). The most prominent performance status (PS) was 1 (19 of 30, 64%). PS 0 and 2 were 7 (23%) and 4 (13%), respectively. Amrubicin was administered as second, third, and fourth-line chemotherapy, and 20 patients (67%) received AMR as second-line treatment. Twenty sensitive relapse (40%) and 18 refractory relapse patients (60%) were included in our study.

3.2. Previous regimens of chemotherapy

In first-line treatments, cisplatin plus etoposide with concurrent irradiation was the most frequent regimen (12 of 30, 40%). Other treatments included cisplatin plus irinotecan (9 of 30, 30%), cisplatin plus etoposide (n = 4), carboplatin plus etoposide (n = 3), and carboplatin plus irinotecan (n = 2). For second-line treatments, carboplatin plus irinotecan was chosen more frequently than any other regimen (5 of 10, 50%). Other second-line treatments were carboplatin plus etoposide (n = 3), cisplatin plus irinotecan (n = 1), paclitaxel plus gemcitabine (n = 1), and cis-

Table 1
Patient characteristics.

Characteristics	No. of patients
Age (years)	
Median	65
Range	47–75
Gender	
Male	20 (67%)
Female	10 (33%)
Performance status	
0	7 (23%)
1	19 (64%)
2	4 (13%)
Initial stage	
Limited disease	13 (43%)
Extended disease	17 (57%)
Administration of amrubicin	
2nd-line	20 (66%)
3rd-line	8 (27%)
4th-line	2 (7%)
Irradiation[a]	
+	17 (57%)
–	13 (43%)
Types of relapse	
Sensitive relapse	12 (40%)
Refractory relapse	18 (60%)

[a] Of the chest, the axial skeleton, or proximal long bones.