Table

Adverse events of in Grade 3 or 4 patients treated with amrubicin

Adverse event	Grade 3		Grade 4		Grade 3 + 4	
	n	%	n	%	n	%
Leukopenia	53	55.8	24	25.3	77	81.1
Anemia	25	26.3	4	4.2	29	30.5
Febrile neutropenia	28	29.5	2	2.1	30	31.6
Neutropenia	21	22.1	64	67.4	85	89.5
Thrombocytopenia	15	15.8	7	7.4	22	23.2
Hyperglycemia	14	14.7	1	1.1	12	12.6
Hyponatremia	11	11.6	5	5.3	16	16.8
Infection	7	7.4	1	1.1	8	8.4
Elevated alanine transaminase level	4	4.2	2	2.1	6	6.3
Elevated aspartate aminotransferase level	4	4.2	0	0	4	4.2

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Clinical Trial

Amrubicin therapy improves patients with refractory small-cell lung cancer: A single-arm confirmatory Chinese clinical study

Mengli Zheng, Naikang Zhou, Lianjun Ma and Wenbo Jin

Department of General Thoracic Surgery, The 309th Hospital of Chinese PLA, Beijing 100-091, China.

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Abstract

Our objective was to evaluate an open-label, multicenter, single-arm study to appraise whether amrubicin therapy improves patients with refractory small-cell lung cancer in Chinese clinical study. Patients (n=95) with refractory small-cell lung cancer received 3 consecutive days amrubicin therapy for 21 days. Overall response rate of response to amrubicin was 39%. Anemia, febrile neutropenia, thrombocytopenia, hyperglycemia, hyponatremia, infection, elevated serum transaminases levels were appeared, but the incidences of adverse events were very few. Our results suggest amrubicin therapy can improve patients with refractory small-cell lung cancer and may be an effective and safe treatment option.

Introduction

The incidence of small-cell lung cancer rises sharply in malignant lung cancer and usually found at a late stage or with metastasis (Cheng and Su, 2010). Amrubicin is a third-generation synthetic anthracycline analogue, of which the pharmacological mechanism is to eventually lead to DNA breaks and inhibition of tumor cell proliferation by inhibiting the activity of TopoII, which has good effect on the treatment of advanced SCLC, but with some adverse reactions (Bosch, 2007; Ding and Zhan, 2013; Sekine et al., 2014).

As a drug of anthracycline, through inhibiting the activity of TopoII, DNA is fractured and amrubicin blocks tumor cells proliferation (Wang et al., 2015). The mechanism of action for amrubicin is distinct with that of adriamycin (Chotenimitkhun et al., 2015). With favorable cardiac safety and great tolerance of patients, amrubicin is better than other anthracycline compounds. Amrubicin is considered as an anti-lung cancer chemotherapeutic drug with high efficiency and huge developmental potential (Ikeda et al., 2014). Clinical studies based on the combined chemotherapy of amrubicin are being conducted both at home and abroad. In 2002, amrubicin appeared on Japan market to cure non-small cell lung cancer and small cell lung cancer (Gervais et al., 2015). 75% of patients with small cell lung cancers and 20% of patients with non-small cell lung cancer showed good curative effects (Ikeda et al., 2014). Compared with other anthracycline drugs, it has better clinical tolerance. Amrubicin has good efficacy in second-line treatment of small-cell lung cancer, and its efficacy is superior to topotecan (Yamaoka et al., 1999). It was effective for the elderly patients with refractory relapsed small cell lung cancer as third-line chemotherapy (Asai et al., 2012).

The present study investigated whether the effect of amrubicin therapy improved patients with refractory small-cell lung cancer in Chinese clinical study.

Materials and Methods

Study design

This study was an open-label, multicenter, single-arm confirmatory research involving 25 institutions in

China. The study protocol was approved by the China Clinical Oncology Group (JCOG) Protocol Review Committee and the institutional review board of each participating institution.

Eligibility criteria

Patients who were chosen were known to be ones of small-cell lung cancer by histological or cytological means, and they were resistant to one or two treatments of making use of chemical substances, with at least one platinum-based treatment. A refractory disease was interpreted as one failing to respond to prior chemotherapy, disease continuation on chemotherapy, or disease continuance <90 days of concluding prior chemotherapy after corroborating a complete response (CR) or partial response (PR). Additional criteria for inclusion consisted of persons aged from 20 to 74, with eastern cooperative oncology group performance status of 0 - 1, measurable disease, no history of chemotherapy with AMR, no history of surgery for small-cell lung cancer, no thoracic radiation therapy ≤4 weeks prior to registration, satisfactory baseline organ function [leukocyte count ≥ 3000/mm^3, absolute neutrophil count ≥1500/mm^3, hemoglobin ≥9.0 g/dL, platelet count ≥100,000/mm^3, total bilirubin ≤2.0 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤ 100 IU/L, serum creatinine level ≤2.0 mg/dL, PaO_2 under room air ≥60 mmHg, and electrocardiographic findings within normal range]. Informed consent in written form was received from all participants. Patients were deemed not qualified providing they suffered from active concomitant malignancy, massive pleural or pericardial effusion, symptomatic brain metastasis, or severe comorbidities such as active infections, uncontrolled hypertension, severe heart disease, uncontrolled diabetes mellitus, bowel obstruction, psychiatric disease, severe emphysema, interstitial pneumonia, or pulmonary fibrosis. Patients who took some medication for systemic steroid and who were pregnant or breastfeeding were not included.

Treatment

Treatment began within the first week following confirmed participation in the study. At an interval of 21 days, patients received amrubicin at 40 mg/m^2/day for three days in succession. Such treatment went on if without worsening of the disease, unbearable toxicity, or refusal on the part of the patient in question. The dosage of amrubicin was reduced to 35 mg/m^2/day assuming that any one of the items listed below was noticed in the process of the previous course: Leukocyte count <1000/mm^3, platelet count <20,000/mm^3, Grade 3 febrile neutropenia, or grade 3 non-hematological toxicity (except nausea, anorexia, weight loss, creatinine, hyponatremia, hyperglycemia or alopecia). The dosage was decreased to 30 mg/m^2/day for the second time in cycles that followed in accordance with the same criteria. In the case of Grade 4 non-hematological toxicity or continued toxicity that might have necessitated a reduction of dosage for the third time, the protocol of the treatment was discontinued.

Evaluation

The response evaluation criteria in solid tumors guidelines (ver. 1.0) wre made use of in order to make an evaluation of any tumor response. Calculated tomography was employed at baseline in at least every two cycles. Verification of a CR or PR was obligatory at least four weeks subsequent to the first corroboration of a response. For those patients whose tumor was found to shrink to a more or less extent, an independent review of any response of the tumor by an independent panel, consisting of at least a diagnostic radiologist, was later conducted. Any detrimental effects were put down in writing by means of the common terminology criteria for adverse events (ver. 3.0). An assessment of cardiotoxicity was carried out as planned according to the judgment of the physician.

Patients were provided with full supportive care as needed, consisting of blood transfusion. The plan for treatment specified that granulocyte colony-stimulating factor (G-CSF) ought to be made use of in compliance with the national health insurance coverage of China. Furthermore, indications for G-CSF administration were stated as follows: a) when fever (for the most part more than 38°C) was noticed with a neutrophil count of ≤1000/mm^3; b) when a neutrophil count of 500/mm^3 was observed; c) during the previous course, if fever (for the most part more than 38°C) with a neutrophil count of ≤1000/mm^3 was observed, or if a neutrophil count of 500/mm^3 was observed, then after concluding the same chemotherapy, if a neutrophil count of ≤ 1000/mm^3 was observed. No more restriction whatever for the purpose of following chemotherapy was necessary after worsening of the disease in this study.

Statistical analysis

Data are presented using SPSS version 17.0 as means ± standard deviation. Statistical significances of differences were determined using Student t-test. A value of $p<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 95 patients (11 women and 84 men; median age, 63 years) from The 309th Hospital of Chinese PLA were enrolled in this study from September 2012 to December 2014 (Table I). Patients were eligible for analysis of the efficacy and safety of amrubicin. All enrolled patients received prior platinum-based chemotherapy, including pretreatment with cisplatin-containing regimens (n = 69; 72.6%), carboplatin-con-

taining regimens (n = 19; 20.0%), cisplatin and carboplatin-containing regimens (n = 7; 77.4%), irinotecan-containing chemotherapy regimens (n = 50; 52.6%), etoposide-containing chemotherapy regimens (n = 43; 45.3%) and topotecan-containing regimens (n = 2; 2.1%).

Response

Among the total study population, complete response was achieved in 5 patients (5.3%), partial response in 32 patients (33.9%), stable disease in 41 patients (43.2%), and progressive disease in 16 patients (16.8%) after treatment with amrubicin (Table II). Thus, for amrubicin therapy, an overall response rate of 39.0% was observed .

Survival

The median follow-up time of all registered patients was 9.1 months (1.3-25.1 months) at the cutoff date for data collection. Of the 95 patients, 78 patients (82.1%) until death, and 94 patients (99.0%) were observed until

Table I

Patient characteristics

Characteristics	Patients (n = 95)	
	n	%
Age (years)	63	
Gender		
Female	11	11.58
Male	84	88.42
Eastern Cooperative Oncology Group performance status		
0	40	42.11
1	55	57.89
Disease extent at entry		
Limited disease	5	5.26
Extensive disease	90	94.74
No. of prior chemotherapy regimens		
1	78	82.11
2	17	17.89
Prior chemotherapy regimen (multiple choices)		
Cisplatin-containing	69	72.63
Carboplatin-containing	19	20.00
Cisplatin and carboplatin-containing	7	7.37
Irinotecan-containing	50	52.63
Etoposide-containing	43	45.26
Topotecan-containing	2	2.11
Response to prior chemotherapy		
Complete response	5	5.26
Partial response	65	68.42
Stable disease	7	7.37
Progressive disease	18	18.95
History of thoracic radiation therapy		
No	74	77.89
Yes	21	22.11

Table II

Response to amrubicin in intent-to-treat population

Response	Number of patients (n = 95)	
Complete response	5	5.3
Partial response	32	33.7
Stable disease	41	43.2
Progressive disease	16	16.8
Not evaluable	1	1.0
Overall response rate	37	39.0

disease progression. The median overall survival of all registered patients was 9.2 months (95% CI, 7.4-11.8 months).

Safety

Of the 95 patients, 53 patients (55.8%) were observed Grade 3 leukopenia, 24 patients (25.3%) were observed Grade 4 leukopenia, and 77 patients (81.1%) were observed grade 3 + 4 leukopenia. Anemia, febrile neutropenia, thrombocytopenia, hyperglycemia, hyponatremia, infection, elevated ALT and AST level were also appeared, but quantity of these adverse events were very few. However, 21 patients (22.1%) were observed Grade 3 neutropenia, 64 patients (67.4%) were observed Grade 4 neutropenia, and 85 patients (89.5%) were observed grade 3 + 4 neutropenia (Table III).

Discussion

Although small-cell lung cancer takes only about 20% of lung cancers, but the degree of malignancy is high. Compared with non-small-cell lung cancer, it is more likely to have distant metastasis, and most patients have metastasis when being treated. The median survival is less than 1 year, and 5-year survival rate is less than 5% (Ding et al., 2012). More and more studies show that the autocrine loop path of body, proto-oncogenes and tumor suppressor genes have an important position in small-cell lung cancer occurrence and development, and epigenetics may affect the occurrence and development of small-cell lung cancer by the regulation of these factors (Zhang et al., 2013). We found that among the total study population, complete response was achieved in 5 patients (5.3%), partial response in 32 patients (33.9%), stable disease in 41 patients (43.2%), and progressive disease in 16 patients (16.8%) after treatment with amrubicin.

Phase III trials of small-cell lung cancer by second-line treatment of amrubicin is underway, and we will look forward to the final release of the results. In the second-line treatment of small-cell lung cancer, the appropriate dose of amrubicin may be 35 mg/m^2 on the first, second and third days, with the repeat of three weeks (Matsunaga et al., 2006). For the second-line chemotherapy of small-cell lung cancer currently, participation in clinical trials was recommended in 2010 by the US National Comprehensive Cancer Alliance; the patients with the relapse within 2-3 months and PS

Table III

Adverse events of in Grade 3 or 4 patients treated with amrubicin

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	n	%	n	%	n	%
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Elevated alanine transaminase level	4	4.2	2	2.1	6	6.3
Elevated aspartate aminotransferase level	4	4.2	0	0	4	4.2

score of 0-2 points can consider the drugs: Different ring phosphoramidite, paclitaxel, docetaxel, gemcitabine, irinotecan and topotecan; the patients with the relapse between 2-3 months and six months can consider the application of topotecan (Level 1 evidence), CAV, gemcitabine, paclitaxel, docetaxel, oral etoposide and vinorelbine; the patients with the relapse after six months can consider the original proposal (Ettinger et al., 2010). In practice, the application of second-line treatment should be combined with full consideration of the general condition of the patient, the situation of first-line chemotherapy and side effects of selected drugs (Shah, 2009). In this study, we found that among Overall response rate was 38.95%, the median follow-up time of all registered patients was 9.1 months (1.3-25.1 months) at the cutoff date for data collection. The median overall survival of all registered patients was 9.2 months. Haruyasu Murakami et al, (2014) reported that overall survival periods were 8.9 months and overall response rate was 32.9% in Japanese patients. Overall response rate and overall survival of our results were higher than findings of Haruyasu Murakami. These differences may be genetic and species difference from Chinese patients and Japanese patients.

Amrubicin has good efficacy in the first and second line treatment of small-cell lung cancer, the median survival time of the patients treated by the combination of amrubicin and cisplatin in the treatment of previously untreated extensive-stage small-cell lung cancer, is more than that of 12.8 months in the IP program group reported in the JCOG 9511 research from Japan (Kobayashi et al., 2010). The combination of amrubicin and carboplatin can also realize good efficacy in the treatment of elderly small-cell lung cancer, with the recommended dose of amrubicin 35 mg/m^2 on the first, second and third days, and carboplatin is calculated according to AUC 4, and used on the first day, with the repeat of three weeks (Igawa et al., 2013). Amrubicin second-line treatment has a good effect of refractory or relapsed sensitive small-cell lung cancer, and Phase II clinical trials have shown superior efficacy to that of Tinto topotecan. European countries are also conducting clinical trials of the treatment of small-cell lung cancer by amrubicin, the Phase III clinical trials of first- or second-line treatment of small-cell lung cancer abroad by amrubicin are underway, of which the final results report is expected.

Amrubicin has better cardiac safety, which may also be a good choice for patients with poor kidney function, and the main side effect is hematologic toxicity, deserving our attention (Ohe et al., 2005; Onoda et al., 2006; Hanada et al., 2007; Hira et al., 2008). In the present study, 53 patients (55.8%) were observed Grade 3 leukopenia, 24 patients (25.3%) were observed Grade 4 leukopenia, and 77 patients (81.1%) were observed Grade 3 + 4 leukopenia. Anemia, febrile neutropenia, thrombocytopenia, hyperglycemia, hyponatremia, infection, elevated ALT and AST level were also appeared, but quantity of these adverse events were very few. However, 21 patients (22.1%) were observed Grade 3 neutropenia, 64 patients (67.4%) were observed Grade 4 neutropenia, and 85 patients (89.5%) were observed Grade 3 + 4 neutropenia.

Conclusion

Amrubicin therapy improves patients with refractory small-cell lung cancer, which showed a favorable tumor response, prolonged survival, and acceptable toxicity. Therefore, amrubicin therapy emerges a standard treatment for refractory small-cell lung cancer.

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Author Info
Naikang Zhou (Principal contact)
e-mail: zhounk2005@163.com