Clinical efficacy and safety of combination of abraxane and trastuzumab in treatment of recurrent ovarian cancer

Yi Yang[1], Zhi-shun Lu[2] and Zhu Zeng[3*]
[1]Department of Oncology, Guizhou People's Hospital, Guiyang, Guizhou, China
[2]Central Laboratory, Guizhou People's Hospital, Guiyang, Guizhou, China
[3]School of Biology and Engineering, Guizhou Medical University, Gui'an New District University City, Guiyang, Guizhou, China

Abstract: Present research work is carried out to compare the clinical efficacy and adverse reactions between combined medication of abraxane and trastuzumab and single medication of trastuzumab in treatment of ovarian cancer. A total of 80 recurrent ovarian cancer patients in Stage III B or IV confirmed by histopathological examination and/or cytological examination were enrolled in this study and divided into two groups, i.e. the combined medication group (n=37) and the single medication group (n=43). Patients in two groups underwent therapy for 4 cycles to evaluate the short-term efficacy and adverse reactions of these two methods. The control rates of the combined medication group and the single medication group were 86.4% and 81.4%, respectively, while the partial response rates were 45.9% and 44.2%, respectively. As for the overall survival (OS), the OS in the single medication group was 7.0 months, while that in the combined medication group was 7.3 months (p=0.63). Incidence of neutropenia in the single and combined medication groups were respectively 51.2% and 40.5%, while the incidence rates of leukopenia in Stage III or IV were 44.2% and 24.3%, respectively (p<0.001) and the differences between two groups were statistically significant. Also, comparison of the incidence rates of thrombocytopenia between the single (53.5%) and combined (23.6%) medication groups showed statistical significance. With promising efficacy, few adverse reaction and high safety, combined medication of abraxane and trastuzumab is more applicable to the treatment of recurrent ovarian cancer.

Keywords: Recurrent, ovarian cancer, abraxane, trastuzumab.

INTRODUCTION

Only after cervical cancer and endometrial cancer, ovarian cancer ranks 3rd in incidence rate of all gynecological cancer. According to the clinical statistics, 5-year survival rate of ovarian cancer is only 25% to 30% (Hennenfent *et al*., 2006) and the mortality rate ranks 1st in all gynecological malignancies. So far, cisplatin-based chemotherapy following the cytoreductive surgery has been regarded as the major treatment strategy. Paclitaxel (PTX), a kind of anti-cancer texanes, is promoted in clinical treatment of a variety of malignancies, including ovarian cancer, breast cancer and non-small cell lung cancer (NSCLC). Moreover, PTX in combination with cisplatin is a standard chemotherapeutical procedure with a high effective rate. Nevertheless, due to the relevantly high recurrence rate, more therapeutic strategies, including second-line or even third-line strategies, are employed, and for the insoluble property of PTX in water, ethoxylate castor oil and anhydrous ethanol serve as the co-solvent, which usually induce the hypersensitivity threatening the health or life of patient (Poveda *et al*., 2007). Albumin-bound paclitaxel, also known as abraxane, is a new type of anti-cancer drug with cytotoxicity, manifesting higher reactivity, longer progression of cancer and fewer allergies. In addition, we hope to develop a kind of effective and safe drug and strategy to further improve the therapeutic efficacy on ovarian cancer. In this study, we aimed to compare the applications of the combined medication of abraxane and trastuzumab with the single medication of trastuzumab

**Corresponding author:* e-mail: uth848@163.com

MATERIALS AND METHODS

General material

In this study, we retrospectively reviewed the cases of 80 patients with recurrent ovarian cancer confirmed by cytological and histopathological examinations who received the treatment in this hospital between June 2014 and May 2017. Inclusion criteria: a) patients who were confirmed with recurrent ovarian cancer in Stage III B to IV through histological or cytological examinations (Calvani *et al.*, 2008); b) patients who should undergo chemotherapy with no history of radiotherapy; c) patients with WHO physical scores (PS) between 0 and 2 points; d) patients with normal liver functions confirmed by bone marrow examination (normal refers to the elimination rate of creatinine of 45 mL/min according to the Cockroft-Gault formula). All patients were divided into two groups, i.e. the combined medication group (n=37) and the single medication group (n=43). In combined medication group, patients aged between 44 and 79 years old with an average of 63 years old and there were 27 patients with PS between 0 and 1 point, and 10 with PS between 1 and 2 points. In single medication group, patients aged between 44 and 73 years old with an average of 65 years old and there were 33 patients with PS between 0 and 1

point, and 10 with PS between 1 and 2 points. This study obtained all the written informed consents of patients and approved by the Ethic Committee of this hospital.

Diagnostic criteria of recurrent ovarian cancer: Measurable lesions, for which RECIST is applicable; for patients with no measurable lesion, level of CA_{125} is higher than 70 KU/L and there is no other primary tumor.

Treatment

Combined medication group

Abraxane (Abraxis BioScience, Reg. No.H20091059) was dissolved as required in instructions (135-175 mg/m^2), and injected intravenously within 20 min. Trastuzumab (Roche, USA; Batch No.J20110020) was applied with reference of the weight of patient (4 mg/kg) and injected intravenously for 90 min. Tropisetron was taken for preventing the vomiting, and electrocardiograph monitoring was carried out for patients during the chemotherapy. Moreover, vital signs of patients were also closely monitored. Dose of drug was reduced by 25% for patients aged at 75 years old or above. One cycle of treatment lasted for 28 days, and patients would undergo a total of 6 cycles.

Single medication group

Patients in this group only received the single medication of trastuzumab. One cycle of treatment lasted for 28 days, and patients would undergo a total of 6 cycles.

Follow-up

Follow-up was carried out at clinic or by telephone. Before chemotherapy and during follow-up, we assessed the adverse reactions of different strategies with CTC (version 3.0).

Efficacy evaluation

During treatment, CA_{125} examination and imaging examination would be carried out before chemotherapy, and the decrease in CA_{125} and shrinkage of lesion served as the indexes for determination of short-term efficacy. Complete remission (CR): CA_{125} is decreased below 35 KU/L with no clinical symptom. Partial remission (PR): CA_{125} is decreased by more than 50% in comparison with the level before chemotherapy. Stable disease (SD): CA_{125} fluctuates around 50% of the original level. Progressive disease (PD): CA_{125} is increased by 50% in comparison with the original level. Evaluation of lesion shrinkage through imaging examination was carried out in following criteria. CR: Lesions and clinical symptoms disappear for 1 month. PR: Shrinkage of lesion is more than 50%. SD: Shrinkage of lesion is not larger than 50%, but less than 25%. PD: Enlargement of lesion is not less than 50%. Control rate of disease = (CR + PR + SD)/Number of Cases ×100%. Response rate (RR) = (CR + PR)/Number of Cases × 100%. Progression-free survival time refers to the period from the start of treatment to the progression of disease.

STATISTICAL ANALYSIS

SPSS 19.0 software was employed to perform statistical analysis of data. Kaplan-Meier method was applied to estimate the survival data of patients, and log-rank test was carried out for comparison of the survival. Hazard ratio (HR) was calculated with Cox proportion. Chi-square test and Fisher exact test were adopted for comparison of the measurement data. $p<0.05$ suggested that the difference had statistical significance.

RESULTS

Clinical features of patients in two groups

Median observation time was 38.7 months, and there were 22 patients in Stage III B, and 58 in Stage IV. Clinical features of patients are shown in table 1 and the comparison between two groups showed no statistical significance ($p>0.05$).

Efficacy of two groups

The averages of treatment cycles of the single medication group and combined medication group were 3.1 and 3.3 months ($p=0.037$), while the PR rates of combined medication group and single medication group were 45.9% and 44.2%, respectively. Patients who fulfilled 4 cycles of treatment occupied 62% in single medication group and 72% in combined medication group ($p=0.030$), while the control rates of the disease were respectively 86.4% and 81.4% (table 2).

Adverse reactions of patients in two groups

The incidence rates of leukopenia at Stage 3 or 4 of patients in the single medication group and combined medication group were 44.2% and 24.3%, respectively ($p<0.001$), incidence rates of thrombocytopenia were 53.5% and 23.6%, respectively, and those of neutropenia were 51.2% and 40.5%, respectively (table 3). Infection was the most frequent event of Stage 3 and 4 in two groups with incidence rates of 9.3% and 8.1% in combined medication group and single medication group, respectively, while the incidence rates of nausea were respectively 4.6% and 2.7% with no statistically significant difference.

Overall survival rate of patients in two groups

The median of overall survival of patients in the single medication was 7.0 months and in the combined medication group was 7.3 months; while the one-year survival rates of the combined and single medication groups were respectively 34% and 31% with no statistically significant difference. Among patients with 0 or 1 point of PS in the single medication group, the median of overall survival was 7.7 months and that of those in combined medication group was 8.7 months; patients with 2 points of PS in the single medication group had a median of overall survival of 5.1 months,

Table 1: Comparison of the clinical features of patients (n, %)

Clinical features	Combined medication (n=37)	Single medication (n=43)	*p*
Age	63 (44 ~ 79)	65 (44 ~ 73)	0.782
PS score			
0-1	27 (73%)	33 (77%)	0.854
2	10 (27%)	10 (23%)	
Clinical stage			
Stage IIIB	10 (27%)	12 (28%)	0.716
Stage IV	27 (73%)	31 (72%)	

Table 2: Analysis of efficacy of patients in two group (n, %)

Efficacy	Combined medication (n=37)	Single medication (n=43)	χ^2	*p*
PR	17 (45.9%)	19 (44.2%)	0.001	0.984
SD	15 (40.5%)	16 (37.2%)		
PD	5 (13.6%)	8 (18.6%)		
CR	32 (86.4%)	35 (81.4%)	0.193	0.726

Table 3: Comparison of the adverse reaction of patients between two groups [n (%)]

Adverse reactions	Combined medication (n=37)	Single medication (n=43)	*P*
Infection	3 (8.1%)	4 (9.3%)	0.74
Nausea	1 (2.7%)	2 (4.6%)	0.48
Anemia			0.85
Grade 3	4 (10.8%)	5 (11.6%)	
Grade 4	1 (2.7%)	2 (4.6%)	
Leukopenia			<0.001
Grade 3	6 (16.2%)	15 (34.9%)	
Grade 4	3 (8.1%)	4 (9.3%)	
Neutropenia			0.026
Grade 3	9 (24.3%)	11 (25.6%)	
Grade 4	6 (16.2%)	11 (25.6%)	
Thrombocytopenia			<0.001
Grade 3	5 (13.5%)	14 (32.6%)	
Grade 4	3 (8.1%)	9 (20.9%)	
Transfusion			0.003
Blood	10 (27.0%)	19 (44.2%)	
Platelet	1 (2.7%)	4 (9.3%)	

while those in the combined medication group had a median of overall survival of 4.3 months, and the difference had no statistical significance.

DISCUSSION

Ovarian cancer is one of the malignancies originated from epithelium in ovary, and, in China, new cases of ovarian cancer has exceeded 400,000. Since there are no evident clinical symptoms in the early stage of ovarian cancer, most of patients have evolved into the median or advanced stage at the time of diagnosis (Floquet *et al*., 2014; Gelderblom *et al*., 2001). Patients who undergo standardized medication with cisplatin are more susceptible to the ascites and recurrence and repeated intervention of chemotherapy usually leads to poor prognosis (Chakravarthi *et al*., 2010). Thus, searching for new drugs and methods for curbing the development of tumor is quite critical to the improvement of life quality and extension of survival.

Scholars have recognized that compared with the optimal treatment strategy, cisplatin-based chemotherapy can improve the life quality, prolong the survival and improve the control of symptoms (Piccart *et al*., 2003). Histological type of ovarian cancer is the key to the stipulation of treatment strategy, and patients with poor PS usually gain little from the chemotherapy. Owing to the considerable progress in abraxane, it can bind to the human albumin to form particles in diameter of 130 nm, which is conducive to the combination with the specific receptor of albumin on the surface of vascular endothelial

membrane, thereby delivering the paclitaxel into the tumor tissues; paclitaxel can function inside the tumor cells through internalization (Huang *et al*., 2014). Enormous clinical studies have indicated that abraxane has potent anti-tumor effect with few adverse reactions and physical requirements on patients, which makes itself an option in treatment of recurrent ovarian cancer. Meanwhile, with the development in biomedicine, target therapy has gained more and more attention. Trastuzumab, as one of the target drugs for anti-angiogenesis, has become a hotspot in research (Calvani *et al*., 2008). Angiogenic factor plays an important role in angiogenesis and can promote the migration and proliferation of endothelial cells, so as to induce the generation of vessels (Gordinier *et al*., 2014). Besides, trastuzumab, a kind recombinant human monoclonal antibody, can bind to the receptor of angiogenic factor to inhibit the regeneration and activation of tumors, which can prolong the progression-free survival of patients without any increase in risk of adverse reactions in chemotherapy (De Geest *et al*., 2010).

In this study, we compared the efficacy and adverse reactions between the single medication of trastuzumab and combined medication of abraxane and trastuzumab in treatment of recurrent ovarian cancer. Results hinted that the overall survival rates, RRs and control rates of disease between two groups were similar, and no statistically significant difference was found in comparison of the survival rates among patients with different PS scores between two groups. After treatment, single medication induced more hematological toxic reactions, but the comparison of overall survival rates showed no statistically significant difference. Thus, the overall survival rates of patients with PS scores between 0 and 1 point were comparable, and the adverse reactions, tolerability and control of disease of these strategies were similar. Besides, patients with recurrent ovarian cancer that received either combined medication or single medication had a similar median survival (7.3 months *vs.* 7.0 months, p=0.63). Of note, we found no correlation between the histological features and survival rates in this study.

CONCLUSION

Abraxane in combination with trastuzumab is expected to be applied as the first-line medicine in treatment of recurrent ovarian cancer with few adverse reactions and high safety.

REFERENCES

Calvani M, Trisciuoglio D and Bergamaschi C *et al* (2008). Differential involvement of vascular endothelial growth factor in the survival of hypoxic colon cancer cells. *Cancer Res.,* **68**(1): 285-291.

Chakravarthi SS, De S and Miller DW *et al* (2010). Comparison of antitumor effi-cacy of paclitaxel delivered in nano and microparticles. *Int. J. Pharm.*, 383(112): 37-44.

De Geest K, Blessing JA and Morris RT *et al* (2010). Phase II clinical trial of ixabepilone in patients with recurrent or persistnetplatinum and taxane-resistant ovarian or primary peritoneal cancer: A gynecologic oncology group study. *J. Clin. Oncol*., **28**(1) : 149-153.

Du Bois A, Floquet A and Kim JW *et al* (2014). Incorporation of pazo-panib in maintenance therapy of ovarian cancer. *J. Clin. Oncol.,* **32**(30): 3374-3382.

Gelderblom H, Verweij J and Nooter K *et al* (2001). Cremophor EL: The drawbacks and advantages of vehicle selection for drug formulation. *Eur. J. Cancer,* **37**(13): 1590-1598.

Gordinier ME, Dizon DS and Weitzen S *et al* (2014). Oral thalidomide as palliative chemotherapy in women with advanced ovarian cancer. *J. Palliat. Medc.,* **10**(1): 61-66.

Hennenfent KL and Govindan R (2006). Novel formulations of taxanes: A review. Old wine in a new bottle? *Ann. Oncol.,* **17**(5): 735-749.

Huang H, Zheng Y and Zhu J *et al* (2014). An updated meta-analysis of fatal adverse events caused by bevacizumab therapy in cancer patients. *PLoS One*, **9**: e89960.

Piccart MJ, Bertelsen K and Stuart G *et al* (2003). Long term follow up confirms a survival advantage of the paclitaxel-cisplatin regimen over the cyclophosphamide cisliatin combination in advanced ovarian cancer. *Int. J. Gynecol. Cancer,* **13**(Suppl 2): 144-148.

Poveda VA, Casado HA and Cervantes RA *et al* (2007). Treatment guidelines in ovarian cancer. *Clin. Transl. Oncol.,* **9**(5): 308-316.