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Effects of bevacizumab and pegylated liposomal doxorubicin for the patients with recurrent or refractory ovarian cancers

Kazuya Kudoh [a,b,1], Masashi Takano [a,c,*,1], Hiroko Kouta [a], Ryoko Kikuchi [d], Tsunekazu Kita [a,e], Morikazu Miyamoto [c], Akio Watanabe [c], Masafumi Kato [c], Tomoko Goto [c], Yoshihiro Kikuchi [a]

[a] Department of Gynecology, Ohki Memorial Kikuchi Cancer Clinic for Women, Tokorozawa, Saitama, Japan
[b] Department of Obstetrics and Gynecology, Nishisaitama-Chuo National Hospital, Tokorozawa, Saitama, Japan
[c] Department of Obstetrics and Gynecology, National Defense Medical College, Tokorozawa, Saitama, Japan
[d] Department of Basic Pathology, National Defense Medical College, Tokorozawa, Saitama, Japan
[e] Department of Obstetrics and Gynecology, Nara Prefectural Nara Hospital, Nara, Nara, Japan

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ABSTRACT

Objectives. Currently, pegylated liposomal doxorubicin (PLD) is regarded as one of the standard treatment options in recurrent ovarian cancers (ROC). Bevacizumab has shown significant antitumor activity for ROC in single-agent or in combination with cytotoxic agents. We have conducted a preliminary study to investigate effects of combination of bevacizumab and PLD for heavily pretreated patients with ROC.

Methods. Thirty patients with ROC were treated with combination therapy with weekly bevacizumab and PLD, 2 mg/kg of continuous weekly bevacizumab and 10 mg/m^2 of PLD (3 weeks on, 1 week off). The treatment was continued until development of disease progression, or unmanageable adverse effects. Response evaluation was based upon Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, and Gynecologic Cancer Intergroup (GCIG) CA125 response criteria. Adverse effects were analyzed according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results. Overall response rate was 33%, and clinical benefit rate (CR + PD + SD) was 73%. Median progression-free survival was 6 months (range: 2–20 months), and a 6-months progression-free survival was 47%. Any hematological toxicities more than grade 3 were not observed. Two cases developed non-hematologic toxicities more than grade 2; a case with grade 3 hand-foot syndrome, another with grade 3 gastrointestinal perforation (GIP). The case with GIP was conservatively treated and recovered after 2 months, and there was no case with treatment-related death.

Conclusion. The present investigation suggested that combination therapy with bevacizumab and PLD was active and well tolerated for patients with ROC. We recommend the regimen be evaluated in further clinical studies.

Introduction

Ovarian cancer is the second most common gynecologic malignancy, but the most lethal gynecologic malignant tumor in the developed countries [1,2]. Combination chemotherapy with paclitaxel and platinum, recognized as 'Gold standard' regimen for ovarian cancer, has significantly improved the survival of the patients with advanced ovarian cancers [3,4]. More than half of the cases, however, will recur despite the treatment with maximal cytoreductive surgery followed by the chemotherapy [5]. For the treatment of platinum-resistant or platinum-refractory ovarian cancers, non-platinum agents such as pegylated liposomal doxorubicin (PLD) and gemcitabine are recommended as single-agent mono-therapy. However, these agents have limited effects for the patients with recurrent or refractory ovarian cancers, and new therapeutic agents including molecular-targeting agents are under investigation. Recently, bevacizumab, a humanized recombinant antibody binding to vascular endothelial growth factor (VEGF), has been recognized to harbor significant activity in recurrent or refractory epithelial ovarian cancers [6–9]. Additive effects of bevacizumab, in combination with paclitaxel and platinum, were also confirmed as the first-line chemotherapy for ovarian, tubal, and peritoneal cancers [10,11]. A report of combination with PLD and bevacizumab showed that standard dose of PLD (45 mg/m^2/4 weeks) and bevacizumab (5 mg/m^2/2 weeks) induced severe toxicities. But decreased dose of PLD (22.5 mg/m^2/2 weeks) significantly decreased toxicities [12]. So we attempted a weekly low-dose regimen for patients with recurrent or refractory ovarian cancers: PLD at a dose of 10 mg/m^2/week and bevacizumab at 2 mg/kg/m^2/week.

* Corresponding author. Fax: +81 4 2996 5213.
E-mail address: mastkn@ndmc.ac.jp (M. Takano).
[1] K. Kudoh and M. Takano contributed equally to this paper.

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Table 1
Patients characteristics ($n=30$).

Variables	Number (%)
Age, years	
Median	55 (range: 34–69)
FIGO stage	
I–II	7 (23)
III	20 (67)
IV	3 (10)
Residual tumor at initial surgery	
Optimal	18 (60)
Suboptimal	12 (40)
Histological subtype	
Serous	13 (43)
Clear cell	7 (23)
Endometrioid	5 (17)
Others	5 (17)
Previous chemotherapy	
1 regimen	3 (10)
2 regimen	6 (20)
3 regimen	10 (33)
4 regimen or more	11 (37)
Previous chemotherapy with pegylated liposomal doxorubicin	
Yes	2 (7)
No	28 (93)
Previous chemotherapy with bevacizumab	
Yes	2 (7)
No	28 (93)
Previous radiotherapy	
Yes	4 (13)
No	26 (87)
Platinum-sensitivity[a]	
Platinum-sensitive	1 (3)
Platinum-resistant	29 (97)

[a] Platinum-sensitivity was evaluated by most recent platinum-based chemotherapy.

Patients and methods

During the period from 2006 until 2009, thirty patients with recurrent or refractory ovarian cancers were treated with bevacizumab and pegylated liposomal doxorubicin (PLD), weekly continuous administration of bevacizumab at a dose of 2 mg/kg and PLD at 10 mg/m^2 (3 weeks on, and 1 week off). Inclusion criteria of the patients were as follows: (1) patients whose tumor specimens were histologically confirmed as epithelial ovarian cancers; (2) patients who received one or more regimens of systemic chemotherapy as postoperative chemotherapy; (3) patients who were diagnosed to have recurrent or refractory tumor at the beginning of the present chemotherapy; (4) patients who received at least two cycles of chemotherapy with PLD and bevacizumab; (5) patients whose clinical information was assessable. Platinum-resistant disease was defined as progression during or within 6 months after completion of most recent platinum-based chemotherapy. The administration of weekly bevacizumab–PLD for recurrent ovarian carcinomas was reviewed and approved by institutional review board (IRB) of Ohki memorial Kikuchi cancer clinic for women. After receiving written informed consent from each patient, the therapy was initiated. The treatment was continued until development of disease progression or unmanageable adverse effects. Bevacizumab is not approved by Japanese Ministry of Health, Labour and Welfare for the treatment of ovarian cancers. So, the patients paid all the cost including drugs by themselves.

The primary endpoint was response rate, and the second endpoints were progression-free survival and toxicities. Response evaluation was based upon Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. In the absence of measurable disease, CA125 level was used to evaluate response by Gynecologic Cancer Intergroup (GCIG) CA125 response criteria [13]. Complete response (CR) was defined as the disappearance of all target and non-target lesions, no evidence of new lesions and normalization of CA125. Partial response (PR) was defined as a 30% or greater reduction in the sum of the longest dimensions of all target lesions and no progression of non-target lesions, or >50% reduction of CA125 levels, lasting at least 4 weeks. Progressive disease (PD) was defined as a 20% or greater increase in the sum of the longest dimensions of target lesions, or the appearance of new lesions, or a doubling of CA125 levels within 8 weeks from the start of chemotherapy. Stable disease (SD) was defined as any condition which did not meet the above criteria. Clinical benefit rate (CBR) was estimated by the rate of the patients with CR, PR and SD. Adverse effects were analyzed according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The time to progression was defined as the interval from the first date of the treatment with bevacizumab and PLD until the date of tumor progression or death due to any cause. Kaplan–Meier method was used for calculation of patient survival distribution. Six-month progression-free survival was estimated based on the Kaplan–Meier method. The chi-square test and Student t test for unpaired data were used for statistical analysis. A P value of <0.05 was considered statistically significant. The Stat View software ver.5.0 (SAS Institution Inc., Cary, NC, USA) was used to analyze the data.

Results

Thirty patients with pretreated recurrent or refractory ovarian cancer (ROC) patients were enrolled in this exploratory study. The characteristics of the patients were summarized in Table 1. Median age of the cases was 55 years, ranging from 34 to 69. Seven patients (23%) with clear cell carcinoma and five cases with endometrioid histology were included. Twenty one patients (70%) had received three or more regimens of chemotherapy. Treatment-free interval from previous chemotherapy was less than three months in 24 (80%) cases, 3–6 months in 5 (17%) cases, and more than 6 months in only 1 (3%) patient. The patients included a case of platinum-sensitive disease and 29 cases of platinum-resistant tumors. Four patients (13%) had received irradiation therapy for recurrent disease. Two cases (7%) received previous PLD regimen, and another two cases (7%) were treated with bevacizumab-containing chemotherapy.

Response evaluation to weekly therapy with bevacizumab and PLD was shown in Table 2. The overall response rate was 33%. Complete response was observed in 7% and a partial response was noted in 27%. Overall CBR was 73% in all the patients. Response according to RECIST criteria was assessable in 25 cases with measurable disease, and 2 (8%)

Table 2
Response evaluation to weekly bevacizumab and pegylated liposomal doxorubicin according to Response Evaluation Criteria in Solid Tumors (RECIST).

Response category	All patients ($n=30$)	Histological subtype				Platinum sensitivity	
		Serous ($n=13$)	Clear cell ($n=7$)	Endometrioid ($n=5$)	Others ($n=5$)	Sensitive ($n=1$)	Resistant ($n=29$)
CR	2 (7%)	1 (8%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	2 (7%)
PR	8 (27%)	5 (38%)	1 (14%)	1 (20%)	1 (20%)	1 (100%)	7 (24%)
SD	12 (40%)	4 (31%)	3 (43%)	2 (40%)	3 (60%)	0 (0%)	12 (41%)
PD	8 (27%)	3 (23%)	2 (29%)	2 (40%)	1 (20%)	0 (0%)	8 (28%)
Response rate	33%	46%	29%	20%	20%	100%	31%
CBR[a]	73%	77%	71%	60%	80%	100%	72%

[a] CBR, Clinical Benefit rate = CR + PR + SD/all patients.