RESEARCH ARTICLE

Salvage Therapy of Gemcitabine Plus Endostar Significantly Improves Progression-free Survival (PFS) with Platinum-resistant Recurrent Epithelial Ovarian Cancer

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Abstract

Anti-angiogenic agents have played crucial roles in the treatment of ovarian cancer in recent years, but potential benefits of endostatin have been largely unexplored. The present retrospective study evaluated its efficacy and toxicity with two cohorts of patients with platinum-resistant recurrent ovarian cancer. One cohort received gemcitabine plus endostar (rh-endostatin), and the second cohort received gemcitabine regimen alone, with totals of 31 and 27 patients, respectively. The main endpoints were disease control rate (DCR), PFS, overall survival (OS) and safety. There were statistically significant differences in DCR (70.9% vs. 40.7%; *P* = 0.02) and PFS (6.3 months vs. 3.2 months, *P* = 0.001) between the two cohorts. Though the endostar cohort also improved median OS by 2.1 months, there was no statistically significant difference compared with gemcitabine alone cohort in this case (12.5 months vs. 10.4 months, *P* = 0.201). Treatment was well tolerated for most patients, and toxicity of endostar was negligible. Gemcitabine plus endostar significantly improved the prognosis in patients with platinum-resistant recurrent ovarian cancer, especially in those with malignant effusion. The endostar-containing regimen is recommended in this setting.

Keywords: Salvage therapy - gemcitabine - endostar - epithelial ovarian cancer

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Introduction

Ovarian cancer is the fifth common malignant tumor in women in china, ranking the second in the gynecologic malignancy, and its incidence is about 12 per 100,000 populations per year. Regrettably, there is not an accurate and effective screening method on a regular basis for ovarian cancer, so more advanced patients are initially diagnosed, leading to a worse outcome for this disease. Although the standard first-line therapy that is constituted of optimal cytoreduction surgery and taxane plus platinum-based chemotherapy has greatly improved median survival to 57 months (Ozols et al., 2003), most patients, including those who have achieved pathological complete remission, will develop platinum-resistant disease and eventually relapse. The preferred regimen for platinum-resistant recurrent diseases was a single non-platinum based agent, such as gemcitabine, liposomal doxorubicin, oral etoposide, etc., which tended to show the similar response rate (RR, approximately 20%) (Rose et al., 1998; Ferrandina et al., 2008), but the median time to second recurrence was brief (5 months) (Roland et al., 1998) and then patients would die in a short time. Thus, treatment for platinum-resistant recurrent ovarian cancer still faces a huge challenge.

Undoubtedly, vascular endothelial growth factor (VEGF) is playing an important role in the occurrence and development of many cancers, including ovarian cancer. Several study confirmed that VEGF expression level was negatively correlated with ovarian cancer prognosis (Hartenbach et al., 1997; Paley et al., 1997). Moreover, stage III clinical trials aslo showed apparent advantages of the anti-angiogenic agent (bevacizumab) in ovarian cancer (Burger et al., 2011; Perren et al., 2011; Aghajanian et al., 2012). Endostatin, a 20 kD potent inhibitor of angiogenesis, was isolated from a murine hemangioendothelioma supernatant (O'Reilly et al., 1997), and amino acid sequencing analysis revealed it was actually the C-terminal fragment of collagen XVIII. Endostar (Shangdong Simcere-Medgenn Bio-Pharmaceutical Co., Ltd, China) is the most frequent anti-VEGF drug used for solid tumors in china, showing exclusive biologic features of inhibiting angiogenesis and tumor growth without obvious toxicity and acquired drug resistance. A randomized multicenter double-blind phase III trial of endostar revealed it exhibited synergistic effects when added to vinorelbine-cisplatin (NP) regimen in the treatment of advanced non-small cell lung cancer

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(NSCLC); endostar plus NP improved response rate (RR), median time to tumor progression and clinical benefit rate with a favorable toxic profile in advanced NSCLC, compared with NP alone (Wang et al., 2005). Although endostar has exhibited activity in many other malignant diseases, such as metastatic colorectal and gastric cancer (Zhou et al., 2011a), its role in ovarian cancer need be further clarified. For this aim, the present study retrospectively evaluated the therapeutic results of gemcitabine plus endostar as salvage therapy in refractory/recurrent epithelial ovarian cancer.

Materials and Methods

Patients

After receiving approval from the Ethics Committees at Zhongshan Hospital of Xiamen University, Cancer Center of Sun-Yat Sen University and Nanshan District Hospital of Shenzhen. Ovarian cancer cases were queried to identify two cohorts of patients with platinum-resistant recurrent ovarian cancer who received treatment between January 2009 and December 2010. One cohort of patients had received gemcitabine plus endostar regimen, and the second cohort had received gemcitabine regimen alone. Inclusion criteria were the following: patients were histologically diagnosed as epithelial ovarian cancer; patients developed relapse/progression (< 6 months after completion of front-line platinum-based chemotherapy), or patients with platinum-sensitive recurrent disease generally received multiple chemotherapy regimens until resistance to platinum; gemcitabine was not included in prior chemotherapy regimens; ECOG performance status ≤ 2, white blood cells ≥ 4×10^9/l, platelets ≥ 100×10^9/l, and hemoglobin ≥ 9 g/dl; there were ≥ 1 measurable lesions evaluated by computed tomograph or magnetic resonance image; adequate liver, renal, and cardiac functions were required. Patients were excluded if they had uncontrolled central nervous system metastases, mental illness, recent surgery, severe hypertension, important organ dysfunction or severe heart disease (including congestive heart failure, uncontrolled abnormal heart rhythms, heart valve disease, angina pectoris and myocardial infarction). Patient medical records were retrospectively reviewed to extract age, performance status, clinical stage, histology and the grade, surgical history, platinum resistance type, site of metastasis, clinical outcomes and adverse events.

Treatment

Treatment consisted of gemcitabine 1000 mg/kg intravenously on day 1, 8 alone or plus endostar 7.5 mg/kg intravenously on day 1 ~ 14 until disease progression or unacceptable toxicity. Each treatment cycle lasted 21 days. The main endpoints were DCR, PFS, OS and safety. All patients were reassessed every 2 cycles, i.e. every 2 months of treatment. Treatment response was defined by response evaluation criteria in solid tumors (RECIST version 1.0) (Therasse et al., 2000). Complete response (CR) was defined as complete disappearance of any measurable lesion as well as a normalization of CA125 level from an elevated level. Partial response (PR) was ≥ 30% reduction in the sum of the longest diameter of each lesion and > 50% decrease in elevated CA125 levels. Progressive disease (PD) was ≥ 20% increase in measurement of the sum of the longest diameter of each lesion or the appearance of new lesions. Stable disease (SD) was defined if it did not meet all the above criteria. PFS was defined from the date of starting gemcitabine or gemcitabine plus endostar until date of disease progression as described above or death from any cause. If no progression or recurrence was noted, the date of last contact was used to censor the data. OS was defined as the date of starting gemcitabine or gemcitabine plus endostar until date of death from any cause. If death did not occur, the data were censored at the date of last contact. The adverse events were evaluated according to the National Cancer Institute's Common Toxicity Criteria (version 3.0). All patients receiving ≥ 1 treatment cycle were included in the safety analysis.

Statistics

Simple descriptive statistics were used to report general clinical information and DCR, and were compared with student t-tests and chi-square tests where appropriate. PFS and OS were calculated using Kaplan-Meier survival analysis. Log-Rank tests were used to perform the comparison of survival rates and univariate analysis of prognostic factors. Multivariate Cox regression models were used to test for independent associations between survival and prognostic factors. Data analysis was performed using SPSS software version 13.0, and all tests were two-sided with statistical significance set at $p < 0.05$.

Results

Patient characteristics

A total of 31 patients were included in the gemcitabine

Table 1. Patient Characteristics

Variable	Gemcitabine plus Endostar (n = 31) Numbers	Gemcitabine (n = 27) (%)	*P* value
Age (years)			0.761
Mean	48	50	
Range	26 ~ 65	35 ~ 64	
FIGO stage			0.555
I/II	5 (16.1)	6 (22.2)	
III/IV	26 (83.9)	21 (77.8)	
Histology			0.517
Serous	22 (70.9)	17 (62.9)	
Others	9 (21.1)	10 (37.1)	
Platinum resistance			0.96
Primary	9 (29.0)	8 (29.6)	
Secondary	22 (71.0)	19 (70.4)	
Performance status			0.671
0 ~ 1	19 (61.3)	18 (66.7)	
2	12 (38.7)	9 (33.3)	
Primary surgery			0.636
Optimal(< 1cm)	20 (64.5)	19 (61.3)	
Suboptimal	11 (35.5)	8 (38.7)	
Site of metastasis			0.974
Pleural effusion	7 (22.6)	6 (22.2)	
Others	24 (77.4)	21 (77.8)	
Tumor grade			0.408
1 ~ 2	15 (48.4)	16 (59.3)	
3	16 (51.6)	11 (40.7)	

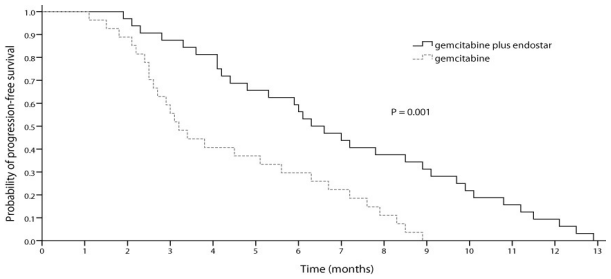

Figure 1. The Median Progression-free Survival (PFS) was 6.3 Months and 3.2 Months for the Endostar Cohort and Gemcitabine Alone Cohort, Respectively. PFS showed statistical differences between the two cohorts

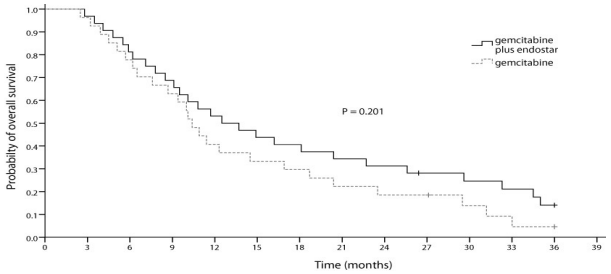

Figure 2. The Median Overall Survival (OS) was 12.5 Months and 10.4 Months for the Endostar Cohort and Gemcitabine Alone Cohort, Respectively. However, there was no statistical difference on OS between the two cohorts

plus endostar cohort and 27 in the gemcitabine alone cohort. The patient characteristics were summarized in Table 1. All patients had received previous standard treatment with platinum and taxane (TC) chemotherapy following the initial surgery. About 60% patients in each cohort underwent the optimal debulking, and the relatively lower surgery satisfaction was probably attributed to more advanced diseases at the initial diagnosis (about 80%). Nearly 30% patients exhibited platinum resistance less than 6 months after six TC regimens, and the median number of previous treatments was 8 (range 6 ~ 14). The common recurrence/metastasis sites were abdominal, pleural effusion, parenchymal liver, mediastinal lymph node and lung. At the time of relapsing, the majority of patients had good performance status (≤ 1). The baseline parameters were well balanced in two cohorts ($P < 0.05$). There were totally 168 cycles given in the endostar cohort (range 2 ~ 16) and 81 cycles in the gemcitabine alone cohort (range 1 ~ 11). The median follow-up period was 23 months (range 4 ~ 36) and 18 months (range 2 ~ 36), respectively.

Efficacy

In the endostar cohort, DCR was 70.9% with a CR in 3 cases, a PR in 7 cases and a SD in 12 cases. Interestingly, the 3 patients experiencing CR were only involved pleural effusion, and 3 in the other 4 cases involved pleural effusion experienced PR. What's more, malignant ascites almost disappeared in 7 of 16 cases with abdominal metastasis, followed by great improvement in quality of life. However, in the gemcitabine alone cohort, DCR was only 40.7% with a PR in 4 cases, a SD in 7 cases. No patients obtained CR, and only 1 of 6 cases with pleural effusion experienced PR, and malignant ascites was partly relieved in only 3 of 13 cases with abdominal metastasis.

Table 2. Univariate Analysis of Overall Survival by Patient Characteristics in the Endostar Cohort

Variable	Hazard Ratio	95% CI	*P* value
Age < 48 vs. ≥ 48	1.001	0.999 ~ 1.002	0.705
FIGO stage I/II vs. III/IV	0.383	0.126 ~ 1.168	0.092
Histology serous vs. others	0.95	0.346 ~ 2.607	0.591
Primary vs. secondary resistance	1.13	1.068 ~ 1.197	0.042
Performance status 0~1 vs. 2	0.931	0.883 ~ 0.981	0.027
Optimal vs. suboptimal surgery	0.713	0.504 ~ 1.008	0.056
Pleural effusion vs. others metastasis	0.498	0.347 ~ 0.716	0.002
Tumor grade 1~2 vs. 3	0.924	0.252 ~ 3.390	0.905

Table 3. Multivariate Analysis of Overall Survival by Patient Characteristics in the Endostar Cohort

Variable	Hazard Ratio	95% CI	*P* value
Performance status 0 ~ 1 vs. 2	0.985	0.927 ~ 1.046	0.083
Primary vs. secondary resistance	1.065	0.949 ~ 1.198	0.094
Pleural effusion vs. others metastasis	0.412	0.244 ~ 0.695	0.032

Table 4. Toxicity of Patients Receiving Treatment

Adverse events (grade)	Gemcitabine plus Endostar (n = 31)	Gemcitabine (n = 27)
	Numbers (%)	
Neutropenia (≥ 3)	10 (32.3)	9 (33.3)
Thrombocytopenia (≥ 2)	6 (19.4)	7 (25.9)
Nausea/vomiting (≥ 2)	9 (29)	6 (22.2)
Diarrhea (≥ 2)	4 (12.9)	2 (7.4)
Constipation (≥ 2)	13 (41.9)	11 (40.7)
Skin rash (≥ 2)	5 (16.1)	4 (14.8)
Fatigue (≥ 2)	11 (35.5)	9 (33.3)
Mucocutaneous bleeding	3 (9.7)	2 (7.4)
Bleeding within CNS	0 (0)	0 (0)
Hypertension (≥ 2)	3 (9.7)	1 (3.7)
Proteinuria (≥ 2)	2 (6.5)	1 (3.7)
Venous thromboembolic event	2 (6.5)	1 (3.7)
Arrhythmia (≥ 2)	1 (3.2)	1 (3.7)
Wound-healing complication	0 (0)	0 (0)

There were statistically significant differences in DCR between the two cohorts ($P = 0.02$).

The median PFS was 6.3 months (95% CI 4.914 ~ 7.686) and 3.2 months (95% CI 2.522 ~ 3.878) for the endostar cohort and gemcitabine alone cohort, respectively. PFS also showed statistical difference ($P = 0.001$) between the two cohorts (Figure 1). Particularly, PFS was more than 12 months in 3 patients with pleural effusion in the endostar cohort, but the longest PFS was about 9 months in the gemcitabine alone cohort. The median OS was 12.5 months (95% CI 6.818 ~ 18.182) and 10.4months (95% CI 8.873 ~ 11.927), respectively. Although median OS was evidently improved in the endostar cohort, there was no statistical difference ($P = 0.201$) when it was compared with that of gemcitabine alone cohort (Figure 2). In the sub-group OS analysis, we found it was statistically longer ($P = 0.046$) in patients with pleural effusion (n = 7) in the endostar cohort than in those with other sites of metastasis (n = 24), while the latter had the similar OS with the gemcitabine alone cohort (n = 27) (Figure 3).

To further investigate the relationship between prognostic factors and OS in the endostar cohort, we then performed the univariate analysis and multivariate regression analysis. Table 2 showed that patients with

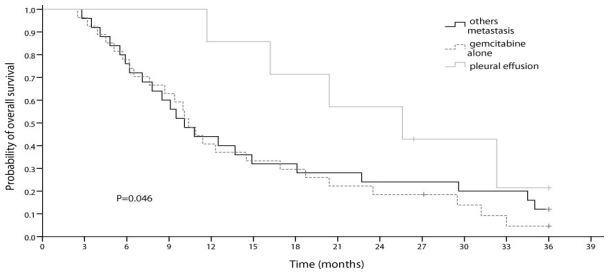

Figure 3. OS was Statistically Longer in Patients with Pleural Effusion (n = 7) in the Endostar Cohort than in Those with Other Sites of Metastasis (n = 24), While the Latter Had the Similar OS with the Gemcitabine Alone Cohort (n = 27)

secondary platinum resistance, good performance status or pleural effusion had better OS ($P < 0.05$). In spite of the early stage, optimal surgery, serous type and low histology grade at initial diagnose and treatment, these factors became no influences on OS ($P > 0.05$) after patients developed platinum-resistant recurrent ovarian cancer. Next, the three positive prognostic factors were included in a Cox proportional hazards regression model in order to identify independent prognostic factors, the results of which were illustrated in Table 3. It showed sites of metastasis was the only independent prognostic factor for OS (HR = 0.412; 95% CI 0.244 ~ 0.695; P = 0.032), which was consistent with treatment efficacy of gemcitabine plus endostar in patients with pleural effusion we observed.

Toxicity

Treatment was well tolerated for most patients (summarized in Table 4), and grade 4 toxicity was uncommon. Except the neutropenia, all other adverse events were ≤ grade 3. 3 patients in endostar cohort suffered from grade 4 neutropenia, and one of these patients experienced febrile neutropenia and got recovery after supportive therapy (G-CSF, anti-infection, and enhancing immunity ability). There were 2 patients involved grade 4 neutropenia in the gemcitabine alone cohort, and no one developed febrile neutropenia. Grade 4 neutropenia was mainly seen in patients with heavily pretreated ovarian caner. Cardiovascular event, proteinuria, bleeding and wound-healing delay didn't show an obvious rise with the addition of endostar to gemcitabine. Although some patients developed skin rash, fatigue and venous thromboembolism, they might be mainly relative to toxicity of gemcitabine, not endostar. Furthermore, severe bleeding didn't occur, and mild mucocutaneous bleeding was related to thrombocytopenia and prior nasal diseases.

Discussion

In recent 2 years, three stage III trials have reported the important roles of anti-angiogenesis on ovarian caner. ICON7 study revealed addition of bevacizumab to initial standard TC regimens improved PFS ($P = 0.04$) after women with ovarian cancer were performed the primary surgery; and patients at high risk for disease progression benefited more with respect to both PFS and OS (Perren et al., 2011). GOG-0218 study showed the use of bevacizumab during and up to 10 months after first-line carboplatin and paclitaxel chemotherapy prolonged the median PFS by about 4 months (95% CI 0.625 ~ 0.824; P < 0.001) in patients with advanced epithelial ovarian cancer receiving debulking surgery (Burger et al., 2011). OCEANS study indicated gemcitabine and carboplatin (GC) plus bevacizumab regimen followed by bevacizumab until progression resulted in a significant improvement in PFS compared with GC plus placebo in platinum-sensitive recurrent ovarian cancer (HR = 0.484; 95% CI, 0.388 ~ 0.605; $P < 0.001$)(Aghajanian et al., 2012). Furthermore, stage III AURELIA study demonstrated chemotherapy plus bevacizumab provided statistically significant and clinically meaningful improvement in median PFS (3.4 months vs. 6.7 months) and objective response rate (ORR, 12.6% vs. 30.9%) in patients with platinum-resistant ovarian cancer, compared with chemotherapy alone, but the ultimate data have not been published. All these high-quality stage III clinical trials have proved anti-angiogenic agents will play a crucial role in the first-line and second-line setting of ovarian cancer. However, as to the other important anti-VEGF drug¬¬-endostar, its role was seldom referred in patients with ovarian cancer.

Endostar was approved by the State Food and Drug Administration of China (SFDA) as a cancer drug, which was the first endogenous angiogenesis inhibitor to receive approval for anticancer therapy (Fu et al., 2009), and had demonstrated activity in many solid tumors. Endostar combining with chemoradiotherapy could improve the early outcome of the advanced cervical cancer, and adverse effects were not encountered (Ke et al., 2012). TC plus endostar seemed to improve ORR (39.3% vs. 23.0%) with a good safety profile in previous untreated advanced NSCLC, compared with TC alone (Han et al., 2011). Endostar suppressed proliferation and triggered cell death in HepG2 cells by autophagy induction in a dose-dependent manner, and the findings provided mechanistic insight into endostar action (Wu et al., 2008). Furthermore, VEGF mRNA expression in endostar plus radiotherapy group was decreased remarkably, and endostar in combination with radiotherapy significantly inhibited the growth of CNE2 tumor, where endostar might act as a radiosensitizer (Zhou et al., 2011b).

To investigate the clinical effect of endostar in ovarian cancer, the current retrospective study was performed. We found addition of endostar to gemcitabine statistically improved DCR (70.9% vs. 40.7%, P = 0.02) and PFS (6.3 months vs. 3.2 months, $P = 0.001$) in platinum-resistant recurrent ovarian cancer, when compared with gemcitabine alone, and the toxicity of endostar was negligible. Generally speaking, malignant pleural effusion or ascites occurring means fairly dismal prognosis in cancers, because there are always no valid methods used to cure or control it till today. Intraperitoneal chemotherapy was once taken as a promising method to deal with malignant ascites, but it was hampered due to intraperitoneal treatment delivery issues (technical problem with catheter placement and management), and severe complications (intraperitoneal adhesion or infection), even it didn't show evident benefits in survival

and quality of life in a lot of cases. Thus, it has not been widely accepted by oncologists. Surprisingly, in the present study, we observed many patients with pleural effusion made excellent outcomes with 3 cases in CR and 4 cases in PR in endostar cohort, and the average OS was about 25 months in the follow-up of 36 months in this small subgroup (n = 7), although all of them ultimately relapsed once again. It was also reported that the use of bevacizumab dramatically improved ascites and the quality of final weeks of life in an 88 year-old woman patients with refractory ovarian cancer and severe symptomatic ascites receiving home hospice care (Hamilton et al., 2008).

Why does endostar show exceptional effect in malignant pleural effusion or ascites? This can be reasonably explained and supported by the following studies. VEGF levels were markedly elevated in malignant ascites, and might play a role in malignant ascites formation by increasing endothelial cell permeability (Zebrowski et al., 1999). And endostatin induced rapid clustering of $\alpha5\beta1$ integrin associated with actin stress fibers and its concomitant colocalization with the membrane anchor protein caveolin-1 in cultured microvascular endothelial cells, mediating inhibition of endothelial cell proliferation and migration (Wickstrom et al., 2002). Moreover, endostatin could bind ovarian cancer cells through integrin $\alpha5\beta1$ and inhibit vessel cooption efficiently and then competitively inhibit tumor cell seeding of the peritoneum in athymic mice. Although both angiostatin and endostatin were potent inhibitors of tumor angiogenesis, peritoneal attachment and vessel cooption was blocked only by the endostatin (Yokoyama et al., 2007). Other ovarian cancer models also showed blocking VEGF could slow tumor progression and inhibit ascites formation (Byrne et al., 2003). Therefore, endostar deserves further study with cytotoxic agents or alone in diseases of malignant effusion.

Though gemcitabine plus endostar improved median OS by 2.1 months in this study, it still had no statistical difference compared with gemcitabine alone (12.5 months vs. 10.4 months, $P = 0.201$), which was mainly attributed to small sample of each cohort and patient characteristics. Age, performance status, tumor histology, and residual tumor volume had proved to be independent predictors of prognosis in patients with stage III epithelial ovarian cancer (Winter et al., 2007). Since clinicopathologic factors have close relation with prognosis, univariate and multivariate analysis were performed to identify certain prognostic factors. Univariate analysis indicated that age, FIGO stage, primary surgery, tumor histology and grade were no longer predictors of prognosis in platinum-resistant recurrent ovarian cancer, although old patients may not tolerate chemotherapy well, mucinous and clear-cell histology types are relative to shorter PFS and OS, and advanced stage and suboptimal surgery at initial diagnosis or treatment mean worse outcomes. The reason why these significant factors became less effective lied in the special populations of endostar cohort. However, performance status, platinum resistance type and sites of metastasis were positive factors in univariate analysis, probably because good performance status means less invasive diseases (besides better toleration of chemotherapy) and, diseases with secondary platinum resistance may be still sensitive to more effective agents than primary platinum resistance. In the Cox regression analysis, sites of metastasis was proved to be the only factor for predicting prognosis on our expectation, chiefly owing to the remarking improvement of malignant effusion with addition of endostar to gemcitabine regimen. Results of the present study can be credible due to stringent criteria on inclusion and exclusion as well as good balance on baseline parameters of the two cohorts. To our knowledge, it is the first time that we report positive results of gemcitabine plus endostar in the platinum-resistant recurrent ovarian cancer. And a prospective study is essentially carried out to further confirm our results.

Collectively, there is still no standard regimen in the platinum-resistant recurrent ovarian cancer at present. Though many agents have showed certain activity in this refractory setting, such as pemetrexed and ifosfamide, the effect is relatively low. But the present study shows better outcome of gemcitabine plus endostar with less toxicity in the setting. Therefore, gemcitabine plus endostar regimen is recommended in patients with platinum-resistant ovarian cancer.

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