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CLINICAL CASE REPORTS

BEVACIZUMAB IN MAINTENANCE THERAPY FOR OVARIAN CANCER PATIENTS

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ABSTRACT

Ovarian cancer is one of the most common cancers in women. Growth and extension of the tumor are associated with active neoangiogenesis regulated by vascular endothelial growth factor (VEGF). Bevacizumab decreases VEGF activity and inhibits the tumor growth.

Purpose of the study. The aim of the study was to evaluate results of bevacizumab in maintenance therapy for ovarian cancer.

Materials and methods. 26 patients with ovarian cancer received maintenance therapy with drop infusions of bevacizumab 15 mg/kg once a day for 21 days in 2014–2019 after completing chemotherapy for relapses.

Results. Bevacizumab mainterned partial response or stabilization in 76.9% of patients. The adverse events were mainly of grades 1–2 (in 88.5% of all adverse events) and could be managed by an appropriate medical correction. Hemorrhagic complications caused the cancellation of bevacizumab in one patient.

Conclusions. Bevacizumab in maintenance therapy after completing chemotherapy for ovarian cancer relapses (both platinum-sensitive and platinum-resistant) significantly improves the treatment results. The toxicity profile of bevacizumab in maintenance treatment is acceptable.

Keywords:
ovarian cancer, relapse, bevacizumab, maintenance therapy, progression-free survival, adverse event

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КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

ОПЫТ ПРИМЕНЕНИЯ БЕВАЦИЗУМАБА В ПОДДЕРЖИВАЮЩЕЙ ТЕРАПИИ У БОЛЬНЫХ РАКОМ ЯИЧНИКОВ

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РЕЗЮМЕ

Одно из наиболее распространенных онкологических заболеваний среди женского населения — рак яичников. Рост и распространение опухоли связано с активным неоангиогенезом, который регулируется фактором роста эндотелия сосудов (VEGF). Бевацизумаб снижает активность VEGF, что подавляет рост опухоли.

Цель исследования. Оценка результатов применения бевацизумаба в поддерживающей терапии рака яичников.

Материалы и методы. В период с 2014 по 2019 годы 26-ти пациенткам с раком яичников проводилась поддерживающая терапия бевацизумабом 15 мг/кг внутривенно капельно 1 раз в 21 день после завершения курсов химиотерапии по поводу рецидивов заболевания.

Результаты. У 76,9% больных проведение поддерживающей терапии бевацизумабом позволило сохранить частичный ответ опухоли на лечение или стабилизацию. Возникшие нежелательные явления были в основном 1–2 степени (в 88,5% случаев от всех возникших нежелательных явлений) и контролировались назначением соответствующей медикаментозной коррекции. У одной больной возникшие геморрагические осложнения послужили причиной отмены бевацизумаба.

Заключение. Введение бевацизумаба в поддерживающем режиме после завершения химиотерапии рецидивов рака яичников (как платиночувствительных, так и платинорезистентных) позволяет значительно улучшить результаты лечения. Профиль токсичности применения бевацизумаба в поддерживающем режиме приемлем.

Ключевые слова:
рак яичников, рецидив, бевацизумаб, поддерживающая терапия, выживаемость без прогрессирования, нежелательные явления

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ABSTRACT

Ovarian cancer is one of the most common cancers in women. In Russia, there is an increase in the incidence of ovarian cancer. In 2008, the prevalence of this disease per 100,000 population was 59.1, and in 2018–76.2.in 2018, the proportion of patients with stage I–II ovarian cancer was 40.3% of the number of patients with a first-time diagnosis, and the remaining patients initially identified stage III and IV. The mortality rate of ovarian cancer patients within a year of diagnosis was 21.3% in 2018. [1] the Frequency of relapses after primary complex treatment in patients with stage III and IV ovarian cancer reaches 80% [2] in the early stages of the disease and the presence of adverse prognostic factors, the frequency of relapses is also high [3, 4]. The occurrence of ovarian cancer recurrence depends not only on the stage of the process, but also on the adequacy of the primary treatment. The appointment of effective schemes of antitumor drug therapy for ovarian cancer is the most important factor in improving the prognosis of this disease.

Vascular endothelial growth factor (VEGF) is an important regulator of physiological and pathological angiogenesis. It is known that in ovarian tumors, the expression of VEGF is higher than in normal tissue, because due to the rapid growth of the tumor and the increasing demand of cells for oxygen and nutrients, rapid neoangiogenesis is necessary. In the tissue of epithelial ovarian tumors, a sharp increase was detected not only in the absolute level of VEGF-A, but also in its ratio to the receptor-1, which shows the content of free endothelial factor and characterizes angiogenic activity in the tissue [5]. Bevacizumab is a recombinant hyperchymeric monoclonal IgG1 antibody that selectively binds and inhibits the biological activity of vascular endothelial growth factor *in vitro* and *in vivo*. Reduced VEGF expression leads to inhibition of vascular growth, which suppresses tumor growth, thereby affecting long-term results [6]. Major international studies of OCEANS (Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease) and AURELIA (Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer) have shown the effectiveness of anti-angiogenic therapy (bevacizumab) together with platinum and non-platinum combinations for platinum-sensitive and platinum-resistant relapses of ovarian Cancer [7, 8]. In a randomized phase III study, OCEANS compared the effectiveness of treatment of patients with platinum-sensitive recurrent ovarian cancer, primary peritoneal or fallopian tube cancer using gemcitabine+carbopaltin+bevacizumab regimens (main group) and gemcitabine+carboplatin+placebo (control group). The average number of cycles of chemotherapy in both groups is 6 (minimum 1 course, maximum 10 courses). Bevacizumab or placebo was administered intravenously on the first day of each cycle of chemotherapy, and after completing cycles of chemotherapy, continued use of bevacizumab or placebo until the disease progressed or intolerant toxicity appeared. The average number of bevacizumab cycles was 12 (from 1 to 43), placebo — 10 (from 1 to 36). Analysis of the results of this study (median follow-up was 24 months) revealed a 2-fold reduction in the risk of disease progression and a statistically significant increase in the period without disease progression in the group of patients receiving bevacizumab. Thus, the median period without disease progression in the main group was 12.4 months, and in the control group — 8.4 months (RR 0.484; 95% CI 0.388–0.605; log-rank $p<0.0001$). Partial response to treatment was observed in 61.2% of patients in the main group (48.3% in the control group). The response time in the main group was 10.4 months, in the control group — 7.4 months (RR 0.534; 95% CI 0.408–0.698). A randomized phase III trial of AURELIA evaluated the effectiveness of bevacizumab and chemotherapy in patients with platinum-resistant recurrent ovarian cancer. The primary endpoint was progression-free survival. In this study, patients were randomized into two groups, one of which received monohymotherapy (pegylated liposomal doxorubicin, paclitaxel, or topotecan), and the second received monohymotherapy in combination with bevacizumab. In the group of patients

who received monohymotherapy in combination with bevacizumab, the median progression-free survival was 6.7 months (95% CI 5.7–7.9), while in the group with only monohymotherapy — 3.4 months (95% CI 2.2–3.7) [9].

According to the practical recommendations of the Ministry of health of Russia and the Russian society of clinical Oncology, patients with recurrent ovarian cancer are recommended to add bevacizumab to the chemotherapy regimen (7.5 or 15 mg / kg IV once every 3 weeks). After the end of chemotherapy, bevacizumab administration is recommended to continue until progression or unacceptable toxicity [10]. The goal of maintenance therapy is to maintain the patient's clinical status achieved by previous treatment [11]. Thus, extending the time until the subsequent progression of the disease is considered a priority when prescribing maintenance therapy. Maintenance therapy continues for a long time, which is limited to establishing the progression of the disease or the appearance of unacceptable side effects. The first drug shown to be used in a maintenance regimen for ovarian cancer was bevacizumab.

Purpose of the study: generalization of the experience of using bevacizumab in maintenance mode for ovarian cancer.

MATERIALS AND METHODS

From 2014 to 2019, 26 patients with ovarian cancer received supportive therapy with bevacizumab after completing chemotherapy for relapses. At the start of primary treatment for ovarian cancer, the patients were aged 45 to 70 years, with an average age of 51 ± 10 years. The distribution of patients by stages of the disease is shown in table 1.

Serous-papillary carcinoma was determined by morphological examination in 12 patients (46.2%), serous carcinoma — in 5 (19.2%), mucinous carcinoma in 3 patients (11.5%), endometrioid carcinoma in 2 patients (7.7%), serous-mucinous carcinoma in 2 patients (7.7%), undifferentiated carcinoma was detected in 2 patients (7.7%). In 16 patients (61.5%), a low degree of tumor differentiation (G3) was detected, in 2 patients (7.7%), a high degree of tumor differentiation (G1), in the remaining patients, the degree of differentiation was not determined. In most cases (18 people (69.2%), primary treatment of ovarian cancer consisted of performing the surgical stage and then conducting 6 courses of polychemotherapy. In 8 patients (30.8%), the first stage was 3 courses of neoadjuvant polychemotherapy, followed by the surgical stage of treatment and continued polychemotherapy.

Most of the patients (22, 84.6% of) recurrence of the disease in terms of more than 6 months from completion of treatment of the primary tumor (platinum-sensitive relapse), in 4 patients (15,4%) were observed latinomericanas relapse of ovarian cancer. More often, the progression of the disease was manifested by a relapse in the pelvis (53.8%), peritoneal metastases (46.1%) and metastases in distant lymph nodes (38.5%). In most cases, 16 patients (61.5%) had not single metastases, but combined lesions of two or more organs (table 2).

In 10 patients (38.5%), bevacizumab was added to the antitumor drug therapy regimen for the treatment of the first recurrence of ovarian cancer. Four patients from this subgroup had received bevacizumab 15 mg/kg intravenously 1 every 3 weeks in conjunction with doxorubicin 50 mg/m^2 intravenously in the 1st day 21-day course, four

Table 1. The distribution of patients by stage of disease (FIGO)

Ovarian cancer stage by FIGO	Absolute number of patients	Percent (*n*=26)
I	2	7.7%
II	2	7.7%
III	16	61.5%
IV	6	23.1%

of the patient — in combination with paclitaxel 175 mg/m^2 intravenously in the 1st day 21-day cycle and carboplatin AUC 5 intravenously in the 1st day 21-day course, two patients with pegylated liposomal doxorubicin 40 mg/m^2 intravenously in the 1st day, 28-day course. In 10 patients (38.5%), bevacizumab was included in the treatment regimens for the second relapse, which the patients continued to receive even after completing chemotherapy. Of this subgroup of patients in the two bevacizumab 15 mg/kg intravenously 1 every 3 weeks was administered in combination with pegylated liposomal doxorubicin 40 mg/m^2 intravenously in the 1st day of the 28 day course, in two patients with paclitaxel 175 mg/m^2 intravenously in the 1st day 21-day cycle and carboplatin AUC 5 intravenously in the 1st day 21-day course, two patients with doxorubicin 50 mg/m^2 intravenously in the 1st day of the 21-day course two — with gemcitabine 1000 mg/m^2 intravenously in the 1st, 8 days 21-day cycle in combination with carboplatin AUC 4 intravenously in the 1st day 21-day course, two patients with etoposide 100 mg orally in 1 to 5 days 21-day cycle and carboplatin AUC 5 intravenously in the 1st day 21-day course. In the event of a third relapse, bevacizumab at a dose of 15 mg / kg intravenously drip once every 3 weeks in combination with chemotherapy was used in 6 patients (23%). Of this subgroup of patients two patients were injected with doxorubicin 50 mg/m^2 intravenously in the 1st day 21-day course, two pegylated liposomal doxorubicin 40 mg/m^2 intravenously in the 1st day, 28-day course, two — doxorubicin 50 mg/m^2 intravenously in the 1st day 21-day cycle and carboplatin AUC 5 intravenously in the 1st day 21-day course. After completing chemotherapy, the patients continued bevacizumab therapy in a supportive mode. In our group, patients received maintenance therapy with bevacizumab 15 mg / kg intravenously drip once every 3 weeks for periods from 3 to 29 months, on average 10.4 ± 5.4 months. Progression-free survival was calculated using the Kaplan-Meyer method, the objective effect of antitumor drug therapy was evaluated according to the RECIST 1.1 criteria, and statistical data processing was performed in the "Statistica 7.0"program.

RESEARCH RESULTS

Partial response to maintenance therapy with bevacizumab was recorded in 12 patients (46.2%), stabilization of the process — in 8 patients (30.7%), progression was detected in 6 patients (23.1%). Annual non-aggressive survival rate of 77%, the median was not reached.

We did not find data on information on the treatment response when bevacizumab was ad-

Table 2. Localization of the tumor process in the progression of ovarian cancer

Tumor localisation	Absolute number of patients	Percent (n=26)
Relapse in the pelvis	14	53.8%
Metastatic lesion of the peritoneum	12	46.1%
Metastases in the lymph nodes	10	38.5%
Liver metastases	6	23.1%
Metastatic lesion of the mesentery of the intestine	4	15.4%
Metastatic pleural lesion	1	3.8%
Metastases to the lungs	1	3.8%
Bone metastases	1	3.8%
Metastatic lesion of the large omentum	1	3.8%

ministered in a maintenance mode without additional administration of chemotherapy drugs. Therefore, we compared our data with the data from the phase III OCEANS study, which used the treatment regimen of carboplatin + gemcitabine + bevacizumab for the treatment of patients with platinum-sensitive ovarian cancer relapses (and continued administration of bevacizumab after completing cycles of chemotherapy). When comparing the data we received on the response to maintenance therapy with bevacizumab with the data from the phase III OCEANS study, we found similar indicators of partial response — in our group it was 46.2%, in the study — 61.2%.

Our data on progression-free survival do not contradict the results of the OCEANS study, where the time interval without disease progression in patients receiving bevacizumab in combination with chemotherapy was 12.4 months.

Among the adverse events, arterial hypertension was most common — 1–2 degrees in 20 patients (76.9%), 3 degrees in two (7.7%) patients. Grade 2 proteinuria on the background of bevacizumab therapy was observed in 1 patient (3.8%). Hemorrhagic complications were observed in 3 patients (11.5%), in one patient (3.8%), the resulting hemorrhagic complications caused the cancellation of bevacizumab. According to a study of OCEANS when adding bevacizumab to the treatment regimen was noted hypertension > grade 3 in 17% of patients, proteinuria more than 3 degrees at 9%. According to our data, the above adverse events were less frequent than in the phase III study, which may be due to the fact that bevacizumab was used in monotherapy in patients of the described group, whereas in the study it was used in combination with gemcitabine and carboplatin.

Clinical case

Patient E., born in 1953, after a planned visit to the gynecologist, on 10.06.2016, an ultrasound examination of the pelvic organs was performed, which revealed a solid cystic formation 86 x 83 x 69 mm posterior to the uterus and to the right. The level of blood cancer markers was determined: CA-125 was 1840 units / ml, Ne-4 89.34 pmol / l. According to computer tomography, no distant metastases were detected. A puncture biopsy of the ovarian tumor was performed, and a cytological analysis was obtained: «carcinoma». 15.07.2016 performed panhysterectomy, extirpation of the large omentum. A histological analysis was obtained during the morphological study: "low-grade serous-papillary carcinoma with the presence of petrificates, solid structures, infiltrative growth, focal small lymphocytic infiltrates in the fatty tissue of the omentum, ectasia and fullness of blood vessels, in the wall of the fallopian tube, mucosal atrophy, sclerosis of the submucosal layer, in the wall of the cervix, minor dysplasia of the integumentary epithelium, leiomyoma with foci of hyalinosis, hypoplastic endometrium." A clinical diagnosis was established-ovarian cancer St III C (rt3cn0m0), the condition after surgical treatment, clinical group 2. the Patient was given 3 courses of polychemotherapy according to the scheme carboplatin AUC 5 V/V drip on 1 day + docetaxel 75 mg/m^2 V/V drip on 1 day, every 3 weeks. Ultrasound examination of the pelvic organs after 3 courses of polychemotherapy revealed continued growth of the tumor (in the pelvis on the right and closer to the iliac region on the right Hypo-echogenic recurrent substrate up to 28 mm, along the posterior arch Hypo-echogenic recurrent infiltrate up to 45 mm with indistinct contours). In this connection, a change of the chemotherapy line was performed and 6 courses of chemotherapy with gemcitabine 1000 mg / m^2 IV / IV drip were performed on days 1, 8, 15 (28 day course). During the next control ultrasound examination of the abdominal and pelvic organs, the following data were obtained:"in the pelvic cavity, an isoechogenic node of 13 x 20 mm is located, a nodular formation along the back surface of the head of the pancreas (36 x 42 mm)". According to the data of spiral x-ray computed tomography of the abdominal organs, the picture of a volumetric pathological formation of the head of the pancreas (39 x 52 x 30 mm). According to magnetic resonance imaging of the abdominal cavity, the picture is characteristic of a cystic solid tumor

located in the area of the head of the pancreas with extra-organ growth in the area of the duodenum, attached to the right renal leg (58 x 44 x 49 mm). The patient was consulted by an abdominal oncologist, this situation is considered as a progression of ovarian cancer. Due to the progression, a change of the chemotherapy line was performed, since 17.05.2017, 9 courses of chemotherapy were performed with pegylated liposomal doxorubicin 40 mg / m^2 intravenously on 1 day, a 28-day course and bevacizumab 15 mg / kg intravenously once every 3 weeks. Next was made of spiral x-ray computed tomography of the chest, abdomen and pelvis and ultrasonography of the abdomen and pelvis (January 2018), which confirmed the stabilization of disease (epigastric and mesogastric Central and more right close to the head of the pancreas adjacent hypoechoic metastatic infiltration confluent character overall dimensions 74 x 28 mm, with isolated anechoic inclusion in the center, with color Doppler mapping (CDM) is weak, mixed flow, recurrence in the pelvis is not revealed). The level of tumor markers decreased to normal values-CA-125 9 u / ml, Ne-4 99.3 pmol / l. In connection with the stabilization of the disease, since January 2018, bevacizumab has been continued to be administered 15 mg/kg intravenously once every 3 weeks in a maintenance mode. Every 3 months, spiral x-ray computed tomography of the chest, abdominal and pelvic organs and ultrasound examination of the abdominal and pelvic organs are performed, and the levels of tumor markers (CA-125 and Ne-4) are determined, confirming the stabilization of the disease. By the time the article is submitted to the journal, the patient has received bevacizumab for 36 months, including 29 months in the maintenance mode. Somatic status on the ECOG 0 scale, the patient takes an active part in social life, continues to work in the specialty. Among the adverse events on the background of bevacizumab therapy, grade 1–2 proteinuria was detected (it first appeared 9 months after the start of bevacizumab therapy) and grade 2 hypertension (blood pressure is controlled by taking an angiotensin II type 1 receptor antagonist, a loop diuretic and a cardioselective beta1-adrenoblocker).

CONCLUSIONS

Administration of bevacizumab in a maintenance mode after completion of chemotherapy for recurrent ovarian cancer (both platinum-sensitive and platinum-resistant) can significantly improve treatment results. In 76.9% of patients in our group, bevacizumab maintenance therapy allowed maintaining a partial response of the tumor to treatment or stabilization. The toxicity profile of bevacizumab in maintenance mode is acceptable. The adverse events that occurred were mainly 1–2 degrees (in 88.5% of cases of all adverse events that occurred) and were controlled by prescribing appropriate medication correction.

Authors contribution:

Vladimirova L.Yu. – research concept and design, scientific editing, data collection, analysis and interpretation, article preparation.

Storozhakova A.E. – research concept and design, technical editing, data collection, analysis and interpretation, article preparation.

Kalabanova E.A. – collection, analysis and interpretation of data, writing text, processing material, preparation of a bibliography, preparation of the article.

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Tikhanovskaya N.M. – data collection, analysis, and interpretation.

Novoselova K.A. – data analysis and interpretation, technical editing.

Selezneva O.G. – data collection, analysis, and interpretation.

Tishina A.V. – technical editing, bibliography design.

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