Case Report

Bevacizumab, Carboplatin and Paclitaxel Combination Treatment in Advanced Stage Ovarian Cancer: The First Experience in Thammasat University Hospital, Thailand: A Case Report

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Background: *Bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), has been approved for concurrent treatment with first line chemotherapy in advanced epithelial ovarian cancer.*
Case Report: *A case of an advanced stage epithelial ovarian cancer (EOC) receiving a combination of bevacizumab, carboplatin and paclitaxel chemotherapy was reported. A 44-year-old woman was presented with abdominal discomfort and distention for 4 months. Bilateral 12 cm diameter ovarian tumors were diagnosed as FIGO stage IIIc after surgical staging operation. Histopathology report showed the mixed type of serous and endometriod adenocarcinoma. The patient was then started on carboplatin/paclitaxel combination chemotherapy for 6 cycles after surgery every 3 weeks. Bevacizumab (7.5 mg/m^2) was concurrently administered with chemotherapy every 3 weeks starting from the 2nd cycle. A complete remission was achieved after the end of the chemotherapy treatment. Bevacizumab was continued for one year after the completion of the standard chemotherapy. Bone marrow suppression, hypertension and proteinuria were not found during Bevacizumab treatment. At bevacizumab treatment completion, a platinum-sensitive recurrent ovarian cancer was diagnosed at the two weeks post program routine check-up. The patient was counseled to start second line chemotherapy treatment and has yet to come back with her decision.*
Conclusion: *Combination of bevacizumab, carboplatin and paclitaxel for first line chemotherapy in advanced EOC in this case had no serious side effects and need further study.*

Keywords: *Ovarian cancer, Bevacizumab, Carboplatin, Paclitaxel*

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Major problem of advanced epithelial ovarian cancer (EOC) is the recurrence of disease even though receiving standard treatment. It composed of cytoreductive surgery and followed by chemotherapy consisting of carboplatin and paclitaxel based on GOG (Gynecologic Oncology Group) 111 protocol[1].

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Vascular endothelial growth factor (VEGF) is a key regulator of physiological angiogenesis during embryogenesis. Pathological angiogenesis of tumors were also implicated. VEGF inhibition was a novel strategy for the prevention of angiogenesis of cancer[2]. Bevacizumab, a humanized, recombinant monoclonal antibody binding to VEGF has shown antineoplastic activity against several solid tumors including colorectal cancer and ovarian cancer[3,4].

In the Gynecologic Cancer Intergroup International Collaboration on Ovarian Neoplasms 7 (ICON7) trial, bevacizumab improved progression-free

survival in patients with ovarian cancer when used in combination with first-line chemotherapy and as a single-drug continuation treatment for 18 cycles[3]. While the Gynecologic Oncology group 218 (GOG 218) trial, bevacizumab dosage was 15 mg/m^2 and gave the same the results[4]. This was the first case of a combination of bevacizumab and chemotherapy at this institute.

Case Report

The authors report the case of 44-year-old woman (para 0-0-0-0) who was sent in the gynaecology clinic, Thammasat University Hospital. Her chief complaint was abdominal discomfort and distention for 4 months. The patient was a healthy-looking, non-smoking and ethnic female. She had a healthy medical history and there were no reports of ovarian, breast and colon cancer in her family history. She had no boyfriend and plan for childbearing.

Pre-operative investigation was done. Complex adnexal cystic mass was detected from current pelvic examination of the patient. A cervical cytology investigated during this visit showed negative result. Chest x-ray, hemogram and liver enzyme profile were all normal. The patient underwent the abdomen-pelvis computerized tomography (CT) scan. The CT reported large, thin-walled, cystic lesion at both ovaries, enhancing solid portion and papillary projection. The measurements were 7.9x5.8x7.2 and 9.9x9.6x6.3 cm on the right and left side of ovary, respectively (Fig. 1). There were pressure effect to sigmoid colon, adjacent small bowel, urinary bladder and both ureters. There was also mild bilateral hydronephrosis.

After thoroughly counseling about her disease, she decided to proceed to surgical staging. Exploratory laparotomy was performed via a midline incision. The operation composed of total hysterectomy, bilateral adnexectomy, infracolic omentectomy, peritoneal biopsy and pelvic lymphadenectomy. A peritoneal cytology examination was performed. Intra-operative gross examination of the uterus showed adenocarcinoma on the uterine serosa. The right and left ovary measured 10x9x8 cm and 10x10x8 cm solid cystic mass containing serous fluid. No metastatic lesions were detected grossly in the rest of the abdominal cavity. Bilateral pelvic lymph node dissection and infracolic omentectomy were then performed. Final histopathological report of both ovaries consisted of a mixed type of endometriod (30%) and serous (70%) adenocarcinoma.

Finally her diagnosis was epithelial ovarian cancer (EOC) stage IIIc (pelvic lymph node metastasis and peritoneal seedlings). However, optimal cytoreduction (no residual tumor or lesser than 1 cm in diameter) was achieved. The patient was counseled including diagnosis, staging, treatment and further management. After thorough counseling, she received six cycles of combined chemotherapy consisting of carboplatin (area under the curve 5) and paclitaxel (175 mg/m^2) every 3 weeks. Bevacizumab (7.5 mg/m^2) was concurrently administered with chemotherapy every 3 weeks starting from the 2nd cycle.

After 5 and 6 courses of bevacizumab and combination chemotherapy (carboplatin/paclitaxel), the complete remission was achieved according to RECIST criteria[5]. Her chest x-ray, whole abdomen tomography, hemogram, liver enzyme profile and tumor marker (CA125 & HE4) were all normal (Fig. 2).

Bevacizumab treatment was continued for 1 year after the completion of chemotherapy (carboplatin/paclitaxel). No serious bone marrow suppression, hypertension and proteinuria were detected during treatment course. This patient was well tolerated. At the end of bevacizumab treatment completion, metastatic cancer survey was performed at the two weeks as program routine checkup.

The patient underwent the third abdomen-pelvis MRI showing a 1.4x1.0 cm oval shaped focus at right internal iliac region. This finding was different

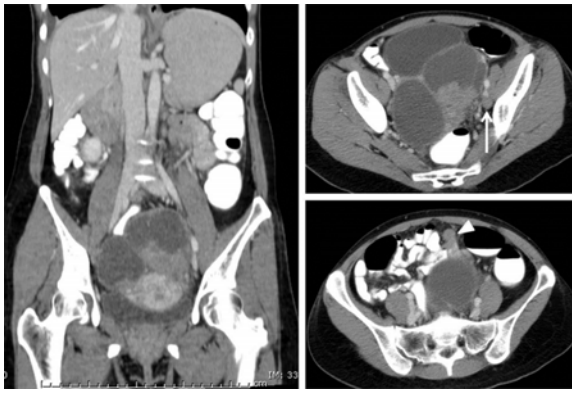

Fig. 1 Abdominal CT scan of this patient, A) Coronal plane of whole abdomen demonstrates bilateral large ovarian thin-walled cystic lesions with enhancing solid portion. B) Axial plane of lower pelvic cavity demonstrates an enlarged left external iliac lymphadenopathy (arrow). C) Axial plane of the upper pelvic cavity demonstrates an irregular enhancing solid nodule which represents peritoneal seeding (arrow head).

compared to the previous CT scan (Fig. 3). There was no ascites fluid. Her tumor markers including CA 125 and HE 4 were slightly elevated (Fig. 2). A platinum sensitive recurrent ovarian cancer was diagnosed[6]. The patient was counseled to start the second line chemotherapy treatment and has yet to come back with her decision.

Discussion

Currently, women diagnosed with advanced epithelial ovarian cancer under went cytoreductive surgery followed by adjuvant platinum (carboplatin) and taxane-based (paclitaxel) chemotherapy. This regimen was widely accepted according to GOG-111 protocol[1]. The recurrence disease was the major problems of advanced EOC even through the patients received optimal cytoreductive surgery followed by standard chemotherapy.

Patients with disease recurrence 6 months after first-line therapy are termed "platinum sensitive", and have response rates in the range of 30-40% to second-line agents[6]. After standard treatment, the minority of women with EOC were actually cured. A promising strategy of ovarian cancer treatment focused on angiogenesis inhibition[7].

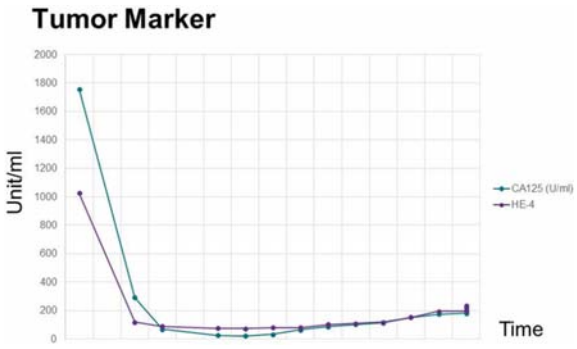

Fig. 2 Tumor marker (composed of CA125 and HE4) after surgery, during chemotherapy and completion of bevacizumab maintenance.

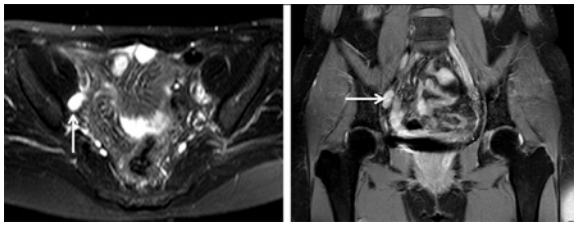

Fig. 3 Pelvic MRI, A) Axial T2-weighted image and B) Coronal post contrast T1-weighted image, demonstrates a new enlarged right external iliac lymphadenopathy (arrow).

Angiogenesis is the process of new blood vessel development that serving tumor growth. Vascular endothelial growth factor (VEGF) was the target of interest. Blocking VEGF pathway will inhibit endothelial cell proliferation[7].

Bevacizumab, a humanized, recombinant monoclonal antibody binding to VEGF has shown antineoplastic activity against several solid tumors including colorectal cancer and ovarian cancer[3,4].

Thailand is one of the countries approving the combination of bevacizumab and chemotherapy for the first line treatment in advanced epithelial ovarian cancer (EOC) under regulation. This case achieved combination of bevacizumab and standard chemotherapy (carboplatin/paclitaxel) according to ICON 7 protocol. Bevacizumab in this case supported by TGCS (Thai Gynecologic Cancer Society) in AVA-POP (Avastin Access Program for Ovarian Cancer Patients) funded by Roche, Thailand.

The most common side effects of bevacizumab include hypertension, proteinuria, thrombotic phenomenon, impaired surgical wound healing and bowel perforation; none was found in this case[7,8].

Unfortunately, despite this case having received the up-front adjuvant chemotherapy combination (bevacizumab/carboplatin/paclitaxel), the case was faced with a recurrent condition. Recurrent ovarian cancer was still problematic and uncommonly cured.

Recurrent ovarian cancer in this patient was diagnosed based on measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) and CA-125 assessable disease according to Gynecologic Cancer Inter Group (GCIG) criteria[5,9]. No histology was proven from this case.

This case was counseled to restart a platinum-based regimen. The chemotherapy regimen in this patient was a combination of pegylated liposomal doxorubicin (30 mg/m^2 intravenously on day 1) and carboplatin (AUC 5 intravenously on day 1) every 4 weeks based on GCIG study[10].

Conclusion

A combination of bevacizumab, carboplatin and paclitaxel for the first line chemotherapy in advanced EOC in this case had no serious side effect and need further study.

What is already known on this topic?

Major problem of advanced epithelial ovarian cancer (EOC) is the recurrence disease even though receiving standard treatment. It composed of cytoreductive surgery and followed by chemotherapy consisting of carboplatin and paclitaxel based on GOG (Gynecologic Oncology Group) 111 protocol[1]. Vascular endothelial growth factor (VEGF) is a key regulator of physiological angiogenesis during embryogenesis. VEGF inhibition was a novel strategy for the prevention of angiogenesis of cancer[2]. Bevacizumab, a humanized, recombinant monoclonal antibody binding to VEGF has shown antineoplastic activity against several solid tumors including colorectal cancer and ovarian cancer[3,4]. In the Gynecologic Cancer Intergroup International Collaboration on Ovarian Neoplasms 7 (ICON7) trial, bevacizumab improved progression-free survival in patients with ovarian cancer when used in combination with first-line chemotherapy and as a single-drug continuation treatment for 18 cycles[3].

What this study adds?

The most common side effects of bevacizumab include hypertension, proteinuria, thrombotic phenomenon, impaired surgical wound healing and bowel perforation were not found at 7.5 mg/m^2 of bevacizumab dosage[7,8]. A combination of bevacizumab, carboplatin and paclitaxel for the first line chemotherapy in advanced EOC in this case had no serious side effects but needs further study.

Potential conflicts of interest

Bevacizumab in this case supported by TGCS (Thai Gynecologic Cancer Society) in AVA-POP (Avastin Access Program for Ovarian Cancer Patients) funded by Roche, Thailand.

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การรักษามะเร็งรังไข่ที่อยู่ในระยะแพร่กระจายโดยการใช้ยาบีวาซิซูแมบ คาร์โบพลาติน และพาคลิแทคเซล: ประสบการณ์ครั้งแรกในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ: รายงานผู้ป่วย

คมสันติ์ สุวรรณฤกษ์, ยุทธเดช ทวีกุล, กริชา ไม้เรียง, เย็นฤดี ภูมิถาวร, กานต์ แตงเที่ยง, วิเชษฐ์ ปิยะวงศ์, กรณ์กาญจน์ ภมรประวัติธนะ

ภูมิหลัง: ยาบีวาซิซูแมบ (โมโนโคลนอลแอนติบอดีคล้ายของมนุษย์ที่มีความความจำเพาะต่อปัจจัยการเจริญเติบโตของเยื่อบุผิวด้านในหลอดเลือด) ได้รับคำรับรองให้เป็นยาอันดับแรกร่วมกับยาเคมีบำบัดในมะเร็งรังไข่ที่อยู่ในระยะแพร่กระจาย

รายงานผู้ป่วย: ผู้ป่วยมะเร็งรังไข่ชนิดเยื่อบุผิวที่อยู่ในระยะแพร่กระจาย อายุ 44 ปี มีอาการอืดอัดแน่นท้องและท้องโตขึ้น เป็นเวลา 4 เดือน ตรวจพบก้อนที่รังไข่ทั้งสองข้างขนาดเส้นผ่าศูนย์กลางประมาณ 12 เซนติเมตร ได้รับการวินิจฉัยมะเร็งรังไข่ระยะ IIIc ภายหลังการผ่าตัดเพื่อกำหนดระยะโรค ผลทางพยาธิวิทยาเป็นมะเร็งเยื่อบุผิวชนิดซีรัส และเอ็นโดเมททริออย ผู้ป่วยได้รับยาเคมีบำบัดชนิดคาร์โบพลาตินและพาคลิแทคเซลจำนวน 6 รอบภายหลังผ่าตัดทุก 3 สัปดาห์ ผู้ป่วยได้รับยาบีวาซิซูแมบขนาด 7.5 มิลลิกรัมต่อพื้นที่ผิวกาย 1 ตารางเมตร ร่วมกับยาเคมีบำบัดเมื่อเริ่มต้น รอบที่สองของยาเคมีบำบัดและเมื่อสิ้นสุดรักษาด้วยยาเคมีบำบัดผู้ป่วยอยู่ในสถานะหายจากโรค จากนั้นผู้ป่วยได้รับยาบีวาซิซูแมบต่อไปภายหลังหยุดยาเคมีบำบัดแล้วเป็นเวลา 1 ปี ไม่พบภาวะกดไขกระดูก ความดันโลหิตสูง และภาวะโปรตีนในปัสสาวะ ในผู้ป่วยรายนี้เมื่อสิ้นสุดการรักษาด้วยยาบีวาซิซูแมบ ผู้ป่วยได้รับการตรวจวินิจฉัยเพิ่มเติมได้รับการวินิจฉัยว่ามะเร็งรังไข่ชนิดกลับซ้ำที่ตอบสนองต่อยาเคมีบำบัดกลุ่มพลาตินั่ม ผู้ป่วยได้รับคำปรึกษาแนะนำเกี่ยวกับการรักษาโดยการใช้ยาเคมีบำบัดรอบสองและอยู่ระหว่างการตัดสินใจ

สรุป: การรักษามะเร็งรังไข่ที่อยู่ในระยะแพร่กระจายโดยการใช้ยาบีวาซิซูแมบ คาร์โบพลาตินและพาคลิแทคเซล ในผู้ป่วยรายนี้ไม่พบข้อแทรกซ้อนที่รุนแรงและยังต้องการผลการศึกษาต่อไป