Cancer and Clinical Oncology; Vol. 5, No. 2; 2016
ISSN 1927-4858 E-ISSN 1927-4866
Published by Canadian Center of Science and Education

Cardiovascular Toxicity of Bevacizumab in Long-term Survival of Recurrent Ovarian Cancer: A Case Report

Yi Pan[1]

[1] Departmetn of Neurology, School of Medicine, Saint Louis University, St. Louis, MO, USA

Correspondence: Yi Pan, MD, Ph.D, Associate Professor, Departmetn of Neurology, School of Medicine, Saint Louis University 1438 South Grand Boulevard, St. Louis, MO 63104, USA. Tel: 1-314-977-6082. E-mail: pany@slu.edu

Received: April 25, 2016 Accepted: May 19, 2016 Online Published: July 18, 2016

doi:10.5539/cco.v5n2p1 URL: http://dx.doi.org/10.5539/cco.v5n2p1

Abstract

Introduction: Bevacizumab has been shown to improve progression-free survival in women with ovarian cancer in multiple clinical trials. Cardiovascular toxicity is reported in the case of a long term survivor of recurrent ovarian cancer. **Case Report:** A 47-year-old woman was diagnosed as stage IIIC, Grade 3 endomitriod adenocarcinoma of the ovary. She had been treated with 4 debulking surgeries and 6 different chemotherapy regimens for 9 years. However, remission diminished over this time period to only one month. Bevacizumab was administrated with additional chemotherapies, and prolonged survival was demonstrated over the next 5 years, including ongoing remission of 18 months to date. New onset hypertension was developed at the 10th month of bevacizumab treatment, and proteinuria was found at the 12th month. Patient presented symptoms of coronary artery disease during the 31th month of bevacizumab treatment, and was soon treated with 4 stents, whereby symptoms resolved. After the 36th month of bevacizumab, the patient had non ST elevated myocardial infarction and peripheral vascular disease. Bevacizumab was terminated thereafter. In the following 18 months, the patient was treated with angioplasty 2 times for coronary artery occlusion, and with an additional stent. This was followed with coronary artery bypass graft. She also had an angioplasty for right femoral artery stenosis. Throughout most of the 14 year disease course, the patient maintained a good quality of life. As patients achieve long term survival from bevacizumab treatment, cardiovascular complications should be recognized and treated aggressively to minimize the adverse effects of cancer therapy.

Keywords: bevacizumab, cardiovascular disease, long-term survival, recurrent ovarian cancer

1. Introduction

Bevacizumab is a vascular endothelial growth factor (VEGF) inhibitor. It has improved progression-free survival in women with ovarian cancer in both first-line chemotherapy (GOG-0218 and ICON7 trials), and second-line chemotherapy in platinum-sensitive (OCEANS trial) and platinum-resistant (AURELIA trial) recurrent ovarian cancer (Burger et al., 2011; Perren et al., 2011; Aghajanian et al., 2012; Pujade-Lauraine et al., 2014). The Food and Drug Administration (FDA) approved bevacizumab for the treatment of patients with platinum-resistant recurrent ovarian cancer in combination with paclitaxel or one other chemotherapy regiment in 2014. The most common vascular toxicities of bevacizumab, from those clinical trials, are hypertension and proteinuria. Coronary artery and peripheral artery diseases as vascular toxicities of bevacizumab are lacking in the literature, which may be due to limited long-term follow up.

As increasing numbers of patients become long-term cancer survivors, the treatment-induced chronic toxicities should receive further attention for cardiac and vascular safeties. Herein is a case of a near 14 year recurrent ovarian cancer survivor who developed coronary and peripheral vascular diseases during 36 months bevacizumab therapy.

2. Case Report

A 47-year-old healthy woman developed abdominal pain, and ovarian cysts were found by ultrasound. She was diagnosed with stage IIIC, Grade 3 endomitriod adenocarcinoma of ovary at an exploratory laparotomy in December of 2002. After optimal debulking surgery, she was treated with 6 cycles of intravenous carboplatin area under the curve (AUC) 6 and paclitaxel 175 mg/m^2. In Augest 2004, recurrent tumors were found in the

spleen, on the liver surface, and pelvic wall by computed tomography (CT). She was treated with 6 cycles of intravenous carboplatin AUC 6 and docetaxel 80 mg/m^2 with a complete response. Nine months later, CT found a 1.5 cm tumor in the spleen of previous location as Febuary of 2006. Splenectomy was performed, followed by 4 cycles of intravenous pegylated liposomal doxorubicin 40 mg/m^2. She was in remission on letrozole 2.5 mg/day for 2 and half years. Upon multiple recurrent tumors were found in the liver, lymph nodes and on the pelvic side wall by whole-body positron emission tomography (PET)/CT in January of 2009, she received the forth chemotherapy regimen with 6 cycles of intravenous carboplatin AUC 6 and gemcitabine 800 mg/m^2. In December 2009, she had an interval debulking surgery for recurrent tumors in pelvis, and between the liver and the right kidney, followed by 4 cycle of intravenous carboplatin AUC 6. In March 2011, another interval debulking surgery was perform for a 3.4 x 3.7 cm^2 tumor on the left pelvic side wall, followed by 5 cycles of intravenous pegylated liposomal doxorubicin 25 mg/m^2. Just one month after this treatment, 3 new recurrent tumors were found by PET/CT in pelvis with CA125 47.8 U/mL in August of 2011. At this time, the patient had received 6 chemotherapy regimens including 4 of them with carboplatin.

Although the patient had persistent chemotherapy induced neuropathy, she had a relative good quality of life, and worked between chemotherapies during the 9 years period. She was 55-year-old with normal blood pressure 98/60mmHg, pulse 68/min, weight 53.7kg, height 167cm and blood tests indicated normal renal and liver functions. She never smoked, had a family history of coronary artery disease and hyperlipidemia, but no family history of hypertension. For the 7th chemotherapy regimen, bevacizumab 10 mg/kg every 2 weeks and paclitaxel 80 mg/m^2 weekly every 3 weeks, were administrated for the patient. She tolerated the treatment well, and CA125 reduced to 22.6 U/mL. After 8 cycles of treatment, bevacizumab was stopped in May of 2012, and the patient was maintained on paclitaxel 80 mg/m^2 weekly every 3 weeks for 5 more cycles. Unfortunately, the patient's CA125 increased to 41.2 U/mL on paclitaxel monotherapy. In October of 2012, the patient returned to the treatment of bevacizumab/paclitaxel in the same dosages as before. Hypertension was noticed as 160/100 mmHg in November of 2012. The patient was treated with lisinopril-hydrochlorothiazide 10-12.5 mg/day initially and changed to lisinopril 20 mg/day one year later. Her blood pressure was well controlled. In January 2013, proteinuria was found, and gradually increased from 18 to 71.9 mg/dL during bevacizumab treatment. CA125 remained abnormal as 40 U/mL after 5 cycles of additional bevacizumab/paclitaxel treatments. At this time, the patient's paclitaxel-induced sensory neuropathy was much worse. In February 2013, the patient's treatment changed to bevacizumab 10 mg/kg every 2 weeks and metronomic oral cyclophosphamide 50 mg/day. After 2 months of the treatment, CA125 returned to normal as 22 U/mL. Ten months after the treatment, no tumor was reviewed on PET/CT. She was on this treatment regimen for total 18 months. In June 2014, the patient felt chest pressure after exertion. Cyclophosphamide was stopped and the patient was on bevacizumab 10 mg/kg every 2 weeks maintenance therapy. Her primary care physician referred her to cardiology for stress test although he found electrocardiogram was normal. Due to abnormal stress test, the patient soon had cardiac catheterization with 1 stent for 80% stenosis of right coronary artery and 3 stents in a long segment for 95% stenosis in the obtuse marginal artery. Meanwhile, she was also treated with clopidogrel 75 mg/day, aspirin 81 mg/day, isosorbide CR 30 mg/day, carvedilol 3.125 mg/day, lisinopril 20 mg/day and rosuvastatin 20 mg/day. In November 2014, the patient had non ST elevated myocardial infarction. In addition, she developed right leg claudication. During this time, bevacizumab was stopped. Carvedilol was increased to 6.25 mg/day and rosuvastatin was increased to 40 mg/day. She had right femoral artery angioplasty for moderate to severe stenosis in March 2015, which resolved the right leg claudication. With the medical treatment, the patient's blood pressure and lipid panel were normal. In November of 2015, the patient had unstable angina and found occlusion of the obtuse marginal artery. She had angioplasty and 1 more stent for the left main coronary artery stenosis. In January 2016, her obtuse marginal artery was occluded again, when she presented intermittent unstable angina. Her cardiologist recommended her coronary artery bypass graft surgery (CABG). She had CABG with 4 vassals bypass grafts in Febuary of 2016. The patient recovered from the surgery well, with no angina, and with no need to take isosorbide CR. To date, she is still in remission of ovarian cancer since stopping bevacizumab in November 2014. The summary of treatment regimens and the duration of remission is listed in Table 1.

Table 1. Summary of surgical and chemotherapy regimens and treatment response

Date	Treatment	Duration of remission (month)
Dec. 2002	optimal debulking followed by carboplatin/paclitaxel 6 cycles	**14**
Sep. 2004	carboplatin/docetaxel 6 cycles	**9**
Feb. 2006	Splenectomy followed by pegylated liposomal doxorubicin 4 cycles	**42**
Feb. 2009	carboplatin/gemcitabine 6 cycles	**6**
Dec. 2009	interval debulking followed by carboplatin 6 cycles	**8**
Feb. 2011	interval debulking followed by pegylated liposomal doxorubicin 4 cycles	**1**
Sep. 2011	paclitaxel weekly with bevacizumab every 2 weeks for 8 months	
May-12	paclitaxel weekly for 5 months	
Oct. 2012	paclitaxel weekly with bevacizumab every 2 weeks for 5 months	
Feb. 2013	cyclophosphamide daily with bevacizumab every 2 weeks for 18 months	
Jul-14	bevacizumab every 2 weeks for 5 months	**18** to date

3. Discussion

The benefit of long term bevacizumab treatment for this patient to date, is 5 more years of good quality and productive life, including currently 18 months progression-free survival. This is after an exhausted previous 6 chemotherapy regimens and total 4 debulking surgeries since she was diagnosed ovarian cancer in December 2002.

Based on clinical trials data, bevacizumab was used for ovarian cancer patients in different doses that ranged from 7.5 mg/kg (ICON7 trial) or 15 mg/kg, every 3 weeks (GOG-0218 and OCEANS trials) to 10 mg/kg every 2 weeks (AURELIA trial). Vascular toxicity, such as hypertension, seams dose dependent. ICON7 used low dose bevacizumab as 7.5 mg/kg every 3 weeks for up to 18 cycles. Hypertension of grade 2 or higher was 18% with bevacizumab vs. 2% with standard therapy, and thromboembolic events of grade 3 or higher were 7% (Perren et al., 2011). In the GOG-0218 trial, bevacizumab was used at 15 mg/kg every 3 weeks for up to 21 cycles. Hypertension of grade 2 or greater was 16.5% in the initial 5 cycles and 22.9% for 21 cycles (Burger et al., 2011). In both trials, bevacizumab was administered during a fixed period of time. In the recurrent setting (OCEANS and AURELIA trials), bevacizumab was continuously administered until disease progression resumed. The optimal treatment dose and duration remain in question. In the present case, the patient was treated with bevacizumab 10 mg/kg every 2 weeks with weekly paclitaxel for 13 months, bevacizumab with metronomic oral cyclophosphamide for 18 months, and bevacizumab monotherapy for 5 months, for a total bevacizumab 36 months. This dose was the same as use in the AURELIA trial. The decision to administer long-term bevacizumab treatment was based on the observations of a raising CA125 after bevacizumab was stopped in the 8th month during treatment for the 7^{th} recurrent disease. The duration of bevacizumab treatment is most likely at least 21 cycles based on the GOG-0218 study report that the benefit of 4 months prolongation of progression-free survival was only seen in the patients with 21 cycles of bevacizumab treatment, but not in the patients with 5 cycles of bevacizumab treatment (Burger et al., 2011).

Although the patient developed new onset hypertension in the 10th month of bevacizumab treatment, hypertension was well controlled by a single antihypertensive agent. Coronary artery disease was found after the 31 month of bevacizumab treatment, and peripheral vascular disease was found after 36 months. The risk factors of the patient for coronary artery disease are hereditary hyperlipidemia and a positive family history of coronary artery disease. Her hypertension, coronary artery disease and peripheral vascular disease were appropriately monitored and treated by her primary physician, cardiologist, and vascular surgeon. In this case, the current 18 month progression-free survival is most likely due to long term bevacizumab treatment because she presented disease progression when bevacizumab was terminated after only 8 months. The longest duration of bevacizumab treatment has been reported in a case of breast cancer (Konigsberg et al., 2014). The patient was treated with bevacizumab at dose from 7.5 mg/kg to 15 mg/kg every 3 weeks until the disease progression for a total of 74 cycles. The patient developed hypertension, but was well controlled with medications.

In a pooled analysis of five randomized controlled trials with 1745 patients, Scappaticci et al found a modest increase in the risk of arterial thromboembolic events among patients with metastatic cancer treated with bevacizumab (Scappaticci et al., 2007). Treatment with bevacizumab and chemotherapy increased the overall incidence of arterial thromboembolic events from 1.7% with chemotherapy alone to 3.8% in combination treatment. The median time to the first event of arterial thromboembolism was 2.1 months in the chemotherapy alone group and 2.6 months in the bevacizumab treated group. Most arterial thromboembolic events were cerebrovascular events (1.7% in combination treatment and 0.5% with chemotherapy alone), angina/myocardial infarction (1.5% in combination treatment and 1% with chemotherapy alone) or others including thrombi in the left ventricle, aorta, or arteries of the mesentery, pelvis, or extremities. They also identified that the risk factors for an arterial thromboembolic event were a history of arterial thromboembolic events, age of 65 years or older, and exposure to bevacizumab.

The mechanism of bevacizumab for cardiovascular risk is unclear. VEGF is essential for normal endothelial homeostasis (Lee et al., 2007). Verheul and Pinedo suggested that angiogenesis inhibitor induced hypertension is caused by the lack of vasodilatory effects, and a decrease in the number of small arteries and arterioles as a consequence of inhibiting new vessel formation. (Verheul and Pinedo, 2007). The molecular mechanisms are: disturbed endothelin function, decreased nitric oxide and prostacyclin production, vascular stiffness, and an inappropriate density of vessels. In their opinion, bevacizumab-induced arterial thrombosis is due to disturbed platelet function and platelet–endothelial cell homeostasis. Endothelial cell apoptosis and lack of endothelial cell renewal would lead to the exposure of the extracellular matrix to circulating blood and result in platelet activation. Mourad and colleagues measured dermal capillary densities in the dorsum of the fingers in colorectal cancer patients before and after a 6-month treatment with chemotherapy and bevacizumab (Mourad et al., 2008). Patients' mean blood pressure was increased from 129/75 to 145/82 mmHg, and mean dermal capillary density at 6 months was significantly lower, as well as pilocarpine-induced vasodilation. Therefore, bevacizumab resulted in reduced spatial density of microvascular networks and endothelial dysfunction. Those changes were closely associated and could be responsible for the rise in blood pressure. They demonstrated that bevacizumab resulted in marked alterations in endothelial function and dermal capillary density. Monocyte chemoattractant protein-1 (MCP-1) is a chemokine involved into the pathogenesis of atherosclerosis and has prognostic value in the acute and chronic phases in patients with acute coronary syndromes (Deo et al., 2004, Piemonti et al., 2009). Piemonti et al found MCP-1 increased in patients with type 2 diabetes and was associated with coronary vascular disease mortality. In a chronic experiment on rodents, bevacizumab showed unexpectedly high overexpression of inflammatory cytokines and MCP-1, both in plasma and in the myocardium in rats (Drimal et al., 2008). Drimal and colleagues utilized spontanuesly hypertensive rats to induce an experiment myocardial infarction. They pre-treated rats with bevacizumab 5 mg/kg intravenously on day 1 and day 7 before the experiment myocardial infarction. They found MCP-1 was significantly higher in bevacizumab pre-treated rats than control rats when measured on day 2 and day 7 after myocardial infarction. These data may suggest an inflammatory hypothesis of atherosclerosis and bevacizumab involvement with cardiovascular disease.

The present case may represent many recurrent ovarian cancer patients who have benefited greatly from emerging target therapies, such as bevacizumab, and have survived longer with an improved quality of life, but also later developed adverse effects including cardiovascular disease. It is a challenge to make decisions such as, how to select patients, and when to initiate or terminate bevacizumab treatment for ovarian cancer. Since the FDA approved bevacizumab for the treatment of patients with platinum-resistant recurrent ovarian cancer in combination with chemotherapy, it seems that after balancing the benefits and risks, bevacizumab may mainly be used in the treatment of recurrent ovarian cancer after failed cytotoxic chemotherapy. It is important to recognize potential cardiovascular complications. Patient's symptoms may be non-specific, as in this case, chest pressure at exertion and leg claudication. These symptoms are common in oncology patients with multiple treatments, complicated with anemia, pulmonary abnormalities, and peripheral neuropathy. Primary care physicians can help oncologists to treat hypertension, monitor cardiovascular complications, and refer to cardiologists and other specialties as needed. To reap the benefits of long term bevacizumab treatment, efforts should be made to diagnose cardiovascular complications and to treat them aggressively to minimize the deleterious adverse effects of cancer therapy.

References

Aghajanian, C., Blank, S. V., Goff, B. A., Judson, P. L., Teneriello, M. G., Husain, A., … Nycum, L. R. (2012). OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol, 30*(17), 2039–2045. http://dx.doi.org/10.1200/JCO.2012.42.0505

Burger, R. A., Brady, M. F., Bookman, M. A., Fleming, G. F., Monk, B. J., Huang, H. … Liang, S. X. (2011). Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med, 365*(26), 2473–2483. http://dx.doi.org/10.1056/NEJMoa1104390

Deo, R., Khera, A., McGuire, D. K., Murphy, S. A., Meo Neto Jde, P., Morrow, D. A., & de Lemos, J. A. (2004). Association among plasma levels of monocyte chemoattractant protein-1, traditional cardiovascular risk factors, and subclinical atherosclerosis. *J Am Coll Cardiol., 44*(9), 1812–8. http://dx.doi.org/10.1016/j.jacc.2004.07.047

Drimal, J., Zurova-Nedelcevova, J., Knezl, V., Sotnikova, R., & Navarova, J. (2006). Cardiovascular toxicity of the first line cancer chemotherapeutic agents: doxorubicin, cyclophosphamide, streptozotocin and bevacizumab. *Neuro Endocrinol Lett, 27*(Suppl 2), 176-179.

Lee, S., Chen, T. T., Barber, C. L., Jordan, M. C., Murdock, J., Desai, S., … Iruela-Arispe, M. L., (2007). Autocrine VEGF signaling is required for vascular homeostasis. *Cell, 130*(4), 691-703. http://dx.doi.org/10.1016/j.cell.2007.06.054

Konigsberg, R., Maierhofer, J., Steininger, T., Kienzer, G., & Dittrich, C. (2014). Long-term remission of a Her2/neu positive primary breast cancer under double monoclonal antibody therapy with trastuzumab and bevacizumab. *Radiol Oncol, 48*(2), 184–188. http://dx.doi.org/10.2478/raon-2013-0083

Mourad, J. J., des Guetz, G., Debbabi, H., & Levy, B. I., (2008). Blood pressure rise following angiogenesis inhibition by bevacizumab. A crucial role for microcirculation. *Ann Oncol, 19*(5), 927-934. http://dx.doi.org/10.1093/annonc/mdm550

Perren, T. J., Swart, A. M., Pfisterer, J., Ledermann, J. A., Pujade-Lauraine, E., Kristensen, G., … Johnson, P. (2011). ICON7 Investigators A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med, 365*(26), 2484–2496. http://dx.doi.org/10.1056/NEJMoa1103799

Piemonti, L., Calori, G., Lattuada, G., Mercalli, A., Ragogna, F., Garancini, M. P., … Perseghin, G. (2009). Association between plasma monocyte chemoattractant protein-1 concentration and cardiovascular disease mortality in middle-aged diabetic and nondiabetic individuals. *Diabetes Care., 32*(11), 2105–2110. http://dx.doi.org/10.2337/dc09-0763

Pujade-Lauraine, E., Hilpert, F., Weber, B., Reuss, A., Poveda, A., Kristensen, G., … Ray-Coquard, I. (2014). Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol, 32*(13), 1302–1308. http://dx.doi.org/10.1200/JCO.2013.51.4489

Scappaticci, F. A., Skillings, J. R., Holden, S. N., Gerber, H. P., Miller, K., Kabbinavar, F., … Hurwitz, H. (2007). Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst, 99*(16), 1232–1239. http://dx.doi.org/10.1093/jnci/djm086

Verheul, H. M., & Pinedo, H. M., (2007). Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. *Nat Rev Cancer, 7*(6), 475-85. http://dx.doi.org/10.1038/nrc2152