Molecular and Cellular Mechanisms of Bevacizumab Actions

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Most ovarian cancer cases are diagnosed at an advanced stage (III or IV), in which a primary debulking surgery combined with adjuvant systemic chemotherapy is the standard management. Since targeted therapy is less toxic to human cells than systemic chemotherapy, it has drawn much attention and become more popular. Angiogenesis is a critical process during the proliferation of ovarian cancer cells. Currently, many studies have put emphases on anti-angiogenetic medication, such as bevacizumab, the first and most investigated angiogenesis inhibitor that can exert anti-neoplastic effects. Bevacizumab is a recombinant humanized monoclonal antibody that has been approved for first-line maintenance treatment of advanced ovarian cancer.

ovarian cancer targeted therapy angiogenesis bevacizumab

1. Introduction

Ovarian cancer ranks fifth place in cancer deaths among women, contributing higher death figures than any other cancer types of the female reproductive system. It is responsible for 14,070 deaths and 22,240 new cases in the United States. Most ovarian cancer cases are diagnosed at an advanced stage (III or IV), in which the overall 5-year survival rate is merely 30% [1]. A primary debulking surgery combined with adjuvant systemic chemotherapy is the standard management for advanced cases. Patients who are considered to be special cases, at risk if undergoing surgery, or with more aggressive diseases would begin with neoadjuvant chemotherapy, followed by an interval debulking surgery and adjuvant chemotherapy [2][3].

Over the past decade, the treatment of ovarian cancer has focused on targeted therapy as well as systemic chemotherapy. Since targeted therapy is less toxic to human cells than systemic chemotherapy, it has drawn much attention and become more popular. Currently, many studies have put emphases on anti-angiogenetic medications. For example, bevacizumab is the first and most investigated angiogenesis inhibitor that can exert anti-neoplastic effects [4]. Bevacizumab is a recombinant humanized monoclonal antibody that was approved by the US Food and Drug Administration (FDA) on 8 May 2020 for use as part of combination therapy with olaparib, a PARP inhibitor for first-line maintenance treatment of homologous-recombination-deficiency (HRD)-positive advanced ovarian cancer [5].

With regard to tumor neoangiogenesis, new blood vessels are essential to supply nutrients in favor of cancer cell growth, and they also contribute to the growth of tumors. Based on the fact, bevacizumab can be attached to vascular endothelial growth factor (VEGF) protein, thus acting on its target to inhibit or offset the growth effect of

tumor cells [6]. While research has not indicated sufficient evidence to prove the increase in patients' longevity [7], the effectiveness of treatment seems to be more obvious when the use of bevacizumab is combined with chemotherapy [8]. Even with dose-dense chemotherapy, the adjuvant bevacizumab has acceptable toxicity [9]. A recent study has also shown that upfront hyperthermic intraperitoneal chemotherapy (HIPEC) combined with bevacizumab-containing adjuvant chemotherapy can improve the prognosis of epithelial ovarian cancer [10]. This phase II, single-arm study enrolled 40 patients affected by advanced ovarian cancer. After complete debulking surgeries, all patients underwent HIPEC with bevacizumab addiction. The results showed maintenance with bevacizumab was feasible in 33 patients (82.5%), and its withdrawal was necessary for 1 patient only (2.5%) due to G3 hypertension. The study has demonstrated that HIPEC can be safely introduced in the upfront therapy of advanced ovarian cancer, along with the usage of bevacizumab [10].

In the past, patients with the BRCA mutation or genomic instability were usually treated with bevacizumab [11]. However, a PARP inhibitor named olaparib, functioning to inhibit polyp ADP ribose polymerase, an enzyme involved in DNA repair, can also be incorporated in the process of maintenance treatment [12]. A randomized, double-blind, international phase III trial investigated the effect of combining maintenance with olaparib and bevacizumab in patients with newly diagnosed, advanced, high-grade ovarian cancers regardless of BRCA mutation status. The median PFS was 22.1 months in the combining group and 16.6 months in the solo group (hazard ratio of disease progression or death: 0.59; $p < 0.001$). Adverse events were consistent with the established safety profiles of olaparib and bevacizumab. In patients with advanced ovarian cancers, combining maintenance with bevacizumab and olaparib could provide a significant progression-free survival (PFS) benefit in ovarian cancer patients with/without a BRCA mutation [12]. To sum up, the progress in medicine and technique has provided weapons, such as bevacizumab and olaparib, for humans to fight with ovarian and breast cancers.

2. Molecular and Cellular Mechanisms of Bevacizumab Actions

Angiogenesis is the formation of new blood vessels by remodeling and expansion of primary vessels. Normal angiogenesis is a highly ordered process under tight regulation, which ensures that developing or healing tissues receive an adequate supply of oxygen and nutrients [13]. Many positively and negatively acting factors influence angiogenesis, and among them the most well-characterized angiogenic factor is vascular endothelial growth factor (VEGF) [14]. VEGF belongs to a heparin-binding glycoprotein family consisting of six isoforms (VEGF-A through E and placental growth factor). VEGF-A shows prominent activity with vascular endothelial cells, primarily through its interactions with the VEGFR-1 and VEGFR-2 receptors found prominently on the membranes of vascular endothelial cells [15]. When VEGF-A binds to its receptor (VEGFR-2), the complex activates a signaling cascade mediated by mitogen-activated protein (MAP) kinase and PI3K/AKT/mTOR and results in the development of angiogenesis, increased vascular permeability, and lymphangiogenesis [6][16].

Although VEGF-A binds VEGFR-1 with a higher affinity than it binds VEGFR-2, the biological effects of VEGF-A are thought to be mediated through VEGFR-2. Since VEGFR-2 is expressed on nearly all endothelial cells, the binding complex can exert widespread actions in the human body. During the process of VEGF-A binding, VEGFR-

2 dimerizes and the tyrosine residues are phosphorylated, resulting in activation of the signal-transduction molecules phospholipase C-r (PLC-r), protein kinase C (PKC), consequent mitogen-activated protein kinase/ERK kinase (MEK), and extracellular signal-regulated kinase (ERK). On the other hand, T-cell-specific adapter (TSAd), Src, PI3K, Akt, and mTOR are also activated by the binding complex of VEGF-A and VEGFR-2 [17] (**Figure 1**).

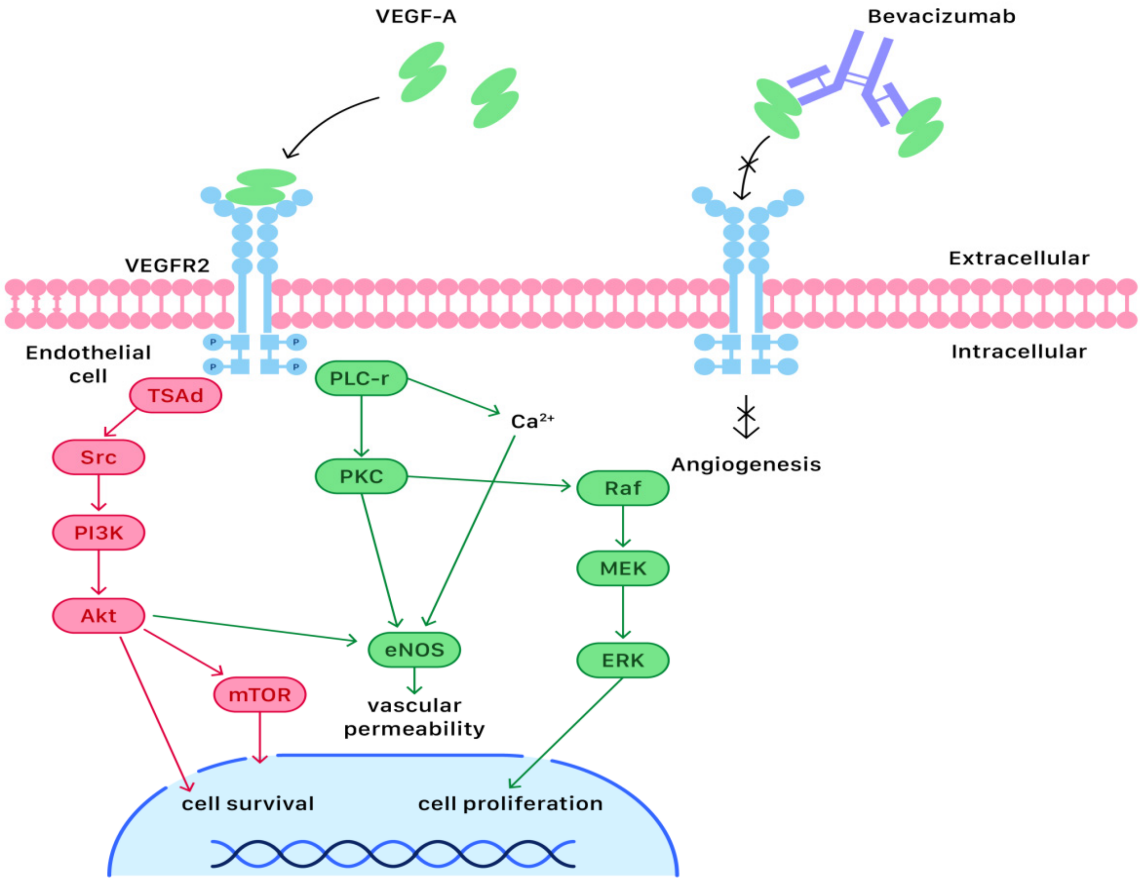

Figure 1. The molecular and cellular mechanisms of bevacizumab in angiogenesis of cancer cells.

In the first pathway, PLC-r stimulates the release of Ca^{2+} and activates PKC, which stimulates the Raf/MEK/ERK pathway and finally promotes cell proliferation. Ca^{2+} mobilization, PKC activation, and Akt activation are the key signaling events in VEGF-A-induced vascular permeability via endothelial nitric oxide synthase (eNOS) activity. In the second pathway, TSAd binds to phosphorylated tyrosine residues and then associates with Src kinases, which are expressed in endothelial cells, thus resulting in regulation of actin stress fiber and mediating VEGF-A-induced PI3K activation. PI3K activation further induces phosphorylation of Akt, thus inhibiting proapoptotic proteins and leading to cell survival [17]. The signaling cascades of both pathways, which are responsible for the development of angiogenesis, increased vascular permeability, and lymphangiogenesis, are illustrated in **Figure 1**.

Angiogenesis is a critical process during the proliferation of cancer cells. The production of VEGF is regulated by local oxygen concentration and usually overexpresses in malignant cells and tumors. Cancer cells often need a continuous supply of oxygen and nutrients, which means that these tissues with cancer cells are in a status of hypoxia. Hypoxia stimulates several complex pathways of cell signaling in cancer cells, including hypoxia inducible

factor (HIF) cell signaling involved in tumor blood vessel formation and metastasis [18]. HIF binds to the hypoxia-response element present in the VEGF gene in a state of hypoxia and induces the transcription and translation of VEGF protein [19][20].

VEGF also enables endothelial and tumor cells to invade adjacent tissues by stimulating the endothelial cells to secrete proteolytic enzymes (e.g., plasmin, matrix metalloproteinases). These enzymes destroy the basement membranes of the precursor blood vessels and weaken the intracellular interactions in the vessel walls. Therefore, the original defense between normal and abnormal tissues is broken under such a condition. Unlike normal angiogenesis, which is highly ordered and strictly regulated, the angiogenesis of cancer cell is fenestrated, chaotic, and abnormal. This disorder creates blood vessels that are structurally and functionally abnormal and impairs the effective delivery of chemotherapeutic agents to the targeted cancer cells, which reduces the effects of chemotherapy [13].

The recurrence and metastasis of epithelial ovarian cancers are featured by the formation and invasion of abnormal tumor cells and vessels, accompanied by the drug resistance of therapeutic chemoagents. Bevacizumab is the first angiogenesis inhibitor to have been approved by the FDA. It is a humanized monoclonal immunoglobulin G antibody that is 93% human and 7% murine in protein sequence and inhibits all active isoforms of VEGF. As an inhibitor of angiogenesis, bevacizumab binds to circulating VEGF-A and thereby inhibits the binding of VEGF-A to its receptors on the surface of endothelial cells [21] (**Figure 1**). Neutralization of VEGF-A prevents neovasculature formation by limiting the blood supply and pruning of immature and abnormal blood vessels. These effects lead to apoptosis of tumor endothelial cells and a decrease in interstitial fluid pressure within the tumors, which allows greater capacity for chemotherapeutic drugs to reach specific targeted sites [22].

Angiogenesis is an ongoing process everywhere in the human tissues that need growth for biologic proliferation, establish transportation for fighting inflammation, and experience repair after sustaining an injury. Although angiogenesis can be divided into normal and abnormal vessel formation, the latter occurs in the majority of tumor tissues and is predominant in all kinds of angiogenesis in the human bodies. Thus, the neoangiogenesis inhibitor bevacizumab can act mainly in tumor tissues and be viewed as a targeted therapy for human cancers. Nevertheless, the inevitable effects of bevacizumab on ordinary vessel formation or normal tissues make its usage limited and account for its side effects in human bodies.

References

1. Torre, L.A.; Trabert, B.; DeSantis, C.E.; Miller, K.D.; Samimi, G.; Runowicz, C.D.; Gaudet, M.M.; Jemal, A.; Siegel, R.L. Ovarian cancer statistics, 2018. CA Cancer J. Clin. 2018, 68, 284–296.
2. Kurnit, K.C.; Fleming, G.F.; Lengyel, E. Updates and New Options in Advanced Epithelial Ovarian Cancer Treatment. Obstet. Gynecol. 2020, 137, 108–121.

3. Wright, A.A.; Bohlke, K.; Armstrong, D.K.; Bookman, M.A.; Cliby, W.A.; Coleman, R.L.; Dizon, D.S.; Kash, J.J.; Meyer, L.A.; Moore, K.N.; et al. Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. J. Clin. Oncol. 2016, 34, 3460–3473.
4. Marchetti, C.; Muzii, L.; Romito, A.; Panici, P.B. First-line treatment of women with advanced ovarian cancer: Focus on bevacizumab. OncoTargets Ther. 2019, 12, 1095–1103.
5. Arora, S.; Balasubramaniam, S.; Zhang, H.; Berman, T.; Narayan, P.; Suzman, D.; Bloomquist, E.; Tang, S.; Gong, Y.; Sridhara, R.; et al. FDA Approval Summary: Olaparib Monotherapy or in Combination with Bevacizumab for the Maintenance Treatment of Patients with Advanced Ovarian Cancer. Oncologist 2020, 26, e164–e172.
6. Stacker, S.A.; Achen, M.G. The VEGF signaling pathway in cancer: The road ahead. Chin. J. Cancer 2013, 32, 297–302.
7. Aghajanian, C.; Goff, B.; Nycum, L.R.; Wang, Y.V.; Husain, A.; Blank, S.V. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol. Oncol. 2015, 139, 10–16.
8. Aravantinos, G.; Pectasides, D. Bevacizumab in combination with chemotherapy for the treatment of advanced ovarian cancer: A systematic review. J. Ovarian Res. 2014, 7, 57.
9. Fleming, N.D.; Coleman, R.L.; Tung, C.; Westin, S.N.; Hu, W.; Sun, Y.; Bhosale, P.; Munsell, M.F.; Sood, A.K. Phase II trial of bevacizumab with dose-dense paclitaxel as first-line treatment in patients with advanced ovarian cancer. Gynecol. Oncol. 2017, 147, 41–46.
10. Paris, I.; Cianci, S.; Vizzielli, G.; Fagotti, A.; Ferrandina, G.; Alletti, S.G.; Costantini, B.; Cosentino, F.; Capoluongo, E.D.; Pasqualoni, M.; et al. Upfront HIPEC and bevacizumab-containing adjuvant chemotherapy in advanced epithelial ovarian cancer. Int. J. Hyperth. 2018, 35, 370–374.
11. Vergote, I.; Ray-Coquard, I.; Anderson, D.M.; Cantuaria, G.; Colombo, N.; Garnier-Tixidre, C.; Gilbert, L.; Harter, P.; Hettle, R.; Lorusso, D.; et al. Population-adjusted indirect treatment comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 trials evaluating maintenance olaparib or bevacizumab or the combination of both in newly diagnosed, advanced BRCA-mutated ovarian cancer. Eur. J. Cancer 2021, 157, 415–423.
12. Ray-Coquard, I.; Pautier, P.; Pignata, S.; Pérol, D.; González-Martín, A.; Berger, R.; Fujiwara, K.; Vergote, I.; Colombo, N.; Mäenpää, J.; et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N. Engl. J. Med. 2019, 381, 2416–2428.
13. Ellis, L.M. Mechanisms of Action of Bevacizumab as a Component of Therapy for Metastatic Colorectal Cancer. Semin. Oncol. 2006, 33, S1–S7.
14. Papetti, M.; Herman, I.M. Mechanisms of normal and tumor-derived angiogenesis. Am. J. Physiol. Physiol. 2002, 282, C947–C970.

15. Kazazi-Hyseni, F.; Beijnen, J.H.; Schellens, J.H. Bevacizumab. Oncologist 2010, 15, 819–825.
16. Aziz, A.U.R.; Farid, S.; Qin, K.; Wang, H.; Liu, B. PIM Kinases and Their Relevance to the PI3K/AKT/mTOR Pathway in the Regulation of Ovarian Cancer. Biomolecules 2018, 8, 7.
17. Van der Ploeg, P.; van der Ploeg, P.; Uittenboogaard, A.; Thijs, A.M.J.; Westgeest, H.M.; Boere, I.A.; Lambrechts, S.; van de Stolpe, A.; Bekkers, R.L.M.; Piek, J.M.J. The effectiveness of monotherapy with PI3K/AKT/mTOR pathway inhibitors in ovarian cancer: A meta-analysis. Gynecol. Oncol. 2021, 163, 433–444.
18. Muz, B.; de la Puente, P.; Azab, F.; Azab, A.K. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. Hypoxia 2015, 3, 83–92.
19. Dzhalilova, D.S.; Makarova, O.V. HIF-Dependent Mechanisms of Relationship between Hypoxia Tolerance and Tumor Development. Biochemie 2021, 86, 1163–1180.
20. Semenza, G.L. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. Oncogene 2009, 29, 625–634.
21. Shih, T.; Lindley, C. Bevacizumab: An angiogenesis inhibitor for the treatment of solid malignancies. Clin. Ther. 2006, 28, 1779–1802.
22. Goel, S.; Duda, D.G.; Xu, L.; Munn, L.L.; Boucher, Y.; Fukumura, D.; Jain, R.K. Normalization of the Vasculature for Treatment of Cancer and Other Diseases. Physiol. Rev. 2011, 91, 1071–1121.