Ovarian function following targeted anti-angiogenic therapy with bevacizumab (Review)

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Abstract. Improvements in cancer therapy have enabled further insight into the long-term effects of treatment, including the highly prevalent gonadal failure. The focus of treatment has been shifted to the preservation of fertility, which may be achieved by preventing ovarian toxicity. To this end, new molecular-targeted agents, including monoclonal antibodies, have been developed and used in a standard procedure for managing different cancers. However, the prolonged antitumor activity of these drugs may cause the emergence of new toxic effects. The aim of the present review was to discuss the leading toxic effect of the anti-angiogenic agent bevacizumab on ovarian function in female patients of reproductive age, which may be observed and expected during in clinical practice. The majority of bevacizumab-induced side effects are expected to be transient and eliminated within the anticipated drug clearance time frame; however, fundamental investigations on these effects are required for generating more evidence-based practice guidelines.

Contents

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1. Introduction

The life expectancy of young cancer patients has significantly increased due to advances in the treatment of malignant diseases. Thus, the focus of medical attention has expanded to include improvements in the quality of life of patients who have undergone cancer treatment. However, cytotoxic damage to ovarian stromal cells and germ cells appears to be progressive and irreversible (1-3) and chemotherapy occasionally exerts detrimental and often unavoidable effects on ovarian function, resulting in female sterility (1-3). Compared with male patients, female patients are more susceptible to gonadal toxicants due to the fact that, unlike men, women are born with an irreplaceable supply of germ cells in their ovaries.

Newly developed molecularly targeted agents, such as monoclonal antibodies, have been utilized as adjuvant or single-agent chemotherapy for over a decade. Bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF), is expected to become the first targeted agent to be approved for the treatment of a wide array of malignancies, including breast, ovarian, lung, colorectal and cervical cancer (4-13). Targeted therapies are considered to obtain a good antitumor response, without causing any major damage to healthy angiogenic tissues. However, introduction of targeted agents with anti-angiogenic properties may negatively affect ovarian function in patients of reproductive age. The effects of bevacizumab therapy on reproductive function have not been clearly determined; however, it is crucial to elucidate this toxicity by investigating the effects of anti-angiogenic agents at the molecular level and what physiologically important roles these processes play in healthy tissues (14). The aim of the present review was to discuss the unintended effects of an anti-angiogenic agent, bevacizumab, on ovarian function, and suggest strategies for the treatment of women of reproductive age.

2. Follicular growth

Invertebrates as well as vertebrates have accessory cells in the ovary surrounding the oocytes that help nourish developing oocytes. These are ordinary somatic cells referred to as follicle cells (Fig. 1), which form an epithelial layer surrounding the oocyte, and are connected to each other and to the oocyte via gap junctions, which allow exchange of only small molecules, but not macromolecules (15,16). Although follicle cells are prevented from providing the oocyte with preformed

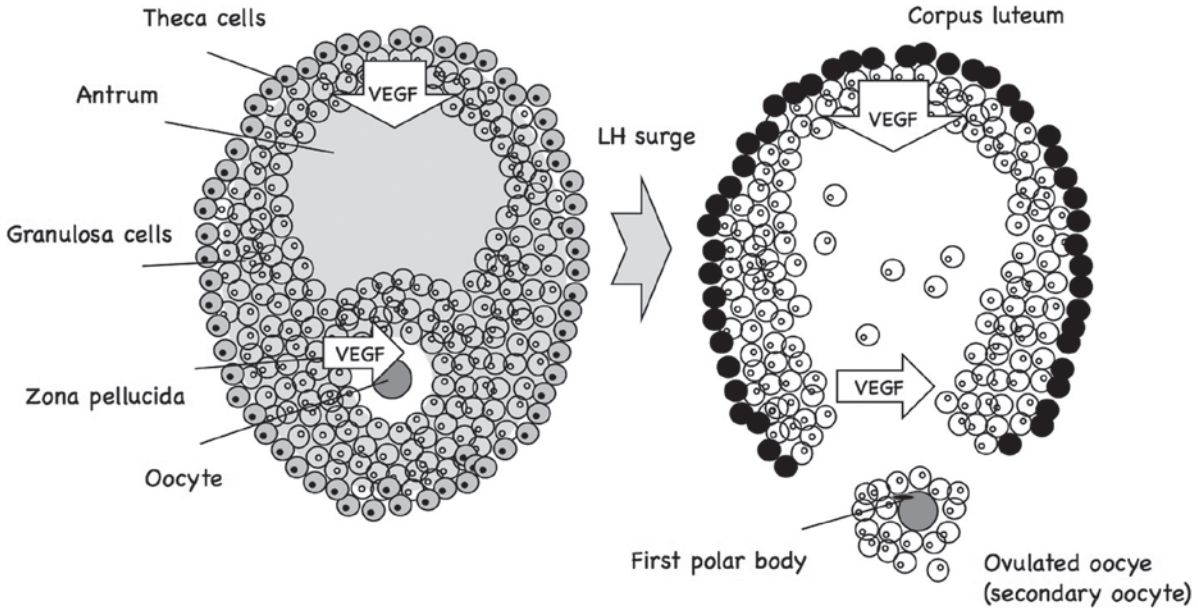

Figure 1. Follicular growth and VEGF. The oocyte is surrounded by granulosa cells, which are separated from an outer layer of theca cells by an intervening basal lamina. LH surge triggers maturation and ovulation of the oocyte and theca cell differentiation to corpus luteum. VEGF and its receptor are expressed in granulosa cells and theca cells in response to gonadotropins, namely FSH and LH. The expansion of the angiogenic networks during follicular development enhances oxygenation and diffusion of several substances important for follicle cells, promoting oocyte maturation. VEGF, vascular endothelial growth factor receptor; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

macromolecules through these gap junctions, they are able to supply smaller precursor molecules from which macromolecules may be synthesized. Of note, the investigation of gap junction communication in mammalian ovaries demonstrated that the gap junction proteins involved in connecting follicle cells to each other differ from those involved in connecting the follicle cells to the oocytes (15,16). By disrupting the genes that encode either of these proteins in mammals, both the follicle cells and oocytes are prevented from normal development, causing female sterility. Follicle cells secrete macromolecules that either contribute to the oocyte coat, are taken up by receptor-mediated endocytosis into the growing oocyte, or act on oocyte surface receptors to control the spatial patterning and axial asymmetries of the oocyte (17-19).

The communication between oocytes and their follicle cells is bidirectional. Coordination of timing is crucial for the developmental processes in the two sets of cells, which appear to be dependent on signals from the oocyte to the follicle cells.

3. Oocyte maturation

The majority of the primary oocytes in female newborns are surrounded by a single layer of follicle cells. Those oocytes and their surrounding follicle cells are referred to as primordial follicles (20-22). Before birth, a small portion of primordial follicles begin to develop multiple layers of follicle cells (granulosa cells) surrounding the growing oocyte. It remains unknown what triggers certain primordial follicles to start growing in this manner. Furthermore, some of these developing follicles develop a fluid-filled cavity, or antrum, and are referred to as antral follicles.

After puberty, approximately once a month, the pituitary gland secretes a surge of follicle-stimulating hormone (FSH), accelerating the development of ~10-12 antral follicles. One of these antral follicles becomes dominant, and a surge in FSH and luteinizing hormone induces ovulation towards the middle of the menstrual cycle: The dominant primary oocyte completes meiosis I, and the resulting secondary oocyte arrests at metaphase II; the rapidly grown follicle then ruptures at the surface of the ovary, releasing the secondary oocyte, which remains surrounded by a shell of granulosa cells embedded in a hyaluronan-rich gel-like matrix (Fig. 1) (20-23). The released oocyte is triggered to complete meiosis II if fertilized by a sperm within ~1 day.

4. VEGF and follicular growth

The reproductive system has a process of vascular development termed angiogenesis. This development of new blood vessels in the ovary is required for delivering necessary nutrients and hormones to ensure follicular growth and formation of the corpus luteum. Since preantral follicles have no vascular supply system of their own, they have to depend on vessels in the surrounding stroma (24,25). However, a vascular sheath consisting of two capillary networks in the theca interna and externa is developed within the thecal layer during antral development. These newly formed ovarian blood vessels are used to supply an increased level of gonadotropins, growth factors, oxygen, steroid precursors and other substances to the growing follicle. The adequate increase of vascular supply may be a rate-limiting step in the selection and maturation process of the dominant follicle to be ovulated (24,25). However, follicular atresia may be caused by degeneration of the capillary bed in follicles that are prevented from developing. Although the ovarian follicle as well as the corpus luteum have been shown to produce some angiogenic factors, VEGFA is considered to play an essential role in regulating angiogenesis in the ovary (24,25). Expression of VEGFA in

ovarian follicles is determined by follicular size, such that in bovine and porcine follicles, the expression of VEGFA is weak during early ovarian follicular development, becoming stronger in granulosa and theca cells as the dominant follicle develops (26-28). The findings were similar in the rat ovary, which also exhibited some secondary follicles with extremely strong VEGFA immunoreactivity in the zona pellucida (28).

VEGFA, a cytokine and homodimeric glycoprotein, has been found in several preantral mammalian follicles, including human (29,30). VEGFA functions as a regulator of angiogenesis in the ovary through the action of its kinase insert domain receptor (KDR; also referred to as fetal liver kinase 1 or VEGFR2) (31,32). A study on mice demonstrated that administering a KDR antibody acts as an inhibitor of gonadotropin-dependent follicular angiogenesis, which in turn impedes development of mature antral follicles (33). It was also observed that inhibition of VEGFA with a VEGFA trap antagonist caused a reduction in follicular angiogenesis and development, as well as a reduction in VEGFR1 (also referred to as FLT1) and KDR expression in monkeys (34). Therefore, ovulation and the subsequent development and functional capacity of the corpus luteum may be inhibited by intrafollicular injection of a VEGFA antagonist (35).

5. Chemotherapy-induced ovarian damage

Several factors affect the rates of permanent infertility and compromised fertility following cancer treatment. Those factors include the drug or size/location of the radiation field, dose, dose-intensity, method of administration (oral vs. intravenous), disease, age and gender of the patient, combination chemotherapy and pretreatment fertility status of the patient (36-40). Older patients are at higher risk of developing ovarian failure. Conversely, younger patients may expect recovery of ovarian function in 30% of the cases at 6-48 months after therapy (37-40). The reason why older patients are clinically observed to be more affected by chemotherapy, is possibly that older women naturally have a smaller ovarian reserve. Therefore, it may be hypothesized that recovery of ovarian function following cancer therapy may be associated with a significant reduction in ovarian reserve.

6. Effect of bevacizumab on ovarian function

Cancer treatment may temporarily or permanently affect female fertility. It may also become apparent later as premature ovarian failure (POF) (2,3,37). It should be noted that female fertility may be compromised, even when there is maintenance or resumption of cyclic menses. The presence of regular menstruation is not a guarantee for normal fertility, as any reduction in ovulatory reserve may reduce the likelihood of subsequent conception and increase the risk of early menopause. Preserved fertility following cancer treatment may be shortened by premature menopause. Due to the risk of POF, these patients should not delay childbearing (41-46). Even if regular menses and a normal reproductive outcome are observed following chemotherapy, it should not be taken as a certain indicator of survival of the ovarian follicular reserve from treatment. Patients who have been exposed to high-dose chemotherapy or radiotherapy are advised not to delay childbearing for long once they recover from ovarian failure (3,37). These patients are encouraged to conceive within a few years of a disease-free period, but to avoid pregnancy <6-12 months after treatment on growing oocytes (38). Histological studies demonstrated that chemotherapy on human ovarian tissue may result in ovarian atrophy, with marked loss of primordial follicles (23).

In view of the functions of anti-angiogenic agents on normal physiological processes (14), it has become more evident that female fertility may be temporarily or permanently affected. The half-life of bevacizumab is estimated to be ~20 days (range, 10-50 days). With doses of 1-20 mg/kg, either weekly or triweekly, drug clearance is estimated to be 100 days (5 half-lives). Time analysis of onset and resolution of the adverse effects of bevacizumab may be found in the literature to a limited extent (47,48). Even if bevacizumab induces ovarian damage, it is likely that this damage is transient and disappears within the expected drug clearance timeframe in the majority of the cases. However, frequent and/or prolonged drug administration may further complicate the anticipated toxicity.

7. Bevacizumab during pregnancy

The availability of data on the use of bevacizumab on pregnant women is currently limited; however, due to its anti-angiogenic and potentially damaging effects on fetal development, its use on pregnant women should be avoided (49). Based on studies on pregnant women exposed to chemotherapy prior to conception, no increase of miscarriages or congenital abnormalities has been reported compared with the general population. It is hypothesized that corrective mechanisms within the oocyte may have taken place, or that undetected miscarriages at a very early stage may have occurred due to dominant lethal mutations, since these pregnancies occurred long after treatment was completed (3,38,39).

8. Conclusion

Considering the importance of VEGF for folliculogenesis and maturation of the oocyte, ovarian dysfunction appears to be a plausible side effect of the angiogenic treatment. The aim of using bevacizumab is obtaining a favorable antitumor response, without damage to healthy tissues. The majority of bevacizumab-induced side effects are expected to be transient and eliminated within the anticipated drug clearance time frame; however, fundamental investigations on these effects are required to generate more evidence-based practice guidelines.

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