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The role of bevacizumab on tumour angiogenesis and in the management of gynaecological cancers: A review

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ABSTRACT

Objective: The study aims to analyze the effectiveness of bevacizumab in addressing the complications associated with gynecological cancers and evaluates effective treatments for various gynecological cancers.
Methods: The study follows a systematic review approach that has been implemented to analyze the qualitative published data from previous studies. Studies related with the trials of angiogenesis and bevacizumab were selected in the review.
Results: In general, the management of gynecological cancers include chemotherapy, surgery and radiation therapy. Results suggest bevacizumab as an effective treatment modality for cervical and several other cancers. Overall, bevacizumab showed promising results in improving the overall survival rate of gynecological cancer patients through the combination of bevacizumab with other chemotherapeutic agents.
Conclusion: Bevacizumab possess less documented adverse effects when compared to other chemotherapeutic agents. The manifestation and severity of adverse effects reported varied according to the chemotherapeutic agent(s) that were used with bevacizumab in combination therapy. Overall, bevacizumab effectively improved the survival rate in patients with several gynaecological cancers.

1. Introduction

Gynecological cancers are a group of cancers involving the female reproductive system, that includes cancers of the ovary, cervix, endometrium, fallopian tube, vagina and vulva [1]. This review focuses on the three most common types of gynecological cancers, which are cervical, endometrial and ovarian cancer.

The current treatment for gynecological cancers include surgery for dissectible tumors; chemotherapy and radiotherapy for in-dissectible tumors [2–9]. However, even with the combination of both chemotherapy and radiotherapy, the prognosis of gynecological cancers remains poor [10] due to tumor angiogenesis [11]. Angiogenesis is defined as the formation of new blood capillaries [11,12], which is a complex process that promotes vascular endothelial growth factor (VEGF) and other proangiogenic factor expression, thus enhancing metastasis [11,12]. Almost 50% of the human cancers known were found to have the expression of the VEGF family and VEGF receptors [13]. These factors are known to worsen the prognosis of cancers of the uterine cervix [14], endometrium [15], and ovary [16–18]. Hence, the novel therapeutics in recent years suggested that Bevacizumab (Avastin®, Genentech), a humanized monoclonal antibody that acts as a direct VEGF inhibitor [12], approved by FDA in 2014 may show some clinical benefit in improving the overall survival rate of gynecological cancer patients [19–21].

Cervical cancer is now ranked the fourth most common female cancer, with an estimated 527,600 new cases diagnosed and resulting in 265,700 mortality worldwide every year [22]. In the United States of America (USA), the estimated number for new cervical cancer cases in 2015 was 12,900 with 4100 estimated number of deaths [23]; among which the squamous cell carcinoma being the major type of cancer [24]. The main etiology of cervical cancer is the chronic infection by Human Papillomavirus (HPV), with the HPV Subtypes 16 and 18 accounted for 70% of all cervical cancer cases worldwide [24]. The incidence of cervical cancer is higher in developing countries with an

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estimated 2.716 million population of ages from 15 to 44 years, who are in the high risk group [24]. Africa, Central and South America are the countries with the highest incidence rates of cervical cancer; whereas developed countries such as North America, Australia, New Zealand and parts of Western Europe have the lowest incidence rates [22]. Overall, 90% of deaths caused by cervical cancer happens in the developing countries [22,24], where India is accounted for one-fourth of the total cervical cancer deaths [22].

Endometrial cancer with an estimated 319,600 new cases globally in 2012 alone [22], is ranked as the sixth most common type of cancer in women [22,25]. Endometrial cancer, which occurs in the lining of the uterus, is the most common type of cancer occurring in the uterus [26]. Unlike cervical cancer, the incidence of endometrial cancer is found higher in high-income and developed countries with the higher risk group being post-menopausal women [25]. North America, Central and Eastern Europe have the highest incidence. On the contrary, countries with middle or low-income such as Western Africa have the lowest incidence [25]. Cancers of the uterine body and endometrium have an estimated total of 54,870 newly diagnosed cases, with an estimated 10,170 fatalities for endometrial cancer in the USA alone in 2015 [10]. Majority of the endometrial cancer cases are of adenocarcinoma origin [26]. For local stage or stage I endometrial cancer that represents 67% of all endometrial cancer cases diagnosed [27,28], the 5-year survival rate is significantly high at 95.3% [28,29] due to presentation of early symptoms [25]. Other stages of endometrial cancers are relatively rare, but associated with worse prognosis [27]. In general, an average of 69% [27] of the diagnosed endometrial cancer patients will survive for 5 years upon detection [25]; hence, endometrial cancer only contributes less than 2% of cancer death cases in women [25,27].

Ovarian cancer has an estimated 238,700 new cases each year with 151,900 estimated deaths in 2012, ranking it as the seventh most common cancer in females [26,27]. In the USA, the incidence of ovarian cancer was estimated to be around 21,290 with about 14,810 deaths in 2015 alone [27]. Almost all the cases diagnosed are of epithelial carcinoma origin [26]. Similar to endometrial cancer, the incidence rate of ovarian cancer is higher in developed countries and the risks increase with age, although, less cases occur in post-menopausal women [26]. In 2012, the incidence rate is more than 9 per 100,000 women in developed countries in Central and Eastern Europe [29]; and on the contrary, the incidence rate is 5 per 100,000 [29] women in developing countries such as parts of Africa [29,30]. The mortality rate was 5 and 3.1 per 100,000 in developed and developing countries respectively [28]. Ovarian cancer is known as a 'silent killer' in females due to absence of symptoms in early stages. Hence, ovarian cancer is usually fatal, with an average of 60% of the diagnosed cases succumbing to death within 5 years upon detection [29–31].

Although the incidence and survival rates between endometrial cancer and ovarian cancer are different, the risks for both cancers are similar. The main reason of higher incidence of both of these cancers in developed countries is due to the use of estrogen-only hormone replacement therapy [32–35]. Other significant factors that increase the risk include sedentary lifestyle, obesity, not bearing children, having early menarche and late menopause [35–40].

Angiogenesis has been the main characteristic feature of these cancers. Antiangiogenic agents such as bevacizumab have been promising in prolonging the survival rate in these patients. The aim of this study is to review the antiangiogenic properties of bevacizumab in the treatment of gynecological cancers.

2. Statement of objectives

The study aims to analyze the effectiveness of antiangiogenic agents such as bevacizumab to address the complications associated with gynecological cancers and evaluate effective treatments for various gynecological cancers.

3. Material and methods

The review was carried out from early 2015 until August 2016. Literature dating until August 2016 were included in the review. Most of the search was performed on the online search engines namely Google, Google Scholar and Medline followed by various other electronic online bibliographic databases. Additional links to electronic research databases were separately searched. For PubMed search, controlled vocabularies such as MeSH (Medical Subject Headings) were used. ERIC Thesaurus terms and a combination of related keywords were also used. The source of data selection was done from reputed international journals.

3.1. Study selection

All relevant studies ranging from clinical trials, pre-clinical studies and laboratory findings were included in the review. Studies concerning other cancers and non-relevant topics were omitted. All included studies and documents were assessed for the quality of the work done. A team of six reviewers among the authors were involved in the assessment of the documents, which included homogeneity, relevance, quality, and language. The recent research studies, which were having a positive correlation of angiogenesis with the effect of bevacizumab, were selected as a source of information to this topic. The effectiveness in treatment of various gynecological cancers was analyzed with a thorough review of the relevant studies. The effectiveness of several other drugs was also examined to compare and correlate the effects and side effects of bevacizumab. There were some studies that have proven the side effects of bevacizumab; however, most of them were favoring the concept.

4. Results and discussion

4.1. Clinical problem

4.1.1. Angiogenesis

Angiogenesis is a process of growing, sprouting or developing new blood vessels from the pre-existing vasculature or intussusception. In other words, angiogenesis is the separation of an existing blood vessel into two and more new blood vessels from the parent blood vessel [41–43]. Angiogenesis is tightly regulated by the balance of proangiogenic and antiangiogenic factors [44]. Generally, angiogenesis undergoes four stages as shown in Fig. 1 [41,45,46].

4.1.2. Types of angiogenesis

Angiogenesis can be classified into two types, which are sprouting and non-sprouting angiogenesis [47]. The latter is also referred to as intussusception [47]. Sprouting angiogenesis is the growth of new blood vessels from the pre-existing blood vessels and usually occurs during the development of yolk sac and embryo [47,48]. On the other hand, non-sprouting angiogenesis is the enhancement of the complexity of the newly formed blood vessels into a vascular network [49]. The development of non-sprouting angiogenesis can take minutes to hours as it does not require endothelial cells to proliferate [49]. Both sprouting and non-sprouting angiogenesis are observed in the development of organs or tissues vascularization such as yolk sac, heart and lungs [47]. Therefore, both types of angiogenesis are equally important in aiding tumor growth because a highly vascularized tumor will ensure tumor survival, growth and allow metastasis to other parts of the body. However, the development into either sprouting or non-sprouting angiogenesis is dependent on the number of existing blood vessels in that specific organ or tumor [50,51].

4.1.3. Occurrence of angiogenesis

Angiogenesis is a common process that occurs during many physiological conditions such as in the development of placenta and fetus