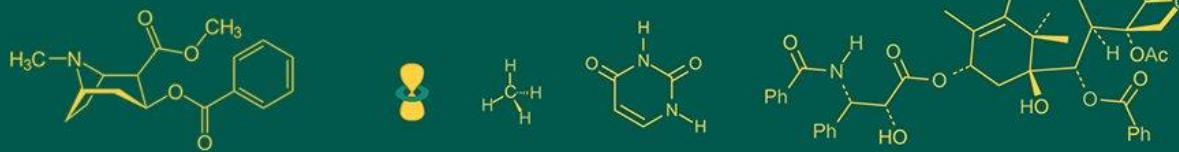


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Inhibition of angiogenesis in the treatment of breast cancer

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Abstract

Worldwide every year, more than 2 million women suffer from breast cancer. The food habit and the current lifestyle, lead to an increase in obesity. Obesity is one of the chief causes of breast cancer. Angiogenesis is highly crucial for tumor growth. The tumor development and metastasis are fully dependent on angiogenesis or the newly formed blood vessels, which supply nutrients for the tumor development. Several early diagnosis methods for detection of breast cancer are there like, mammography, which is an X-ray technique to visualize inside the breast. This technique is used for the early detection of breast cancer. Antiangiogenic treatment plays a major role in treating breast cancer, as it inhibits the supply of nutrients which is essential for tumor growth. Our review will be focusing on the anti-angiogenic drugs which inhibit the formation of new blood vessels. Inhibiting angiogenesis is an effective way to treat breast cancer as it is a safe and effective method.

Keywords: Angiogenesis, breast cancer, tumor, antiangiogenic treatments

Introduction

Cancer is a type of disease in which the body cells divide uncontrollably and spread to other parts in some cases. There are various types of cancer, but the main focus of our review is breast cancer. Breast cancer is a heterogeneous disease, which includes a broad variation prognosis^[1], named after the location where it is found. It is more common in women than men. The chance of an individual dying of breast cancer is 1 in 35^[2].

Breast cancers are the most common carcinoma with approximately 1 million deaths per year. It is the second most common non-skin cancer and it is the fifth most common type of cancer^[3]. Breast cancer comprises 7% of the total deaths caused due to cancer worldwide and includes almost 1% of the total deaths^[4].

Cancerous cells are similar to the cells from where they have originated (have similar DNA and RNA but they are not identical to the cells) and hence, the immune system is unable to recognise the cancerous cells. Cancer is caused due to the modification or mutation of the genetic material, DNA, or RNA. The mutation of the genetic material results from various factors.

UK cancer registry data shows that there is an increasing trend of breast cancer worldwide from age 30 to 35. At the age of 60-65 years, it achieves its highest peak (Fig. 1). Average Women in India under 40 years are more prone to have breast cancer unlike UK^[52].

Factors leading to the cancer cells

- **Evolution:** The cancerous cells grow by somatic cell evolution. In such processes when a clone cell is produced, it acquires many genetic changes over time and then proliferates to generate highly complex cancer^[5].
- Aging of the genetic material (DNA or RNA) is also an important factor contributing to mutations. Aged cells are hypoactive with accumulated disadvantageous mutations, cell division inability, and a decreased ability for energy production and consumption^[6].
- **Advanced age:** Breast cancer occurs in females with advancing age, doubling about every 10 years until she reaches menopause. It is also noticeable in certain countries that there is a flattening of the age incidence curve after menopause^[7].

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- **Poor diet:** Poor dietary habits are directly related to causing cancer in humans. Studies have indicated that obesity is a risk factor resulting in 13 different types of cancer in humans [8].
- **Micro-organisms (bacteria and viruses):** Double-stranded DNA breaks in HeLa cells were induced by bacteria like *E. coli* and *Staphylococcus epidermidis*. Another bacteria *Fusobacterium* sp. is a well-known cancer-promoting pathogen [9].
- **Parasites:** Certain parasites like *Schistosoma haematobium*, *Echinococcus granulosus*, *Theileria* sp., *Fasciola hepatica*, *Opisthorchis viverrini*, bladder cancer, cholangiocarcinoma are associated to cause cancer. Certain plasmodium parasites like *Plasmodium falciparum* are indirectly a reason for the cause of cancer [10].
- **Fungi:** 7 fungal families *Aspergillus* sp, *Candida* sp, *Coccidioides* sp., *Cunninghamella* sp., *Geotrichum* sp, *Pleistophora* sp., and *Rhodotorula* sp. are seen to be present in more than 1 type of cancer [11].
- **Chemicals:** Chemical substances that are responsible for causing cancer are called carcinogens. These substances cause cancer only when they are in contact with the body in a specific way like touching, swallowing, or intense exposure. Some carcinogenic substances include asbestos, cadmium, radon, benzidine, benzene, and vinyl chloride which are capable of increasing the risk of cancer [12].
- **Nuclear radiation:** Exposure to ionizing radiation is capable to cause mutation in normal cells causing the cells to transform into cancerous cells [13].
- **Injury to the cells:** Cell injury indicates that lifestyle is a major upstream initiator of cancer development, however, this does not exclude randomness as an unavoidable contributor to the disease [14].
- **Irritation of cells:** A particular type of inflammation called ‘chronic inflammation’ begins and does not stop, which throughout time can result in damaging DNA affecting the cell growth and cell division eventually leading to cancer and tumors [15].
- **Free radicals:** These are oxygen-containing molecules with an uneven number of electrons. The uneven number allows free radicals to easily react with other molecules. Free radicals can cause large chain chemical reactions in the body because they react easily with other molecules. At higher concentrations, free radicals are capable of damaging major components of the cells including components like DNA, proteins, and even cell membrane. When free radicals damage DNA, it results in the development of cancer [16, 17].
- The organ, the breast is composed of two types of tissues namely, the glandular tissue and the stromal tissue. The stromal tissues perform the supporting function including the connective tissues, whereas the glandular tissues include the glands producing the milk and helping in the passage of milk (lobules and ducts). Tumors can be found in different parts of the breast. This tissue cancer commonly begins in the ducts or lobules [18]. Major factors contributing to causing breast cancer include age [19], an iodine-deficient diet [20], high hormonal levels [21, 22], and economic status [23].

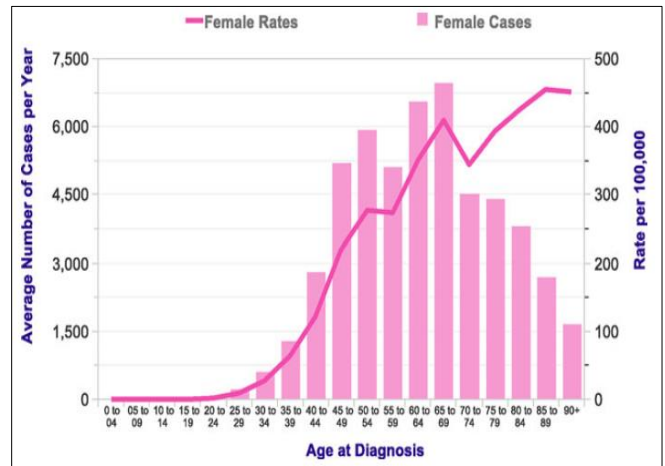


Fig 1: Trends for age distribution among UK cancer registry. [52]

Types of breast cancer

- Breast cancer is commonly divided into three major groups, including:
 - **Non-invasive Breast Cancer:** It is a type of breast cancer that is confined to the location where it originates and does not spread to the surrounding tissues of the breast. Example: Ductal carcinoma (this cancer is initiated in the cells that line the milk duct)
 - **Invasive Breast Cancer:** It is a type of breast cancer that can spread within the breast or nearby lymph nodes or tissues. Example: Infiltrating Lobular
 - Carcinoma is commonly called Invasive Lobular Carcinoma (this cancer initiates in the milk gland known as lobules and has the capability of spreading to other parts)
 - **Metastatic Breast Cancer:** It is an advanced type of invasive breast cancer (stage 4) in which the cancerous cells advance and enters the blood vessels or lymph vessels, from where the cancerous cells can travel into the bloodstream or lymphatic system to reach different body parts [24, 25].

Genetics of Breast Cancer

In cancers, malignant cells are formed which reduces the rate of apoptosis. Apoptosis is a series of molecular steps that eventually lead to the death of the cells. Apoptosis involves many pathways or complex mechanisms. Apoptosis involves activation of caspases followed by DNA and protein breakdown finally leading to membrane changes and recognition by phagocytic cells [26]. In the beginning, phosphatidylserine is expressed in the plasma membrane, allowing recognition of dead cells by macrophages causing phagocytosis without the release of pro-inflammatory cellular components, the DNA breaks down and inter-nucleosomal cleavage is initiated and oligo nucleosomes by the endonuclease. Then cysteine proteases are activated leading to the breakage of nuclear scaffolds and cytoskeleton [27]. The two major pathways of apoptosis include the extrinsic [29] and intrinsic pathways [30]. In the extrinsic pathway, dead ligands bind to the dead receptor. Ligands like type1 TNF receptor (TNFR1) and FAS (CD95) and intracellular death domains TRADD and FAS associated death domain FADD, as well as caspases, result in forming death-inducing signaling complex DISC [27, 28].

If a defect occurs at any point during the sequential process of apoptosis, it can lead to the formation of malignant cells, cells that are tumor metastatic, and cells resistant to anticancer drugs. In such cases, the balance between cell division and cell growth is lost, for example: during down-regulation of the p53 gene, which reduces apoptosis and enhances the growth of tumor cells, the inactivation of which leads to cancer. Apoptosis can be considered as both the solution and the problem, leading to either cancer treatment or carcinogenesis. The main reason for a reduced rate of apoptosis includes disruption of the balance between proapoptotic and anti-apoptotic proteins, reduced function of caspases, and impaired death receptor signaling^[31]. Deregulation of apoptosis in affected cells may be due to the overexpression of one or more apoptotic proteins or a combination of both. (Rebecca SY Wong 2015)^[32] reported that overexpression of BCL2 led to the inhibition of TRAIL, which is involved in inducing apoptosis in neuroblastoma, glioblastoma, and breast cancer cells. Overexpression of BCL2-XL is a multi-drug resistance phenotype tumor cells and also prevents the cells from apoptosis^[32].

- About 85% of breast cancers occur without a family history of the disease, indicating BRCA-1 and BRCA-2 mutations^[33]. Approximately 5% of all breast cancers are hereditary^[34]. Scientists have dedicated many years to identify the genes that are responsible for causing breast cancer^[35]. The major concern was BRCA-1 since it was related to the early onset of breast cancer. BRCA-1 gene is located on chromosome 17q21, it plays an undefined protective role, BRCA-1 is seen to strongly express itself in epithelial cells that undergo a high level of proliferation in association with differentiation.^[35, 36] Another gene called BRCA-2, located on chromosome 13q12-q13 has been identified, in which loss of heterozygosity of 13q was observed in 25% of sporadic breast tumors. This indicates that BRCA-2 is a tumor suppressor gene^[35, 36]. Another gene called Vascular Endothelial Growth Factor or VEGF affects the endothelial cells which line the blood vessel in several ways, it can cause proliferation by activating extracellular kinases and MAP kinases signal-transducing pathways. It can induce the proteins to break down the protein-membrane allowing the endothelial cells to migrate and invade;^[37] these proteins include Matrix Metalloproteinases (MMP), urokinase-type plasminogen activators, and its receptor UPAR and plasminogen activator^[38]. It makes vessels more permeable allowing molecules and fluids to leak. When MMP is secreted into the extracellular spaces it degrades the extracellular matrix allowing pro-angiogenic factors to reach the vasculature within the extracellular matrix degraded. Pro-angiogenic factors including VEGF, can reach receptors on the endothelial cells surrounding the tumor thus stimulating angiogenic signal. Also, VEGF helps the new endothelial cells to survive by up-regulating the factors of apoptosis. VEGF activates the endothelial cells to express proteins necessary for new blood vessel formation. The result is the formation of new blood vessels, which facilitates tumor growth. Studies have mainly focused on targeting VEGF and its receptors which can be used to treat tumors in clinical practices^[38]. Genes like TP5 (tumor suppressor gene) located in the short arm of chromosome 17 (17p 13.1) encodes p53. Mutation of p53 results in the addition of

oncogenic functions and plays a vital role in cancer. More than 50% of human cancers are a result of p53 defects. If the mutant p53 is silenced, the downregulation of such mutant p53 expression would result in a reduced rate of cellular growth in humans.^[39] Also, other genes like the Androgen receptor (AR) and ataxia-telangiectasia (AT) were seen to be associated with breast cancer^[34].

Tissues require nutrients and oxygen supply for their growth, therefore, angiogenesis plays an important role in the formation of cancer. Angiogenesis is a biological mechanism that involves the formation of new blood vessels from pre-existing vessels in response to tissues^[40]. It is a vital process required for growth and development and also contributes to the healing and formation of granulation tissues. During angiogenesis, the blood vessels grow by specific processes called sprouting and splitting. From the precursor of mesodermal cells and neovascularization, endothelial cells are formed^[41]. Angiogenesis is an important step that results in the transition from a benign tumor to a malignant tumor. Hence, 'angiogenesis inhibitors' can prevent tumor growth by blocking the requirements, this is achieved by certain drugs like lenalidomide tamoxifen, pazopanib, bevacizumab, cabozantinib, and many other anti-angiogenic drugs, whose usage is not widely accepted due to its rare but severe side effects like blot clot, heart failure, serious bleeding, and a bowel perforation^[41]. Many scientists have clinically studied these drugs and have revealed that proper understanding of synergistic treatment modalities of angiogenesis inhibitors as well as they have indicated their broad range of cellular targets, which could act as an effective tool for future therapies for many types of cancer^[40].

Mechanism of antiangiogenic drugs

Angiogenesis inhibitors are cancer-fighting agents capable of blocking the growth of blood vessels that supports tumor growth thereby preventing the growth of the tumor^[42]. Angiogenesis inhibitors interfere in different steps that are involved in the formation of blood vessels. Certain angiogenic inhibitors are monoclonal antibodies that specifically recognize and bind to vascular endothelial growth factor (VEGF). When VEGF is attached to the drug, the receptor is inactivated. Other angiogenesis inhibitors are capable of binding to either VEGF or its receptor or even both, as well as to other receptors on the surface of endothelial cells, or they bind to other proteins in the downstream signaling pathways thereby, blocking their activities. Some angiogenesis inhibitors function as immunomodulatory drug agents that stimulate or suppress the immune system and also possess antiangiogenic properties. In some cancers, angiogenesis inhibitors are more effective when they are combined with additional therapies. Because angiogenesis inhibitors work by slowing or stopping tumor growth without killing cancer cells, they are given over a long period^[42].

Lenalidomide

Biologically active Vitamin D is well established as a cancer cell growth inhibitor in addition to maintaining bone mineralization. Immunomodulatory drug lenalidomide restores a vitamin D sensitive phenotype to the vitamin D resistant breast cancer cell line MDA-MB-231 through inhibition of BCL-2: potential for breast cancer therapeutics.

The enhancement of apoptosis and cell cycle arrest improves with the inhibition of angiogenesis and metastasis. The survival of the patient is related to the vitamin D receptor on breast cancer cells.

Lenalidomides were treated on the cell lines which represent non-tumorigenic, tumorigenic and vitamin D resistant lines i.e. MCF-12A, MCF-7 and MDA-MB-231.

Lenalidomide did not affect these alone but it had an effect of 50% cell growth inhibition when it was treated additionally with $1\alpha, 25$ Dihydroxyvitamin D₃, and 1 μ m lenalidomide in resistant cells. This inhibitory effect is through annexin-V-expression and apoptosis. The combination of $1\alpha, 25$ -dihydroxy vitamin D₃, and Lenalidomide has an increasing effect on the proapoptotic proteins and a decrease in the BCL-2 inhibition. BCL-2 inhibition is regarded as the mechanism of action for the combined drugs in the MDA-MB-231 cell lines. This does not affect the vitamin D-resistant cell lines [43].

Tamoxifen

It is a very common and widely used drug. It is used mostly before and after menopause. The TAM has the primary action by inhibition of estrogen receptors, but nonestrogen receptor mechanisms also exist. The nonestrogen mechanism includes modulation of signaling proteins such as protein kinase C. Transforming growth factor β and the proto-oncogene [43].

Bevacizumab

It is an antiviral drug that is approved for the treatment of metastatic breast cancer [44]. It functions as a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) which is a regulator of angiogenesis and vascular permeability, this inhibits the function of VEGF in vascular endothelial cells that do not allow angiogenesis in the tumor, hence, preventing the growth and metastasis of tumor [44]. The vascular endothelial growth factor is a pro-angiogenic growth factor that is involved in stimulating the proliferation, migration, and survival of endothelial cells. Bevacizumab is produced by incorporating 6 VEGF binding residues from murine anti-human VEGF monoclonal antibodies into the human IgG framework and binding to vascular endothelial growth factor, preventing binding to the receptor (VEGFR-1 or VEGFR-2) mostly on the endothelial cell [45].

Cabozantinib

Cabozantinib is a drug that acts as a targeted agent against MET and vascular endothelial growth factor receptor-2 [46]. There is an aggressive subtype of breast cancer called triple-negative breast cancer (TNBC) that requires targeted therapeutics for treating the patients. Receptor tyrosine kinase (RTK) is greatly expressed in the patients suffering from this subtype of breast cancer, triple-negative breast cancer (TNBC). MET tyrosine kinase is involved in cancer growth, survival, migration, metastasis, and also angiogenesis which is highly expressed in several TNBC subtypes. The upregulation of MET plays a vital role to acquired anti-VEGF resistance [47].

Pazopanib

Pazopanib is a drug effect that can decrease the size of the tumors and stabilize disease in several patients suffering from breast cancer and another type of cancers. It is a multi-targeted tyrosine kinase inhibitor, which targets vascular endothelial growth factor receptor (VEGFR), platelet-derived

growth factor receptor, and c-kit, key proteins that are responsible for the growth and survival of tumors [47]. Pazopanib is important against all human VEGFR and is closely related to tyrosine kinase [48].

Table 1: Antiangiogenic drugs and their targets

Angiogenic Drug	Target
Lenalidomide	BCL-2 Inhibition
Tamoxifen	Modulation of Protein Kinase C
Bevacizumab	VEGF
Cabozantinib	MET & VEGF-2
Pazopanib	VEGFR

Metronomic Chemotherapy

The proliferating cells are targeted by the dose-dense drugs while the metronomic chemotherapy targets the activated endothelial cells of the newly formed tumors [49].

Thrombospondin 1, metronomic cyclophosphamide, and methotrexate have increased the level of endogenous antiangiogenic activity, this combination is also reported to reduce the serum VEGF level in breast cancer.

A combination of drugs bevacizumab with metronomic cyclophosphamide and methotrexate in stage IV breast cancer gives a promising result of ORR and TTP [50].

Treatment Safety of Antiangiogenic Drugs

The addition of bevacizumab or TKIs to other chemotherapy regimens has usually been correlated with additional overall toxicity.

The antiangiogenic drugs usually don't have any adverse effects, they can cause a few symptoms in some rare cases which include hand-foot syndrome, diarrhoea, fatigue, hypothyroidism, and hypertension.

In very recent studies it has been found that cardiovascular toxicity has been increased with a potential adverse effect of some antiangiogenic drugs.

Bevacizumab is a highly effective antiangiogenic drug but it has some effect on elderly patients which results in some thromboembolic events and potentially a cardiac risk when they are taking sorafenib [51].

Conclusion

As there is a rise in breast cancer globally among women so an effective and safe treatment method is needed to cure them. Antiangiogenic treatment can be an alternative method for treating breast cancer. From this review, we conclude, that the antiangiogenic drugs have a promising result with minimal side effects. It has a high recovery rate compared to the other treatments.

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