Lessons about antiangiogenesis treatment of breast cancer in the current era

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Abstract

Metastatic breast cancer has a complex biology, high incidence, with variable clinical behaviors and different therapeutic responses, psychological and economic burden on societies, incurability, all of which have made this disease a very important and interesting issue in clinical medicine. But inside these complexities, angiogenesis and VEGF-VEGFR system, is a landscape for a deep understanding of these kinds of biological systems. Until now, unfortunately, the antiangiogenesis therapy has not changed the rate of survival in breast cancer treatment, but this does not mean that this mode of treatment will not be effective in the future, because in every phase of breast cancer activity from carcinogenesis to recurrence and metastasis, angiogenesis will always have a role in this movement and subsequent therapeutic interventions will change this natural course. In this complexity, for optimal treatment, it is necessary to examine the mechanisms of angiogenesis switch, to analyze the precise situation of specific drugs in the current practice. This review is a reminder that for this heterogeneous disease, it is a constant challenge to determine the correct timing of antiangiogenesis treatment in breast cancer.

Keywords: breast cancer, antiangiogenesis, metastasis, VEGF and VEGFR system

1. Introduction

Tumor growth depends on angiogenesis formation of new blood vessels. It was first proposed by Judah Folkman[1] in 1971 and is now a widely confirmed hypothesis. The concomitant growth of new blood vessels or a means of coopting existing capillary networks allows tumors to expand beyond a size regulated by diffusional distance to invade local tissues and to metastasize to distant sites. Vascular endothelial growth factor (VEGF) has a major role in this process; it is an essential growth factor for endothelial cells[2,3], VEGF is involved in endothelial cell proliferation, migration, morphogenesis. The term Angiogenesis switch refers to the loss of balance between angiogenesis inhibitors and angiogenesis inducers that trigger angiogenesis. Angiogenesis switch is changed by disturbance in matrix metalloproteinase (MMP) and tissue inhibitor of metalloproteinase (TIMP).

The angiogenic program requires the degradation of basement membrane, endothelial cell migration, invasion of extracellular Matrix and endothelial cell migration and invasion of extracellular and capillary cell lumen formation. Induction of angiogenesis relies on there being a balance between angiogenic control and proangigenic factors including bFGF, PDGF angiopoietin, and TGF beta1.[4]

Angiogenesis is important in breast cancer development and invasion and metastasis, transfections of tumor cells with angiogenic stimulating peptide adds invasiveness to the primary tumors.

Inhibition of VEGFR, the complex molecular pathway that regulates tumor angiogenesis is a target for treatment of tumor cells that are genetically unstable and is a cause of tumor resistance.[5]

2. Angiogenic behaviors in breast cancer

A - In Triple negative breast cancers with high proliferative index and enhanced angiogenesis which supports rapid growth and early metastasis with high level of VEGF, antiangiogenesis therapy has a role.

B - In Hormone positive breast cancer, activation of angiogenesis in advanced setting with expression of angiogenic markers, response to antihormone therapy is poor.

C - In advanced HERE2 positive breast cancers, a combined therapy of trastuzumab and bevacizumab is rational but toxicity of the drugs needs to be considered.[6]

D - In Early breast cancer and angiogenesis, it seems that without biomarkers we cannot benefit from antiangiogenic treatment because angiogenesis signaling is activated during metastatic settings and tumor recurrence.[7]

Results of the antiangiogenic treatment in advanced breast cancer, especially in second line or third line is due to increased numbers of survival pathways in cancer cells, so it is expected that the results are not clear; therefore, if it is planned to start the drug earlier in first line metastatic the results will be better but the amount of data is scarce.

For adjuvant treatment, the antiangiogenic treatment seems to be better but the problem is lack of biomarkers; if biomarkers are based on selection of patients, better therapeutic results be achieved and toxicity of drugs would be decreased.

What are the unexpected results of antiangiogenic treatment and breast cancer?

a - Changing the behavior of the cancer, mostly positive on survival, but this is not true for every tumor.

b - Decreasing and delaying the life threatening metastatic sites, such as central nervous system to allow the oncologist to have time for therapeutic maneuvers.

c - Antiangiogenic therapy occasionally leads to aggressive course.

d - The side effects of antiangiogenic therapy need to be matched by the efficacy and clinical status of patient.

e - It is possible at one time in the course of the breast cancer to assess the patient as to whether the tumor may be angiogenesis dependent.

f - Ways need to be developed to select patients who are most likely to benefit from each antiangiogenic agent at each time and phase of the disease and determine the time for starting antiangiogenesis treatment. Each try needs to be started at an early phase because the bulk of tumor is low and the number of activating factors is not high so pathways can be controlled with antiangiogenic therapy.[8,9]

Is the site of breast cancer metastasis a guide for using antiangiogenic treatment?

It is better for life threatening sites and tumor activity on metastatic sites which did not respond to chemotherapy to undergo a try of antiangiogenesis treatment.

3. Overall results of antiangiogenic treatment

Considering the molecular pathways in angiogenesis there are three classes of these drugs monoclonal antibody against VEGF and receptor of small molecule inhibitors of angiogenic receptors neutralizing angiogenic factors VEGF trap aflibercept .[10,11]

Bevacizumab is a humanized monoclonal antibody against VEGF-A it has limited anticancer effects when administered alone but with cytotoxic drug it has antitumor activity, it normalizes the blood flow to tumor and increases the cytotoxic effects of chemotherapy agents on the tumor. Inhibition of the various regulators of VEGF regulators, their expression and production is a potential strategy for antiangiogenic therapy .

Bevacizumab, sorafenib, sunitinib, thalidomide, aflibercept, vascular matrix metalloproteinase regulators, vascular disrupting agents VDA, Taxol are routine antiangiogenic agents.

Inhibiting one pathway is in favor of activation of other pathways, Sunitinib, an oral agent is effective against VEGFR, PDGFR and C-kit; Sorafenib, targets VEGF receptors, PDGFR, c-kit and FLT3.

Simultaneous safety of blocking VEGF and epidermal growth factor receptors are present. Integrins which are receptors that mediate between cell and extracellular matrix and antagonists to integrin alfavbeta3, alfavbeta5 have an antiangiogenic potential. [12,13]

The selection of patients for antiangiogenic therapy is important and earlier treatment with antiangiogenic therapy is more effective.

The development of highly specific drugs needs to be matched to develop biomarkers for response. It is thought that highly vascularized tumors are good responders to antiangiogenic drugs but this does not mean that less vascularized tumors do not respond.

Estrogen enhances VEGF expression and HIF mediated TAM and antiestrogenes have antiangiogenic activity; Anti-inflammatory agents also induce antiangiogenesis.

AntiVEGF therapy clearly affects the growth of the breast cancer, but combination therapy is more effective.[14.15,16]

Antiangiogenesis treatment normalizes flow initially, resulting in important tissue oxygenation and decreased interstitial pressure increasing the delivery of cytotoxic agents. They confer better efficacy in combination with chemotherapy and earlier treatment because late stage breast cancer expresses many different angiogenic factors such as fibroblast growth factors; in contrast, early cancers express more VEGF.

Several receptor tyrosine kinase inhibitors that target the VEGFR1, VEGFR2 have been tested, ZD6474 against VEGFR2 is not effective in metastatic breast cancer, and after initial response they soon relapse. General antiangiogenic control also needs inhibition of EGFR, HER2, COX2HIF1alfa.[17,18,19]

Antiangiogenic agents are hypothesized to inhibit cancer growth by controlling new blood formation, survival growth and metastasis. Different tumor types use different genetic pathways to establish a blood supply, oncogenes and tumor suppressor genes are frequently associated with transformation for angiogenesis switch; Ras, Myc, Raf, HER2, C-Jun and SRC are associated with angiogenesis activity.

In tumors, due to abnormal vasculature, drug and oxygen delivery is poorer than normal vasculature. Hypoxia is the result of an abnormal microcirculation.

The response to hypoxia is by HIF response, the HIF changes the behavior of cancer.[20]

Early studies of antiangiogenic agents predominantly assessed their use as single agent therapy and in heavily treated cases Phase III trial showed promise for progression free survival for antiangiogenic treatment in advanced breast cancers.[21]

Tumor markers are the best for selection of antiangiogenic treatment, this has been shown previously with HERE2 positive breast cancer because nonselective treatment has little effect on survival in contrast with HER2 positive cases with dramatic change in survival with antihere2 therapy. The other approach is to obstruct VEGF mediated angiogenesis by use of small molecule inhibitors VEGFR tyrosine kinase.

Notch signaling, an adhesion, molecular and cellular system is activated in breast cancer. The notch pathway is important in angiogenesis, mediated with gamma secretase; blocking gamma secretase is important in cancer therapy.

In antiangiogenesis treatment, also tumor endothelial cells are sensitive to low dose chemotherapy and anticoagulation, with the mechanisms of antithrombin activity and antiplatelet can also control the tumorigenic angiogenesis.[22,23]

4. Mechanisms of antiangiogenesis resistance

Compensatory angiogenesis initiates with antiangiogenesis treatment and can be reactivated after discontinuation of the drug. Angiogenic independent tumor growth, vessel co-option, growth by intussusception, vascular mimicry and vasculogenesis decrease the tumor dependence on classical angiogenesis, so

there is resistance to classic antiangiogenesis treatment. Incorporation of circulating EPC into the capillary wall and the tumor vasculature is another mechanism of tumor resistance to antiangiogenic treatment, EPC is able to migrate and home to tumor site and is the cause of tumor resistance. The role of EPC in promoting tumor angiogenesis and metastasis has been the target of many studies .[24,25,26,27]

Tumor stroma and cancer associated fibroblast, Bone marrow derived endothelial cells are modes of resistant mechanisms of VEGF targeted treatment. Angiogenic factor redundancy, activation of survival factors, antiapoptotic mechanisms, mutations in oncogenes, vessel co-option, vascular mimicry and variation on VEGF [28,29], are diverse resistance mechanisms.

Another angiogenic pathway, delta-like ligand 4 notch signaling is induced by VEGF and is reactivated by inhibiting angiogenesis.

Tumors engage in bad angiogenesis system and bad stroma, also cancer stem cells produce more VEGF with resulting aggressive tumors. TAM induce breast cancers with poor prognostic clinical course. It seems that drug resistance in antiangiogenesis therapy is less than in chemotherapy so this discriminates this type of treatment from chemotherapy; this is due to stability of genetic changes in endothelial cells. The term vascular mimicry, VM, is defined as a complex capillary network composed of tumor cells rather than endothelial cells, these tumors do not respond to conventional antiangiogenic therapy.

5. General side effects of antiangiogenic treatment

Antiangiogenic therapy can induce negative responses in carcinomas including progression to high grade cancers; with bevacizumab there is hypertension, bleeding, proteinuria, problem in wound healing and thromboembolic events and gastrointestinal perforation, posterior encephalopathy.[30]

6. Future of antiangiogenesis and breast cancer

Regarding the exciting biologic nature of the breast cancer and unsolved issues in tumor angiogenesis, antiangiogenesis treatment of breast cancer needs to be considered in every phase of the disease. Regarding the stages of breast cancer, it can change the natural course of the disease and using biomarkers and circulating tumor cells is a new concept for this therapeutic entity in future. Until now, the antiangiogenesis treatment of breast cancer has not changed the survival of breast cancer patients, so the toxicity of chronic antiangiogenic therapy is undefined and this requires many large clinical trials be done in future.

Rethinking these mechanisms of failure can help researchers to find new trials to discover these complex situations. Regarding the complexity of biological systems in cancer and incurability of this disease, we cannot expect to find a safe therapeutic goal to affect cancer survival in the next decades, and data about antiangiogenic drugs is not enough, so continuing therapeutic interference with these agents is needed in future, and absence of inadequate dramatic response of antiangiogenesis treatment is not in favor of inefficacy of these agents.[31,32]

7. Conclusion

In routine practice, failure of antiangiogenesis treatment of breast cancer in survival benefit is not the end of this type of treatment category in breast cancer, but it is a starting point for dissection of the mechanisms of biology of this disease. It is certain that angiogenesis will have many roles in diagnosis and treatment of breast cancer in the future. Regarding the role of angiogenesis in every phase of breast cancer activity, many clinical trials are needed to define the precise situation of this mode of therapy with the hope that in adjuvant and in metastatic breast cancer it can control and increase survival of the patients.

Conflict of interest

The author declares no conflicts of interest.

ABBREVATIONS:

VEGF=vascular endothelial growth factor

PDGF=platelet derived growth factor

PDGFR=platelet derived growth factor receptor

EGFR=epidermal growth factor receptor

MMP=matrix metalloprotease

TIMP=tissue inhibitor metalloprotease inhibitors

CNS=central nervous system

CTS=circulating tumor cells

VM=vascular mimicry

EPC=endothelial progenitor cells

TAM=tumor associated macrophage

C-JUN=june gene, a proto-oncogene

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