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Vascular Endothelial Growth Factor Inhibitors: Blocking Angiogenesis and Improving Outcomes

Ahmed M. Malki[1,2*], **Hassan A. Aziz**[1] **and Mona O. Mohsen**[1]

[1]*Health Sciences Department, Biomedical Science Program, College of Arts and Sciences, Qatar University, Doha, Qatar*

[2]*Biochemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt*

[*]**Corresponding author**: Malki AM, Health Sciences Department, Biomedical Science Program, College of Arts and Sciences, Qatar University, Doha, Qatar, Tel: 974 4403 3333; E-mail: ahmed.malki@gmail.com

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Editorial

Tumor tissues are just like normal tissues; require nutrients, oxygen and the ability to evacuate waste products and CO_2, the process of angiogenesis or (tumor-associated vascularization) addresses these needs to tumor tissues. The process of angiogenesis in tumors is continuously activated; triggering the normal vasculature to sprout out new vessels to sustain the tumor growth. The resulting new blood vessels "feed" growing tumors with oxygen and nutrients, allowing the cancer cells to invade nearby tissue and metastasize around, forming new colonies of cancer cells. This process is governed by several inducing and opposing factors, some of these factors are signaling proteins, which bind to the cell-surface receptors on the vascular endothelial cells causing their stimulation or inhibition. Vascular Endothelial Growth Factor-A or for short "VEGF-A" is a well-known angiogenic inducer.

VEGF-A is encoded by Vascular Endothelial Growth Factor A gene, this gene orchestrates the growth of new blood vessels during embryonic development and in other pathological and physiological situation in adults, such as wound healing and reproductive cycles. VEGF-A signaling pathway is a complex process regulated via three main receptors (VEGFR-1, 2 & 3), furthermore Metalloproteases such as "MMP-9" is capable of releasing and activating the sequestered VEGF-A ligands in the extra cellular matrix. The up-regulation of "FGF" or fibroblast growth factor is also implicated in supporting the angiogenesis process and sustaining the growth of tumor tissues.

The discovery of VEGF inhibitors is a fertile area in cancer drug therapy now a day. These drugs act by inhibiting the activity of the tyrosine-kinase receptors capable of modulating and inducing angiogenesis. Several angiogenesis inhibitors have been approved by the FDA, for example bevacizumab ® is a monoclonal antibody that recognize and binds effectively to VEGFR-1. This binding would inhibit the activation of the receptor and the downstream signaling pathway. Bevacizumab® has been used efficiently in treating cases of Glioblastoma, colorectal cancers, metastatic renal cell cancer and non-small cell lung cancers. Other inhibitors would act by blocking the endothelial receptors or downstream signaling pathway proteins such as, Sorafenib (Nexavar®) for hepatocellular carcinoma and different types of kidney cancer, Sunitinib (Sutent®) for neuroendocrine tumors and Pazopanib (Votrient®) for kidney cancer.

In addition to the above approved drugs, several other drugs are in clinical trials, waiting to prove their safety and effectiveness in the treatment of different cancers. Nevertheless, clinical trials are testing now the possibility of combining both angiogenesis inhibitors and other drugs that target blood vessels such as tumor-vascular disrupting agents, which damage existing tumor blood vessels. Furthermore, preclinical investigations in animal models will explore the potential use of angiogenesis inhibitor therapy to treat cancer metastasis and hopefully clarify the role of angiogenesis inhibitors in the arsenal of breast cancer therapies.

A recent study in 2015 has shown that Quercetin inhibits cell proliferation and tube formation in RF/6A cell lines by targeting VEGFR-2 pathway in a dose-dependent manner. Therefore, it can act as a potent and effective drug in choroidal and retinal angiogenesis.

Lenvatinib (Lenvima®) is a multi-kinase inhibitor for VEGFR2 and 3, the drug was granted to treat different types of thyroid cancer which do not respond to radioiodine in both USA and Japan in 2012 and in Europe in 2013. Clinical trial phase-I for this drug was conducted in 2006 and followed by several phase-II trials in 2011. Phase III was launched in 2011 with encouraging results, the drug has been recently granted approval by the FDA. The New England Journal of Medicine has published on Feb 2015, a recent study on Lenvatinib, the oral VEGFR-1, 2 and 3 inhibitor in patients with differentiated thyroid cancer. Lenvatinib is also an inhibitor for FGF, PDGF, RET and KIT. The study involved 261 patients and 131 controls on placebo. Lenvatinib has shown a significant progression free survival rate of 18.3 months compared to placebo group with 3.6 months only. The response rate was also obvious in the Lenvatinib group compared to the control, the adverse effect occurred in 40% of the patients and include, hypertension, diarrhoea, fatigue and decreased appetite. The study has concluded that Lenvatinib is associated with significant improvement in the response rate and progression free survival rate in these patients. The Children Oncology Group at USA is currently recruiting participants for the study of VEGFR inhibitor Axitinib (Inlyta®) in children suffering from refractory solid tumours. The aim of phase I trial is to determine the "MTD" maximum tolerated dose of Axitinib or the recommended dose for phase II. It also aims to determine the toxicity profile of this drug. Axitinib is a VEGFR inhibitor, which has shown significant potency against breast cancer xenografts. It has received FDA approval in 2012 for the treatment of renal cell carcinoma. Furthermore, a recent study in 2015 has shown that Axitinib can effectively inhibit T315l mutation in patients with chronic myeloid leukemia and lymphoblastic leukemia who acquired resistance to conventional therapy.

Conclusion

Innovative, significant and remarkable development have been made in angiogenesis, the above-mentioned drugs have delivered hope for cancer patients and enhanced the progression free-survival rate dramatically to improve the overall outcomes of cancer patients.