Vascular normalization window: A positive prognostic foresight for head and neck cancer

M. L. Asha, Aprajita Dua, Basetty Neelakantam Rajarathnam, H. M. Mahesh Kumar, Poulomi Dey, P. Deepak

Department of Oral Medicine & Radiology, Dr. Syamala Reddy Dental College, Hospital & Research Centre, Bengaluru, Karnataka, India

Abstract

Tumor angiogenesis is a hallmark of advanced cancers which is critical for the continued growth and progression of solid tumors owing to the metastatic spread of tumor cells. This knowledge has led to the concept of targeting the tumor vasculature as a therapeutic modality. Several retrospective studies support the positive prognosis for the implications of angiogenic markers for head and neck squamous cell carcinoma (HNSCC), currently making them an attractive target oriented treatment. Radiotherapy (RT) being the conventional treatment for HNSCC, makes it imperative in this present era to recognize the communication between antiangiogenic therapy and RT, thus developing a combination therapy to achieve progress in the outcome of clinical practice. The combination of antiangiogenic agents and ionizing radiation involve many interactions between the cells, the stroma of the tumor and tissue vasculature. Increased angiogenesis is responsible for the proliferation of tumor cells and its metastasis which ultimately leads to tumor hypoxia. Any agent targeting the tumor vasculature can modulate the tumor microenvironment thus normalizing it and enhancing the therapeutic response of hypoxic cells of head and neck cancers. This review provides insight into the mechanisms by which the antiangiogenic therapy combined with RT improves the tumor response to radiation, thereby suggesting a promising prognostic treatment modality of HNSCC in the time ahead.

Keywords

Antiangiogenesis, head and neck cancer, targeted therapy, vascular endothelial growth factor receptor/platelet-derived growth factor receptor inhibitor

Introduction

Cancers of the oral cavity, oropharynx, hypopharynx, pharynx, and larynx, are included in head and neck squamous cell carcinoma (HNSCC), which being the sixth most common cancer worldwide constitutes about 5% of all cancers globally, with about 0.7 million new cases being diagnosed annually in India. Radiotherapy (RT) is the standard of care for the initial stages of HNSCC, while RT plus chemotherapy, particularly cisplatin, is used for non-resectable and locally advanced cases of HNSCC. Though advantageous, combination therapies are associated with an increased risk of toxicity, with the average survival of patients being as low as 12 months, depending on various prognostic factors. This warrants the discovery of novel treatment strategies to improve the overall survival outcome of HNSCC.

Novel molecule-targeting agents having non-coinciding adverse effects and potential to be combined with current treatment modality of HNSCC are being focused on recent studies for improving the outcome of clinical practice. It has been seen that antiangiogenic agents have rapidly found a place in mainstream clinical practice over the past 5 years. Angiogenesis being the hallmark of advanced cancers, can be targeted by the combination of antiangiogenic agents and radiation, thus increasing the feasibility of treatment, and warranting further investigation for this approach.

The Process of Angiogenesis in Carcinogenesis

Angiogenesis is the process of new blood vessel development from existing vessels and primarily venules. Angiogenesis is the hallmark feature of carcinogenesis which sustains the growth of cancer cells leading to proliferation and invasion of the tumor cells and is thus responsible for the malignant potential of the tumor. Increased angiogenesis leads to an alteration in the tumor microenvironment and vasculature leading to the tumor growth resulting in increased oxygen consumption creating a hypoxic environment. Hypoxia-inducing factor 1a is the key transcription factor which is upregulated by the hypoxic tumor cells and is responsible for increase in the expression of vascular endothelial growth factor (VEGF).
leading to resistance to conventional therapy. The tumor growth, progression, and metastasis depend on angiogenesis.

The basic process of angiogenesis has been described in Figure 1.[8]

**VEGF and its Receptors**

VEGF has a key role in neoangiogenesis and its significance in HNSCC is well-known.[9] The ligands included in the VEGF family of proteins are VEGF A-E and placenta growth factor 1 and 2.[11] The receptors of VEGF and their role in angiogenesis have been described in Flowchart 1.[8]

Based on these processes, antiangiogenic agents were introduced as novel therapeutics in the treatment of head and neck cancer.

**Antiangiogenic Agents**

- The first generation: Single target antiangiogenic inhibitors, VEGF is targeted.
  Eg: Bevacizumab, nimotuzumab
- Second generation: Multi target angiogenesis inhibitor, VEGFR platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor are targeted.
  Eg: Vandetanib, sunitinib, sorafenib, motesanib, linifanib
- Third generation: Broad spectrum angiogenesis inhibitor.
  Instead of acting by a single mechanism of inhibition, these agents make use of intricate mechanisms (like stimulating integrin α5β6, α5β3, matrix metalloproteinase) that counteract several processes to inhibit the downstream angiogenic phenotype, regardless of which angiogenic factor has initiated the stimulus.[11]
  Eg: ABT510.

Antiangiogenic agents alone like cetuximab and ABT 510 have gained approval for use for the treatment of head and neck cancers.[12]

RT being the conventional treatment for HNSCC makes it imperative in this present era to recognize the communication between antiangiogenic therapy and RT, thus developing a combination therapy to achieve progress in the outcome of clinical practice.

**Antiangiogenic Interactions and Radiation**

Antiangiogenic agents with radiation have been tested in experimental conditions with various tumor models. The tumor size can affect oxygen tension, nutrient supply, and pH, which are all elements that determine the response of the tumor to radiation. The sequence of steps involved in antiangiogenesis has been explained in Flowchart 2.[8]

**Antiangiogenesis Agents Combined with Radiation in Head and Neck Cancer**

Antiangiogenic agents target the process of angiogenesis by inhibiting the factors stimulating the development of new blood vessels.

---

**Flowchart 1:** The role of receptors of vascular endothelial growth factor in the process of angiogenesis

---

**Figure 1:** The basic process of angiogenesis
Overview of the combination of antiangiogenic agents with radiation acting on a single target is given in Table 1,\(^{(2,13-16)}\) and those acting on multiple targets is given in Table 2.\(^{(17-24)}\)

**Bevacizumab (Avastin)**

Bevacizumab is a recombinant monoclonal antibody, targeting VEGF A. Being approved by the US Food Drug Administration for its use in clinical practice in 2004, it had an initial indication for colorectal cancer in combination with 5-fluorouracil-based conventional chemotherapy.\(^{(25-27)}\) Bevacizumab is approved recently for treatment of non-small cell lung cancer, glioblastoma, breast cancer, metastatic renal cell cancer in addition to advanced colorectal cancer.\(^{(28)}\)

Bevacizumab along with cetuximab has been recently used in Phase II clinical trial for the treatment of metastatic HNSCC. The median progression-free survival and overall survival were >2.5 and >7.0 months, respectively, and this combination was well tolerated.\(^{(29)}\)

The combination of bevacizumab, erlotinib (an EGFR tyrosine kinase inhibitor), and radiation has been employed by Bozec et al., in a head and neck orthotopic model.\(^{(14)}\) Angiogenesis in tumor vasculature was observed to be significantly increased with radiation therapy alone while the supra-additive reduction in the size of the tumor was observed with simultaneous drug administration. This triple combination had the highest effect on the inhibition of tumor growth.

In 2012, a clinical trial used the combination of bevacizumab, erlotinib, and chemo-radiation, and it was found to have a clinical response of >95% in 27 advanced head and neck cancer patients after concurrent chemo-RT. Three-year estimated progression-free survival, disease-specific survival and overall survival rates were 82%, 89%, and 86%, respectively.\(^{(30)}\)

Adverse effects: Mucositis, leukopenia, lymphopenia, anemia, throat pain, and fatigue.\(^{(30)}\)

**Nimotuzumab**

Nimotuzumab is a humanized therapeutic monoclonal antibody which acts against the EGFR. The use of nimotuzumab for the treatment of squamous cell carcinoma of head and neck (SCCHN), nasopharyngeal cancer, and glioma has been approved in different countries.\(^{(31)}\)

In India, at three multispecialty centers, an open-label, randomized, multicentric study have been conducted to evaluate the utility of the combination of chemotherapy and RT with nimotuzumab or RT alone with nimotuzumab in patients having advanced SCCHN (Stage III or IVA) which is documented histologically. At month 60, overall survival was 57% with CRT + nimotuzumab and 39% with RT + nimotuzumab. It was concluded that the concurrent use of nimotuzumab with CRT/RT is safe and provides long-term survival benefit.\(^{(32)}\)

Adverse effects: Fever, chills, pruritus, urticaria/rash, headache, hypertension, and fluctuation in blood pressure.\(^{(32)}\)

**Vandetanib (ZD6474, Zactima)**

Vandetanib is a novel antiangiogenic agent which is orally available and inhibits VEGFR-2 as well as EGFR. An in vivo study, conducted in the year 2008, showed that the combination of vandetanib and radiation effectively acts on both EGFR and VEGFR-HNSCC tumor xenograft models. Vandetanib inhibits the signaling of PI3K/AKT when acting on EGFR, while in VEGFR - tumors, the antitumor activity of vandetanib against VEGFR 2 was enhanced by radiation due to antiangiogenesis in the tumor caused by vandetanib.\(^{(17)}\) The anti-tumor and anti-metastasis effects of radiation therapy on nasopharyngeal carcinoma (NPC) is also potentiated by the use of vandetanib.\(^{(17)}\)

The combination of vandetanib with cisplatin and RT has been employed in a randomized Phase II clinical trial in patients with high-risk Stage III/IV head and neck cancer and is being evaluated further.\(^{(31)}\)

Adverse effects: Diarrhea, colitis, hypertension and hypertensive crisis, fatigue, hypocalcemia, rash, and QT interval prolongation.\(^{(31)}\)

**Sunitinib**

Sunitinib inhibits receptor tyrosine kinase which is responsible for the proliferation and angiogenesis of the cells of the tumor. It has multiple targets, and its inhibiting mechanism involves VEGFR-1, 2, and 3, PDGFR-a and -b, stem cell factor receptor (Kit), and fms-like tyrosine kinase
A Phase II clinical trial combining sunitinib with hypofractionated image-guided RT was carried out in 25 cancer patients which included 4 head and neck cancer cases having incurable distant metastases was reported. The 18 months follow-up showed >55% progression-free rate and >70% overall survival rate.

Adverse effects: Anemia, neutropenia, fatigue, liver function test abnormalities, thrombocytopenia, mucositis/stomatitis, nausea/vomiting, skin changes, diarrhea, hypertension, bleeding, metabolic abnormalities, and increased creatinine.

**Sorafenib**

Sorafenib inhibits the serine/threonine protein kinases and also tyrosine kinase receptors, such as VEGF-R2, 3, PDGFR, Flt-3, and c-kit. Advanced renal cell carcinoma (RCC), thyroid cancer, and hepatocellular carcinoma, are being treated by sorafenib. The efficacy and safety of sorafenib as a single agent in patients with metastatic HNSCC and NPC has been determined. (Adverse effects: Fatigue, mucositis/stomatitis, lymphopenia, anemia, hand-foot skin reactions, and hypertension.)
Motesanib
Motesanib potentially inhibits VEGFR-1, 2, and 3, PDGFR, and kit receptors. It has been known to inhibit the formation and proliferation of tumor by its antiangiogenic effects in the endothelial cells in a preclinical study. When combined with radiation, it is known to reverse the hypoxic conditions of tumor cells and accelerate the killing of the cancer cells of head and neck region, both in vivo and in vitro.[4,5] No discernible adverse effects noted in mice model.[23]

Linifanib (ABT-869)
Linifanib inhibits tyrosine kinase receptors of the VEGF and PDGF family by an ATP dependent competitive inhibition mechanism. Studies done previously have shown linifanib as an inhibitor of PI3K/AKT, mitogen-activated protein kinase pathways in acute myeloid leukemia[36,37] and also the expression of VEGF in several types of cancers.[38,39] The combination of linifanib with radiation has shown better results than either of them being employed alone according to the preliminary data available. This combination has ultimately inhibited the growth of tumor cells and has induced apoptosis by down-regulating the signal transducer and activator of transcription 3 signaling pathway.[41] Linifanib radiosensitizes HNSCC cells and thus, its combination with radiation may prove to be a promising prognostic foresight for the treatment of patients with head and neck cancer.[8]

Adverse effects: Fatigue, decreased appetite, hypertension, diarrhea, nausea, palmar-plantar erythrodysesthesia, and proteinuria.[40]

Conclusion
Increased cellular toxicity seen with chemotherapy has led to the emergence of targeted therapy such as antiangiogenic agents leading to a promising therapeutic approach for the treatment of head and neck cancer. These agents when used in combination with radiation or other chemotherapeutic agents or both, enhances the tumor response to radiation and increases the overall survival rate of patients. When an antiangiogenic agent is applied alone, cancer cells might switch from angiogenic sprouting to intussuscepted mode[42] which eventually promotes a second wave of angiogenesis.[42] This angiogenic switch of the tumor vasculature makes it more resistant to antiangiogenic agents or radiation therapy since the vessels become mature, rigid, and less vulnerable to VEGF inhibition.[43-45]

Thus, optimal doses and schedule of these antiangiogenic drugs designed according to the angiogenic profile of tumors can normalize tumor vasculature and its microenvironment without causing harm to the normal tissues. Here, we have shown antiangiogenic therapy is an attractive option to overcome tumor hypoxia and radioreistance. Antiangiogenic therapy in combination with RT is a promising strategy, which could lead to decreased morbidity and increased efficiency while treating HNSCC.[4]

References
17. Gustafson DL, Frederick B, Merz AL, Raben D. Dose scheduling of the dual VEGFR and EGFR tyrosine kinase


