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Targeting angiogenesis in head and neck cancer

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SUMMARY

Angiogenesis is a crucial step in tumor growth and metastasis. Head and neck squamous cell carcinomas (HNSCC) highly express angiogenesis factors, such as vascular endothelial growth factor (VEGF), which are associated with patient prognosis. Antiangiogenesis agents can potentially modulate tumor microenvironment and induce radiosensitivity and chemosensitivity. In this review, we discuss the molecular mechanisms underlying angiogenesis involved in HNSCC, preclinical data with antiangiogenesis agents as well as potential predictive biomarkers. We also review novel therapies under investigation and summarize the results of clinical trials using antiangiogenesis agents alone or in combination with conventional therapies in HNSCC.

Introduction

Growth and expansion of the vascular network through a process known as angiogenesis is a crucial event during the natural history of cancer since the proliferation and migration of cancer cells depend on sufficient oxygen and nutrient supply. The role of angiogenesis, a hallmark of tumorigenesis, has been investigated in many types of cancers, including squamous cell carcinoma of the head and neck (HNSCC) [1,2]. Angiogenesis constitutes an important target of anticancer treatment and antiangiogenesis agents are currently available and beneficial in the treatment of several solid tumors (Table 1). In HNSCC, angiogenesis targeting remains experimental as definitive clinical trials are still ongoing and, therefore, these agents should not be used in routine clinical practice. An understanding of the biology of HNSCC is essential for the development of these new therapies. This review focuses on the role of angiogenesis in HNSCC and elaborates on the current status and challenges in the development of antiangiogenesis therapies for HNSCC.

Angiogenesis in cancer: VEGF pathway

The downstream signaling of the angiogenesis pathway is mainly mediated by the production of vascular endothelial growth factors (VEGF), a member of the platelet-derived growth factor (PDGF) superfamily, which also includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor [3] (Fig. 1). These alternative splicing-derived variants have different functions and specificity to VEGF receptors [4]. Among these factors, VEGF-A is the most common and usually referred to as VEGF. This is a vascular permeability factor produced in response to upstream activators, including growth factors, cytokines, environmental stimuli and oncogenes. Hypoxia is a major factor inducing VEGF expression through the expression of hypoxia-inducible factor-a (HIF-1α) [5] and a key regulator of tumor angiogenesis. Numerous other factors are involved in cancer neovascularization such as prostaglandins, COX-2, IL-6, PDGF and epidermal growth factor (EGF) [6].

A group of specific receptors on the surface of endothelial as well as tumor cells interact with VEGF triggering downstream angiogenesis-related signals. This group of VEGF receptors include the receptor tyrosine kinases (RTKs) VEGFR1, VEGFR2 and VEGFR3. VEGFR2 is the major VEGF tyrosine kinase receptor mediating the angiogenesis signalling pathway in endothelial cells [7]. It was originally believed that VEGF receptors are expressed on endothelial cells only but it was later demonstrated that they can be expressed on tumor cells as well [8]. The binding of VEGF ligands to their specific cell surface RTKs, such as, VEGFR-1, VEGFR-2, and VEGFR-3 results in activation of downstream signaling [9] (Fig. 1). Despite the existence of multiple variants of both VEGF

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Table 1
Currently FDA approved antiangiogenesis agents in solid tumors (none in HNSCC).

Anti-angiogenesis agent	Mechanism of action	FDA approval
Bevacizumab	Humanized monoclonal antibody against VEGF	Colorectal cancer, NSCLC, renal cell cancer, ovarian cancer, glioblastoma, cervical cancer
Ramucirumab	Fully human monoclonal antibody against VEGFR2	Gastric cancer, NSCLC
Sunitinib	Multitargeted TKI, including VEGFR-1,VEGFR-2, VEGFR-3, PDGFR, RET and c-kit	GIST, pancreatic neuroendocrine tumors and metastatic renal cell cancer
Sorafenib	Multitargeted inhibitor of the serine/threonine protein kinases B-Raf, C-Raf and a TKI of VEGFR-2, -3, PDGFR, Flt-3, and c-kit	Advanced renal cell carcinoma, unresectable hepatocellular carcinoma and thyroid cancer
Vandetanib	Multitargeted TKI targeting EGFR, VEGFR-2 and RET	Unresectable medullary thyroid cancer
Axitinib	VEGFR TKI of receptors 1, 2, and 3	Advanced renal cell carcinoma
Pazopanib	Multitargeted TKI with activity against VEGFR, FDGFR, PDGFR, and c-kit	Renal cell carcinoma, soft tissue sarcomas
Regorafenib	Multitargeted TKI, including VEGFR	Colorectal cancer, GIST

Abbreviations: VEGF, vascular-endothelial growth factor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; GIST, gastrointestinal stromal tumors; VEGFR, vascular-endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; and FDGFR, fibroblast-derived growth factor receptor.

receptors and ligands, the main angiogenesis downsteam signal is mediated by VEGF-A and VEGFR-2 [10].

VEGF signalling may affect several significant tumor functions independent of vascular permeability and neovascularization. Autocrine VEGF signalling can promote tumor cell proliferation, migration as well as cancer invasion [11,12] by activating predominant pathways in tumorigenesis, such as the MAPK and PI3K–AKT. Moreover, VEGF can affect the host immune response by interacting with the function of immune cells within the tumor microenvironment [13]. VEGF signalling may have an autocrine and paracrine effect on the function of cancer stem cells [8]. VEGF has also been implicated in chemotherapy resistance as it may induce autophagy that counteracts chemotherapy-induced stress [14].

Angiogenesis markers as prognostic factors in HNSCC

High levels of VEGF expression are commonly observed in HNSCC and have been associated with disease aggressiveness and worse patient outcome [1,15,16]. In addition to VEGF, other promoters of angiogenesis, such as interleukin-8 (IL-8) and EGFR, are found in high levels in HNSCC. VEGF as well as EGFR plasma levels have been reported as potentially prognostic and predictive factors in HNSCC [1]. IL-8, a key mediator of hypoxia, along with other hypoxia-regulated cytokines and angiogenic factors (VEGF, IL-4 osteopontin, growth-related oncogene α, eotaxin, granulocyte-colony stimulating factor, and stromal cell derived factor 1α) were reported to comprise a high risk signature predictive for progression following induction chemotherapy with carboplatin, paclitaxel and cetuximab in HNSCC [17]. Another study of serum samples from patients treated with cetuximab-containing therapy showed that baseline VEGF and IL-6 are of potential prognostic significance [18]. Furthermore, Le et al. reported that plasma IL-8 is an independent prognostic factor irrespective of treatment in an analysis of large randomized trial of chemoradiotherapy with or without tirapazamine [19]. Several other proangiogenesis factors related to inflammation, hypoxia or apoptosis, such as COX-2, Bax, BcL-xL, BcL-2, VEGFR/KDR, pKDR/KDR and survivin, have been related to adverse clinical outcomes [1].

Additionally, hypoxia is a key feature of locally advanced tumors and major driving force of neovascularization in a wide variety of cancers including HNSCC [5]. Hypoxia-associated transcription factor, HIF-1 a and its target proteins CA-9 and GLUT-1 are often overexpressed in HNSCC contributing to angiogenesis and worse clinical outcome [1]. Lactate is another hypoxia-related factor and its accumulation has been associated with more aggressive phenotype in many tumors, including HNSCC [1].

A gene profiling study in HNSCC tumors of 323 patients who were enrolled in a randomized study testing the hypoxic modifier nimorazole with radiation against placebo plus radiation, uncovered a hypoxia-related gene classifier including 15 hypoxia-responsive genes predictive of the outcome of radiotherapy with nimorazole [20]. According to this study, tumors with upregulated hypoxia-related genes showed a worse clinical outcome but a better response to treatment with the hypoxic modifier. Hence, this gene classifier might be helpful to identify patients likely to derive benefit from radiotherapy combination with hypoxia-modifying radiosensitizers [20]. A biomarker adaptation study is being conducted by DAHANCA and EORTC in p16 negative HNSCC and aims to answer the question of whether hypoxic gene classifier positive HNSCC derive benefit from the addition of nimorazole to chemoradiotherapy (NCT01880359).

Another important aspect of HNSCC biology is the role of immune response in tumor microenvironment which may be stimulated by antiangiogenesis-induced vascular normalization and can subsequently enhance immunotherapy response against cancer cells [21]. Hence, the level of tumor-cytotoxic CD8+ has been described as a potential biomarker for vascular normalization and response to antiangiogenesis treatment [22].

VEGF and angiogenesis as therapeutic targets

The functional significance of VEGFs and their receptors has provided opportunities for the development of new therapeutic agents and strategies. These approaches can potentially promote tumor regression, reduce the probability of recurrence and enhance the response to standard chemotherapy and radiotherapy [8]. So far, these therapeutic approaches have been based on either antibody-mediated inhibition of VEGF or VEGFR, or inhibition of VEGF RTK activity using tyrosine kinases inhibitors (Fig. 1). In a study in head and neck cancer cell lines and xenograft models, bevacizumab in combination with radiation showed significantly decreased angiogenesis, inhibition of tumor growth and increased tumor cell apoptosis compared to radiation alone [23]. A study evaluating bevacizumab in combination with the EGFR-TKI erlotinib and radiation in a head and neck cancer orthotopic model demonstrated that radiation alone induced increased angiogenesis, whereas combination therapy led to increased tumor inhibition [24]. These observations suggest that activation of EGFR upregulates VEGF inducing resistance to EGFR inhibitors and support the rationale for several studies that evaluated the combination of anti-EGFR and anti-VEGF therapy in HNSCC [25,26].

Interactions with chemotherapy and radiation

Anti-VEGF therapies can normalize tumor vessels presumably leading to increased delivery of chemotherapy. This is an

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