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REVIEW BASED BOOK CHAPTER

TARGETING TUMOR ANGIOGENESIS IN HNSCC: THE ROLE OF VEGF INHIBITORS AND COMBINATION THERAPIES

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Abstract

Abnormalities in the vasculature of tumors, including undeveloped structure, increased permeability, and a disorganized microenvironment, are important characteristics of cancer. The problems are caused by malfunctioning endothelium and mural cellular structures, in addition to disrupted connections with the extracellular matrix (ECM). Tumor endothelial cells (TECs) derived from cancer stem cells undergo detachment, resulting in an elevation of vascular permeability and promoting the dissemination of the tumor. Pericyte detachment exacerbates these issues by augmenting mechanical strain and interrupting blood circulation, resulting in a hypoxic, acidic environment that promotes tumor proliferation and the production of ascites. Increased levels of Vascular Endothelial Growth Factor (VEGF) promote angiogenesis, which are abnormal in structure and limit the efficient delivery of drugs. Tumors can also employ vasculogenic mimicry, which involves the formation of vascular systems resembling those found in embryos, in order to get food. VEGF and its related proteins (VEGF-A, VEGF-C, VEGF-D) play a crucial function in facilitating the development of new blood vessels in Head and Neck Squamous Cell Carcinoma (HNSCC). Anti-VEGF therapies, comprising monoclonal antibodies and small molecule inhibitors, offer potential benefits but face challenges associated with resistance. Inhibiting VEGF receptors with tyrosine kinase inhibitors (TKIs) can enhance advancement survival without complications and response rates, particularly when combined with immune checkpoint inhibitors (ICIs). Currently, there is ongoing research on FDA-approved tyrosine kinase inhibitors (TKIs) such as sunitinib, sorafenib, and lenvatinib, in addition to novel medicines like zanzalintinib. Future research endeavors to augment medicines that target VEGF, incorporate immunotherapy, and identify biomarkers to boost treatment outcomes for HNSCC.

Keywords
Tumor Angiogenesis, Vascular Endothelial Growth Factor (VEGF) Pathway, Head and Neck Squamous Cell Carcinoma (HNSCC), Tyrosine Kinase Inhibitors (TKIs), Tumor Microenvironment

1. Introduction

1.1. The Tumor Vasculature Abnormalities

The genotypes of cancer cells are indicative of six physiological alterations that make cancer treatment more complex. Angiogenesis is a prominent characteristic of human cancer [1]. Angiogenesis induction is a key characteristic of human cancer. Scientists have observed physical distinctions between tumoral and normal vasculature, which has prompted them to consider the concept of normalizing tumor vasculature [2]. Tumor blood vessels show significant variations from normal blood vessels, frequently demonstrating underdeveloped design, elevated permeability, and a disordered microenvironment. The root cause of these problems lies in defective endothelium and mural cells and their modified interactions in conjunction with the extracellular matrix (ECM). Oncogenic stem cells have the ability to differentiate into atypical tumor endothelial cells (TECs), cells resembling smooth muscle, and pericytes. Tumor endothelial cells (TECs), which are not arranged in a regular pattern along the blood arteries of the tumor, detach and cause the vessels to become permeable, enabling tumor cells infiltrate the bloodstream and propagate to other regions of the body [3, 4]. In addition, the separation of pericytes, which typically provide support to the construction of blood vessels, worsens problems with permeability. The atypical permeability of the tumor microvasculature leads to an elevation in mechanical stress, resulting in the leakage of plasma into the adjacent tissues. This leakage increases the pressure of the fluid between cells, disturbs the flow of blood, and changes the way blood vessels are arranged in tumors [5].

Tumors experience increased pressure in the fluid between cells, which squeezes blood vessels. This changes the way tumor endothelial cells respond to mechanical forces and leads to the development of a low-oxygen, acidic environment. This environment promotes the rapid multiplication and dissemination of cancer cells and

the accumulation of fluid in the abdomen, known as ascites [6, 7]. Elevated VEGF levels within tumors intensify the process of angiogenesis, hence aggravating vascular irregularities and diminishing the effectiveness of medicine transportation. Tumor endothelium cells (TECs), which have increased expression of VEGF receptors, exhibit heightened sensitivity to VEGF in comparison to regular endothelial cells [8, 9]. Tumor endothelial cells (TECs) display differing degrees of heterogeneity based on the tumor's aggressiveness. In the instance of highly metastatic tumors, there is typically a lower presence of pericytes and a higher abundance of juvenile arteries. In highly metastatic TECs, the activation of the PI3K-Akt signaling pathway results in enhanced proliferation and elevated levels of VEGF [10, 11].

1.2. Mechanism of Angiogenesis

Angiogenesis in both healthy tissues and malignancies can occur through multiple mechanisms. These processes include sprouting angiogenesis, neo-vascularization, intussusception, co-opting pre-existing arteries, and vascular mimicry [6]. Typically, endothelial cells are inactive. When the body experiences low oxygen levels or a lack of nutrients, it initiates sprouting angiogenesis. This process is activated by VEGF, which stimulates tip cells to direct stalk cells in the angiogenesis. Mural cells provide assist to these arteries, and the disruption of VEGF receptor 2 inhibits this function [12, 13]. VEGF promotes the recruitment of endothelial progenitor cells and blood-forming cells derived from circulating mature endothelial cells within the microenvironment of a tumor, and also form hematopoietic stem cells and myeloid cells during tumor vasculogenesis. These cells continue to differentiate into endothelial cells (ECs) or aggregate to form a lumen resembling blood vessels [6]. Intussusception is a process in which the transluminal pillars fuse together and new branches from existing capillaries fold inward, causing a rapid expansion of the capillary network. This phenomenon was initially identified in the circulation of rat lungs [14]. Intussusceptive angiogenesis involves the expansion of vascular networks without the need for endothelial cell growth, in contrast to sprouting angiogenesis. Intussusceptive angiogenesis is a rapid process that leads to the duplication and reorganization of the existing vascular network [15]. In melanoma metastases in humans, the presence of

intravascular pillars emphasizes the significance of intussusception in the development of malignancy. Tumors transition from sprouting to intussusception as a result of exposure to radiation or anti-angiogenic medications, which are used to facilitate vascular repair [16, 17]. Fibroblast growth factors, angiopoietin-1, ephrins, and VEGF isoforms are essential in the transition from sprouting angiogenesis to intussusceptive angiogenesis [18]. Tumors have the ability to employ vasculogenic mimicry instead of the typical processes of sprouting angiogenesis, vasculogenesis, and intussusception used by normal tissues. During this process, malignant cancer cells create vascular structures similar to those found in embryos to provide nourishment to the tumor. This process is controlled by pericytes and pro-angiogenic proteins in an oxygen-deprived environment [19]. Hypoxia stimulates the formation of vasculogenic mimicry and vascular co-option in multiple malignancies, including melanoma and ovarian cancer. Co-opted vessels assimilate into preexisting arteries, maintaining the host structures, cancer cells have the capacity for trans-differentiation. These mechanisms, commonly seen in tumors with elevated blood flow, facilitate the development of resistance to anti-angiogenic therapy [20].

1.3. Function of VEGF in Tumor Angiogenesis

The relationship between VEGF-A and VEGF receptor 2 modulates various processes in endothelial cells, including survival, proliferation, migration, permeability, and capillary lumen creation. VEGF plays a crucial function in angiogenesis by activating several intracellular pathways. Besides its effect on endothelial cells, VEGF additionally plays an essential function in coordinating the creation of tumor blood vessels through its diverse biological effects.

The importance of integrating VEFG-TKIs with immune checkpoint inhibitors as a promising treatment strategy for SCCHN and other diseases must be emphasized. Angiogenesis is the process by which new blood vessels grow from old ones in tumors. This helps the tumors meet their increased metabolic needs and allows them to grow [21].

Immunohistochemical methods demonstrate detectable VEGF expression in tumor cells of HNSCC. The limited research available indicates that VEGF levels vary

according to the subtype of HNSCC and the tumor stage. This emphasizes the variations in patterns and intensity of VEGF expression [22].

Angiogenesis in HNSCC is stimulated by VEGF family members, specifically VEGF-A, VEGF-C, and VEGF-D. These proteins facilitate the proliferation, motility, and maturation of endothelial cells, leading to angiogenesis. Additional factors, such as bFGF and PDGF, contribute to angiogenesis. Hypoxia, a condition commonly found in solid tumors, triggers the activation of hypoxia-inducible factors (HIFs). Proteins like this help keep angiogenic factors like VEFG-A stable and boost their synthesis. In HNSCC, tumor angiogenesis is facilitated in part by HIF's activation of pro-angiogenic genes [23, 24].

In HNSCC, the tumor microenvironment plays a pivotal role in promoting angiogenesis. Secreted by cancer cells and stromal cells, including immune cells and cancer-associated fibroblasts, are a number of angiogenic agents and cytokines that foster an environment helpful to angiogenesis. The transition to an angiogenic phenotype depends on maintaining a precarious equilibrium both pro-angiogenic and anti-angiogenic agents [25].

There is a correlation between the level of tumor angiogenesis and poor prognosis and clinical outcomes in HNSCC. Tumor aggressiveness, metastasis, and prognosis rates are all worse when micro-vessel density (MVD) is high or when angiogenesis-related markers, like VEFG-A expression, are high [26]. The approach for addressing angiogenesis in HNSCC involves the use of anti-VEGF therapeutics, such as monoclonal antibodies and small molecule inhibitors. These drugs may be utilized independently or in conjunction with conventional therapies. Tumors have elevated levels of VEGF-A as a result of genetic mutations, hypoxia, and inflammation, which subsequently induces the formation of abnormal blood vessels [27, 28]. VEGF-A interacts with VEGFR-2 receptors on endothelial cells, initiating signals that promote their proliferation, migration, and survival. This process promotes the development of new blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis). Increased VEGF-A levels in HNSCC correlate with a more aggressive tumor phenotype,

heightened invasiveness, and a greater probability about lymph node metastasis. This arises from the promotion of tumor growth and lymphatic dissemination [29].

VEGF-C and VEGF-D promote the formation of new lymph nodes through their interaction with VEGFR-3. Increased levels of these proteins correlate with the spread of cancer cells to lymph nodes and a poor prognosis for individuals with head and neck squamous cell carcinoma (HNSCC). To develop therapies that can limit tumor growth and improve therapy outcomes, VEFG and angiogenesis must be the primary targets [30, 31].

1.4. Therapeutic Targeting of VEGF in HNSCC

Head and neck squamous cell carcinoma (HNSCC), A common and highly aggressive cancer frequently exhibits abnormal angiogenesis, making vascular endothelial growth factor (VEGF), a crucial therapeutic approach. Monoclonal antibodies and small chemical inhibitors that target VEFG have demonstrated promise in preclinical studies by lowering tumor angiogenesis, growth inhibition, and metastasis reduction. However, a comprehensive assessment of the effectiveness, safety, and constraints of these treatments is necessary through rigorous examination in clinical studies [32, 33]. Reducing VEFG can lessen HNSCC cell invasiveness, block tumor cell migration, and stop distant metastases from developing, according to studies [34]. The metastasis of HNSCC tumor cells could be halted by blocking VEFG, which inhibits angiogenesis. Alternate angiogenic pathways, compensatory signaling, and genetic alterations in the VEFG system are among the resistance mechanisms that have been elucidated by preclinical investigations [35, 36].

Knowing resistance mechanisms is essential for improving the efficacy of VEGF-targeted therapies. Clinical trials demonstrate that VEGF-targeted treatments, such as monoclonal antibodies and tyrosine kinase inhibitors, enhance progression-free survival and response rates in head and neck squamous cell carcinoma (HNSCC), though benefits vary by study and patient [37, 38].

1.5. VEGF-TKI Monotherapy in Solid Tumors

1.5.1. Monoclonal Antibody Therapy

Bevacizumab, a monoclonal antibody, binds to VEGF-A, obstructing its interaction with receptors. This action inhibits the angiogenesis, reduces blood vessel leakage, and slows down tumor growth in HNSCC. Combining bevacizumab with radiation or chemotherapy increases overall survival and progression-free survival, according to empirical studies. However, the extent among these advantages is subject to variation based on individual patient and tumor factors [39].

While VEFG-targeted monoclonal antibodies usually have a low incidence of side effects, they can increase the risk of hypertension, proteinuria, bleeding, and wound healing issues. Primary and acquired resistance are challenges that can restrict the effectiveness of treatment in HNSCC [40]. Additional investigation is required on the selection of patients, the duration of treatment, and the identification of prognostic biomarkers for medicines that target VEGF. The integration of these antibodies with immune checkpoint inhibitors, chemotherapy, or targeted treatments shows promise for enhancing outcomes in HNSCC, highlighting the need for continued research [41].

1.6. Tyrosine Kinase Inhibitors (TKIs)

Tyrosine kinase inhibitors (TKIs) selectively attach to the intracellular domain of VEGF receptors, thereby obstructing downstream signaling cascades and disrupting the blood supply to tumors in head and neck squamous cell carcinoma (HNSCC). Although there are a number of tyrosine kinase inhibitors (TKIs) on the market, including sunitinib and sorafenib, which show some benefits including increased rates of tumor response and progression-free survival, the results in clinical trials are still not clear. Patient selection, treatment methods, and tumor features are among the variables that affect the efficacy of TKIs in HNSCC [42].

VEGF-TKIs demonstrate potential efficacy in solid tumors, indicating possible advantages for SCCHN, particularly when used in conjunction with immune checkpoint inhibitors (ICIs). The fusion of PD-1 inhibitors and anti-angiogenic medicines shows a synergistic effect, making it a viable therapy with documented advantages in multiple

types of cancer. Sunitinib, a multikinase inhibitor licensed by the FDA, enhances response rates, extends progression-free survival and improves overall survival in patients with advanced illness RCC [43]. Subsequent research provided a clearer understanding of the most effective treatment schedules for managing the significant toxicity associated with it [44]. Additionally, it has received approval for the management of gastrointestinal stromal tumor (GIST) [45].

Sorafenib is a type of medication called a multikinase inhibitor. It specifically targets and inhibits the participation in VEGFRs, PDGFR, c-Kit, RET, and Raf. It was granted approval for the management of renal cell carcinoma (RCC), hepatocellular carcinoma, and thyroid cancer that is refractory to radioactive iodine therapy (RAI-refractory). In clinical trials, it exhibited improved progression-free survival and a higher probability of stable disease in RCC. Nevertheless, there was no first statistically meaningful improvement in overall survival [46].

Lenvatinib, a potent inhibitor of many kinases including VEGFR, FGFR, PDGFR, RET, and KIT, has been authorized for the management of thyroid cancer resistant to radioactive iodine therapy. It has demonstrated enhanced rates of survival without disease progression and increased response rates. Additionally, it received approval as a combined treatment with everolimus for advanced metastatic RCC after showing substantial enhancements in average survival and response rates [47].

Axitinib is a second-generation tyrosine kinase inhibitor (TKI) that specifically targets the vascular endothelial growth factor receptor (VEGFR). In two phase III trials, patients with recurrent metastatic renal cell carcinoma (RCC) were found to have better outcomes with axitinib compared to sorafenib in terms of progression-free survival (PFS) and objective response rate (ORR). However, neither trial exhibited substantial changes in overall survival (OS) [48]. As a result, the medication is currently not sanctioned by the FDA for first-line therapy.

Cabozantinib is a novel multi-kinase inhibitor (MKI) that effectively inhibits the activities of VEGFR, RET, AXL, MET, and KIT. These proteins have been recognized for their function in imparting resistance to VEGF inhibitors in renal cell carcinoma (RCC) [49]. After a phase III trial demonstrated that Cabozantinib improved OS, PFS, and ORR

compared to everolimus in patients with advanced or metastatic renal cell carcinoma (RCC) whose condition worsened despite prior treatment with VEFG inhibitors, the FDA approved the drug [50]. Further, following advancement following first-line VEGFR-targeted treatment, it can be used as a second-line therapy for patients with locally progressed or metastatic RAI-refractory differentiated thyroid cancer [51]. The prolonged plasma half-life of cabozantinib led to the development of zanalintinib (XL092), which is used during first therapy to prevent drug production. As a multi-kinase inhibitor, XL092 targets VEGFR, MET, and the TAM kinases (TYRO3, AXL, MER), much like cabozantinib. However, its half-life is significantly shorter [52]. In order to determine, if XL092 is effective in treating advanced solid tumors when combined with immuno-oncology medicines, a Phase 1b clinical trial is now underway (NCT05176483). Tyrosine kinase inhibitors (TKIs) can induce adverse reactions and develop resistance. However, the combination of therapeutic approaches and the utilization of biomarkers have the potential to enhance treatment results.

2. Combination Therapy

2.1. Immunotherapy in Solid Tumors with VEFG-TKIs with Combination Therapy

Combining avelumab and axitinib considerably improved progression-free survival in patients with renal cell carcinoma (RCC) as compared to sunitinib alone, according to the Javelin renal 101 study. However, the two therapy groups did not differ significantly in terms of overall survival, and the occurrence of adverse events was also similar [48].

Patients with advanced renal cell carcinoma (RCC) had substantially enhanced overall survival, progression-free survival, and objective response rate when treated with axitinib and pembrolizumab in comparison to sunitinib alone, according to the KEYNOTE 426 trial. Both groups experienced similar adverse effects; however, combination therapy had lower rates of discontinuation, indicating the need for more research [49].

In patients with renal cell carcinoma (RCC), the CHECKMATE 9ER study found that nivolumab plus cabozantinib considerably improved progression-free survival, overall survival, and objective response rate compared to sunitinib alone. In addition,

the two therapy groups had similar rates of adverse events. The CLEAR research indicated that the combination of lenvatinib with pembrolizumab produced the most positive results. The findings highlight the promise of integrating VEGF-TKI with ICI for the management of SCCHN.

2.2. Combination of VEFG-TKIs with EGFR Inhibitors or Chemotherapy for SCCHN

Clinical trials with 47 individuals diagnosed with squamous cell carcinoma of the head and neck (SCCHN) found that different treatment regimens involving apatinib had varying effects. Clinical trials with 47 individuals diagnosed with squamous cell carcinoma of the head and neck (SCCHN) found that different treatment regimens involving apatinib had varying effects [50].

As part of a phase II clinical research, 49 patients were involved who had locally progressed squamous cell carcinoma of the head and neck (SCCHN). Apatinib and S-1 oral chemotherapy were administered to the patients. Despite a very high objective response rate of 97.4%, the overall survival percentage at three years was 64.2%. Out of the 30 patients tested for oropharyngeal, 14 of them had p16 positive. The study emphasized the necessity of regular HPV testing, a technique that was previously not implemented [51].

A clinical investigation comparing the efficacy of docetaxel alone to docetaxel combined with vandetanib shown a small inclination towards enhanced reaction rates and time to remission were measured. However, these findings did not have any significant clinical relevance [52]. A randomized experiment was conducted to evaluate the possible synergy of combining cetuximab with sorafenib. However, the results did not demonstrate any meaningful therapeutic advantage. The response rates exhibited no significant difference, both standing at 8%. The total survival duration was 9 months without sorafenib and 5.7 months with sorafenib [53].

Results from a clinical trial using 54 patients with advanced nasopharyngeal cancer showed promise when sorafenib was given alongside cisplatin and 5-fluorouracil. With 1 complete response and 41 partial responses, the treatment obtained a response rate of 77.8%. The median time between treatments was 11.8

months for overall survival and 7.2 months for progression-free survival. Additional randomized studies are required [54].

Researchers have looked into tazopanib, a tyrosine kinase inhibitor (TKI), both alone and in combination with other medications. Pazopanib is now authorized for the treatment of soft-tissue sarcomas and has demonstrated promise in metastatic renal cell carcinoma (RCC) [53, 55, 56]. In a phase II trial, pazopanib monotherapy had a partial response in 2 out of 33 patients with nasopharyngeal carcinoma. A median of 10.8 months was the time that patients survived. Two complete responses and nine partial responses were observed in a phase Ib clinical trial where pazopanib and cetuximab were administered together. The overall percentage of survivors was 9.5 months [57]. Pazopanib significantly improved patients' health and was well-tolerated in both studies. Famitinib is now under investigation as a possible treatment for a variety of cancers, including renal cell carcinoma (RCC), colorectal cancer, breast cancer, and others [58–60]. In a phase II clinical trial, 58 patients with nasopharyngeal cancer who had recurred or spread to other areas of the body were assessed for the efficacy of famitinib as a monotherapy. The results showed that 3.2 months of progression-free survival (PFS), 5 patients had a partial response, and 16 patients had stable disease. Researchers found that famitinib was highly effective in the clinic and had just mild to moderate side effects [61]. Phase I trials with famitinib and concomitant chemotherapy in individuals with locoregionally advanced nasopharyngeal carcinoma showed acceptable tolerability but limited clinical efficacy [62]. High vigilance is required during VEFG-targeted therapy because to the potential side effects of hypertension, proteinuria, and others. Combination therapy and biomarkers are necessary for effectively addressing resistance concerns. The selection of therapy for HNSCC patients is determined by factors such as tumor stage, biomarkers, performance, and comorbidities. The specific criteria for selection may change depending on the protocol being followed.

2.3. Prospective Pathways and Barriers

The challenges in VEFG-targeted treatment for HNSCC encompass the diversity of tumors, the intricate nature of angiogenesis, and an appearance of resistance. The

research is centred on creating new VEGF inhibitors, such as small compounds and bispecific antibodies, with the goal of enhancing effectiveness, safety, and the ability to combat resistance [63, 64].

Potential immunotherapeutic techniques for HNSCC treatment include adoptive cell therapy and immune checkpoint inhibitors. Research mainly aims to improve the activation and durability of tumor-infiltrating lymphocytes by targeting PD-1/PD-L1, tumor-specific antigens, and other similar targets [65]. The objective of molecular profiling advancements is to discover predictive biomarkers that can be used to customize treatments, target specific mutations, and enhance therapies for HNSCC [66].

There is currently no recognized biomarker for head and neck squamous cell carcinoma, however the molecular criteria for anti-VEFG therapy are progressing. Research focuses on identifying and validating biomarkers like genetic mutations and protein expressions to guide treatment and predict outcomes. Understanding the tumor microenvironment and its components is crucial for developing personalized therapies and managing resistance [67].

Continued progress in treating HNSCC, it is necessary to tackle obstacles such as the diversity of tumors, the mechanisms of resistance, choosing the right patients, and maximizing the use of combination medicines. Efficient administration of medication and proper handling of adverse effects are also essential. Effective collaboration among scientists, researchers, and clinicians is crucial for converting scientific findings into practical medical applications and assessing the efficacy of novel treatments.

3. Conclusion

When thinking about how to treat SCCHN in the future, studies on VEFG-TKIs show promise for increasing their applicability. Given the limited therapy options now available for SCCHN, this is of utmost importance. Latest findings regarding the synergistic effects of VEGF kinase inhibitors (VEGF-TKIs) and immunotherapy suggests that this approach holds promise. The combination offers clinical benefits from both types of agents, without any additional side effects when using Immune Checkpoint

Inhibitors (ICIs). Furthermore, this strategy is widely applicable as it does not require specific biomarkers or patient selection. As a result, it has a high potential for effectively treating Squamous Cell Carcinoma of the Head and Neck (SCCHN) and potentially other types of Squamous Cell Carcinomas (SCCs). With the growing emphasis on targeted medicines and customized care in cancer treatment and research. The importance of integrating VEFG-TKIs with immune checkpoint inhibitors as a promising treatment strategy for SCCHN and other diseases must be emphasized.

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J. Narayanan & R. Sridevi: Conceptualization, Literature Review, Writing – Original Draft Preparation.
V. Manimaran & K. Manikandan: Literature Review, Writing – Review and Editing.
V. Chitra: Supervision, Critical Revision and Final Approval of the Manuscript.

Conflicts of interest

The authors do not have conflict of interest.

References

[1] Hanahan, D. 1997. Signaling vascular morphogenesis and maintenance. Science, 277, 48–50.
[2] Jain, R.K. 2005. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science, 307, 58–62.
[3] Ayoub, N.M., Jaradat, S.K., Al-Shami, K.M., Alkhalifa, A.E. 2022. Targeting angiogenesis in breast cancer: current evidence and future perspectives of novel anti-angiogenic approaches. Frontiers in Pharmacology,13, 838133.
[4] Hida, K., Maishi, N., Takeda, R., Hida, Y. 2022. In: Sergi, C.M. (Ed.), The Roles of Tumor Endothelial Cells in Cancer Metastasis, Metastasis, Brisbane (AU).
[5] Lugano, R., Ramachandran, M., Dimberg, A. 2020. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cellular and Molecular Life Sciences, 77, 1745–1770.
[6] Majidpoor, J., Mortezaee, K. 2021. Angiogenesis as a hallmark of solid tumors-clinical perspectives. Cellular Oncology, 44, 715–737.
[7] Moghaddam, S.M., Amini, A., Morris, D.L., Pourgholami, M.H. 2012. Significance of vascular endothelial growth factor in growth and peritoneal dissemination of ovarian cancer. Cancer and Metastasis Reviews, 31, 143–162.
[8] Zanotelli, M.R., Reinhart-King, C.A. 2018. Mechanical forces in tumor angiogenesis. Advances in Experimental Medicine and Biology, 1092, 91–112.

[9] Matsuda, K., Ohga, N., Hida, Y., Muraki, C., Tsuchiya, K., Kurosu, T., Akino, T., Shih, S. C., Totsuka, Y., Klagsbrun, M., Shindoh, M., Hida, K. 2010. Isolated tumor endothelial cells maintain specific character during long-term culture. Biochemical and Biophysical Research Communications, 394, 947–954.
[10] Hida K, Maishi N, Takeda R, et al. 2022. The Roles of Tumor Endothelial Cells in Cancer Metastasis. In: Sergi CM, editor. Metastasis [Internet]. Brisbane (AU): Exon Publications; Chapter10.
[11] Eelen, G., Treps, L., Li, X., Carmeliet, P. 2020. Basic and therapeutic aspects of angiogenesis updated. Circulation Research, 127, 310–329.
[12] Ribatti, D., Crivellato, E. 2012. Sprouting angiogenesis", a reappraisal. Developmental Biology, 372, 157–165.
[13] Burri, P.H., Tarek, M.R. 1990. A novel mechanism of capillary growth in the rat pulmonary microcirculation. The Anatomical Record, 228, 35–45.
[14] Pasut, A., Becker, L.M., Cuypers, A., Carmeliet, P. 2021. Endothelial cell plasticity at the single-cell level. Angiogenesis, 24, 311–326.
[15] Pandita, A., Ekstrand, M., Bjursten, S., Zhao, Z., Fogelstrand, P., Le Gal, K., Ny, L., Bergo, M.O., Karlsson, J., Nilsson, J.A., Akyurek, L.M., Levin, M.C., Boren, J., Ewald, A.J., Mostov, K.E., Levin, M. 2021. Intussusceptive angiogenesis in human metastatic malignant melanoma. American Journal of Pathology, 191, 2023–2038.
[16] Hlushchuk, R., Riesterer, O., Baum, O., Wood, J., Gruber, G., Pruschy, M., Djonov, V. 2008. Tumor recovery by angiogenic switch from sprouting to intussusceptive angiogenesis after treatment with PTK787/ZK222584 or ionizing radiation. The American Journal of Pathology, 173, 1173–1185.
[17] Saravanan, S., Vimalraj, S., Pavani, K., Nikarika, R., Sumantran, V.N. 2020. Intussusceptive angiogenesis as a key therapeutic target for cancer therapy. Life Sciences, 252, 117670.
[18] Zhang, Y., Brekken, R.A. 2022. Direct and indirect regulation of the tumor immune microenvironment by VEGF. Journal of Leukocyte Biology, 111, 1269–1286.
[19] Belotti, D., Paganoni, P., Manenti, L., Garofalo, A., Marchini, S., Taraboletti, G., Giavazzi, R. 2003. Matrix metalloproteinases (MMP9 and MMP2) induce the release of vascular endothelial growth factor (VEGF) by ovarian carcinoma cells: implications for ascites formation. Cancer Research, 63, 5224–5229.
[20] Nishida, N., Yano, H., Nishida, T., Kamura, T., Kojiro, M. 2006. Angiogenesis in cancer. Vascular Health and Risk Management, 2(3): 213-219.
[21] Meadows, K.L., Hurwitz, H.I. 2012. Anti-VEGF therapies in the clinic. Cold Spring Harbor Perspectives in Medicine, 2(10): a006577.
[22] Holmes, D.I., Zachary, I. 2005. The vascular endothelial growth factor (VEGF) family: angiogenic factors in health and disease. Genome Biology, 6(2), 209.
[23] Carmeliet, P. 2005. VEGF as a key mediator of angiogenesis in cancer. Oncology 69(Suppl 3), 4-10.
[24] Pradeep, C.R., Sunila, E.S., Kuttan, G. 2005. Expression of vascular endothelial growth factor (VEGF) and VEGF receptors in tumor angiogenesis and malignancies. Integrative Cancer Therapies, 4(4), 315-321.
[25] Yang, X., Zhang, Y., Hosaka, K., Andersson, P., Wang, J., Tholander, F., Cao, Z., Morikawa, H., Tegnér, J., Yang, Y., Iwamoto, H., Lim, S., Cao, Y. 2015. VEGF-B promotes cancer metastasis through a VEGF- A-independent mechanism and serves as a marker of poor prognosis for cancer patients. Proceedings of the National Academy of Sciences of the United States of America, 112(22), E2900-E2909.
[26] Niland, S., Eble, J.A. 2019. Neuropilins in the context of tumor vasculature. International Journal of Molecular Sciences, 20(3), 639.
[27] Domingues, A., Fantin, A. 2021. Neuropilin 1 regulation of vascular permeability signaling. Biomolecules, 11(5), 666.

[28] Sopo, M., Anttila, M., Hämäläinen, K., Kivelä, A., Ylä-Herttuala, S., Kosma, V.M., Keski-Nisula, L., Sallinen, H. 2019. Expression profiles of VEGF-A, VEGF-D and VEGFR1 are higher in distant metastases than in matched primary high grade epithelial ovarian cancer. BMC Cancer, 19(1), 584.
[29] Favier, B., Alam, A., Barron, P., Bonnin, J., Laboudie, P., Fons, P., Mandron, M., Herault, J.P., Neufeld, G., Savi, P., Herbert, J.M., Bono, F. 2006. Neuropilin-2 interacts with VEGFR-2 and VEGFR-3 and promotes human endothelial cell survival and migration. Blood, 108(4), 1243-1250.
[30] Savory, L.J., Stacker, S.A., Fleming, S.B., Niven, B.E., Mercer, A.A. 2000. Viral vascular endothelial growth factor plays a critical role in orf virus infection. Journal of Virology, 74(22), 10699-10706.
[31] Dewerchin, M., Carmeliet, P. 2014. Placental growth factor in cancer. Expert Opinion on Therapeutic Targets, 18(11), 1339-1354.
[32] Kieran, M.W., Kalluri, R., Cho, Y.J. 2012. The VEGF pathway in cancer and disease: responses, resistance, and the path forward. Cold Spring Harbor Perspectives in Medicine, 2(12), a006593.
[33] Shibuya, M. 2011. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for anti- and pro-angiogenic therapies. Genes Cancer, 2(12), 1097- 1105.
[34] Patel, S.A., Nilsson, M.B., Le, X., Cascone, T., Jain, R.K., Heymach, J.V. 2023. Molecular mechanisms and future implications of VEGF/VEGFR in cancer therapy. Clinical Cancer Research, 29(1), 30-39.
[35] Ramakrishnan, S., Anand, V., Roy, S. 2014. Vascular endothelial growth factor signaling in hypoxia and inflammation. Journal of Neuroimmune Pharmacology, 9(2), 142-160.
[36] Niu, G., Chen, X. 2010. Vascular endothelial growth factor as an anti- angiogenic target for cancer therapy. Current Drug Targets, 11(8), 1000-1017.
[37] Wagner, K.D., El Maï, M., Ladomery, M., Belali, T., Leccia, N., Michiels, J.F., Wagner, N. 2019. Altered VEGF splicing isoform balance in tumor endothelium involves activation of splicing factors Srpk1 and Srsf1 by the Wilms' tumor suppressor Wt1. Cells, 8(1), 41.
[38] Hutson, T.E., Lesovoy, V., Al-Shukri, S., Stus, V.P., Lipatov, O.N., Bair, A.H., et al. 2013. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. The Lancet Oncology, 14(13), 1287–94.
[39] Motzer, R.J., Escudier, B., Tomczak, P., Hutson, T.E., Michaelson, M.D., Negrier, S., et al. 2013. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. The Lancet Oncology, 14(6), 552–62.
[40] Yakes, F.M., Chen, J., Tan, J., Yamaguchi, K., Shi, Y., Yu, P., et al. 2011. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Molecular Cancer Therapeutics, 10(12), 2298–308.
[41] Choueiri, T.K., Escudier, B., Powles, T., Mainwaring, P.N., Rini, B.I., Donskov, F., et al. 2015. Cabozantinib versus everolimus in advanced renal-cell carcinoma. The New England Journal of Medicine, 373(19), 1814–23.
[42] Brose, M.S., Robinson, B.G., Sherman, S.I., Jarzab, B., Lin, C.C., Vaisman, F., et al. 2022. Cabozantinib for previously treated radioiodine-refractory differentiated thyroid cancer: Updated results from the phase 3 COSMIC-311 trial. Cancer, 128(24), 4203–12.
[43] Hsu, J., Chong, C., Goon, L., Balayan, J., Wu, S., Johnson, E., et al. 2020. XL092, a multi-targeted inhibitor of MET, VEGFR2, AXL and MER with an optimized pharmacokinetic profile. European Journal of Cancer, 138, S16.
[44] Choueiri, T.K., McGregor, B.A., Shah, N.J., Bajaj, A., Chahoud, J., O'Neil, B., et al 2022. A phase 1b study (STELLAR-002) of XL092 administered in combination with nivolumab (NIVO) with or without ipilimumab (IPI) or bempegaldesleukin (BEMPEG) in patients (pts) with advanced solid tumors. Journal of Clinical Oncology, 40 (16_suppl), TPS4600–TPS4600.

[45] Motzer, R.J., Penkov, K., Haanen, J., Rini, B., Albiges, L., Campbell, M.T., et al. 2019. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. The New England Journal of Medicine, 380(12), 1103–15.
[46] Rini, B.I., Plimack, E.R., Stus, V., Gafanov, R., Hawkins, R., Nosov, D., et al. 2019. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. The New England Journal of Medicine, 380(12), 1116–27.
[47] Choueiri, T.K., Powles, T., Burotto, M., Escudier, B., Bourlon, M.T., Zurawski, B., et al., 2021. Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma. The New England Journal of Medicine, 384(9), 829–41.
[48] Motzer, R., Alekseev, B., Rha, S.Y., Porta, C., Eto, M., Powles, T., et al., 2021. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. The New England Journal of Medicine, 384(14), 1289–300.
[49] Wu, Q., Liu, J., Li, S., Wang, J., Zhong, Y. 2022. Apatinib in recurrent or metastatic head and neck cancer patients. Journal of Clinical Oncology, 40(16_suppl), e18010–0.
[50] Jiang, W., Li, R., Zhang, L., Dou, S., Ye, L., Shao, Z., et al. 2023. Efficacy and feasibility of Apatinib and S-1 as a novel oral induction therapy in locally advanced head and neck squamous cell carcinoma: an exploratory phase 2 open-label, single-arm trial. Frontiers in Oncology, 13, 1072538.
[51] Limaye, S., Riley, S., Zhao, S., O'Neill, A., Posner, M., Adkins, D., et al. 2013. A randomized phase II study of docetaxel with or without vandetanib in recurrent or metastatic squamous cell carcinoma of head and neck (SCCHN). Oral Oncology, 49(8), 835–41.
[52] Gilbert, J., Schell, M.J., Zhao, X., Murphy, B., Tanvetyanon, T., Leon, M.E., et al. 2015. A randomized phase II efficacy and correlative studies of cetuximab with or without sorafenib in recurrent and/or metastatic head and neck squamous cell carcinoma. Oral Oncology, 51(4), 376–82.
[53] Xue, C., Huang, Y., Huang, P.Y., Yu, Q.T., Pan, J.J., Liu, L.Z., et al. 2013. Phase II study of sorafenib in combination with cisplatin and 5-fluorouracil to treat recurrent or metastatic nasopharyngeal carcinoma. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 24(4), 1055–61.
[54] Nguyen, D.T., Shayahi, S. 2013. Pazopanib: approval for soft-tissue sarcoma. Journal of the Advanced Practitioner in Oncology, 4(1), 53–7.
[55] Wang, B., Song, J.W., Chen, H.Q. 2020. First-line pazopanib treatment in metastatic renal cell carcinoma: real-world data from a single chinese center. Frontiers in Pharmacology, 11, 517672.
[56] Adkins, D., Mehan, P., Ley, J., Siegel, M.J., Siegel, B.A., Dehdashti, F., et al. 2018. Pazopanib plus cetuximab in recurrent or metastatic head and neck squamous cell carcinoma: an open-label, phase 1b and expansion study. The Lancet Oncology, 19(8), 1082–93.
[57] Chen, L., Jiang, Y.Z., Wu, S.Y., Wu, J., Di, G.H., Liu, G.Y., et al. 2022. Famitinib with camrelizumab and nab-paclitaxel for advanced immunomodulatory triple-negative breast cancer (FUTURE-C-plus): an open-label, single-arm, phase II trial. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 28(13), 2807–17.
[58] Qu, Y.Y., Zhang, H.L., Guo, H., Luo, H., Zou, Q., Xing, N., et al. 2021. Camrelizumab plus famitinib in patients with advanced or metastatic renal cell carcinoma: data from an open-label, multicenter phase II basket study. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research, 27(21), 5838–46.
[59] Xu, R.H., Shen, L., Wang, K.M., Wu, G., Shi, C.M., Ding, K.F., et al. 2017. Famitinib versus placebo in the treatment of refractory metastatic colorectal cancer: a multicenter, randomized, double-blinded, placebo-controlled, phase II clinical trial. Chinese Journal of Cancer, 36(1), 97.
[60] Huang, Y., Zhang, L., Pan, J.J., Hu, G., Gang, W., Xiong, J.P., et al. 2013. A phase II, multicenter, open-label, single-arm trial of famitinib in patients with advanced recurrent and/or metastatic nasopharyngeal carcinoma (NPC) after two previous treatment regimens. Journal of

Clinical Oncology: Official Journal of the American Society of Clinical Oncology, 31(15_suppl), 6026–6.
[61] Chen, Q., Tang, L., Liu, N., Han, F., Guo, L., Guo, S., et al. 2018. Famitinib in combination with concurrent chemoradiotherapy in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 1, open-label, dose-escalation study. Cancer Communications, 38(1), 66.
[62] Cheng, G., Dong, H., Yang, C., Liu, Y., Wu, Y., Zhu, L., Tong, X., Wang, S. 2021. A review on the advances and challenges of immunotherapy for head and neck cancer. Cancer Cell International, 21(1), 406.
[63] Barzaman, K., Samadi, M., Moradi-Kalbolandi, S., Majidzadeh-A, K., Salehi, M., Jalili, N., Jazayeri, M.H., Khorammi, S., Darvishi, B., Siavashi, V., Shekarabi, M., Farahmand, L. 2021. Development of a recombinant anti-VEGFR2-EPCAM bispecific antibody to improve antiangiogenic efficiency. Experimental Cell Research, 405(2), 112685.
[64] Mei, Z., Huang, J., Qiao, B., Lam, A.K. 2020. Immune checkpoint pathways in immunotherapy for head and neck squamous cell carcinoma. International Journal of Oral Science, 12(1), 16.
[65] Chan, J.Y.K., Zhen, G., Agrawal, N. 2019. The role of tumor DNA as a diagnostic tool for head and neck squamous cell carcinoma. Seminars in Cancer Biology, 55, 1-7.
[66] Kordbacheh, F., Farah, C.S. 2021. Current and emerging molecular therapies for head and neck squamous cell carcinoma. Cancers (Basel), 13(21), 5471.
[67] Somara, S., Kwatra, S.G., Kwatra, M.M. 2022. Biomarkers in head and neck squamous cell carcinoma: unraveling the path to precision immunotherapy. Drug Resistance Updates, 60, 100806.