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An Enquiry on the Present Status of Drugs Inhibiting Neo-Angiogenesis in Treatment of Oral Cancers

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1. Abstract

The occurrence of locoregional recurrences, distant metastasis and second primaries has limited the efficacy of treatment for oral cancer. Despite improvements and modifications in treatment paradigms, there has not been significant reduction in the numbers of post treatment disease events in such patients. The research on antiangiogenesis which began systematically in the 1970s, has evolved to a point where several agents have been approved for treatment of cancers such as lung, colon, breast and thyroid. Some of these drugs are being used as combination therapy for oral cancers also, while others are being investigated by clinical trials. This review covers the principles of angiogenesis, its mechanisms and its history; we give an overview of the current scenario of use of antiangiogenic drugs for oral cancers. The use of angiogenesis inhibitors in chemoprevention for oral premalignant lesions is examined and future directions are discussed.

2. Introduction

The development of cancer in any part of the body involves complex, multiple and evolving pathways [1]. These pathways involve both genetic and epigenetic changes and are also influenced by factors in the host environment [2].

Of the numerous processes involved in the development of a tumor, angiogenesis has emerged as a rate limiting step for progression of a premalignant to a malignant lesion and for progression, invasion and metastasis of a malignant growth [3]. Angiogenesis is described as one of the eight critical changes that occur on the pathway of any cell to becoming cancerous [4].

2.1. Definition

As the name implies, angiogenesis or neo-angiogenesis means the formation of new blood vessels. A tumor will be unable to grow or invade and metastasize if not for its own system of blood vessels [5]. These new vessels are different from normal ones, both architecturally and in the fact that they are not quiescent and retain the ability to continue propagating [2]. The development of these blood vessels involves an evolved and intricate process, with numerous alternate pathways, convergent and divergent routes and points of host-tumor interaction, as is examined in the following paragraphs.

2.1.1. History of the study of tumor angiogenesis

Angiogenesis as a critical part of progression of malignant tumors has been studied systematically since the 1940s [6], though the concept itself has been under discussion from the nineteenth century onwards. The term - 'angiogenesis' -was coined two centuries earlier (1787) by John Hunter, a surgeon [7]. Virchow, in 1865, in his publications on surgical pathology, described the abundance of blood vessels in a tumor as well as the presence of distinctive stroma in its surroundings [7]. The ability of transplanted tumours to rapidly produce new capillaries was observed [8, 9]. The presence of a definite substance produced by malignant tumors that could incite this angiogenesis was demonstrated [10]. Further work in

this direction lead to the naming of this substance as tumor angiogenesis factor or TAF [6]. In addition, the possibility of countering malignant growth by producing an antiserum to TAF was suggested [6]. These pioneers also laid the foundation for using animal or tissue models for the study of factors related to angiogenesis[7].

2.1.2. Proof of concept for anti-angiogenesis - the theory of dormancy

'Dormant' malignant cells show a balance between proliferation and apoptosis and lack of neovascularization. Thus, both the primary growth and metastases if any are suppressed [11]. Angiogenic dormancy is one of the mechanisms of reaching this state, the other being cellular dormancy [12]. Dormancy of cells has been observed in tumors in conditions such as in the presence of indigenous angiogenic inhibitors [13]. Human derived angiostatin has been shown to inhibit, at least in part, tumor metastases in mouse models [14, 15]. An extensive review of issues related to dormancy of tumours has been covered elegantly elsewhere [16] Thus, employing anti-angiogenic agents should logically induce dormancy, which is the premise behind the extensive effort that is being pursued in this field [17].

2.1.3. The Process of and Regulation of Angiogenesis

The transformation of a cell into a potentially malignant one is determined by genetic changes such as loss, deletion, translocation which in turn may be brought on by hereditary or environmental factors. The latter may be, as in the majority of oral squamous cancers, substances such as tobacco and alcohol. The next step in the evolution of any cancer cell is to grow and invade. The growth of a tumor cells up to a limit may proceed unaided, however, to grow beyond the size of a few square millimeters, there is required a system of dedicated vasculature for nutrition and waste disposal. This comes from the process of angiogenesis [5]. Animal models have led workers to identify the factors that are involved in stimulating and inhibiting angiogenesis [18].

This so called 'angiogenic switch', in the body is now known to be a multi-step process involving upregulation of pro-angiogenic factors and also downregulation of angiogenesis suppressor proteins.

The presence of hypoxia [19] releases Hypoxia Inducible Factor (HIF) that in turn upregulates and downregulates genes that would eventually stimulate angiogenesis. In addition the switch may be triggered by oncogenes such as cmyc, ras and p jun [20, 21].

The upregulation of these oncogenes in turn target products of the EGFR system, most importantly VEGF, FGF, PLGF that are overexpressed by tumor cells [20]; others being angiopoietins -especially Angiopoietin 2 or Ang 2 [22], ephrins [23], apelin (APLN) [24] and chemokines [25]. These factors are often expressed simultaneously, effectively co-operating at different stages of tumor angiogenesis [18].

2.1.4. The role of tumor microenvironment

That the host environment around the tumor or the 'microenvironment' is relevant for its further growth was described quite early when there was realisation of a tumor's ability for angiogenesis and the host stroma in the process (26). The tumor microenvironment comprises tumor and host stromal cells, extracellular matrix, and various secreted factors- this milieu being likened to an ecosystem [27]. Both these sides influence each other via proteins, enzymes, inhibitors and stimulators that would eventually lead to angiogenesis and invasion [28]. For instance, fibroblasts in or near the tumour bed begin to produce pro-angiogenic factors [29] and tumours recruit progenitor endothelial cells from bone marrow [30].

2.1.5. The role of inflammatory cells

The theory that angiogenesis is stimulated by inflammation-based mediators produced by the tumour itself has also been put forward by many authors over the decades, even before the molecular basis of this fundamental phenomenon was elucidated. Virchow in the 1860s described the phenomenon of inflammatory cells at the margins of certain malignancies [31]. Tumors have been likened to 'wounds that do not heal' and which instead recruit the duality of the healing mechanism for their own survival and growth [32]. The interdependence of the leucocytes-macrophage system and the endothelial cell system is initially used by the tumor until a critical phase is reached, after which it becomes autonomous [33]. The tumor microenvironment as mentioned above also comprises immune and inflammatory cells namely macrophages, myeloid derived suppressor cells, neutrophils and lymphocytes [18]. Inflammation products Prostaglandin E, nitric oxide, interleukin1& 8 and Tumor necrosis factor all stimulate angiogenesis. The new abundant blood vessels in turn allow influx of more inflammatory cells along with the oxygen and nutrients required to sustain them [34].

2.1.6. Angiogenic growth factors

The more well studied and ubiquitous of these factors are Vascular endothelial growth factor (VEGF), Platelet derived growth factor (PGDF), Fibroblast growth factor (FGF). These are described with a short note on the evolution of their discovery.

Michaelson, in 1948, proposed that a diffusible angiogenic "factor X" produced by the retina is responsible for retinal and iris neovascularization in proliferative diabetic retinopathy [35]. In 1968, the first experiments to directly test the hypothesis that tumors produce angiogenic factors were performed. Greenblatt and Shubik and Ehrmann and Knoth separately demonstrated that transplantation of melanoma or choriocarcinoma cells promoted blood vessel formation despite the interposition of a Millipore filter between tumor and host. They thus showed that tumor angiogenesis was mediated by diffusible factor(s) produced by the tumour cells [35].

2.1.7. Vascular endothelial growth factor or VEGF

In 1979, Dvorak isolated a supernatant from animal and human tumor cells which had the special property of generating a blue hue from Evans blue dye due to extravasation. This was in contrast

to normal cells which retained the dye in the cells [35]. Similarly, in 1983, Senger et al succeeded in purifying partially, a protein from guinea pig tumor cell lines, that was able to induce vascular leakage in the skin, which was named "tumor vascular permeability factor" [35]. In 1989, Ferrara et al and Henzel, Plouet et al separately reported the purification of an endothelial cell-specific mitogen which they named respectively vascular endothelial growth factor (VEGF) and vasculotropin. Subsequent molecular cloning of VEGF and VPF revealed both molecules to be one and the same [7].

VEGF is produced by tumor cells as well as stromal cells such as macrophages and platelets. It is crucial for angiogenesis but also contributes to other physiological processes such as osteogenesis, hematopoiesis, wound repair and development [36, 37].

2.1.8. Fibroblast growth factors or FGFs

Fibroblastic growth factor or FGF: Though it was known that a fibroblast stimulating substance existed in animal embryos as early as 1939 [38], it was in 1973 that a protein named Fibroblastic growth factor was isolated [39] and this substance was purified over the next decade [40, 41]. FGFs are secreted by macrophages and have a seminal role in embryonic development, influencing regulation of cell proliferation, migration and differentiation. FGFs are important for tissue repair and response to injury. Some members of the FGF family are known to contribute to tumor angiogenesis when present in the milieu of malignant growth [42].

2.1.9. Platelet derived growth factor or PGDF

PDGF was first identified and purified from the platelets that stimulate proliferation of fibroblasts, smooth muscle cells, and glial cells [43]. Apart from platelets, PGDFs are also secreted by endothelial and epithelial cells [44].

It has important functions in embryonic development, inflammation and wound healing. It drives processes such as cell survival and chemotaxis [45].

PGDF is a potent stimulator of tumor angiogenesis and recruits smooth muscle and endothelial cells [46]. It confers angiogenic, proliferative and survival abilities to cancer cells and influences the ability to metastasise [47]. PGDF also has a role in stimulating production of VEGF from endothelial cells [48]. The overexpression of PDGFRs and/or their ligands has been described in many solid tumors [49].

2.1.10. Other pro angiogenic factors

Matrix Metalloproteinases (MMPs)

These are enzymes that promote cancer invasiveness by degrading extracellular matrix [50]. These promote tumor angiogenesis by increasing availability of VEGF and FGF the microenvironment [51]. The levels of MMPs may be found raised even in early stage oral cancers [52] and correlates with invasive ability of the neoplasm [53].

2.1.11. Epigenetics

Micro RNAs or miRNAs influencing expression of angiogenetic factors and host endothelial cell activity are called angiomiRNAs (angiomiRs) [54, 55]. miRNAs act in both pro and anti angiogenic ways. Some (miR 132 AND 146a) stimulate endothelial cells proliferation and promote tube formation while other (miR 138 and 497) directly target factors such as vascular endothelial growth factors (VEGF) and impair angiogenesis. The balance between these two groups of miRNAs decides suppression or stimulation of the given tumor [56]. These properties of miRNAs have been the basis of investigations into their role in diagnostics and therapeutics of oral cancers [57], though it is yet to translate into clinical practice.

2.1.12. Immune escape

Tumor cells have the ability of escaping the normally immune response by several mechanisms [58]. This 'immuno-privileged 'status is achieved due to loss of adhesion molecules, such as ICAM1, from the angiogenic endothelial cells [59]. Thus, leucocytes are unable to recognise these abnormal endothelial cells as non-self. Additionally, antigen presenting cells themselves, called Dendritic cells are defective in a tumor microenvironment [60]. VEGF is known to inhibit maturation of these dendritic cells [61]. Myeloid derived suppressor cells or MDSCs are seen to accumulate in the tumor microenvironment; these cause tumor immunoprotection by reducing anti-tumor T cell activity [62]. VEGF also can induce reduced NK cell activity [63] and an increase in tumor associated macrophages and monocyte levels [64]. Anti-angiogenic Immunotherapy has been thought to have an advantage over solely anti-angiogenic agents in their ability to work on more than one pathway, thus circumventing resistance and resulting in additive efficacy [65].

2.1.12. Endogenous Inhibitors of angiogenesis

Apart from protective genes, such as p 53(2) and Rb (21), endogenous inhibitors are important in maintaining the balance of pro and anti-angiogenic factors; the discovery and study of these are spurred by the possibility of employing them as pharmacological agents. The more studied and clinically relevant of these have been reviewed below.

Arresten [66] is a component of the basement membrane of blood vessels and inhibit endothelial tubal formation and acts via integrins which are collagen receptors.

Canstatin [67] also acts via integrins and inhibits endothelial cell migration and is an inducer of apoptosis.

Endostatin [68] is a collagen derived inhibitor that works at different points in the process of angiogenesis. It downregulates several angiogenic genes and signalling pathways, apart from blocking the effects of FGF, VEGF and Tumor necrosis factors.

Tumstatin [69] is another antiangiogenic and proapoptotic agent seen to inhibit tumor growth in animal models and cell lines.

Angiostatin [70] is a product of plasminogen cleavage and unlike its parent compound, it possesses anti angiogenic and apoptotic activities; these have been determined to be present more against immature endothelial cells.

Interferons [71] were one of the earliest inhibitors identified and work at different levels to inhibit angiogenesis. On the one hand they upregulate genes that are anti angiogenic and on the other they inhibit endothelial cells directly. They may also have a role in downregulation of VEGF and FGF gene expression, though this is as yet unclear [68].

Interleukins(IL) are a family of proteins with diverse physiological functions, one of them being angiogenesis. IL 6 [72] and IL 8 [73] are pro-angiogenic, while others such a IL 4 [74]. IL 12 [75] and IL 18 or IFN gamma [76] are potent anti angiogenics. IL 1 [77] has been a confounding cytokine sine it has shown endothelial suppressive properties in vitro and in vivo, however, it has been seen to be upregulated in solid tumors of the head and neck [78]. It upregulates expression of VEGF and proangiogenic IL 8 [79]. It has efficacy for disorders of chronic inflammation such as rheumatoid arthritis but its utility in cancers is currently under trial [80].

3. Anti Angiogenic Agents for Oral Cancer

As described above there is a myriad number of activators, inhibitors and promoters present at the molecular level , all of them converging to specific critical nodal points on the road to progression and metastasis of a tumour. Many of these factors influence more than one pathway; several of them are known to 'cross-talk'. Therefore, it would be assumed possible to develop therapeutic agents that simultaneously inhibit more than one critical step in the progression of malignancy [81]. However, this translation into clinical use in head neck and especially oral cancers has not yet equalled expectations. Several animal models that demonstrated measurable therapeutic efficacy have not translated into clinically viable efficacy [82]. Even in other head neck non squamous cancers, despite several drugs being approved the success of anti-angiogenic therapy has been low, with limited survival benefits and development of resistance [83].

The anti angiogenics that are currently in use or are in advanced clinical trials for oral cancers are described below. Since the majority of oral malignancies are squamous cancers, we have focused on this histology and any mention of 'oral cancer' should be taken to mean oral squamous cancers.

- **Cetuximab**

Cetuximab is a well-known EGFR (epidermal growth factor receptor) inhibitor and has been used in that capacity for Head and neck squamous cancers(HNSCCs) [84]. It is being used as an adjunct with radiation in locally advanced HNSCCs including oral cancers, for patients unfit for cisplatin or carboplatin [85]. The EGFR related activity of Cetuximab may occur via the HIF-1α and Notch1 pathways as established in HNSCC cell lines, where Cetuximab was found to down -regulate HIF-1α and Notch1, both pro-angiogenic factors [86]. Hence, we include Cetuximab in the list of angiogenesis inhibitors in clinical use for Oral cancers.

- **Nimotuzumab**

Nimotuzumab, an EGFR inhibitor and an anti-angiogenic agent [87], when combined with weekly cisplatin and radiotherapy conferred improved progression free survival, locoregional control and disease free survival in patients with locally advanced HNSCC including oral cancers [88]. The authors suggest that this regime may be used as an alternative to weekly (instead of 3 weekly) cisplatin regimes in concomitant chemoradiation protocols.

- **Bevacizumab**

Bevacizumab has been used as trial drug in combination therapy for locally advanced cancers.

The trial results suggested that the combination of 2 weekly bevacizumab and erlotinib daily can be safely and effectively incorporated into a Chemoradiation protocol [89]. In another trial, adding bevacizumab to cetuximab and radiation increased toxicity did not result in improvement in efficacy, which, incidentally, counters the hypothesis that dual EGFR–VEGF targeting would overcome radiation resistance, and enhance clinical benefit [90].

Bevacizumab has been administered in recurrent metastatic head neck/oral cancers

The combination of erlotinib and bevacizumab was well tolerated in a cohort of recurrent or metastatic squamous-cell carcinoma of the head and neck, the cohort including oral cancer patients [91]. A few patients seemed to derive a sustained benefit and complete responses were attained.

- **Lenvatinib**

Lenvatinib provides not only anti-angiogenic effects but also causes direct antitumor effects through inhibition of VEGF and FGF signalling pathway in cancer cells [92]. It has been found to have efficacy along with pembrolizumab (an immunotherapeutic agent) in recurrent metastatic oral cancers [93, 94].

- The Angiogenic inhibitors currently under early clinical trials or in pre-clinical investigation for oral cancers are described below**Pazopanib**

Pazopanib, an angiogenesis inhibitor when administered along with cetuximab to patients of recurrent metastatic head neck cancer- a third of which were of oral cancers- showed encouraging response rates; although with grade 3 adverse effects. The authors suggest further validation with randomized trials [95].

- **Matrix metalloproteinases or MMPs**

The more well-known MMPs under study as anti-angiogenic agents are Batimastat, Marismastat, Salimatat, Prinomastat and Tanomastat; however, their clinical usefulness is as yet not established [96].

MMPs have been found to have effect on human head neck cancer cells and several such experiments are enlisted in this review [97]. Since MMPs have broad-spectrum roles in physiology, their therapeutic effects need to be isolated and refined; in addition, the occurrence of adverse effects need to be addressed for MMPs to become viable treatment options [98].

- **Thalidomide**

Thalidomide is a repositioned drug, found to possess immunomodulatory, anti-inflammatory, and antiangiogenic properties. It is currently under study for various clinical conditions including cancer [99]. The potential uses of thalidomide and its synthetic analogues have been reviewed here [100]. It has been found to induce apoptosis in human cancer cell lines individually [101] and as combination with low dose cisplatin in mouse models [102]. It has not emerged as a popular anti-cancer agent possibly due to its adverse effects and potential for teratogenicity [100].

- **Paclitaxel**

Paclitaxel is a widely used chemotherapeutic agent that has additional anti-angiogenic properties [103]. It was found that paclitaxel, in cell lines, inhibited human endothelial cell proliferation, migration, and tube formation at a tenth of the concentration needed to achieve a similar effect without this combination. The authors expect further studies to establish possibility of reduction in requisite doses of both radiation and paclitaxel [104].

Micro RNA inhibitors

1. mi R 21 is the most consistently altered and over expressed micro RNA in tongue carcinoma [105]. In vivo, the suppression of this miRNA in a tongue cancer cell line is seen to suppress growth and to reduce angiogenesis [106]. However clinical uses are still awaited. A combination of miR 145-5p is a potential biomarker for application of photodynamic therapy (PDT) of superficial oral cancers as found by workers in a study. They demonstrated that cell lines, both of primary and metastatic cancers, showed a much greater response to PDT when they showed overexpression of this particular miRNA [107].

- **NK Cells**

A phase I clinical trial that involves use of Natural Killer Cells for unresectable or metastatic head neck cancers, including cancers involving the maxillary sinus found some clinical response with no serious adverse effects [108]. This study also found that nasal submucosal administration of the therapeutic agent was feasible and safe.

- **Interleukins**

A phase I/II trial looked at the efficacy of IL 12 administered with cetuximab in EGFR expressing recurrent/metastatic unresectable HNSCCs including those of buccal mucosa and tongue. The investigators found a longer Progression free survival (PFS) in those given IL 12 [109]. This study found encouraging results, justifying further focussed trials on IL 12.

- **P 53 Gene therapy**

Unmutated p53, an established tumor suppressor gene, with a virus vector which is either given intra-arterially or intralesionally has seen very promising results in trials with patients with oral premalignant lesions and treatable oral squamous cancers. A review of these trials is given here [110].

- **Aflibercept (VEGF Trap or AFL)**

AFL is a known anti angiogenic drug and when used in combination with another anti angiogenic drug bevacizumab, showed additive effect on human cancer cell lines [111]. Aflibercept along with Chinese traditional medicine Arsenic trioxide significantly reduced endoglin and VEGF expression on human oral cancer cell lines [112].

Natural and traditional agents with angiogenesis inhibitory effects and the role of phytochemicals (with reference to oral cancers)

That vegetables and fruits have tumor preventive activity has been known and proven from epidemiological findings and studies on animals [113]. Some of these molecules with anti angiogenic effects found naturally are Lycopene (present in red fruits and vegetables such as tomato, carrot, watermelon and papaya), Beta carotene (present in green, orange and yellow fruits and vegetables such as carrots tomatoes spinach), Curcumin, Aloe vera, Green tea, Ginger, Chamomile and Genisteine (from soyabean and its products) [114, 115]. This has led to investigative pre-clinical and clinical trials on the possibility of incorporating these chemopreventive chemicals into drug formulations [115].

The active component of green tea (EGCG or epigallocatechin gallate) has been found to inhibit human oral cancer cell in vitro [116].

Oridonin [117] is a diterpenoid isolated from a herb called Rabdosia Rubescens used in Chinese and Japanese medicine and had been described as possessing anti-tumor effects in 1976. Its anti angiogenic effect and inhibition of human cancer cell lines have been reaffirmed [118].

Sulforaphane, an angiogenesis inhibiting isothyocyanate found in broccoli, has been found to inhibit, in a dose dependant manner, human oral cancer cell lines selectively [119].

Resveratrol, polyphenol found in berries and grapes, has both pro and anti angiogenic effects [120], however, it has been found to induce autophagy and apoptosis in cell lines of oral cancer cells that were resistant to cytotoxic chemotherapy [121].

A combination of resveratrol and quercetin (another angiogenesis inhibiting polyphenol found in apples, onions, grapes and green tea) has been seen to inhibit cell growth, induce DNA damage and cell cycle arrest in oral cancer cells as compared to normal oral mucosal cells [122].

4. Angionesis Inhibitors for Chemoprevention

Head and neck squamous cancers (HNSCCs)of the head and neck,

particularly those originating in the aerodigestive tract, are usually consequent to chronic exposure to external carcinogenic substances such as tobacco and alcohol. The progression of normal mucosa to premalignant and finally to malignant cells has been studied. It has been established that this progression takes a tangible period of time, with the population of normal, premalignant and malignant cells having an identifiably distinct genetic profile [123]. Since there is a sequence to the acquisition of malignant features, with newer genetic changes being accumulated at each step, HNSCCs are suitable for development of agents to intervene at each step and thus putatively prevent cancers [124]. This reasoning could also be extended for the prevention of second primary tumors in HNSCC survivors [125]. Hereunder are some of the compounds investigated or used for chemoprevention in the oral cavity.

1. Cox 2 (cyclo-oxygenase 2) inhibitors: Cox 2 is an enzyme, which is induced by the presence of carcinogens such as those in tobacco and also by factors that are known to be dysregulated and in high concentration in HNSCCs, such as Ras and Protein Kinase C [126]. Cox isoenzymes (both Cox 1 and 2) are over-expressed in malignant as well as premalignant cells. Cox induces angiogenic factors in tumor cells as well as in the surrounding cells, thus causing tumour progression [127]. The prostaglandins produced by Cox suppress both cellular and humoral defense mechanisms against tumour proliferation thus contributing to malignant proliferation. In addition, Prostaglandins in turn promote tumour angiogenesis [128]. Finally, COX-2 augments VEGF expression [129]. A Cox inhibitor, nimesulide, was seen to retard growth of cancers in a head neck animal model presented with a carcinogen [130].

Celecoxib in combination with EGFR has additive efficacy for chemoprevention in vivo [131]. Salvianolic Acid-B, a natural anti-inflammatory (selective COX-2 inhibitor) and antioxidative agent has chemopreventive activity on HNSCC. One of its modes of action is by inhibition of angiogenesis. It has shown preclinical efficacy with no serious adverse effects.; its clinical application may be warranted [132].

2. A combination of Green tea and curcumin was found to reduce serum levels of biomarkers Ki 67, cyclin D1 and p 53 in patients with oral premalignant lesions when treated topically and systemically for 12 weeks [133]. Other natural phytochemicals studied for such lesions have been examined here before and in this review [115].

5. Markers of Angiogenesis

5.1. VEGF

VEGF is a marker for advanced stage oral cancers as measured by immunohistochemistry or by Western and Northern blot analysis [134], but not for early stage oral cancers.

Urinary VEGF measurement has been found in one study to estimate progression free survival, 1 year after completion of radiation [135].

5.2. Endoglin

Endoglin or CD 105 is a hypoxia inducible protein and is a receptor for Transforming Growth Factor (TGF). It is expressed abundantly in the tumor endothelial cells that are involved in neo-angiogenesis. It has been correlated with higher Tumor (T) stage [136]. High expression of endoglin was also associated with high levels of VEGF and translated to possibility of nodal metastases [137]. Levels of Endoglin in the oral mucosa of chronic tobacco users has been found to be elevated, thus raising the possibility of its use as a marker for patients at high risk for oral cancer [138]. Since Endoglin is shed in blood, it can be measured by employing specific antibodies. On tagging it with Technetium 99, it has been seen to localize in CD 105 bearing tumor cells in renal cancers. This molecule, then, could emerge as a prognostic, diagnostic and a therapeutic agent for malignancies [139].

5.3. Thymidine Phosphorylase(TP)

This is an enzyme involved in DNA synthesis. It is similar to PGDF and has been associated with angiogenesis, radiation response levels and mutant p53 levels in Head neck squamous cancers [140]. Assay of TP levels is suggested as a marker for radiation resistance [141].

5.4. Lysyl Oxidase

This enzyme promotes proliferation and angiogenesis in oral cancer cell lines [142] . They are over expressed in oral cancers as well oral dysplasias [143]. The enzyme is also associated with higher risk of lymph node metastases and with poorer prognosis [143].

5.5. Microvessel Density (MVD)

MVD is a good indicator of angiogenesis, however, there is inconsistency in its results across series, possibly owing to lack of standardized immunohistochemical techniques. Thus it cannot be relied upon for prognostication or estimate of progression [144, 145].

5.6. Imaging of Angiogenesis

Tumor vessels are leaky, that is, they have large gaps between endothelial cells. This property is exploited in imaging for neovascularization in modalities such as CT perfusion studies, Dynamic contrast enhanced MRIs, PET with specialized radiotracers, Ultrasound Doppler and molecular imaging [146]. This technology may also be used to monitor the effect of anti angiogenic therapy [147, 148].

6. Metronomic Chemotherapy (MCT) and Angiogenesis

Most conventional chemotherapeutic agents do possess anti -angiogenic effects, but these are marginalized or lost due to repair by the tumor vasculature in the long interval (usually 3 weeks) between doses [148]. This problem can, it follows, be rectified if the drug is scheduled metronomically, which means frequent administration of low doses of the agent with no long drug-free interval [149]. It has been shown, also, that the endothelial cells of

newly formed tumor vessels are specifically sensitive to low doses of several chemotherapeutic agents [150]. There is evidence that the anti angiogenic effect of MCT is not due to direct effect on the endothelial cell but is via mediators such as Thrombospondin 1, an endogenous inhibitor of angiogenesis [151]. Therefore, adverse effects such as myelosuppression is not seen with MCT. A randomized controlled trial comparing Celecoxib and Methotrexate MCT to intravenous 3 weekly cisplatin in unresectable head neck cancers including oral cancers showed that MCT was not only superior as regards Overall survival, but it also provided better quality of life [152]. A retrospective analysis of MCT for palliation of patients with recurrent HNSCCs, most of whom had oral cancers, revealed that though, overall, MCT showed promising results for palliation when time to recur was over 6 months of initial treatment, oral cancers especially tongue carcinomas had lower response rates [153]. MCT is thus a potential treatment option in selected patients of oral cancer; although the issues concerning correct dosing and possibility of delayed adverse effects require to be tackled [149].

7. Adverse Effects of Angiogenic Inhibitors Used for Oral Cancers

VEGF inhibitors such as Bevacizumab and Cetuximab have cardiovascular side effects such as bleeding, thromboembolism, cardiac ischaemia, arrythmias and cardiac failure [154]. Nimotuzumab has a relatively safe profile but may cause asthenia, dizziness, hematuria, vomiting, diarrhoea, fever, rash, headache and hypertension [155]. Cetuximab may also cause an acne like rash, abdominal pain, nausea and vomiting [156].

8. Resistance to Anti-Angiogenic Drugs

Response to anti angiogenic drugs, if present in a particular tumor, is observed to often reduce or disappear after a certain period of time. This 'resistance' develops by various ways - a) Anti angiogenic drugs induce hypoxia which in turn stimulate hypoxia related factors and anti- apoptotic genes [157]. b) Alternate pathways of angiogenesis are uncovered [158], c) p 53 mutated cells can resist hypoxia and become more invasive and metastatic in hypoxic conditions such as that created by antiangiogenic medication; p 53 cells get selected in the tumor due to the effect of the drug [159]. d) Alternate methods of vascular growth is adopted by the tumor such as sharing the host vessels by a process called 'co-option' [160], e) release of pro angiogenic factors from bone marrow [161]. f) Intrinsic resistance to an agent targeting a single factor such as VEGF due to presence of redundant pathways already in operation especially in advanced tumors [162, 163].

Deploying therapeutic agents that target more than one pathway of angiogenesis [164] or using a combination of drugs thus targeting more than one pathway [165] are ways of circumventing resistance. Some of these combinations are also covered further in this text.

9. Further Possible Applications of Angiogenesis and its Inhibition

9.1. Nanotechology for Antiangiogenic Treatment

The deployment of nanovehicles for drug delivery may enhance efficacy, reduce adverse effects and prevent development of resistance in antiangiogenic treatment, thus exponentially improving their clinical applicability [166].

9.2. Antiangiogenesis -Imaging for Guiding Radiation

A phase I trial of bevacizumab in combination with chemoradiation for HNSCCs also included imaging for observing antiangiogenic effects of bevacizumab. It was found that such imaging could demonstrate tumor perfusion, proliferation and hypoxia. The authors concluded that these findings could be the basis for personalized precision radiation in the future [167, 168].

The risk of recurrence in advanced oral cancers despite adequate locoregional therapy, distant metastasis in spite of adequate local control and use of systemic therapy and the phenomenon of second primaries in cases of survivors have all been the limiting factors in the outcomes of treatment of oral cancers. The 5-year survival of advanced stage oral cancers, after surgery and concomitant radiochemotherapy is around 50% [169, 170]. The addition of neo-adjuvant chemotherapy to the treatment protocols has not much improved these figures [171]. 10% of patients with advanced oral cancers develop distant metastasis while 3% patients with early disease have distant metastasis [172]. The annual incidence of second primary malignancies in patients with treated oral cancers is 5% [173]. The risk of having an event (recurrence or distant metastasis or second primary) after treatment for oral cancer has been found to be 17% at 1 year, 30% at 5 years and 37% at 10 years [174]. These outcomes have been the basis of continuing effort towards improving treatment combinations, delivery systems and patient selection over the years. The research in developing angiogenesis inhibiting agents can potentially provide clinicians with an option to improve control rates; though at present the number of antiangiogenic drugs proven to be useful in oral cancers is low. Despite this, evidence continues to emerge to support the principle of angiogenesis inhibition and it is hoped that the tremendous volume of research and effort by workers all over the world in this field will culminate in the development of viable treatment options for patients with oral cancers.

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