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Angiogenesis in Head and Neck Cancer

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Abstract

Locally advanced Head and Neck Squamous Cell Carcinoma (HNC) is a challenging disease for the lack of effective therapies even in the era of molecular medicine (the five-year survival does not exceed 40%). For patients with metastatic and recurrent HNC the standard treatment is the combination of Cetuximab/Platinum and Fluorouracil but median overall survival rate for this population remains lower than 11%. The main reasons of these disappointing outcomes include acquired drug resistance, anti Epidermal growth factors variants, epithelial to mesenchymal transition and tumor hypoxia.

Angiogenesis plays a crucial role in HNSCC development and proliferation. Drugs may interfere with the angiogenic process via different mechanisms and there is a sound rationale for combining anti-angiogenic agents with chemotherapy or multiple anti-angiogenic strategies. Promising preclinical results with angiogenic inhibitors have engendered a number of trials, but until now there are not yet conclusive data on the value of anti-angiogenic therapy in HNC.

This paper aims to review the role of angiogenesis inhibitors in head and neck cancer.

Keywords: Angiogenesis; Head and neck cancer; Target therapies

Abbreviations: Cet: Cetuximab; Pem: Pemetrexed; Beva: Bevacizumab; TXT: Docetaxel; PTX: Paclitaxel; 5FU: 5 Fluorouracil; OS: Overall Survival; PFS: Progression Free Survival; DCR: Disease Control Rate; RR: Response Rate; TTP: Time to Progression; ORR: Overall Response Rate; RT: Radiotherapy; M: Months; CDDP: Cisplatin; W: Weekly; biW: Biweekly; LRFS: Locoregional Recurrence Free Survival; DMFS: Distant Metastasis Free Survival *Naso pharyngeal Cancer; **At 2 Years.

Introduction

Head and neck cancer (HNC) is the sixth most common cancer with 500,000 diagnoses per year worldwide [1]. Despite the advances in the multidisciplinary approach to locally advanced disease, about 50% of patients will relapse. Actually, HNC is a poorly chemo sensitive tumor and no one chemotherapeutic single agent is able to offer more than 15% objective response rate [2]. Moreover concurrent radiochemotherapy (CRT) often leads to severe acute and late toxicities that negatively impact on patients' quality of life. On the other hand, patients with relapsed or metastatic disease have a worse prognosis with an overall survival of approximately 7–10 months [3]. New therapeutic protocols and agents should be developed to improve survival while limiting treatment-related toxicities.

Angiogenesis (formation of new blood vessels) is associated with tumor growth and metastasis in patients with solid tumors, including HNC. Dr. Judah Folkman pioneered the concept that tumors growth is angiogenesis-dependent [4].

Antiangiogenic agents are to date available and useful for the treatment of many tumors. For HNC definitive evidence in the form of a pivotal trial is still pending.

Preclinical and early clinical data show that the vascular endothelial growth factor (VEGF), a key mediator of angiogenesis, and the respective receptors (VEGFR1-3) play a central role for cell proliferation, differentiation and survival (up to 90% of HNSCC express VEGF). Many studies support the associations among angiogenic markers and poor prognosis [5]. The most studied strategy to interrupt the angiogenic process is to inhibit the VEGF [5].

Preclinical studies showed anti-angiogenic therapies synergism with traditional therapies, eg, radiation (RT) and chemotherapy (CT). Moreover they may overcome drug and RT resistance. Clinical use of anti-angiogenic agents for HNC, including bevacizumab, sorafenib, sunitinib, and others, is currently limited to clinical trials, and several larger trials are still ongoing. We did not include angiogenic inhibitors approved or under investigation in radioiodine resistant thyroid cancer but only those used in HNSCC.

This paper is aimed at evaluating the anti-angiogenic therapies in HNC and to hint future perspectives. We considered clinical trials only reporting emerging prospective from preclinical studies.

Materials and Methods

Searches were conducted to identify published and unpublished clinical Trials (selected retrospective and phase II trials were also considered). Medline was used for research. Electronic search results were supplemented by hand searching of selected papers, expert consensus meeting notes and reference lists from selected articles. The literature search was limited to articles in English starting in 1990 up to date. The following Medical Subject Headings terms and keywords were used in the search: Head and neck cancer, angiogenesis, angiogenic inhibitor, target therapies.

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After a comprehensive literature search we discussed the literature, taking into account the previously reported reviews on this matter.

Results of Preclinical Data

Several studies reported strong correlation between high micro-vessel counts and both recurrent or metastatic disease in HNSCC [6,7]. In 2005 a meta-analysis confirmed previous data about levels of VEGF and risk of lymph node metastases (1.88-fold higher risk of death at 2 years) [8]. Williams et al. showed high levels of angiogenesis markers in locally advanced HNSCC [9].

In HNSCC preclinical models, anti-VEGF therapies showed radiosensitizing properties, with increased oxygenation, and additive/supra-additive antitumor effects.

Although a number of demonstrations about angiogenesis's role in HNC no anti angiogenetic therapies have achieved satisfactory results in vivo [5].

Preclinical data have demonstrated that targeting angiogenesis may impair tumor cell proliferation and inhibit tumor growth. Multiple anti-angiogenic agents were investigated: monoclonal antibodies against VEGF, soluble VEGF receptors such as VEGF-trap, tyrosine kinase inhibitors, metalloproteinases and integrin antagonists [10].

The blockage of angiogenesis during RT and/or CT has significantly improved the efficacy of the regimens in experimental models [11].

Radiotherapy induce a strong and very significant increase in tumour angiogenesis.

Angiogenic inhibitors act normalizing vasculature through destruction of immature non-functional vessels. They allow other drugs distribution in the microenvironment and provide a better blood flow reducing tumour hypoxia [5]. A direct enhancement of endothelial cell or tumor cell cytotoxicity has also been hypothesized. VEGF expression has been shown to be enhanced by radiation, and in vitro studies suggested the enhanced cytotoxicity of the combination of RT and antibody anti- VEGF depends on the increase of endothelial cell death. Therefore angiogenic inhibitors may neutralize VEGF protective role on endothelial cells exposed to ionizing radiation [12].

Of interest in xenograft models is the addition of Bevacizumab to CT, such as Irinotecan or to Epidermal Growth Factor Receptor (EGFR) inhibitors, such as Erlotinib. The combination markedly increases the antitumor efficacy [13,14]. In HNSCC EGFR variant III is associated with Cetuximab resistance and leads to auto-activation and up-regulated VEGF further augmenting this pathway [15].

It is possible that a dual inhibition of EGFR and VEGFR may help to stop the proliferation pathway [15].

Yigitbasi et al. reported that dual inhibition of EGFR and VEGFR is an effective therapeutic strategy in murine oral cancer model. Hypoxic tumours show a propensity to metastasize, have higher local failure rates, and carry on an overall worse prognosis [16].

Inhibition of tyrosin kinase endothelial (TIE) hypoxic induced factor 1 α (HIF-1 α) and c-Met are current under investigation and appear alternative anti-angiogenic targets.

Hsu et al. showed that Linifanib (ABT-869) enhances radiosensitivity and and has and additive effect on citotoxicity with poly ADP ribose polymerase inhibitor veliparib [17].

Cilengitide an integrin inhibitor in combination with RT and CDDP showed to be a feasible option for clinical development [18].

Results of Antiangiogenic Therapy in HNC

Combining antiangiogenic agents with CRT in HNSCC relies on a strong biological rational, but clinical experience is limited.

In the past 10 years, many positive data have been provided from preclinical and early clinical trials with anti-angiogenic therapies in HNCC but no standard angiogenic CRT associations have been approved in phase III trials. Multi target angiogenic agents such as Sorafenib and Sunitinib have been used in phase II trials both as single agents or in combination [19].

In a study reported by Elser et al., Sorafenib was used in patients with recurrent/metastatic disease in first or second line therapy [20]. Median overall survival was 4.2 months with 6- and 12-month overall survival rates of 34.7% and 11.6% respectively. Angiogenic inhibitors, such as squalamine, Cediranib, Axitinib, Dalantarcept, Semaxanib and Sunitinib have been evaluated without satisfactory results [15]. Cilengitide was added to standard first line CT-Erbitux without showing PFS benefit over standard PF-Cet [21]. Bevacizumab (Avastin°), a monoclonal antibody, binding VEGF, is the more promising anti-angiogenic drug.

Seiwert et al. reported enthusiastic results of the combination Bevacizumab (B), FHX (fluorouracil [FU], hydroxyurea [HU], radiation) chemo-radiotherapy with median overall survival of 10.3 months with a 2-year cumulative incidence of death resulting from disease of 51.7%. However 11.6% and 9.3% patients with fistula and ulceration/tissue necrosis respectively underline the concern about the side effects of the treatment [22]. Moreover these favourable outcomes were not confirmed by the phase II trial [23].

Recently Hainsworth JD et al. in a phase II trial reported the safety and the efficacy of a combined modality treatment with Bevacizumab, Erlotinib and CRT. In this study patients received 6 weeks of neoadjuvant chemotherapy/Bevacizumab followed by concurrent CRT with weekly Paclitaxel, Bevacizumab (3 weekly) and daily Erlotinib (150 mg). Although the median progression free and overall survival rates have not been reached, the authors point out a 3 years estimated progression free and overall survival rates of 71 and 85%, respectively [24].

The combination of Erlotinib and Bevacizumab has been studied based on the finding that in preclinical models VEGF expression may abrogate EGFR inhibition. In a phase II trial Vokes et al. reported encouraging results with an overall response rate of 15% and median survival of 6.8 months [25].

A phase I/II triasl of Erlotinib and Bevacizumab in patients with recurrent or metastatic HNC showed promising results (mOS 7.1 m and PFS 4.1m) [26]. A dual VEGF/EGFR inhibition has been also studied by Yoo et al. [27]. In a prospective trial on 29 patients they reported that Bevacizumab Erlotinib can be integrated with CRT with efficacy that compares favourably with historical controls albeit with an increased risk of osteoradionecrosis. Authors suggest to accurately select patients using early DCE-MRI to identify patients at high risk of failure [27].

A phase II trial on the combination of Bevacizumab and Pemetrexed was recently published by Argiris et al. reporting encouraging data with a median time to progression (TTP) of 5 months, and a median OS of 11.3 months. This study enrolled 40 patients and achieved an overall response rate of 30%, including a complete response rate of 5%, with 86% of disease control [28].

Yao et al. reported safety and efficacy of combination of bevacizumab, docetaxel and radiotherapy; due to promising results (3 year PFS, OS, locoregional recurrence free survival and distant metastasis free survival was 61.7%, 68.2%, 84.5%, and 80.5%, respectively) this study on 30 pts is worthy of further study in appropriate subset of patients receiving chemoradiation therapy [29]. Definitive results of further studies of Bevacizumab with chemotherapy, chemoradiation and/or with target therapies (cetuximab or erlotinib) are still pending. Mature data from these studies will provide detailed information on locoregional and distant control, survival and toxicity of Bevacizumab integrated treatment for HNC [17].

Aflibercept is designed to sequester circulating vascular endothelial growth factor (VEGF) by preventing VEGF from binding to its receptors. Preclinical studies have reported that VEGF-Trap can be combined effectively with both chemotherapy and radiotherapy. No mature clinical data have been published up to date [17].

Unsatisfactory results were also reported using Vandetanib, (a VEGFR, EGFR and Ret TKI)plus docetaxel in a phase II trial by Limaye et al., with only a minor trend towards improved PFS [30].

Promising results may derive also form Motesanib and Ramucirumab according to terrific data in Non-small cell lung cancer [31,32].

Data from some of the most impressive clinical trials are detailed in Table 1.

Angiogenic therapies toxicities

Typical Bevacizumab side effects include hypertension (significant hypertension develops in 15%-60% of patients), hemorrhagic complications, thromboembolic events, wound healing complications, perforation, hypothyroidism, cardiac dysfunction, immunosuppression, proteinuria, oedema, and hand-foot syndrome. However the most feared side effects, above all in HNC, are idiosyncratic bleeding events, wound and ulcer healing complications, and gastrointestinal perforations, which can be fatal. In the phase II trial by Hainsworth et al., a fatal cerebral-vascular accident , grade3-4 mucosal toxicity in 78 pts% and nearly half of the population that needed enteral or parenteral alimentation during treatment with erlotinib bevacizumab and paclitaxel were registered [24]. The same Bevacizumab toxicity profile was confirmed with a 15% Grade 3 to 5 bleeding events, including 2 fatal events by Argiris et al. [28].

Discussion

Present and future prospective

Despite dramatic advances in surgical and non-surgical treatment options, HNSCC cure rates remain unchanged over the past 30 years. Angiogenesis inhibitors are an attractive treatment approach to these tumors. Bevacizumab, in combination with targeting agents and/or chemotherapy, showed activity in many phase II trials in relapsed/metastatic disease, with attractive median overall survival. Unfortunately, the toxic profile is severe, but it is possible that Bevacizumab could play a role in specific situations, rather than being employed in all the patients with relapsed/metastatic disease. The optimal therapeutic synergy appears to be dependent on the dose and schedule of this monoclonal antibody. Results from the phase III trial ECOG 1305 (a phase III trial evaluating efficacy and toxicity of standard platinum-based CT with or without Bevacizumab) may provide further data. Concerns about serious bleeding events remain but it should be reminded that hemorrhagic complications are not uncommon in the natural history of HNC, therefore it is sometimes difficult to discern the contribution of study drugs to these events. Probably an adequate selection of patients could reduce the incidence of tumor related bleeding. Concerning about safety has in our opinion reduced the interest of researches on antiangiogenic treatment of HNSCC. In our opinion the relevance of antiangiogenic therapy remains largely under evaluated in clinical trials. New antiangiogenic drugs (Cediranib

Study	pts	Treatment	PFS	OS
Williamson et al. [33]	41	Sorafenib 400 mg/mq 28 days	4m	9m
Elser et al. [20]	26	Sorafenib 400 mg/mq d1-2	NR	4,2m
Vokes et al. [25]	51	Bevacizumab + erlotinib	3.8m	6.8m
Feinstein et al. [34]	25	Pem+ Beva	NR	RR =36% DCR =95%
Gibson et al. [35]	28	Cetuximab +Beva	2.8m	RR =27%8.1m DCR 76%
Savvides et al. [36]	23	TXT +RT+Beva	78%	89% DCR 74%
Pfister et al. [37]	42	CDDP+IMRT+Beva	83%	88% DCR100%
Cohen et al. [26]	48	Erlotinib + Beva	4.1m	7.1 RR15%
Salama et al. [23]	26	Beva +Hydroxyurea +5FU + RT	59% at 2 yr	OS= 58% LRC =67% RR= 86%
		+Hydroxyurea +5FU +RT	89% at 2 yr	OS= 89% LRC 100% RR= 100%
Argiris et al. [28]	37	Pem +Beva	TTP = 5 m	median OS= 11.3m ORR= 30%, CRR = 5%, DCR= 86%.
Harari et al. [41]	10	wCDDP+Beva+RT	NR	22.4
Lee et al. [38]	44*	Beva + CDDP+IMRT→ 3x(Beva+CDDP+5FU)	71.7%**	90.9%**
Argiris et al. [39]	46	Cetuximab+Beva	2.8m	7.6m DCR=73%
Yao et al. [29]	30	TXT+RT+Beva biW	3y 61.7%	3y OS=68.2% LRFS= 84.5% DMFS = 80.5%
Yoo et al. [27]	29	Beva-erlotinib →RT+ Beva-erlotinib+ CDDP	3y 82%	3y OS 86% 3y LRFS=85% 3y DMFS= 93%
Hainsworth et al. [40]	60	Beva-5FU-PTX-CDDP →RT+ Beva-erlotinib+ PTX	3y 71%	3y OS 82%

Table 1: Clinical trials on antiangiogenic therapies.

in a phase III trial conducted at Massachusetts General Hospital, Dalantercept, Ramucirumab, Aflibercept, dual inhibitors, integrins αvβ-αvβ5 inhibitors and multi target antiangiogenic agents in phase I/II trials) may overcome safety problems and improve outcomes.

A better definition of predictive factors of response and an improvement of safety profile may help to establish exactly the importance of antiangiogenic drugs in this heterogeneous tumor. Continued investigations and the collaborative effort of all physicians caring for head and neck cancer patients will be necessary to determine if antiangiogenic approaches will ultimately improve survival.

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