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Original Article

Bleeding Complications and Possible Resistance Patterns of Anti-angiogenesis Treatments in Recurrent/Metastatic Head-and-neck Squamous Cell Carcinoma – Reflections from a Phase II Study of Pazopanib in Recurrent/ Metastatic Head-and-neck Squamous Cell Carcinoma

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Abstract

Background: Due to smoking, alcohol, and betel nut use, head-and-neck squamous cell carcinoma (HNSCC) is a serious public health problem in Taiwan. **Materials and Methods:** We performed a single-arm Phase II trial of pazopanib in patients with platinum-refractory recurrent or metastatic HNSCC in 2011. **Results:** We screened 43 patients in about 6 months. Thirty-three of the patients were excluded due to easy bleeding and vessel contact resulting from the advanced tumor status. The remaining ten patients were included in this study. An objective response was seen in one patient; six patients had clinical benefits, which was comparable with the outcomes of sorafenib or sunitinib in this patient group. Four patients experienced at least Grade 3 bleeding. The tumor response was usually seen in the central cavity; the rim of the cavity extended outside, reflecting peripheral invasion and future resistance. **Conclusion:** The early use of anti-angiogenesis treatments is necessary for better tumor control and to prevent bleeding and potential resistance. In future, vascular endothelial growth factor receptor and/or epidermal growth factor receptor tyrosine kinase inhibitors may be used in combination with immunotherapy to increase the clinical benefits and avoid the risk of hyperprogression.

Keywords: Anti-angiogenesis treatments, bleeding complications, head-and-neck squamous cell carcinoma, pazopanib

Introduction

As smoking, alcohol, and betel nut use is quite common in Taiwan, head-and-neck squamous cell carcinoma (HNSCC) is a serious public health problem, with more than 6,000

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new patients/year. Even with multiple treatment modalities, still half of all patients with HNSCC finally succumb to the diseases within 5 years. In recurrent or metastatic disease, conventional chemotherapy often only palliates symptoms but does not prolong overall survival. Adding cetuximab to cisplatin and 5-fluorouracil treatment has been shown to offer survival benefits (7–10 months in overall survival) compared with chemotherapy alone in frontline treatment.[1] EPF has been covered by the National Health Bureau for the first-line treatment since early 2017. Afatinib is used for the second-line treatment of recurrent or metastatic recurrent/metastatic (R/M) HNSCC, and it has been shown to provide a borderline significant benefit in progression-free survival. However, the absolute benefit has been reported to be only 0.7 months, and severe diarrhea is common.[2] Patients with p16-negative status, epidermal growth factor receptor (EGFR) amplification, low human epidermal growth factor receptor 3, and intact PTEN have been shown to have a greater clinical benefit. Excitingly, immune checkpoint inhibitors (anti-PD1 monoclonal antibody), such as nivolumab, have been shown to provide survival benefits over chemotherapy in the second-line treatment of R/M HNSCC; however, treatment is expensive.[3] Tumor and stromal PDL1 levels may be biomarkers, and investigations are warranted to identify more biomarkers. Immunotherapy has been shown to potentially be more beneficial in Asian patients and especially in Taiwan.[4-6] Tumor or stromal PDL1 status, PDL2, p16/human papillomavirus (HPV) status, smoking, mutational or neoantigen load, INDEL signatures or frameshift mutations, APOBEC signatures, MSI status, DNA damage response or copy number alterations, cell cycle control (MDM2/4 or CCND1 or CDK4/6), inflammation gene expression profiles, angiogenesis, vascular endothelial growth factor (VEGF)-C level, gene changes of extrinsic apoptosis, antigen presentation, innate immunity, stromal Treg/myeloid-derived suppressor cell (MDSC)/tumor-associated macrophages type 2, fecal microbiota, epigenetic modifications, dynamic changes of plasma Treg or PD1 + effector CD8 cells, and T-cell reinvigoration (Ki67 + PD1 + CD8 cells/tumor burden) may influence the effects of immunotherapy.[7-11]

Betel nut chewing causes inflammation of the mucosa in head-and-neck areas. Chronic inflammation initiates DNA damage, angiogenesis, and several kinds of signal transduction favoring early carcinogenesis.[12] In addition, HNSCCs often become large tumors with central necrosis contributing to hypoxia. Hypoxia induces further signals, such as increased expressions of VEGF, platelet-derived growth factor (PDGF), placental growth factor, and stromal growth factor.[13] Blocking these signals may be able to control refractory HNSCC.

Although subgroup analysis of the EXTREME study showed a greater benefit with EPF for oral cavity cancers, we previously found that EPF did not have a good response in the induction or R/M setting of oral cavity cancer caused by betel nut exposure in Taiwan compared with Western countries.[14,15] The lower incidence of EGFR-dependent oncogenesis in oral cavity cancers in Taiwan is quite particular. Instead, a high response rate has been reported for bevacizumab (targeting VEGF) combined with PF in induction[16] and salvage settings (unpublished data); however, attention should be paid to bleeding, necrosis, and fistula formation. Bevacizumab with erlotinib[17] or bevacizumab combined with pemetrexed[18] has been associated with clinical benefits in the second-line setting of R/M HNSCC. However, the E1305 study comparing bevacizumab combined with chemotherapy alone in the first-line setting of R/M HNSCC showed no 5-year survival benefit,[19] although significantly improved response and progression-free survival rates with survival benefits were noted in the initial 4 years.

Multi-targeted VEGF tyrosine kinase inhibitors, such as sorafenib and sunitinib, have shown a disappointing overall response (below 10%) in cisplatin-refractory R/M HNSCC but a disease control rate of 40%–50%.[20-23] In one trial of sunitinib, 10% of the patients had Grade 5 bleeding and 40% had skin ulcers and fistulas,[23] very similar to our experience (unpublished data). If the distance of the tumor from the carotid artery is below 0.5 cm, sunitinib should not be used, possibly due to PDFGR inhibition causing pericyte maturation arrest and rupture of fragile vessels.

Pazopanib is an active multi-targeted tyrosine kinase inhibitor, which blocks VEGF-A, B, C, and fibroblast growth factor (FGF) pathways and may suppress tumor angiogenesis and growth in HNSCC. For the first-line use of pazopanib in metastatic renal cell carcinoma, pazopanib has been shown to have similar efficacy but better toxicity profiles compared with sunitinib.[24] Our group planned a Phase II trial of pazopanib for cisplatin-refractory R/M HNSCC[25] due to the lack of standard treatments before 2010. However, this trial had some obstacles which we believe may be common in other anti-angiogenesis treatments in this patient group. We found that (1) bleeding complications are very common in heavily treated advanced R/M HNSCC, and anti-angiogenesis treatments may be contraindicated; (2) possible resistance mechanisms of anti-angiogenesis treatments were shown in special imaging patterns; and (3) earlier use of anti-angiogenesis treatments with novel combinations, such as chemotherapies, drugs modifying epithelial-mesenchymal transition (EMT), and immunotherapies, was warranted.

Materials and Methods

We performed a single-arm Phase II trial of pazopanib (800 mg/day) in patients with platinum-refractory R/M HNSCC at National Taiwan University Hospital in 2011. The trial was registered at "ClinicalTrials.gov: NCT01377298-Pazopanib in patients with recurrent or metastatic HNSCC." The trial was approved by the IRB of National Taiwan University Hospital, registered on June 21, 2011.

The inclusion criteria were as follows: (1) histologically confirmed HNSCC; (2) recurrent or metastatic setting, refractory to previous cisplatin, or carboplatin-based

chemotherapy; (3) at least one measurable lesion (according to the RECIST v 1.1 criteria); (4) Eastern Cooperative Oncology Group performance status 0–2; (5) age >18 y/o, ≤70 y/o; (6) adequate bone marrow, hepatic, and renal functions as evidenced by the following: (a) absolute neutrophil count ≥1,500 cells/μL, platelet count ≥100,000 cells/μL, and hemoglobin ≥9 g/dL; (b) total bilirubin ≤1.5 × ULN and AST/ALT ≤3.0 × ULN; and (c) creatinine ≤1.5 mg/dL; and (7) patients who could provide written informed consent.

The exclusion criteria were as follows: (1) second malignancy; (2) locoregional recurrence amenable to definite surgery or further radiation treatment; (3) brain/meningeal metastasis with IICP or bone metastasis with spinal cord compression; (4) pregnancy or nursing women; (5) having received more than two prior lines of intravenous chemotherapy in a palliative setting; (6) having received anti-angiogenesis agents in a palliative setting; (7) having received chemotherapy or radiation therapy or surgery within the past 3 weeks; (8) patients with major systemic diseases making them unsuitable for systemic chemotherapy according to the clinicians' professional judgment; (9) mental status not fit for a clinical trial; (10) clinically significant gastrointestinal abnormalities that may have increased the risk of gastrointestinal bleeding including, but not limited to: (a) active peptic ulcer disease; (b) known intraluminal metastatic lesions with a risk of bleeding; (c) inflammatory bowel disease (e.g. ulcerative colitis or Crohn's disease) or other gastrointestinal conditions with an increased risk of perforation; and (d) history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning the study treatment; (11) corrected QT interval >480 ms using Bazett's formula; (12) poorly controlled hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg; (13) concomitant diseases that may be aggravated by the investigational drugs including: (a) active or noncontrolled infection; (b) severe upper gastrointestinal bleeding; and (c) history of any one or more of the following cardiovascular conditions within the past 12 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina, symptomatic peripheral vascular disease, and Class III or IV congestive heart failure, as defined by the New York Heart Association; (14) hemoptysis within 6 weeks of the first dose of pazopanib, prior major surgery within 4 weeks of the first dose of pazopanib, and the presence of any nonhealing wounds/fractures; and (15) tumors located within 0.5 cm of large blood vessels (such as internal/external carotid arteries, internal/external jugular veins, superior vena cava, subclavian artery/vein, ascending/descending aorta, pulmonary artery/vein, and mediastinal vessels).

Toxicity was recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 published by National Cancer Institute (located in 9609 Medical Center Drive, Rockville, Maryland 20850, United States) on May 28, 2009 Initially, 43 patients were expected to be enrolled. Follow-up images after pazopanib were also examined for patterns of failure.

Results

We screened 43 patients in about 6 months, of whom 10 were enrolled in the study. All patients were male, all had a history of smoking and drinking, and nine had a history of betel nut chewing. Three criteria were commonly met in R/M HNSCC: (1) hemoptysis within 6 weeks of the first dose of pazopanib; (2) presence of any nonhealing wounds; and (3) tumors located within 0.5 cm from large blood vessels (such as internal/external carotid arteries, internal/external jugular veins, superior vena cava, subclavian artery/vein, ascending/descending aorta, pulmonary artery/vein, and mediastinal vessels). Thirty-three of the 43 patients (77%) were excluded due to easy bleeding and vessel contact resulting from an advanced tumor status. Betel nut chewing can induce severe inflammation, local tissue destruction, regional huge masses, and queer metastatic sites. Many patients developed metastatic lesions in the pleura, pericardium, and mediastinum, and also locoregional lesions around carotid vessels causing unhealed fistulas or ulcers. Therefore, there was a high exclusion rate in this patient group due to concerns about bleeding complications.

Of the ten enrolled patients [Table 1], one had a partial response and five had stable disease; therefore, six patients had clinical benefits, which was comparable with the outcomes of sorafenib or sunitinib in this patient group. Two patients experienced severe fatal bleeding; one patient suffered from Grade 3 bleeding, and the other patient suffered from Grade 4 bleeding. The first of these patients had a partial response initially but then died from massive hemoptysis soon thereafter; therefore, this patient was not categorized as having a partial response. The other case of fatal bleeding also had massive hemoptysis (tumor progression and treatment effect were both likely). The third case of bleeding also occurred rapidly, with Grade 4 left lingual artery bleeding (tumor progression favored). This patient was stabilized by emergent transarterial embolization. One patient with stable disease initially and pulmonary cavity formation [Figure 1] finally had tumor progression and Grade 3 bleeding. Because of the high exclusion rate and severe bleeding complications, the trial was terminated early (from June 2011 to May 2013).

Two oropharyngeal patients, with histories of smoking, alcohol, and betel nut exposure, were HPV negative. However, one had a partial response after pazopanib treatment, and the duration of response was 157 days; the other patient had a prolonged duration of stable disease for 450 days and survived for 2 years and 11 months after subsequent intra-arterial chemotherapy. Another gingival cancer patient had stable disease for 140 days under pazopanib, and his pazopanib dose was tapered to 400 mg/day due to repeated Grade 3 hand and foot syndrome. He then received bio-chemotherapy, afatinib, and erlotinib with everolimus and survived for 594 days.

Table 1: All ten of the enrolled patients

Diagnosis	Disease status during trial entry	Response to pazopanib	Toxicity	Survival time
Laryngeal cancer (HPV-, BQ+)	Multiple metastasis failing PF, metronomic UFUR/Endoxan, & cetuximab-TPF	Unconfirmed PR (by CXR) due to grade 5 bleeding then	Grade 5 bleeding (massive hemoptysis) probably related to tumor response	20 days
Laryngeal cancer (HPV-, BQ+)	Multiple metastasis failing salvage PFL & palliative RT for right chest wall	Stable disease (cavity formation over chest wall lesion)	Grade 2 to 3 HTN & grade 3 bleeding (hemoptysis) probably related to tumor progression	121 days
Oropharyngeal cancer (HPV+, BQ+)	Persistently refractory neck lymph nodes failing cetuximab-TPF	Prolonged SD (less enhancement in MRI) for 450 days	Hand and foot syndrome, grade 1	1068 days (2Y11M); prolonged survival due to subsequent intra-arterial Bio-CT (bevacizumab- MEP/ TPF alternatively); afatinib & erlotinib/everolimus ever used
Buccal cancer (HPV-, BQ+)	Loco-regional recurrence refractory to PF	Progression	Mucositis, grade 2	91 days
Gingival cancer (HPV-, BQ+)	Neck recurrence with thyroid, tracheal , & skull base invasion failing cetuximab-TPF	Not assessed	Grade 4 bleeding related to tumor bleeding; tumor progression favored and stabilized after TAE	79 days
Buccal cancer (HPV-, BQ+)	Persistent right submandibular lymph node necrosis after salvage PF	Stable disease	Nil	143 days
Oropharyngeal Cancer (HPV+, BQ+)	Multiple metastasis failing cetuximab-PF	Partial response	Hypothyrodism, lightening of hair & skin color, grade 2 hand and foot syndrome	171 days
Gingival cancer (HPV-, BQ+)	Right maxillary and orbital floor recurrence refractory to PF	Stable disease	Hand and foot syndrome, grade 3	594 days; progression due to lung metastasis; prolonged survival due to subsequent cetuximab-docetaxel and bevacizumab- TPF; afatinib & erlotinib/everolimus ever used
Tongue base cancer (HPV-, BQ-)	Lung and bilateral adrenal metastasis refractory to PF & cetuximab-TPF	Stable disease	Anorexia, grade 2	218 days (brain metastasis thereafter, subsequent therapy with erlotinib and everolimus)
Tongue cancer (HPV-, BQ+)	Lung and bone metastasis refractory to PF	Not assessed	Grade 5 bleeding (massive hemoptysis; tumor progression or treatment effect both likely)	38 days

*PF: cisplatin, 5-fluorouracil *TPF: Docetaxel, cisplatin, 5-fluorouracil *BQ: betel nuts *PR: partial response. *PFL: weekly low dose cisplatin, 5-fluorouracil, & leucovorin *HPV: human papillomavirus *SD: stable disease. *N/A: no applicable. *Bio-CT: bio-chemotherapy. *MEP: mitomycin, epirubicin, cisplatin *TAE: trans-arterial embolization

The median duration of response in the evaluable patients was 112 days. The median progression-free survival was 82 days, and the median overall survival was 132 days. The image pattern of tumor response was usually central cavity or necrosis formation, typical of the effect of anti-angiogenesis treatments previously reported in the literature [Figure 1].[16,17] However, the rim of the cavity after anti-angiogenesis treatments extended outside, possibly reflecting peripheral invasion, and finally led to future resistance [Figure 1].

Discussion

Tumor bleeding is usually seen in the end-stage of R/M HNSCC, and it is always the cause of death. The risk of bleeding in our patient group (R/M HNSCC patients refractory to platinum) was very high (about 77%) in our screening process for enrollment into the anti-angiogenesis agent trial. The disease status at this stage was very advanced, which resulted in unpredictable bleeding events and death, and the risk for receiving anti-angiogenesis treatments was too high. The strict eligibility criteria in this advanced disease status were warranted. Therefore, the outcomes of these patients were even worse than usually expected, and further earlier interventions are urgently needed. Three of the four cases with at least Grade 3 bleeding had hemoptysis, and two died (one with an unconfirmed response); the other patient initially had stable disease with pulmonary cavity formation and finally had tumor progression with Grade 3 hemoptysis. Therefore, great vessel involvement in the head and neck is a risk factor for bleeding, and multiple lung lesions with cavity formation before or after pazopanib may be another important risk factor. In addition, peripheral invasion seen in our cases is a possible resistance pattern of anti-angiogenesis treatments, which may result from tumor invasion/migration signals and EMT. This phenomenon may further aggravate bleeding complications due to easy vessel rupture.

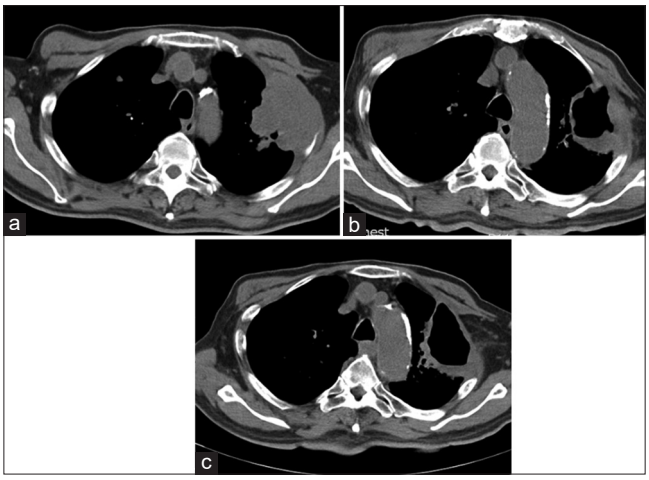

Figure 1: Prepazopanib versus postpazopanib images in case 2. (a) Before pazopanib use. (b) Pazopanib use for 6 weeks: The lesion became cavitated. (c) Pazopanib use for 12 weeks: The lesion became more cavitated and the rim of the cavity seemed to invade further peripherally

The treatment of HNSCC in Taiwan is still very challenging and may be related to betel nut use. Betel nut chewing has been reported to cause: (1) strong inflammation and angiogenesis; (2) strong invasion ad queer metastatic sites;[26] (3) easy recurrence or metastasis, usually accompanied with hypercalcemia; (4) poor response to chemotherapy and EGFR inhibitors;[14,15] (5) relatively good response to VEGF inhibitors combined with chemotherapy;[16] and (6) difficult wound healing and repair. Novel mechanism-guided treatments in betel nut-related HNSCC in Taiwan are urgently needed. Molecular classification for betel nut-related HNSCC in Taiwan will also be needed for the development of further precision medicine.

In VGH studies in Taiwan, huge HNSCCs from betel nut chewing have frequently been reported to cause tumor central necrosis and hypoxia and to mediate the EMT through the upregulation of Twist, Snail, and Slug. *Let7i* would be suppressed, resulting in increased H-Ras/RAC activity and enhanced tumor migration. EMT signals and suppressed *let7i* would also induce body mass index-1 expression and cause tumor stemness. Acetylated Snail has been shown to confer cisplatin resistance and induce M2 polarization by upregulating exosomal miR-21. M2 polarization has been shown to lead to enhanced tumor angiogenesis and migration, while miR-21 has been shown to cause NLRP3 ubiquitination and poor inflammasome activity. Acetylated Snail and exosomal miR-21 may also increase tumor MDSC and Treg.[27-30] Therefore, betel nut-related HNSCC in Taiwan may harbor possible resistance mechanisms to immunotherapy from strong angiogenesis and EMT. Targeting angiogenesis, EMT, and M2 polarization with immunotherapies may be important in this special phenotype.

Earlier combinations of anti-angiogenesis treatments with chemotherapy and immunotherapy, even in neoadjuvant settings, may result in greater benefits and enhance cure rates of definite surgery or CCRT in HNSCC, especially betel nut-related phenotype in Taiwan. This kind of earlier

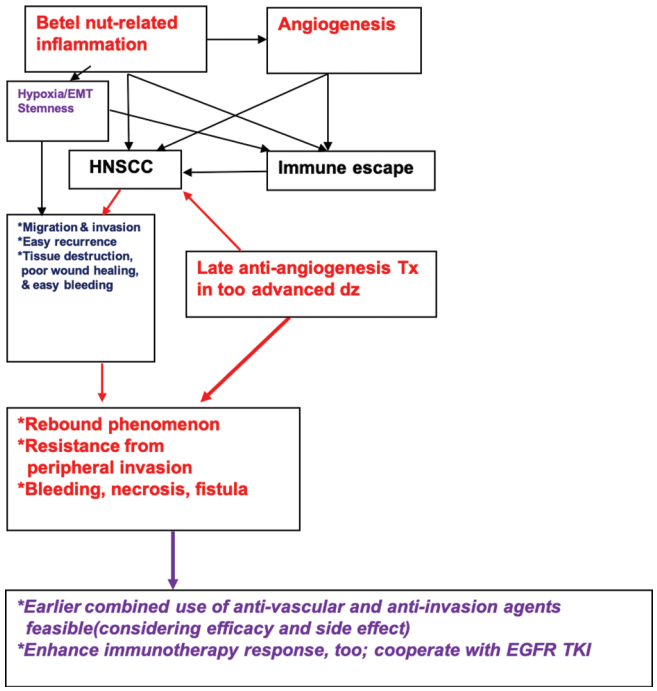

Figure 2: Anti-angiogenesis treatments for betel nut-related head-and-neck squamous cell carcinoma

intervention could possibly avoid the EMT, bleeding, and treatment refractoriness in advanced settings. Anti-angiogenesis treatments in betel nut-related HNSCC in Taiwan in future may be introduced early in three situations. First, with neoadjuvant chemotherapy (even with immunotherapy in future) in huge borderline resectable T4bN3 oral cavity cancer, such as the APF regimen in our institute.[16] Second, with immunotherapy in relatively frontline recurrent or metastatic settings (such as multi-targeted lenvatinib, targeting VEGF receptor (VEGFR1/2/3), PDGFR, FGF receptor, c-kit, RET, and some other invasion signals, combined with pembrolizumab which have been shown to result in 41% response rate and over 90% disease control[31]) to increase clinical benefits and avoid fatal bleeding, fistulas, and necrosis if later-line use. A first-line randomized placebo-controlled study of lenvatinib combined with pembrolizumab has been initiated (LEAP-10).[32] Third, with the use of EGFR monoclonal antibodies, such as cetuximab, in R/M settings. A Phase 1b study of pazopanib plus cetuximab in R/M HNSCC reported a complete response of 6%, an objective response rate of 35%, and a disease control rate of 81%. In cetuximab- and cisplatin-naïve patients, an objective response rate of 55% was reported, compared to 25% in patients who failed cetuximab and 28% in patients who failed cisplatin.[33]

Besides the VEGFR pathway, EGFR inhibition may cause immune modulation and overcome tumor immune escape. In our retrospective analysis, afatinib (EGFR tyrosine kinase inhibitor) 40 mg/day with pembrolizumab 200 mg/3 weeks was given to 51 refractory recurrent or metastatic Taiwanese patients with HNSCC (afatinib 30 mg/day and pembrolizumab 100 mg/3 weeks in patients with poor KPS or who could

not tolerate the original dosage).[34] The objective response rate was 55.8% and the disease control rate was 79%. The median duration of response was 7.5 months, the median PFS was 8.3 months, and the 1-year survival was 59.2%. Most patients only received four cycles of pembrolizumab, but a durable response was observed in the responders. The toxicity profiles were tolerable and manageable. The high therapeutic index of the combination of afatinib and pembrolizumab in betel nut-related HNSCC in Taiwan has already led to the opportunity to initiate a Phase II study to further investigate this regimen, and the ALPHA study has already begun.[35] The preliminary results of the ALPHA study in ASCO2021 showed an objective response rate of 41.4%, median progression-free survival of 4.1 months, and median overall survival of 8.4 months. High tumor PDL1 and EGFR amplification predicted a good response; MTAP loss or mutation predicted a poor response.[36] Besides, a study conducted by a Harvard group using a colon cancer model showed that EGFR TKIs (such as erlotinib and afatinib) could enhance CD8 cytolytic activity by increasing MHC/HLA/beta2-microglobulin expression, STAT1 activation, PDL1 suppression, STAT3 inhibition, and NKG2D/KIR modulation in a mouse model. The authors mentioned our clinical experiences of afatinib and pembrolizumab in HNSCC in their article.[37] Furthermore, EGFR was shown through M2 polarization to promote carcinogenesis in a hepatocellular carcinoma mouse model.[38] EGFR has also been shown to increase CTLA4 + Treg and MDSC and suppress dendritic cell maturation, natural killer cell tumor killing, and TIL infiltration in the tumor microenvironment.[39]

In this study, two oropharyngeal patients were HPV negative but had relatively good outcomes with a prolonged duration of response. Some patients had a long survival due to a relatively prolonged duration of response under pazopanib and subsequent treatments, such as intra-arterial bio-chemotherapy, afatinib, and erlotinib with everolimus. Immunotherapy was still not readily available during the study enrollment period. From 2011 to 2013, afatinib[40] and erlotinib with everolimus[41] were shown to have salvage efficacy under a cisplatin-refractory setting in early abstracts. Aggressive subsequent therapy for R/M HNSCC in Asia could also prolong survival in a recent immunotherapy trial.[5,42]

Conclusion

The early use of anti-angiogenesis treatments is necessary for better tumor control and to prevent bleeding and potential resistance. It may be combined with current immunotherapy regimens to enhance immune-mediated tumor killing. Furthermore, this combination may overcome potential resistance to immunotherapy by blocking profound angiogenesis and the EMT in betel nut-related HNSCC in Taiwan [Figure 2].

In future, VEGFR and/or EGFR tyrosine kinase inhibitors may be used in combination with immunotherapy to increase clinical benefits and avoid the risk of hyperprogression.

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Conflicts of interest

There are no conflicts of interest.

References

1. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, *et al.* Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.
2. Machiels JP, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB, *et al.* Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): An open-label, randomised phase 3 trial. Lancet Oncol 2015;16:583-94.
3. Ferris RL, Blumenschein G Jr., Fayette J, Guigay J, Colevas AD, Licitra L, *et al.* Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med 2016;375:1856-67.
4. Tahara M, Muro K, Hasegawa Y, Chung HC, Lin CC, Keam B, *et al.* Pembrolizumab in Asia-pacific patients with advanced head and neck squamous cell carcinoma: Analyses from KEYNOTE-012. Cancer Sci 2018;109:771-6.
5. Kiyota N, Hasegawa Y, Takahashi S, Yokota T, Yen CJ, Iwae S, *et al.* A randomized, open-label, Phase III clinical trial of nivolumab vs. therapy of investigator's choice in recurrent squamous cell carcinoma of the head and neck: A subanalysis of Asian patients versus the global population in checkmate 141. Oral Oncol 2017;73:138-46.
6. Chen WC, Chu PY, Lee YT, Lu WB, Liu CY, Chang PM, *et al.* Pembrolizumab for recurrent/metastatic head and neck squamous cell carcinoma in an Asian population. Medicine (Baltimore) 2017;96:52-9.
7. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. Nature 2017;541:321-30.
8. Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. Cell 2015;160:48-61.
9. Turajlic S, Litchfield K, Xu H, Rosenthal R, McGranahan N, Reading JL, *et al.* Insertion-and-deletion-derived tumour-specific neoantigens and the immunogenic phenotype: A pan-cancer analysis. Lancet Oncol 2017;18:1009-21.
10. Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, *et al.* T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature 2017;545:60-5.
11. Fankhauser M, Broggi MA, Potin L, Bordry N, Jeanbart L, Lund AW, *et al.* Tumor lymphangiogenesis promotes T cell infiltration and potentiates immunotherapy in melanoma. Sci Transl Med 2017;9:eaal4712.
12. Chang MC, Chiang CP, Lin CL, Lee JJ, Hahn LJ, Jeng JH. Cell-mediated immunity and head and neck cancer: With special emphasis on betel quid chewing habit. Oral Oncol 2005;41:757-75.
13. Haddad RI, Shin DM. Recent advances in head and neck cancer. N Engl J Med 2008;359:1143-54.
14. Lou PJ, Liao CT, Wang CP, Huang SF, Cheng SJ, Hsu CL, *et al.* A phase II study of cetuximab-based neoadjuvant and adjuvant treatment strategies, with or without surgery, in patients with locally very advanced squamous cell carcinoma of the oral cavity. Journal of Clinical Oncology 2012; 30suppl.:e16050.
15. Yen CJ, Tsou HH, Hsieh CY, Chu CY, Chiu CF, Chen CC, *et al.* Sequential therapy of neoadjuvant biochemotherapy with cetuximab, paclitaxel, and cisplatin followed by cetuximab-based concurrent bioradiotherapy in high-risk locally advanced oral squamous cell carcinoma: Final analysis of a phase 2 clinical trial. Head Neck 2019;41:1703-12.
16. Huang HC, Kao HF, Liao BC, Hong RL. A phase II study of neoadjuvant chemotherapy with APF(bevacizumab, cisplatin, and 5-FU) and AP(bevacizumab and cisplatin)- bio-chemoradiation, followed by curative surgery for locally advanced squamous cell carcinoma of head and neck. ESMO Asia 2016 Poster1296.
17. Cohen EE, Davis DW, Karrison TG, Seiwert TY, Wong SJ, Nattam S, *et al.* Erlotinib and bevacizumab in patients with recurrent or metastatic

squamous-cell carcinoma of the head and neck: A phase I/II study. Lancet Oncol 2009;10:247-57.
18. Argiris A, Karamouzis MV, Gooding WE, Branstetter BF, Zhong S, Raez LE, *et al.* Phase II trial of pemetrexed and bevacizumab in patients with recurrent or metastatic head and neck cancer. J Clin Oncol 2011;29:1140-5.
19. Argiris A, Li S, Savvides P, Ohr JP, Gilbert J, Levine MA, *et al.* Phase III randomized trial of chemotherapy with or without bevacizumab in patients with recurrent or metastatic head and neck cancer. J Clin Oncol 2019;37:3266-74.
20. Williamson SK, Moon J, Huang CH, Guaglianone PP, LeBlanc M, Wolf GT, *et al.* Phase II evaluation of sorafenib in advanced and metastatic squamous cell carcinoma of the head and neck: Southwest oncology group study S0420. J Clin Oncol 2010;28:3330-5.
21. Fountzilas G, Fragkoulidi A, Kalogera-Fountzila A, Nikolaidou M, Bobos M, Calderaro J, *et al*. A phase II study of sunitinib with recurrent and/or metastatic non-nasopharyngeal head and neck cancer. Cancer Chemother Pharmacol 2010;65:649-60.
22. Choong NW, Kozloff M, Taber D, Hu HS, Wade J, Ivy P, *et al*. Phase II study of sunitinib malate in head and neck sqaumous cell carcinoma. Invest New Drugs 2010;28:677-83.
23. Machiels JP, Henry S, Zanetta S, Kaminsky MC, Michoux N, Rommel D, *et al.* Phase II study of sunitinib in recurrent or metastatic squamous cell carcinoma of the head and neck: GORTEC 2006-01. J Clin Oncol 2010;28:21-8.
24. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, *et al.* Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722-31.
25. NCT01377298-Pazopanib in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma. Available from: https://clinicaltrials.gov. [Last accessed on 2011 Jun 21].
26. Shao YY, Hong RL. Pleural metastases as a unique entity with dismal outcome of head and neck squamous cell carcinoma. Oral Oncol 2010;46:694-7.
27. Yang MH, Hsu DS, Wang HW, Wang HJ, Lan HY, Yang WH, *et al.* Bmi1 is essential in Twist1-induced epithelial-mesenchymal transition. Nat Cell Biol 2010;12:982-92.
28. Yang WH, Lan HY, Huang CH, Tai SK, Tzeng CH, Kao SY, *et al.* RAC1 activation mediates Twist1-induced cancer cell migration. Nat Cell Biol 2012;14:366-74.
29. Hsu DS, Wang HJ, Tai SK, Chou CH, Hsieh CH, Chiu PH, *et al.* Acetylation of snail modulates the cytokinome of cancer cells to enhance the recruitment of macrophages. Cancer Cell 2014;26:534-48.
30. Hsieh CH, Tai SK, Yang MH. Snail-overexpressing Cancer cells promote M2-like polarization of tumor-associated macrophages by delivering MiR-21-abundant exosomes. Neoplasia 2018;20:775-88.
31. Taylor MH, Lee CH, Makker V, Rasco D, Dutcus CE, Wu J, *et al.* Phase IB/II trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. J Clin Oncol 2020;38:1154-63.
32. NCT04199104 – A Study of Pembrolizumab with or Without Lenvatinib as First Line Intervention in a Programmed Cell Death-Ligand 1(PD-L1) Selected Population with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC) (LEAP-10). Available from: https://clinicaltrials.gov. [Last accessed on 2021 Nov 29].
33. Adkins D, Mehan P, Ley J, Siegel MJ, Siegel BA, Dehdashti F, *et al.* Pazopanib plus cetuximab in recurrent or metastatic head and neck squamous cell carcinoma: An open-label, phase 1b and expansion study. Lancet Oncol 2018;19:1082-93.
34. Kao HF, Hong RL. Pembrolizumab and afatinib for recurrent or metastatic head and neck squamous cell carcinoma-a single center experience. Annals Oncology 2018; 29 suppl 8:viii372-99.
35. NCT03695510 – Afatinib and Pembrolizumab for Head and Neck Squamous Cell Carcinoma (ALPHA Study). Available from: https://clinicaltrials.gov. [Last accessed on 2021 Feb 26].
36. Kao HF, Liao BC, Huang YL, Huang HC, Chen CN, Chen TC, *et al*. Afatinib and pembrolizumab for recurrent or metastatic head and neck squamous cell carcinoma(ALPHA study): A phase II study with biomarker analysis. Journal of Clinical Oncology 2021;39: Abstract6024.10.
37. Lizotte PH, Hong RL, Luster TA, Cavanaugh ME, Taus LJ, Wang S, *et al*. A High-throughput immune-oncology screen identifies EGFR inhibitors as potent enhancers of antigen-specific cytotoxic T-lymphocyte tumor cell killing. Cancer Immunol Res 2018;6:1511-23.
38. Lanaya H, Natarajan A, Komposch K, Li L, Amberg N, Chen L, *et al.* EGFR has a tumour-promoting role in liver macrophages during hepatocellular carcinoma formation. Nat Cell Biol 2014;16:972-81.
39. Concha-Benavente F, Ferris RL. Oncogenic growth factor signaling mediating tumor escape from cellular immunity. Curr Opin Immunol 2017;45:52-9.
40. Seiwert TY, Fayette J, Cupissol D, Del Campo JM, Clement PM, Hitt R, *et al*. A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. Ann Oncol 2014;25:1813-20.
41. Massarelli E, Lin H, Ginsberg LE, Tran HT, Lee JJ, Canales JR, *et al.* Phase II trial of everolimus and erlotinib in patients with platinum-resistant recurrent and/or metastatic head and neck squamous cell carcinoma. Ann Oncol 2015;26:1476-80.
42. Yen CJ, Kiyota N, Hanai N, Takahashi S, Yokota T, Iwae S, *et al.* Two-year follow-up of a randomized phase III clinical trial of nivolumab vs. The investigator's choice of therapy in the Asian population for recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141). Head Neck 2020;42:2852-62.