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Durable Overall Survival in Recurrent Locally Advanced Tongue Base Squamous Cell Carcinoma (SCC) With Combination Targeted Therapy Agents That Are Not Conventionally Used for Head and Neck SCC (HNSCC)

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Abstract

Background: Over 90% of cancers in the oral cavity have been identified as oral SCC (OSCC) or oropharyngeal SCC (OPSCC). However, the 5-year survival rate of OSCC and OPSCC through multimodal treatment has not significantly improved over the past 20 years.

Case Presentation: We share the case of a patient with recurrent advanced tongue base squamous cell carcinoma (OPSCC), who experienced complete remission (CR) from stage IVA initially. He went into CR again from recurrent disease with negligible adverse drug reactions through combination target therapy guided by molecular genomic analysis of cells in the re-biopsied recurrent tumor specimen. He had prolonged overall survival of 1449 days that greatly exceeded the large-scale statistical medium survival range of 395 to 415 days.

Conclusions: It is still under debate whether either basket or umbrella trials could be applied to strategies of personalized precision medicine for patients with advanced or intractable malignant diseases. Despite this, the utilization of somewhat corresponding targeted agents, which are not generally considered for conventional treatment, on druggable genomic or signaling pathways aberrance via next generation sequencing (NGS) analysis of the cells in the biopsied or resected specimen could bring improved clinical benefits, as shown through the patient we present.

Keywords: Tongue base SCC; Next-generation sequencing (NGS); Precision medicine

List of Abbreviations: ADCC: Antibody-Dependent Cellular Cytotoxicity; ADR: Adverse Drug Reaction; CGP: Comprehensive Genomic Profiling; cGy: centigray (Gy: gray, SI unit for radiation dose); CR: Complete Remission; CT: Computer Tomography; DBD: DNA binding domain; ECOG: Eastern Cooperative Oncology Group (a measurement of how a disease affects a patient's daily living abilities); EGFR: Epidermal Growth Factor Receptor; FFPE: Formalin-Fixed, Paraffin-Embedded; FGFR: Fibroblast Growth Factor Receptor; HNSCC: Head And Neck Squamous Cell Carcinoma; ICT: Induction Chemotherapy; LA: Locally Advanced; LOF: Loss Of Function; Mb: Megabase; MP: Molecular Profiling; MRI: Magnetic Resonance Imaging; MSS: Microsatellite Stability Status; NGS: Next Generation Sequencing; OPSCC: Oropharyngeal Squamous Cell Carcinoma; OSCC: Oral Squamous Cell Carcinoma; OS: Overall Survival; PDGFR: Platelet-Derived Growth Factor Receptor; PD: Progressive Disease; PET: Positron Emission Tomography; PFS: Progression-Free Survival; PlGF: Placental Growth Factor; PR: Partial Remission; R/R: Relapsed And Refractory; SCC: Squamous Cell Carcinoma; TKI: Tyrosine Kinase Inhibitor; TMB: Tumor Mutational Burden; VEGF: Vascular Endothelial Growth Factor; VEGF-A/C/D: Vascular Endothelial Growth Factor A/C/D; VEGFR: Vascular Endothelial Growth Factor Receptor; VEGFR1, 2, 3: Vascular Endothelial Growth Factor Receptor 1, 2, 3

Introduction

With an estimated 500,000 new cases each year [1], oral cancer (when oropharyngeal sites are included) is the sixth most common cancer in the world, with over 90% of cancers in the oral cavity identified as oral SCC (OSCC) or oropharyngeal SCC (OPSCC). Etiologic factors of OSCC and OPSCC include smoking (by far the most important cause), alcohol, betel nuts [2] and other intrinsic factors (e.g. candidiasis, syphilis, and oncogenic viruses) [3].

In general, salvage treatment with a combination of probable chemotherapy, reirradiation, and surgical resection would be considered for the second primary head and neck squamous cell carcinoma (HNSCC) or recurrent locoregional disease. However, its effectiveness is still inadequate, and the low 5-year survival rate of OSCC and OPSCC in all stages has not greatly improved over the past 20 years and remains at approximately 27.8% [4,5,6]. Furthermore, the majority of these patients who refuse salvage surgical resection or have unresectable disease would fail to respond to the salvage reirradiation or chemo-radiotherapy and could potentially suffer from major drawbacks also possibly seen in surgical intervention, such as speech problems, mucositis, local infection, aspiration pneumonia, malnutrition, myelosuppression, and organ function impairment (e.g. swallowing or vocal dysfunction) [7,9]. Molecular profiling (MP) through next generation sequencing (NGS) may be able to guide treatment models for advanced or relapsed and refractory (R/R) malignant diseases and provide clinically relevant benefits of prolonged progression-free survival (PFS) or overall survival (OS) with less serious treatment-related side effects than the conventional heavy treatment used as a rescue model [7,8,10-13].

Herein we present a patient with recurrent locally advanced (LA) tongue base SCC (OPSCC) who achieved complete remission (CR) through combination target therapy guided by molecular genomic analysis. The treatment course timeline has been summarized in Figure 1.

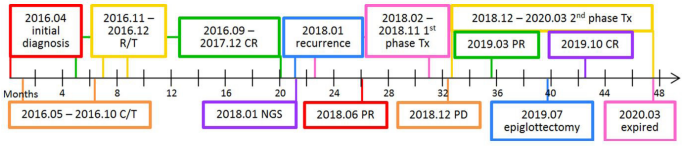

Figure 1: Treatment timeline: Treatment course of advanced tongue base SCC from diagnosis until expiration

Case Presentation

The 59-year-old male was initially diagnosed with locally advanced tongue base squamous cell carcinoma (OPSCC), stage IVA (T2N2cM0), through biopsy of tongue base tumor and neck lymph nodes on April 5th, 2016 and PET scan on April 27th, 2016, when he was 55. He refused surgery and got CR according to neck CT, PET scan, and laryngoscopy from September 2016 to December 2017, after receiving four cycles of induction chemotherapy (ICT) with cisplatin, docetaxel, and fluorouracil, combined with cetuximab, and sequential radiotherapy with 7000 cGy from May to December 2016. Regretfully, recurrent tongue base SCC (rT2N0M0, stage II) was noted through PET scan (Figure 2) on January 12th, 2018 and proved through biopsy of the recurrent tongue base tumor on January 17th, 2018. The patient refused conventional salvage treatment, including surgery he had never had before, and consented to MP analysis-guided treatment instead. The genomic DNA was extracted from the formalin-fixed, paraffin-embedded (FFPE) recurrent tumor sample, and comprehensive genomic profiling (CGP) with a 440 cancer-related gene panel was then analyzed through NGS after it was reviewed by pathology. The resultant analysis identified eighteen non-synonymous mutations, including single nucleotides and small insertion and deletion variants. Detected among them were two loss-of-function (LOF) mutations, located in p.H179L and p.R181P of TP53 coding regions with respective allele frequencies of 13.3% and 14.0% (Figure 3), and an amplified genomic region encoding epidermal growth factor receptor (EGFR) gene at chromosome 7p11.2 with copy number of 15 (Figure 4). The tumor mutational burden (TMB) was 15.4 mutations/Mb (with the cutoff value at 17 mutations/Mb), and the microsatellite stability status was stable (MSS).

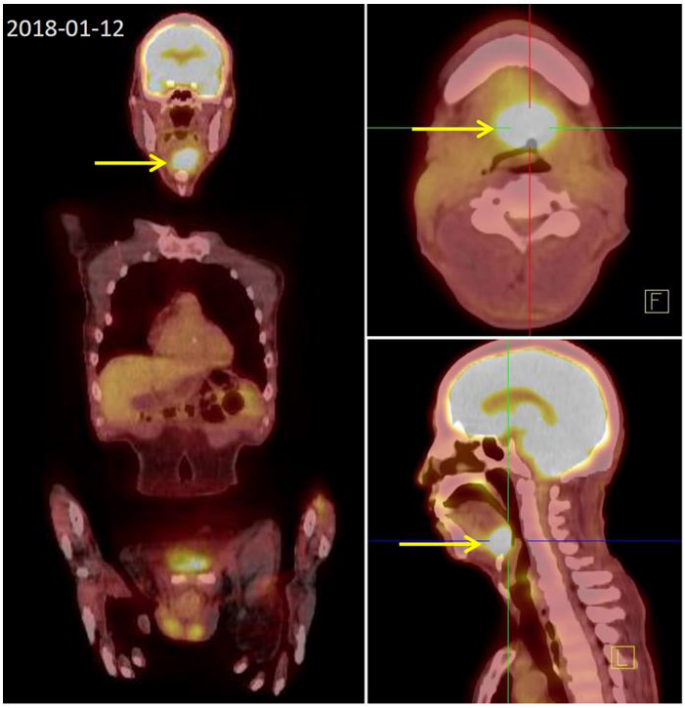

Figure 2: PET scan (Jan.12, 2018): recurrent local oropharyngeal tumor (rT2N0M0, stage II) over tongue base, vallecula, and epiglottis

Gene	Accession Number	Chr	Exon	cDNA Change	Amino acid change	Coverage	Allele Frequency
TP53	NM_000546	17	5	c.542G>T	Arg181Pro	801	14.0%
TP53	NM_000546	17	5	c.536A>T	His179Leu	792	13.3%

Figure 3: Clinically relevant mutations of TP53, detected in patient's re-biopsy specimen

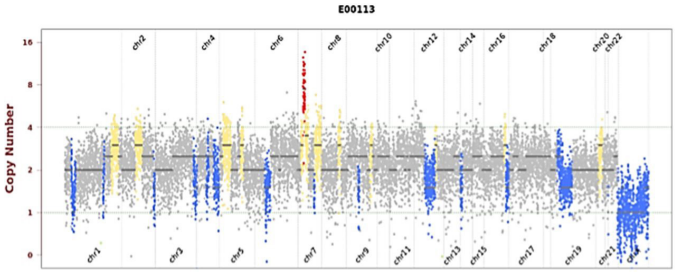

Figure 4: Copy number profile of the re-biopsy sample. Amplified regions of chromosome 7 are indicated by red "dots," which cover the EGFR coding regions

Figure 5: (a) PET scan (Jun.19, 2018); **(b)** MRI (Jun.4, 2018): corresponding images illustrating smaller local tumor through the first phase genomic analysis-guided target therapy, with MRI (b) as the baseline follow-up image with enhanced tongue base, vallecula, and epiglottis

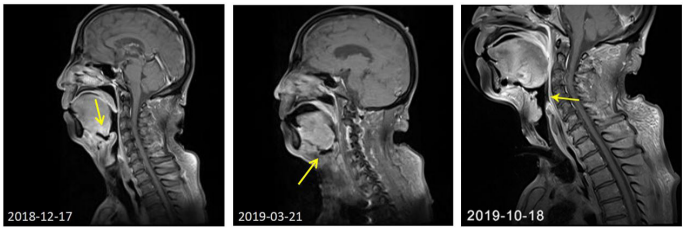

Figure 6: (a) MRI (Dec.17, 2018): progressive local enhanced tumor after the first phase target therapy; **(b)** MRI (Mar.21, 2019): less enhanced (remitted) local tumor through the second phase target therapy; **(c)** MRI (the last follow-up image, Oct.18, 2019): invisible enhanced local tumor (previously over tongue base, vallecula and epiglottis), during the second phase target therapy, after partial epiglottectomy of necrotic part of epiglottis

The patient went into CR after two consecutive phases of combination target therapy with multi-tyrosine kinase inhibitors (TKI) and inhibitors of EGFR and angiogenesis, guided by genomic analysis [14-16]. Partial remission (PR) could be seen through PET (Figure 5a) and MRI (Figure 5b) in June 2018 during the first phase therapy, which was given from February to November 2018 and comprised of cetuximab, aflibercept, and pazopanib. Progressive disease (PD) was subsequently noted through MRI in December 2018 (Figure 6a), and PR was noticed soon through MRI in March 2019 (Figure 6b) during the second phase therapy, which was given from December 2018 until March 2020 and consisted of cetuximab, ramucirumab, and lenvatinib. CR was assured through MRI (Figure 6c) on October 18th, 2019 and nasopharyngolaryngoscopy on December 16th, 2019. The patient was not caught with any noticeable adverse drug reactions (ADR). He once received hyoid bone resection and partial epiglottectomy of necrotic part of epiglottis due to an episode of sudden massive hemoptysis in July 2019, but pathology revealed only necrotic tissue without malignant cells. Unfortunately, he passed away on March 23rd, 2020 due to suffocation after an episode of aspiration from food with an overall survival of 1449 days (3.97 years) and an ECOG performance status of mainly grade 2 during the treatment period.

Discussion

Combination of cetuximab with ICT, comprising of docetaxel and cisplatin-5-fluorouracil, provides significant overall survival benefit over cisplatin-5-FU, which has been the conventional chemotherapy backbone in advanced, recurrent, inoperable or metastatic HNSCC for the past several decades [17,18]. The overall median survival was 515 days (1.41 years) for patients with all stages of OSCC and OPSCC in a large-scale analysis. Among them, the medium survival of patients with stage III and IV was 415 days, patients having alcohol consumption was 484 days, and patients without radical surgery resection was 395 days [6].

As cancer is a genetic disease driven by heritable or somatic mutations, there is no doubt that new DNA sequencing technologies will have a significant impact on new management, diagnostic, prognostic, and therapeutic models. CGP through NGS allows simultaneous testing of multiple genes and saves time for patients with clinically limited options by identifying genomic variants that could be targeted by these authorized therapeutic agents [19,20].

EGFR is overexpressed in up to 90% of HNSCCs, and high levels of EGFR expression and EGFR gene amplification have been associated with poor prognosis in patients with advanced HNSCC [21-24,30]. Cetuximab binds competitively to the extracellular domain of EGFR and induces antibody-dependent cellular cytotoxicity (ADCC) [23]. However, one of the proposed mechanisms to resist cetuximab in various types of cancer is through elevated vascular endothelial growth factor (VEGF) signaling pathway, which not only induces EGFR inhibitor resistance, but also increases migratory potential and activates multiple downstream signaling pathways, such as the RAS/MAPK pathway to regulate cell proliferation and gene expression, the PI3K/AKT pathway to regulate cell survival, and the RhoA/ROCK pathway to stimulate vessels de novo [25-30,39]. On the other hand, TP53 mutations have been

found in about 50% of human tumors and reported in about 74% of HNSCCs. These TP53 gene mutations result in a p53 protein in cells with mutated or damaged DNA that has less ability to induce apoptosis and inhibit tumor growth [31,32]. TP53 gene mutations also upregulate VEGF-A and VEGF receptor 2 (VEGFR2). Therefore, TP53 alterations may predict the sensitivity of cancer cells to VEGF/VEGFR inhibitors in the clinic and be a biomarker ready for treatment with antiangiogenesis agents [14,33-35].

Co-alterations of TP53 DNA-binding domain (DBD) (residues 94-292) mutations and EGFR amplification are prevalent in 5% of primary and metastatic HNSCC. As a result, studies have demonstrated that the combination of anti-EGFR agent and inhibitor of VEGF signaling pathway has greater efficacy than either agent alone [14,35-39].

Aflibercept, with a 45- to 92-fold greater blocking potency than bevacizumab, binds to both VEGF-A and placental growth factor (PlGF) and essentially renders multiple VEGF-A isoforms and PlGF ligands unable to bind to or activate cell receptors [40,41]. Pazopanib, an approved corresponding drug for TP53 mutation, is one of the best known multi-targeted TKIs that blocks VEGFR1, 2, 3 and platelet-derived growth factor receptor (PDGFR) signaling and can produce remarkable tumor response rates when combined with cetuximab [42-47].

Ramucirumab binds to VEGFR-2 and acts as an antagonist to VEGF-A, VEGF-C, and VEGF-D. With the resultant attenuation of vascular permeability and of the survival, proliferation, and migration of endothelial cells (anti-hemangiogenesis and anti-lymphangiogenesis), it ultimately suppresses tumor growth and dissemination of metastasis via blood and lymph vessels [48-52]. Lenvatinib is a multi-kinase inhibitor that primarily inhibits kinase activities of VEGFR1, 2, and 3, as well as other kinases relevant to pathogenesis, angiogenesis, tumor growth, and cancer progression, such as fibroblast growth factor receptors (FGFR) 1, 2, 3, and 4, PDGFR alpha (PDGFRα), c-Kit, and the RET proto-oncogene. It is crucial for the inhibition of endothelial cell growth [32,53-55].

It has not been confirmed whether patients with different intractable cancers can receive the same treatment strategy that targets similar or specific biomarkers or genetic aberrance and subsequently have extraordinary clinical outcome [56,57]. However, we share a patient who received treatment through targeted molecular aberrance and had noteworthy clinical benefit with prolonged overall survival (1449 days, 3.97 years) that greatly exceeded the large-scale statistical medium survival range of 395 to 415 days [18], as well as neglected ADRs. This reflects the feasibility of treatment models with combined targeted agents that are generally not considered in the conventional treatment regimens and are involved in druggable genomic or signaling pathway aberrance.

Conclusions

Molecular profiling (MP) through next generation sequencing (NGS) of cells in biopsied or resected specimen may offer the opportunities for controlling advanced or relapsed and refractory (R/R) malignant diseases with druggable genomic or signaling pathway aberrance. As demonstrated through the case we shared, even though the disease was initially partially remitted with the first phase therapy, the progressive condition was still under control up to complete remission with the second phase therapy. The medication agents in the two phases of salvage therapies were all involved with mechanisms related to genomic or signaling pathway aberrance through NGS analysis.

Precision medicine could characterize treatment strategy for advanced malignant disease via molecular genomic analysis. Although basket trials for intractable cancers have not been confirmed yet, these "personalized" druggable targets and signaling pathways bring a hopeful opportunity to have not only higher disease control rates and less ADRs, but also a better quality of life [56]. Nevertheless, further approaches should be implemented to enhance scientific validity, pinpoint the target, and reduce misunderstandings and risks so that the benefits to both society and trial participants could be maximized [57].

Ethical Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient's next of kin to publish this paper. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of St. Martin De Porres Hospital (IRB No. 20B-016, 12/08/2020).

Authors' Contributions

Conceptualization, S.C.H.; Investigation, S.C.H.; Resources, S.C.H., C.T.N.; Writing - Original Draft, S.C.H.; Writing - Review & Editing, S.C.H.; Visualization, S.C.H.; Supervision, S.C.H. All authors have read and agreed to the published version of the manuscript. All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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