Sorafenib for treating head and neck adenocarcinoma of unknown primary site: a case report

Jingxian Chen¹, Chien-shan Cheng²,³, Jie Chen⁴, Lingling Lv¹, Xiaoheng Shen¹ and Lan Zheng¹

Abstract
The aim of the present study was to report a rare case of head and neck adenocarcinoma with an unknown primary site in a 59-year-old man. After disease progression followed by multiple cycles of chemotherapy and radiotherapy, genetic screening using next-generation sequencing identified vascular endothelial growth factor A amplification and the TP53 R209Kfs mutation. Treatment with the multi-targeted protein kinase inhibitor sorafenib controlled the patient’s symptoms and improved his quality of life.

Keywords
Cancer of unknown primary, adenocarcinoma, head and neck cancer, sorafenib, adverse events, next-generation sequencing

Date received: 18 April 2020; accepted: 11 September 2020

Introduction
Sorafenib is a multi-targeted protein kinase inhibitor that has been approved for the treatment of advanced renal cell carcinoma, advanced hepatocellular carcinoma, and

¹Department of Traditional Chinese Medicine, Ruijin Hospital, Jiaotong University School of Medicine, Shanghai, China
²Department of Integrative Oncology, Fudan University Shanghai Cancer Center, Shanghai, China
³Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China
⁴Department of Orthopedics, Shanghai Institute of Traumatology and Orthopedics, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Corresponding author:
Lan Zheng, Department of Traditional Chinese Medicine, Ruijin Hospital, Jiaotong University School of Medicine, 197 Ruijin 2nd Road, Huangpu District, Shanghai 200025, China.
Email: zl10558@rjh.com.cn
advanced thyroid cancer. Sorafenib exhibits activities against vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, and ubiquitous serine/protein kinases. Sorafenib confers survival benefits in patients with specific gene alterations or intolerance or unresponsiveness to standard therapies. However, its efficacy in the treatment of metastatic adenocarcinoma of the head and neck with an unknown primary site has not been reported.

Cancer of unknown primary site (CUP) accounts for 3% to 5% of all malignancies. Current treatment with platinum or taxane-based chemotherapy is associated with a response rate of only 20% and a median survival of 6 months. Unlike the improvement in treatment outcomes for squamous cell carcinoma achieved by the addition of cetuximab, adenocarcinoma of the head and neck has limited therapeutic options and poses challenges to oncologists. With the recent advancements in genomic technology, targeted “panel” sequencing of selected mutations for individual patients or molecular profiling has been increasingly available for diagnostic purposes and for tailoring cancer treatments. In this study, we reported a case of head and neck adenocarcinoma of unknown primary site with an unsatisfactory response to chemotherapy and radiotherapy that was treated with sorafenib based on the results of next-generation sequencing (NGS).

Case report

A 59-year-old man who had a left submandibular mass for more than 30 years presented with a posterior mass in the left ear and facial swelling that had persisted for 3 months. The patient’s past medical history was unremarkable. Contrast-enhanced computed tomography (CT) of the maxillofacial region revealed a left submandibular gland lesion, as well as left neck lymph node enlargement at levels I to V and subcutaneous soft tissue thickening (Figure 1a). Enhanced magnetic resonance imaging (Figure 1b–d), positron emission tomography–CT (Figure 1e–h), and immunohistochemical investigations (Figure 2, Table 1) failed to identify the primary site of the lesion. Fine-needle aspiration and biopsies of the left postauricular mass identified a poorly differentiated metastatic adenocarcinoma.

The multidisciplinary team (MDT) recommended parotidectomy. The patient chose conservative treatment because of fears regarding surgery. The TP chemotherapy regimen was selected (paclitaxel 175 mg/m² and cisplatin 75 mg/m², day 1), and treatment was terminated because of severe myelosuppression (grade IV) despite the improvement of facial swelling and shrinkage of the tumor (Figure 3a–c) in the first cycle. Subsequent radiotherapy (DT: 66GY/33F; Figure 3d) was followed by three cycles of paclitaxel 140 mg/m² on day 1 of each 21-day cycle. The treatment failed to relieve the facial swelling or delay disease progression (Figure 3e), and the patient exhibited symptoms including migraine and a sensation of obstruction upon eating.

Genetic screening via NGS was then applied (Table 2), indicating that the patient would not benefit from any treatment recommended in current guidelines. Sorafenib was provided as compassion therapy to the patient based on amplification of the vascular endothelial growth factor A gene and the TP53 R209Kfs mutation according to NGS. Treatment was administered after discussion among MDT members, ethics committee approval, and patient consent.

After sorafenib (200 mg bid) was administered for 8 days, the patient’s facial swelling had subsided completely (Figure 4a–c).
Figure 1. A lesion in the left submandibular gland was detected via plain computer tomography (a), T1-weighted magnetic resonance imaging (b), T2-weighted magnetic resonance imaging (c), and contrast-enhanced computed tomography (d). Subcutaneous soft tissue mass in the left neck with increased metabolism on positron emission tomography–computed tomography (e–h).

Figure 2. Hematoxylin and eosin staining of the subcutaneous soft tissue mass biopsy specimen revealing adenocarcinoma. Magnification, $\times50$ (a), $\times200$ (b), and $\times400$ (c). Staining for cytokeratin AE1/AE3 (d), CK7 (e), and negative-control antibodies (f).
However, facial swelling reappeared 10 days after the start of sorafenib treatment (Figure 4d). We hypothesized that this symptom may have been caused by sorafenib opposed to rapid disease progression. Then, the combination of promethazine (25 mg, i.m., qd, for 14 days) and furosemide (20 mg, i.v., qd, for 14 days) was administered together with sorafenib, followed by continuous loratadine therapy (10 mg, p.o., qd) after discharge. This regimen controlled the patient’s symptoms (Figure 4e) and substantially improved his quality of life. In addition, this treatment strategy resulted in stable disease for 2.5 months (Figure 5). Ultimately, the patient died of other complications of disease progression.

Written consent for publication of this study was obtained from the patient’s caregiver, and the study was approved by the Ethics Committee of Ruijin Hospital of Shanghai Jiaotong University (Shanghai, China).

| Positive markers | Negative markers |
|------------------|------------------|
| AE1/AE3          | CK20             |
| CK7              | P63              |
|                  | P40              |
|                  | PSA              |
|                  | TTF-1            |
|                  | CDX2             |
|                  | Villin           |
|                  | ER               |
|                  | PR               |
|                  | GATA             |
|                  | muc2             |
|                  | muc5AC           |

Figure 3. Submandibular contrast-enhanced computed tomography (a), T1-weighted magnetic resonance imaging (b), and T1-weighted magnetic resonance imaging (c) revealed a thickened and enhanced soft tissue mass on the left side of the neck after three cycles of paclitaxel/cisplatin chemotherapy. Enhanced computed tomography before radiotherapy (d) and after radiotherapy and three cycles of paclitaxel monotherapy (e) revealed disease progression.
Discussion

Sorafenib has been approved by the FDA for the treatment of liver, thyroid, and kidney cancers. Sorafenib exhibits broad oral antitumor efficacy across various cancers. In metastatic adenocarcinoma, several phase II placebo-controlled clinical trials evaluated the efficacy, safety, and tolerability of sorafenib in combination with chemotherapy. The GEMSO study (NCT00661830) evaluated the combination of gemcitabine and sorafenib as a first-line palliative therapy in 102 patients with chemotherapy-naïve advanced or metastatic biliary tract adenocarcinoma (BTC). The results demonstrated that although the addition of sorafenib to gemcitabine did not improve progression-free survival (PFS) or overall survival (OS) versus gemcitabine alone, patients with liver metastasis after resection of primary BTC who received the combination regimen displayed longer survival than those treated with placebo ($P = 0.019$). Common adverse events caused by sorafenib include rash, diarrhea, elevated blood pressure, and redness, pain, swelling, or blisters on the palm or foot. The most common treatment-related adverse events are diarrhea, rash/scum, fatigue, skin reactions on the hands and feet, hair loss, nausea, vomiting, itching, high blood pressure, and loss of appetite. The risk–benefit ratio is acceptable in the context of an apparent clinical benefit in patients with fatal disease. Currently, the therapeutic options for patients with advanced previously treated cancer are limited, and sorafenib has produced promising results. In heavily pretreated patients with soft tissue sarcomas, the use of sorafenib resulted in a median time to disease progression of 45 days and acceptable toxicity. Similarly, sorafenib monotherapy was associated with tumor stabilization in patients with heavily pretreated high-grade glioma and median PFS of 3 months.
However, there are only limited data on sorafenib in the setting of heavily pretreated patients with recurrent disease.

CUP often presents with multiple clinical manifestations, and most patients have poor prognoses. In head and neck cancers and other than squamous cell carcinoma, the treatment outcomes are far from satisfactory. Several conventional chemotherapy regimens and novel targeted agents have been used in adenoid cystic carcinoma without success. A case report by Dammrich et al. described a case of adenoid cystic carcinoma with lung metastasis that was treated with sorafenib, observing stable disease for more than 6 months. To date, a few phase II clinical studies investigated the effectiveness of sorafenib against advanced salivary gland carcinoma. A study by Williamson et al. evaluated the efficacy and safety of single-agent sorafenib in chemotherapy-naïve patients with metastatic or recurrent squamous cell carcinoma of the head and neck reported a poor response rate of approximately 2%. Conversely, the PFS and OS of the therapy compared favorably with the findings of the Southwest Oncology Group study, and the drug was well tolerated. Another study by Thomson et al. involved 23 patients. Among the 19 patients with evaluable lesions, 68% (13/19) exhibited stable disease for more than 6 months. Research by Locati et al. reported a stable

**Figure 4.** Facial swelling 2 days before sorafenib treatment (a) and 2 days after the start of treatment (b). Complete resolution of swelling 1 week after the start of sorafenib treatment (c). Facial edema 10 days after the start of sorafenib treatment (d) and relief (e) after the intervention.
disease of 59% (22/37), and 50% of patients exhibited stable disease for >6 months. In Thomson’s study, sorafenib was reasonably well tolerated, and 13 patients (57%) experienced grade 3 toxicity, exceeding the rates observed in previous trials of sorafenib in renal cell carcinoma and hepatocellular carcinoma and a phase II study of patients with head and neck squamous cell carcinoma.15–17 In Locati’s study, 11 patients (29.7%) experienced grade 3 or higher toxicity, and the toxicity was in line with other studies of sorafenib.14

The rarity, variety of histological types, unknown primary sites and patterns of metastases, and course of the disease explain the difficulty in accumulating sufficient data and information about heavily treated patients with CUP. Often, there is not sufficient evidence to support treatment decisions. In this case study, the therapeutic process indicated that the treatment of this chemotherapy-resistant tumor might require simultaneous inhibition or blockade of multiple oncogenic pathways. More research must be conducted in this particular population to identify the mechanisms of tumorigenesis that may be induced in this malignancy to identify potential targets for therapeutic development. To identify risks, molecular profiling of genomic analysis can provide targeted drug information based on candidate drive gene amplification and mutation. Mild toxicity or drug-related side effects were observed during treatment. Therefore, sorafenib may be a new treatment option for advanced head and neck tumors with VEGFR mutations. However, clinical trials are needed to confirm its effectiveness and safety.

Conclusion
In the MDT setting, individual genomic findings may be integrated into patient care, permitting the creation of tailored treatment plans for patients with advanced cancer. Genomic technology, molecular targeted therapy, and molecular profiling can provide target drug information based on candidate driver gene amplification and mutation. Sorafenib may be applied in patients with advanced head and neck adenocarcinoma and evident VEGFR mutations detected via NGS; however, some unforeseen side effects and uncertain clinical outcomes illustrated the need for more data for clarification. Our experience

Figure 5. Stable disease on computed tomography (a), T1-weighted magnetic resonance imaging (b), and T2-weighted magnetic resonance imaging (c).
indicates that a MDT of clinicians and genomic sequencing can create a paradigm in which genetically based treatment is integrated into the care of patients with late-stage cancer. In conclusion, the efficacy and safety of sorafenib in patients with advanced head and neck adenocarcinoma should be further evaluated in a large prospective study.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

Funding
This research was financially supported by the Famous Chinese Medicine Academic Research Studio of Shanghai (No. SHGZS-20170111) to Xiaoheng Shen and Shanghai Science and Technology Committee Scientific Research (19401971100) to Jingxian Chen.

ORCID iD
Lan Zheng https://orcid.org/0000-0003-4393-9264

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