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Successful treatment switch from lenvatinib to sorafenib in a patient with radioactive iodine-refractory differentiated thyroid cancer intolerant to lenvatinib due to severe proteinuria

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ABSTRACT

Sorafenib and lenvatinib showed efficacy for patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) in pivotal phase 3 clinical trials. Although the efficacy of lenvatinib in patients who received previous treatment with multi-target kinase inhibitors (m-TKIs), including sorafenib, was reported, the efficacy of sorafenib in patients who previously received lenvatinib remains unknown. A 75-year-old woman diagnosed as RAI-refractory poorly differentiated carcinoma with multiple lung metastases and started treatment with lenvatinib. She continued to receive lenvatinib but with repeated dose interruptions and reductions due to continuous proteinuria. Because of severe and persistent proteinuria as well as newly developed renal impairment, lenvatinib was suspended after two years of treatment. After the 7-month suspension, her proteinuria and renal impairment were partially improved, but her lung metastases progressed. Because she was unable to tolerate previous treatment with lenvatinib, sorafenib was started. At 7 months of treatment with sorafenib, her lung metastases shrank and she could continue sorafenib without exacerbation of proteinuria or renal impairment. This case may suggest that sorafenib does not exacerbate the proteinuria or renal impairment induced by lenvatinib, and may be an effective treatment option for RAI-refractory DTC patients who are unable to tolerate lenvatinib.

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1. Introduction

Advanced differentiated thyroid cancer (DTC) can be treated with surgery followed by radioactive iodine (RAI) therapy and thyroid stimulating hormone (TSH) suppression. However, about 5% of patients develop distant metastasis and become refractory to RAI therapy [1]. Sorafenib is an oral multi-target tyrosine kinase inhibitor (m-TKI) of the vascular endothelial growth factor receptor (VEGFR) 1-3, RET, Raf-1, and platelet-derived growth factor receptor (PDGFR) β [2]. Lenvatinib is also an oral m-TKI of the VEGFR 1-3, fibroblast growth factor receptor (FGFR) 1-4, PDGFR α, RET, and KIT [3]. Both sorafenib and lenvatinib significantly improved progression-free survival (PFS) compared to placebo in patients with RAI-refractory DTC, including poorly differentiated carcinoma, in two pivotal phase 3 clinical trials, DECISION and SELECT [4,5]. In the SELECT trial, this PFS benefit with lenvatinib was also observed in patients who had received a prior TKI, including sorafenib. However, the efficacy of sorafenib in patients who had received lenvatinib remains unknown. Both lenvatinib and sorafenib are m-TKIs, which mainly inhibit the VEGF pathway, and induce various adverse effects. Hypertension and proteinuria are well-known class-effects of VEGF-targeted therapy. Regarding lenvatinib, hypertension is usually manageable with anti-hypertensive agents, but proteinuria is often difficult to manage and sometimes causes renal impairment despite appropriate supportive care.

Here, we report a case of RAI refractory (RR) poorly differentiated thyroid carcinoma patient successfully treated with sorafenib without exacerbation of proteinuria that precluded continuation of lenvatinib treatment.

2. Case report

A 75-year-old woman was diagnosed with thyroid cancer with multiple lung metastases. Histological examination revealed that poorly differentiated carcinoma associated with papillary carcinoma component (Fig. 1A, B). After total thyroidectomy and neck dissection, she received RAI therapy for lung metastases up to a cumulative iodine-131 activity of 450 mCi. At 6 months after the last RAI treatment, her lung metastases showed progression on a chest computed tomography (CT). She started lenvatinib at a dose of 24 mg/day as part of a phase II clinical trial for RR-DTC. On day 15, lenvatinib treatment was interrupted because of proteinuria, with quantitative urine protein of 810 mg/day (normal range, 20–120 mg/day). On day 22, the proteinuria was resolved, and lenvatinib was restarted at a dose of 20 mg/day. Despite the dose reduction to 20 mg/day, repeated dose interruptions and reductions of lenvatinib were required due to the severity of her continuing proteinuria. On day 57, lenvatinib at a dose of 10 mg/day was interrupted because of quantitative urine protein of 2680 mg/day. After a week, quantitative urine protein was partially reduced to 1390 mg/day, and lenvatinib was restarted at the same dose. On day 127, lenvatinib was finally reduced to a dose of 8 mg/day because of persistent proteinuria, at which time her lung metastases were noted to have shrunk.

This response was maintained for two years (Fig. 2A, B) and serum thyroglobulin (Tg) remained stable at around 400 ng/mL (normal range, <33.7 ng/mL) without detection of anti-Tg antibody in her whole treatment course of lenvatinib. However, despite repetitive dose interruptions of lenvatinib, severe and prolonged proteinuria continued; quantitative urine protein was 2970 mg/day. At the time of treatment suspension, her urine protein to creatinine ratio (UPCR) was 6.61 g/g Cr (normal range, <0.15 g/g Cr) and renal impairment had newly appeared, and serum creatinine (sCr) was elevated from 0.58 mg/dL before treatment to 1.15 mg/dL (normal range, 0.47–0.79 mg/dL), and eGFR decreased from 75.6 mL/min/1.73 m^2 before treatment to 45.1 mL/min/1.73 m^2 (normal range, >60.0 mL/min/1.73 m^2). After suspension of lenvatinib for 7 months, her proteinuria and renal impairment had partially recovered, with UPCR of 0.85 g/g Cr, sCr of 0.97 mg/dL and eGFR of 42.5 mL/min/1.73 m^2, but her lung metastases showed progression on chest CT (Fig. 2C) and serum Tg level was elevated to 4897 ng/mL. We assessed that she was unable to tolerate lenvatinib because of persistent proteinuria during her whole treatment course of lenvatinib and prolonged proteinuria despite of over half-year suspension of lenvatinib. Therefore, we decided to switch to sorafenib at dose of 800 mg/day. At 7 months after the initiation of sorafenib, her lung metastases had shrunk on chest CT (Fig. 2D) and serum Tg level had decreased at 1443 ng/mL, and she was able to continue sorafenib without exacerbation of proteinuria or renal insufficiency (Fig. 3).

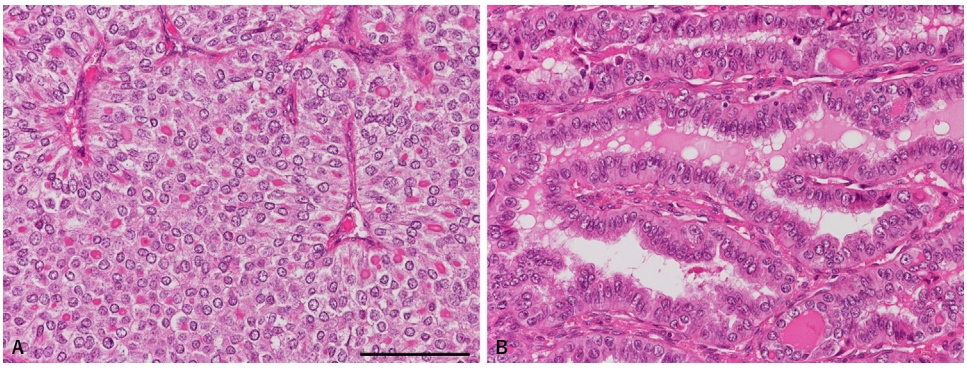

Fig. 1. Microscopic findings of surgical specimens of total thyroidectomy. Component of poorly differentiated carcinoma (A) and papillary carcinoma (B). The scale bar indicates 100 μm.

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