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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

Hideaki Goto[1)], Naomi Kiyota[1)2)], Naoki Otsuki[3)], Yoshinori Imamura[1)], Naoko Chayahara[1)], Hirotaka Suto[1)], Yoshiaki Nagatani[1)], Masanori Toyoda[1)], Toru Mukohara[1)], Ken-ichi Nibu[3)], Toshihiko Kasahara[4)], Yasuhiro Ito[5)], Akihiro Miya[5)], Mitsuyoshi Hirokawa[6)], Akira Miyauchi[5)] and Hironobu Minami[1)2)]

1) Division of Medical Oncology/Hematology, Department of Medicine, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
2) Kobe University Hospital Cancer Center, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
3) Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
4) Department of Internal Medicine, Kuma Hospital, 8-2-35, Shimoyamate-dori, Chuo-ku, Kobe 650-0011, Japan
5) Department of Surgery, Kuma Hospital, 8-2-35, Shimoyamate-dori, Chuo-ku, Kobe 650-0011, Japan
6) Department of Diagnostic Pathology, Kuma Hospital, 8-2-35, Shimoyamate-dori, Chuo-ku, Kobe 650-0011, Japan

Corresponding author

Naomi Kiyota, M.D., Ph.D.

Department of Medical Oncology/Hematology and Cancer Center, Kobe University Hospital, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan

E-mail: nkiyota@med.kobe-u.ac.jp

Phone: +81-78-382-5820

Fax: +81-78-382-5821

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.

Key words

radioactive iodine-refractory differentiated thyroid cancer, lenvatinib, sorafenib, proteinuria, renal impairment

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.

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 2,680 mg/day. After a week, quantitative urine protein was partially reduced to 1,390 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 2,970 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/1.73m^2 before treatment to 45.1 ml/min/1.73m^2 (normal range, > 60.0 ml/min/1.73m^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/1.73m^2, but her lung metastases showed progression on chest CT (Fig. 2C) and serum Tg level was elevated to 4,897 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 1,443 ng/mL, and she was able to continue sorafenib without exacerbation of proteinuria or renal insufficiency (Fig. 3).

Informed Consent

This patient was provided written informed consent for the treatment as well as this report. The Research Ethics Board approved this report (permission number: 1481).

Discussion

We identified two important clinical suggestions from this case. First, sorafenib can be safely prescribed without exacerbation of proteinuria and renal impairment in patients who experienced severe proteinuria during prior treatment with lenvatinib. Second, sorafenib may be effective in RAI-refractory patients who are intolerant to lenvatinib.

Proteinuria is a well-known class effect of VEGF-targeted therapy. Podocytes

constitute an important component of the filtration barrier of renal glomeruli, and express VEGF, which activates VEGFR-2 on glomerular capillary endothelial cells and maintains the normal filtration barrier [6]. VEGFR-TKIs are considered more likely to induce podocytopathies such as minimal change disease and/or collapsing-like focal segmental glomerulosclerosis than endothelial damage like renal thrombotic microangiopathy [6]. No patient in the DECISION trial, a phase 3 clinical trial of sorafenib for patients with RR-DTC, developed proteinuria [4]. In the SELECT trial, in contrast, lenvatinib induced proteinuria of any grade in 31% and of grade 3 or higher in 10%. Incidence was higher in the Japanese subset, at 63% and 31%, respectively [5, 7]. As described in the Introduction, the target molecules of sorafenib and lenvatinib differ slightly, although their main targets are both VEGFR. In addition, based on 50% inhibitory concentrations (IC50) of lenvatinib for VEGF-R 1-3, lenvatinib is a much more potent inhibitor of the VEGF pathway than sorafenib [8]. These factors may explain the difference in the incidence and severity of proteinuria between sorafenib and lenvatinib. A switch from lenvatinib to sorafenib may be an effective management strategy in cases with continuous proteinuria and renal impairment despite dose reduction and interruption of lenvatinib. In our patient, lenvatinib caused severe proteinuria after 2 months from treatment initiation, and she was finally unable to tolerate to lenvatinib. Although sorafenib was started after the discontinuation of lenvatinib due to severe and persistent proteinuria, she was able to continue sorafenib without exacerbation of proteinuria for 7 months.

In the SELECT trial, lenvatinib showed an improvement in median PFS in patients with RR-DTC compared to placebo. This PFS benefit with lenvatinib was also observed in patients who had received a prior TKI, including sorafenib [5]. However, the efficacy of sorafenib in patients who had received lenvatinib remains unknown because sorafenib

was developed well before lenvatinib and other TKIs. A retrospective analysis reported that sorafenib did not induce a clinical response when used as second-line treatment for DTC, but that the median PFS of sorafenib in second-line treatment was similar to that in first-line treatment [9]. The growth and development of DTC is influenced by a number of molecular pathways, including VEGF, RET/PTC, BRAF, RAS, FGF, and MET [10-12]; given this, the fact that the various m-TKIs have different target molecule inhibitory profiles may offer a rationale for the treatment switching from one m-TKI to another. Indeed, the m-TKI cabozantinib, which inhibits c-MET, RET, and VEGFR, showed efficacy in patients with RR-DTC refractory to at least one prior VEGFR-targeted therapy [13]. Sequential treatment with m-TKIs has also shown efficacy in patients with metastatic renal cell cancer [14, 15]. Also in our present patient, sorafenib showed efficacy after she had received lenvatinib for about 3 years and she was unable to tolerate lenvatinib.

In conclusion, this case suggests that sorafenib can be safely administered without exacerbation of lenvatinib-induced proteinuria and renal impairment, and can show efficacy even after previous treatment with lenvatinib. Accordingly, a treatment switch from lenvatinib to sorafenib may be an effective treatment option in patients with RAI-refractory DTC patients unable to tolerate lenvatinib.

Disclosure Statement

Naomi Kiyota has received honoraria from Bayer C.C. and honoraria and a research grant from Eisai Inc.

Hironobu Minami has received a research grant from Bayer C.C.

The other authors declare no interests.

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Figure Legends

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.

Fig. 2. Axial sections of the lung on chest computed tomography (CT) scans

Before treatment of lenvatinib (A); before suspension of lenvatinib (B); progression of pulmonary metastases after a 7-month suspension of lenvatinib (C); and objective response in pulmonary metastases 7 months after starting sorafenib (D).

Fig. 3. Time course of urine protein to creatinine ratio (UPCR) and thyroglobulin (Tg) values

LEN, lenvatinib; SOR, sorafenib.

Figure 1.

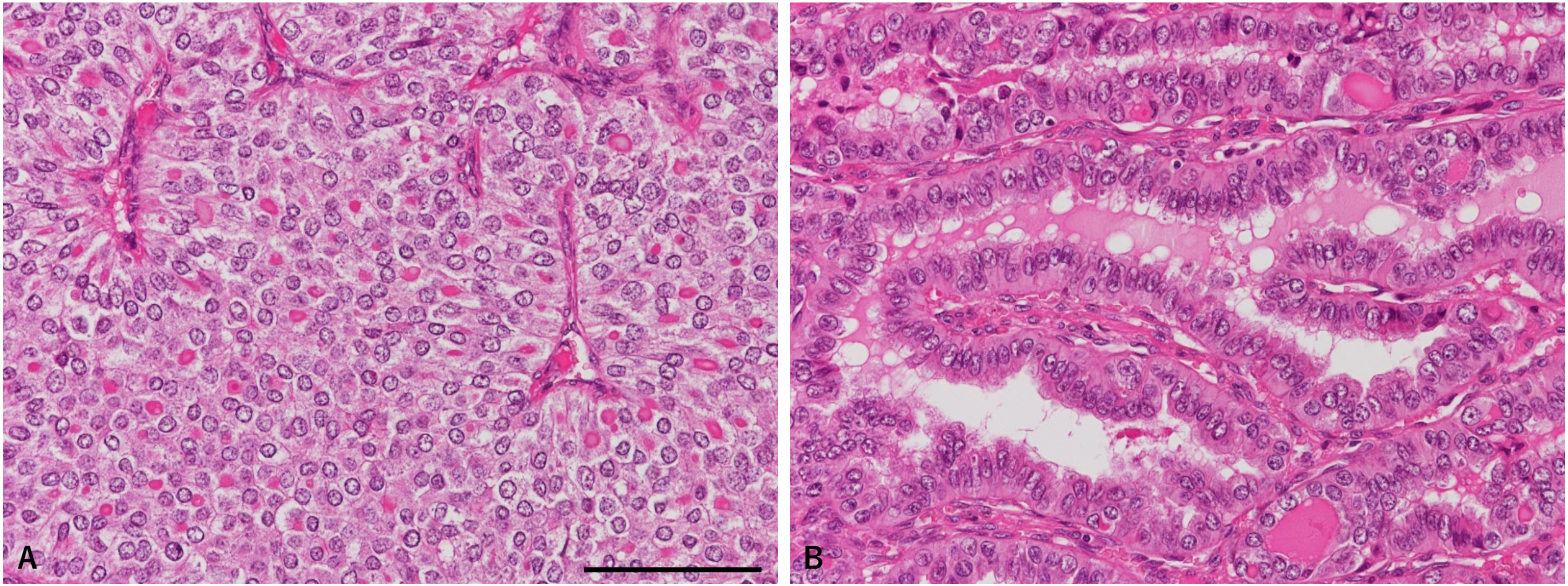

Figure 2.

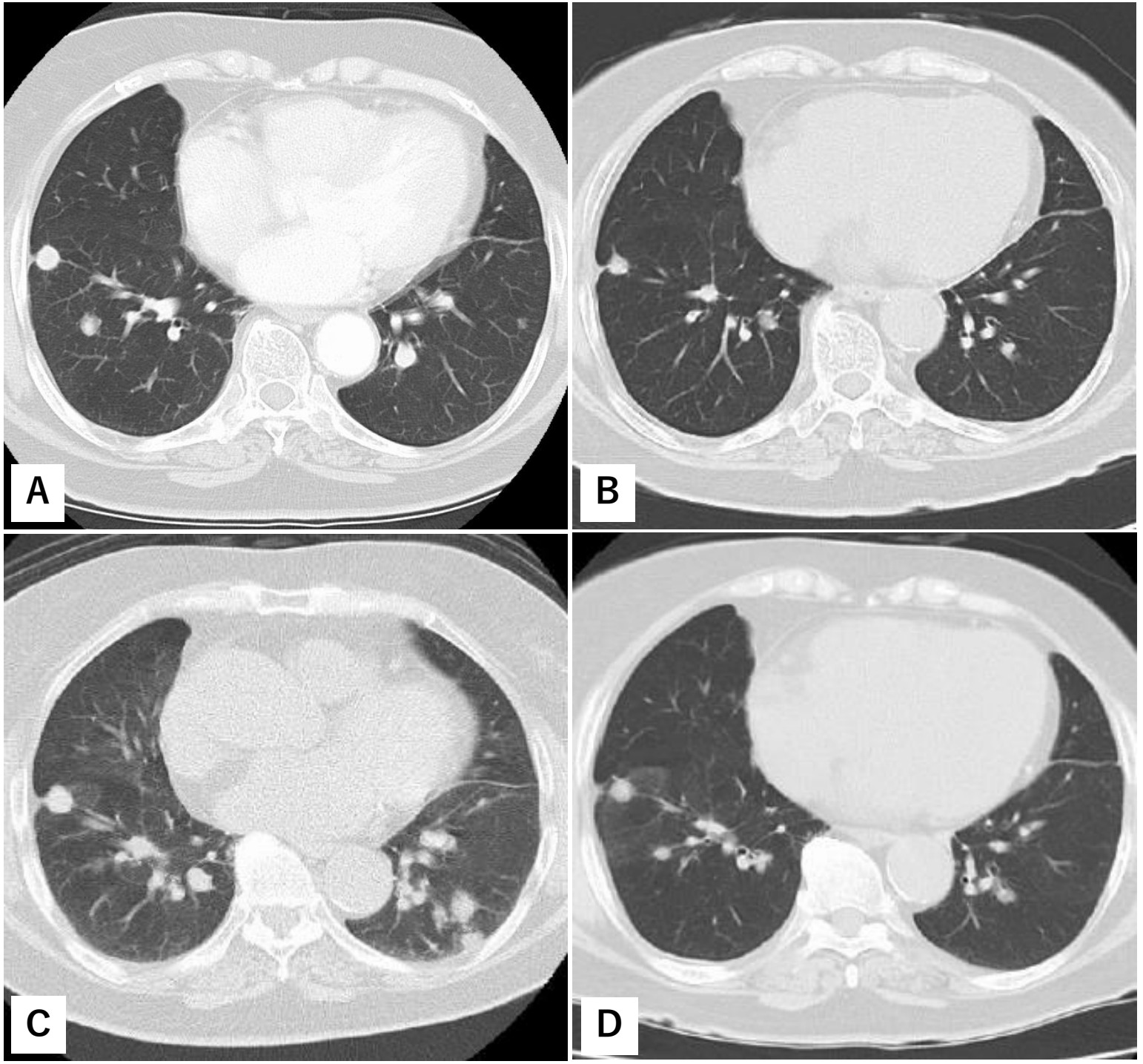

Figure 3.

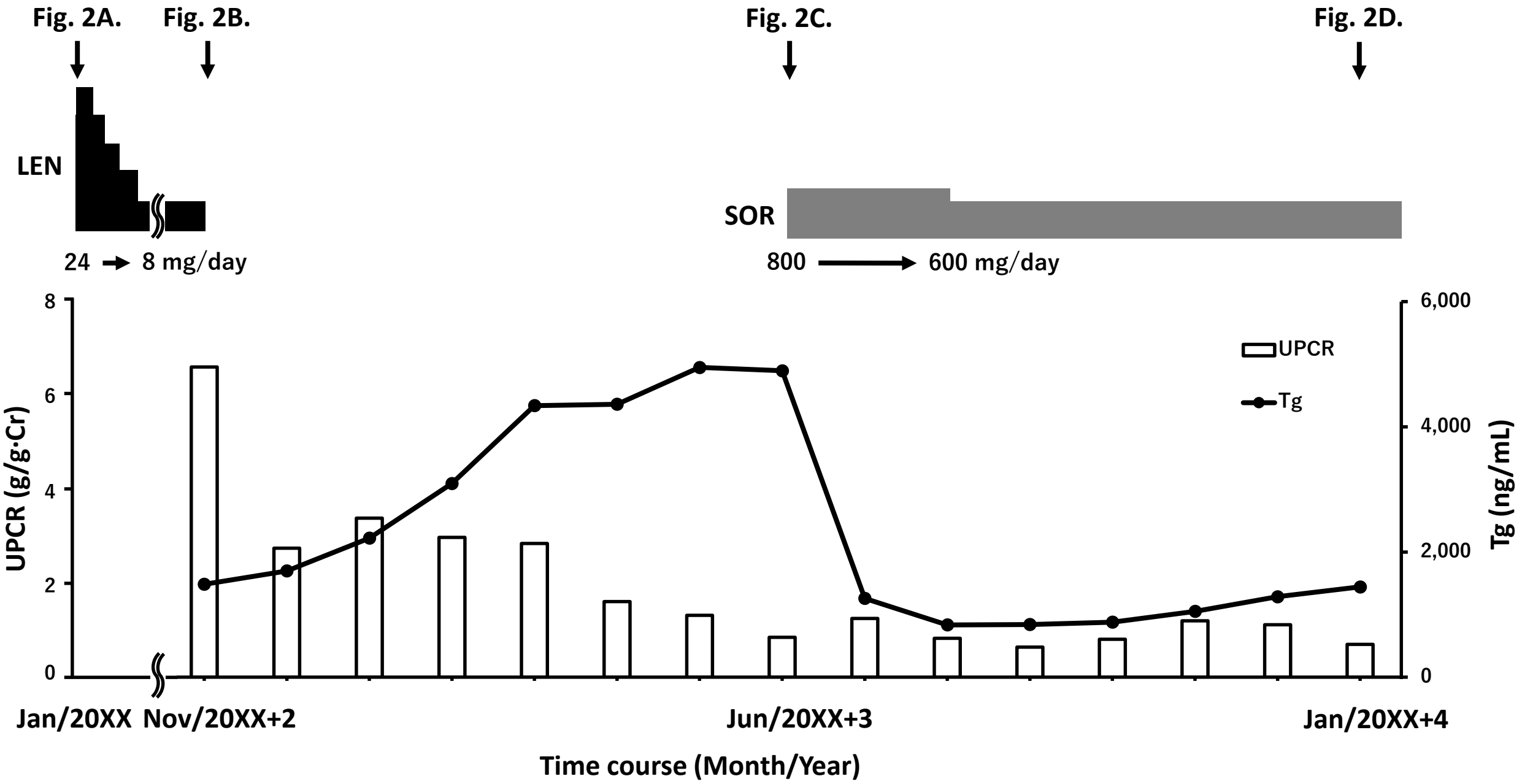
Fig. 2A.
Fig. 2B.
Fig. 2C.
Fig. 2D.
LEN
24 → 8 mg/day
SOR
800 → 600 mg/day
UPCR
Tg
UPCR (g/g·Cr)
Tg (ng/mL)
0
2
4
6
8
0
2,000
4,000
6,000
Jan/20XX
Nov/20XX+2
Jun/20XX+3
Jan/20XX+4
Time course (Month/Year)