中文題目：使用 Lenvatinib 治療甲狀腺乳突癌併發之皮膚黏膜廔管與顱內出血：案例報告

英文題目：Effective Lenvatinib Treatment Complicated with Secondary Mucocutaneous Fistula and
Intracranial hemorrhage in Patients with Advanced Thyroid Papillary Carcinoma

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Introduction:

The incidence of thyroid papillary cancer increased from 4.8 to 13.46 per 100,000 from 1975 to 2018 based upon the Surveillance, Epidemiology, and End Results (SEER) database[1]. Patients with thyroid papillary carcinoma have a relatively good prognosis,
with a 5 year-survival rate of 98.3%, however 30% of patient have disease recurrence. Although radioiodine ablation following thyroidectomy is standard treatment in metastatic differentiated thyroid cancer, about 25–50% of patients with locally advanced or metastatic disease become refractory to RAI therapy.[2]

Small-molecule tyrosine kinase inhibitors, including Vandetanib, Cabozantinib, Sorafenib, and Lenvatinib are now FDA-approved for thyroid cancer, have shown clinical benefit in advanced thyroid cancer. Lenvatinib targets including VEGFR1-3, FGFR1-4, PDGFR-alpha, RET and KIT proto-oncogenes, and is approved for locally recurrent or metastatic, progressive, radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). Recently, a retrospective study composed of 23 Japanese patients with thyroid cancer treated with Lenvatinib showed an incidence of 39.1% grade 3 or higher treatment-related adverse events [3]. Hypertension was the most common adverse effect (AE), while headache, gastrointestinal discomfort, rare complications such as tumor fistula, bleeding and carotid blowout syndrome were also described . Here we report a cases with T4aNxM0 thyroid papillary carcinoma complicated with mucocutaneous fistula and intracranial hemorrhage.

Case presentation:

A 50 year old woman was diagnosed with left thyroid papillary carcinoma, initial staging pT4aNxM0, stage I. She received total thyroidectomy with close margin(<1mm) and lymphadenectomy, following radioactive iodine-131 ablation therapy. Followed head and neck CT showed residual tumor and neck metastasis, extension to left internal jugular vein with thrombosis formation, rcT2N1b, and she received surgery with neck mass excision and selective neck dissection (level III, IV) and internal jugular vein ligation , following radioactive iodine-131 ablation therapy. After the surgery, partial encasement of the left proximal common carotid artery was noticed, stenting was performed in case of carotid blow-out syndrome because extensive necrosis surrounded the artery, on Aspirin after the procedure. However, followed PET scan showed local recurrence at left thyroid tumor bed(Figure 1). She then started on Lenvatinib 10 mg daily.

One month later, she experienced redness and pain over left anterior neck , dysphagia, odynophagia, easy choking, she could barely tolerate liquid diet. She presented to our emergency room for shortness of breath and chest tightness. Erythematous skin with tenderness at left anterior lower neck was noticed. Computed tomography (CT) studies revealed a localized air-filled cavity near left thyroid fossa, subcutaneous layer, and abutting anterior wall of the cervical esophagus, as well as mucocutaneous fistula formation (Figure 2). Esophageal diverticulum or focal perforation was also suspected. Lenvatinib was ceased because life-threatening adverse effects triggered by tumor shrinkage. Local wound debridement for abscess drainage was performed, which revealed tissue necrosis, leaving an non healing open wound for pus drainage(Figure 3). Percutaneous endoscopic gastrostomy was created for bypass oral feeding. The patient was stabilized with the breathing status and infection control after wound debride, antibiotics treatment, and PEG feeding.
Two month later, oral medication was shifted to Sorafinib for thyroid cancer treatment. For better control for left carotid stent stenosis, Cilosrazol was added with Aspirin. However, she was admitted again for spontaneous left frontal-occipital intracerebral hemorrhage (Figure 4) and sepsis related to left CCA septic necrotic tissue/emboli. She then received mechanical thrombectomy of left ICA occulusion and antibiotics treatment. Cancer treatment medications were discontinued because unwanted side effects mentioned above.

Discussion:

A Multicenter RCT trial of Lenvatinib in 2015[4] showed significant improvements in progression-free survival and the response rate of 64.8% among patients with iodine-131–refractory thyroid cancer. This study also demonstrated up to 75.9% patients reported grade 3 or higher AEs with the standard dose of 24mg Lenvatinib daily.
Despite reduced dose with 10mg daily, our patient still developed mucocutaneous fistula formation with poor wound healing and intracranial hemorrhage. Although Lenvatinib led to massive tumor necrosis and shrinkage, it then unfortunately resulted in
significant morbidities, including tracheal perforation and fistula formation.

Conclusion:

Regardless of the dose used, close monitoring of clinical symptoms, signs and regular imaging follow up will be helpful to minimize risks of rapid tumor shrinkage leading to AEs. Physicians should be aware of this potentially high-risk treatment and closely monitor the clinical status of patients treated with Lenvatinib.

References:

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