Original Paper: Clinical Thyroidology

Lenvatinib for anaplastic thyroid cancer and lenvatinib-induced thyroid dysfunction

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Key words

Lenvatinib, Anaplastic thyroid cancer, Chemotherapy, Hypothyroidism, Tyrosine kinase inhibitor

Abstract

Background: Lenvatinib is an oral multitargeted tyrosine kinase inhibitor that has an anticancer action in patients with differentiated thyroid cancer that is refractory to radioiodine. Knowledge of the efficacy and safety of lenvatinib in patients with anaplastic thyroid cancer (ATC) is limited. Tyrosine kinase inhibitors frequently cause hypothyroidism; the incidence of hypothyroidism with lenvatinib is unclear.

Objectives: We conducted a retrospective study to investigate the efficacy and safety of lenvatinib in ATC.

Methods: Five patients with unresectable ATC were enrolled. Lenvatinib 24 mg once daily was administered until disease progression, unmanageable toxicity, withdrawal, or death occurred. We retrospectively analyzed objective response rate (ORR), time to progression (TTP), overall survival, and safety.

Results: Three of the five patients (60%) had a partial response, and two (40%) had stable disease. ORR was 60%. Median TTP was 88 days, and overall survival was 165 days. Hypothyroidism was a common treatment-related adverse effect; four patients (80%) had

hypothyroidism of any grade. These four patients had not undergone total thyroidectomy prior to lenvatinib administration, and the other patient had undergone total thyroidectomy. Treatment-related adverse effects of any grade were hypertension in 80% of patients, diarrhea in 40%, fatigue in 80%, and decreased appetite in 80%.

Conclusions: Lenvatinib is an effective treatment and may improve the prognosis of unresectable ATC. Four of five patients had hypothyroidism, which may have been associated with treatment-induced injury of the thyroid gland. There were many treatment-related adverse effects, most of which were manageable by dose modification and medical therapy.

Introduction

Anaplastic thyroid cancer (ATC) is one of the most aggressive cancers, and death usually occurs within a few months after diagnosis [1]. Surgery is the most effective treatment to improve the prognosis [2-4]; however, most cases cannot be managed because of locally extensive disease or distant metastases at the initial diagnosis. Current chemotherapies have limited efficacy and cannot demonstrate a significant increase in overall survival [5]. Thus, new therapeutic strategies are required to improve the prognosis.

Lenvatinib is an oral tyrosine kinase inhibitor targeting VEGFR1-3, FGFR1-4, RET, KIT. and PDGFRβ [6-8]. It was associated with a marked improvement in progression-free survival in patients with radioiodine-refractory differentiated thyroid cancer [9]. Lenvatinib also has the possibility of improving disease control and prognosis in ATC [10, 11]. However, the efficacy and safety of ATC have not been sufficiently considered. In Japan, lenvatinib has already been approved for the treatment of unresectable ATC since 2015; therefore, we could use lenvatinib to treat patients with ATC.

Tyrosine kinase inhibitors frequently present several specific adverse effects, such as fatigue, diarrhea, rash, and endocrine-related disorder [12, 13]. Treatment-related hypothyroidism is a major adverse effect of other tyrosine kinase inhibitors [14]. The reported rates of

hypothyroidism range from 53% to 85% for sunitinib, 20% to 36% for sorafenib, and 10% to 29% for pazopanib [14]. Treatment-related hypothyroidism from lenvatinib for thyroid cancer has been rarely reported; most patients undergo total thyroidectomy prior to lenvatinib treatment [10]. Therefore, treatment-related hypothyroidism from lenvatinib for untreated thyroid cancer has never been discussed.

Patients and Methods

Between June 2015 and December 2016, five patients diagnosed with unresectable ATC were enrolled in this study. The pathological diagnosis was determined by a pathologist from fine-needle aspiration cytology. Liquid-based cytology and cell block cytology techniques were combined with the conventional technique. Only case 5 was histologically diagnosed using lymph node biopsy because of the insufficient information from fine-needle aspiration cytology. Lenvatinib 24 mg once daily was administered until disease progression, unmanageable toxicity, withdrawal, or death occurred. Dose modification was performed based on the adverse reaction management guideline on the lenvatinib website. The management of treatment-related adverse effects was performed with the cooperation of a medical oncologist. We retrospectively analyzed objective response rate (ORR), time to progression (TTP), overall survival, and safety. ORR was evaluated based on the Response Evaluation Criteria in Solid Tumor version 1.1 with computed tomography. Radiological

evaluation was first performed 4–8 weeks after the first administration of lenvatinib and repeated every 4–8 weeks thereafter. Safety of the treatment was evaluated based on the Common Terminology Criteria for Adverse events, version 4.0.

The protocol of the investigation was approved by the Institutional Review Board of Tottori University Hospital (No. 1706A061).

Results

Five male patients with a mean age of 58.8 years were enrolled in this study (Table 1). Four patients were newly diagnosed with de novo ATC, and the other patient experienced anaplastic transformation from poorly differentiated thyroid cancer. The four de novo ATC patients had received no treatment prior to lenvatinib; the remaining patient (case 2) had undergone total thyroidectomy and radioactive iodine treatment prior to receiving lenvatinib. The four patients except case 1 were diagnosed with unilateral recurrent laryngeal nerve paralysis, and unilateral recurrent laryngeal nerve were resected at initial surgery in case 2. Case 5 was first diagnosed as unknown primary squamous cell carcinoma by cervical lymph node biopsy and was treated with two cycles of cetuximab, cisplatin, and 5-fluorouracil. Subsequently, a biopsy specimen from the thyroid revealed ATC with squamous cell and papillary cell carcinoma.

Three of the five patients (60%) had a partial response, and two (40%) had stable disease; therefore, the ORR was 60% (Figure 1). Clinical benefit rate was 100%. Case 1 showed remarkable tumor reduction at 4 and 12 weeks post-lenvatinib treatment compared with baseline (Figure 2). The median TTP was 88 days, and the median overall survival was 165 days. One patient continued over 6 months of treatment with lenvatinib because of a continued partial response. Two patients who presented unilateral recurrent laryngeal paralysis at the diagnosis developed bilateral recurrent laryngeal paralysis. However tracheostomy was performed only in case 5 due to tracheal obstruction by the tumor. Hypothyroidism was a common treatment-related adverse effect; four patients (80%) had hypothyroidism of any grade within 4 weeks after the initiation of lenvatinib (Figure 1). These four patients had not undergone total thyroidectomy, and the thyroid organ was preserved during lenvatinib administration. The treatment-related adverse effects of any grade were hypertension in 80% of patients, hand-foot syndrome in 20%, diarrhea in 40%, fatigue in 80%, decreased appetite in 80%, proteinuria in 100%, and weight loss in 80% (Table 2). There was no discontinuation of treatment due to adverse effects of lenvatinib. Adverse effects were manageable by dose modification, temporary treatment interruption, and addition of therapeutic medication. The clinical course of case 1 is shown in Figure 3.

Discussion

Treatment efficacy of lenvatinib for ATC has been reported in only one phase 2 study, which reported an ORR of 24% [10]. A high ORR was seen in the present study, indicating that lenvatinib is an effective treatment for ATC. The difference in ORR during the two studies might have resulted from the patient characteristics, especially in a previous treatment prior to lenavtinib. In the previous study, most patients received multiple treatments with surgery, chemotherapy, and radiotherapy prior to lenvatinib, which might have induced acquired resistance to chemotherapy [15]. Median TTP was 88 days, which is slightly higher than that with the use of other drugs (i.e., less than 2 months) [16, 17]. Median survival of ATC was reported to be 147 days for Stage IVB and 81 days for Stage IVC [1]. In the study, median overall survival was 168 days; therefore, lenvatinib may show promise to potentially extend survival. Most patients with ATC present at a very advanced stage, with a high-volume tumor invading the surrounding organs and resulting in several symptoms, such as neck pain, neck stiffness, airway obstruction, hoarseness, and dysphagia [18]. Tracheotomy should be considered carefully because tracheotomy for patients with unserectable ATC impairs their quality of life because of tumor plugging, erosion, and bleeding [19]. The incidence of tracheotomy reached 30% of patients with ATC [20]. In the present study, only one patient (20%) underwent tracheostomy due to airway obstruction by the tumor. Therefore, lenvatinib may improve quality of life of patients with ATC by controlling tumor growth and avoiding

tracheotomy.

The adverse effect profiles were similar to those in previous studies of lenvatinib [9, 10]. Most of the patients presented with hypertension, diarrhea, fatigue, decreased appetite, and proteinuria of any grade. However, adverse effects were manageable by dose modification, temporary interruption of treatment, and addition of therapeutic medication. A major difference between the present study and previous studies regarding adverse effects is that 80% of the patients had hypothyroidism. In previous studies, most patients had undergone total thyroidectomy prior to participation, and thyroid hormone was replaced by oral levothyroxine [9, 10]. In the present study, the four patients who presented with hypothyroidism had not received any treatment prior to lenvatinib, and the thyroid organ was preserved as it was. Several studies reported that tyrosine kinase inhibitors induce hypothyroidism through various mechanisms, such as destructive thyroiditis and tissue ischemia [14, 21]. In this study, the difference in thyroid gland integrity may have resulted from treatment-related hypothyroidism, which was induced by the mechanisms mentioned above. Hypothyroidism was observed within 4 weeks after the initiation of lenvatinib, and therefore we should frequently examine thyroid function in the early period after the initiation of lenvatinib.

Lenvatinib is an effective treatment for ATC and may show promises to potentially improve the prognosis; however, overlooked hypothyroidism might decrease the quality of life. Therefore, the physician should pay attention to treatment-related hypothyroidism if the patient has a residual thyroid organ.

Conclusions

Lenvatinib is an effective treatment for ATC and may improve the prognosis of unresectable ATC. Four of five patients had hypothyroidism, which may have been associated with treatment-induced injury of the thyroid gland. The patients had many treatment-related adverse effects, most of which were manageable by dose modification and medical therapy.

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Figure legends

Figure 1. Time to progression, treatment response, survival, and time to hypothyroidism of the patients.

Figure 2. Representative treatment response of case 1. Treatment with lenvatinib revealed remarkable tumor reduction 4 and 12 weeks after lenvatinib initiation compared with baseline.

Figure 3. Clinical course of adverse effects in case 1. Grade 2 hypothyroidism was observed 2 weeks after lenvatinib initiation. Medication with levothyroxine was effective to control thyroid function.

Table 1. Patient characteristics

PDC, poorly differentiated thyroid cancer; TTX, total thyroidectomy; C-mab; cetuximab; FP, CDDP + 5FU.

Table 2. Treatment-related adverse effects in each patient

Fig. 1.

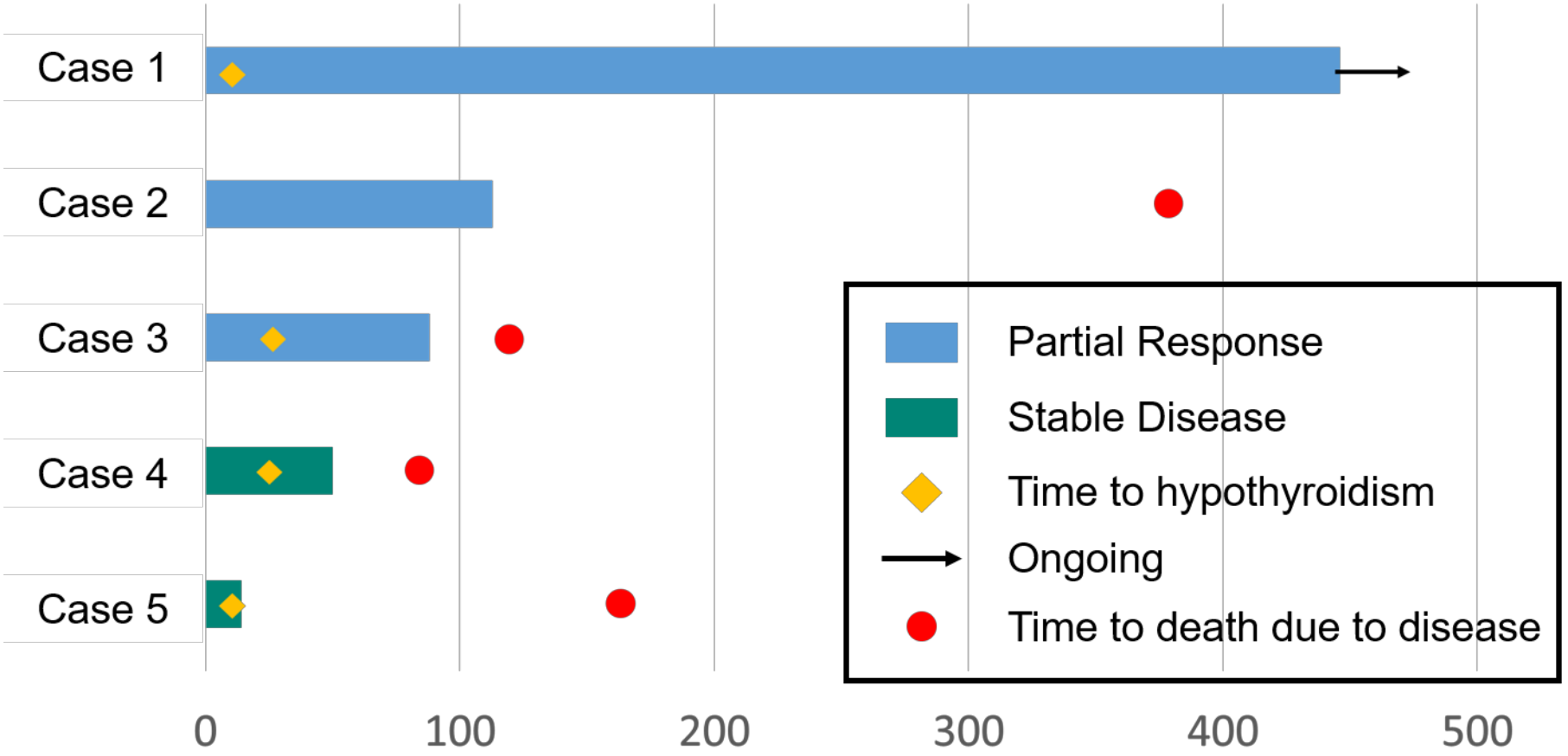
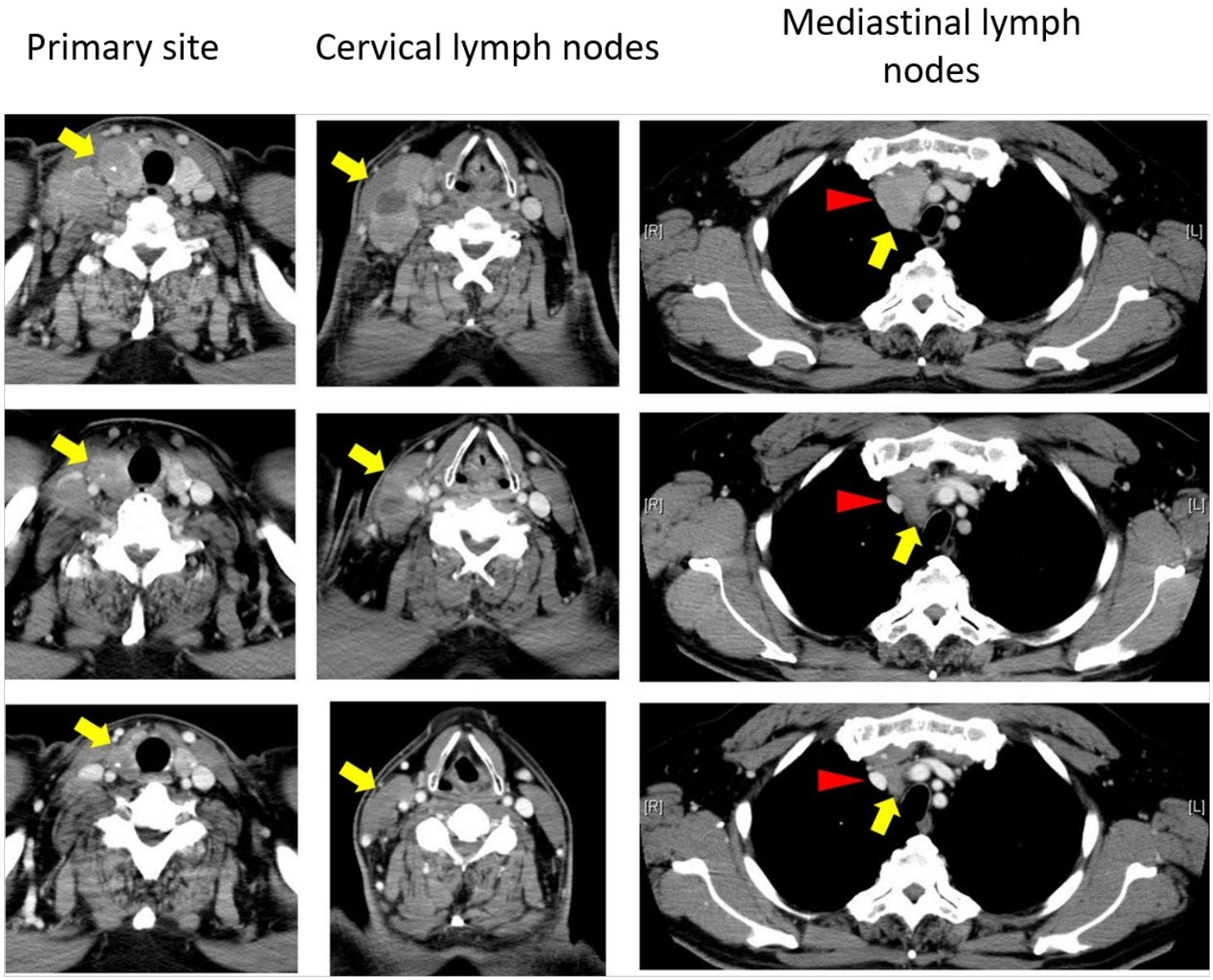

Case 1
Case 2
Case 3
Case 4
Case 5
0
100
200
300
400
500
Partial Response
Stable Disease
Time to hypothyroidism
Ongoing
Time to death due to disease

Fig. 2.



Yellow arrow, tumor sites; Red arrowhead, tumor invasion to brachiocephalic artery

Fig. 3.

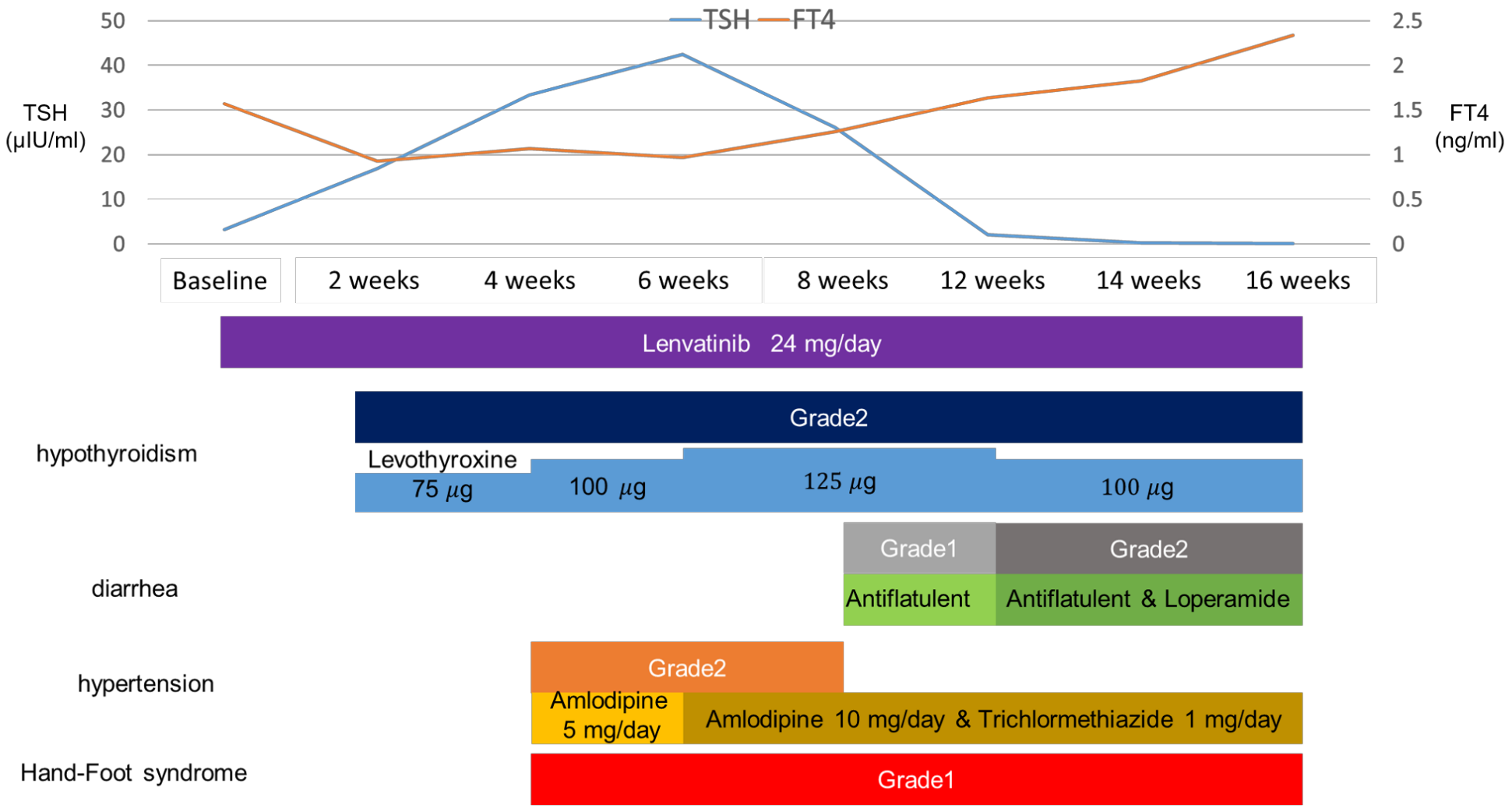

TSH
FT4
50
40
30
20
10
0
TSH (μIU/ml)
2.5
2
1.5
1
0.5
0
FT4 (ng/ml)
Baseline
2 weeks
4 weeks
6 weeks
8 weeks
12 weeks
14 weeks
16 weeks
Lenvatinib 24 mg/day
hypothyroidism
Grade2
Levothyroxine
75 μg
100 μg
125 μg
100 μg
diarrhea
Grade1
Grade2
Antiflatulent
Antiflatulent & Loperamide
hypertension
Grade2
Amlodipine 5 mg/day
Amlodipine 10 mg/day & Trichlormethiazide 1 mg/day
Hand-Foot syndrome
Grade1

Table 1

Case no.	Age/sex	Presenting symptom	Unilateral recurrent laryngeal nerve paralysis	Thyroid function TSH (μIU/ml)/FT4 (ng/ml)	de novo	Stage at diagnosis	ECOG PS	Previous Treatment			Tracheotomy
								Surgery	Chemotherapy	Radioactive Iodine	
1	58/M	Dysphagia and neck mass	No	Euthyroid 3.17/1.57	Yes	IVB	0	None	None	None	No
2	69/M	Aggressive metastases	Yes	Euthyroid (levothyroxine) 0.802/1.94	No (anaplastic change of PDC)	IVC	0	TTX	None	6 cycles	No
3	61/M	Neck mass	Yes	Euthyroid 0.79/1.43	Yes	IVC	0	None	None	None	No
4	51/M	Hoarseness	Yes	Euthyroid 1.82/1.01	Yes	IVC	0	None	None	None	No
5	50/M	Hoarseness and pharyngeal pain	Yes	Euthyroid 2.18/1.19	Yes	IVC	0	None	C-mab+FP	None	Yes

Table 2

	Case number				
	1	2	3	4	5
Hypothyroidism	Grade 2		Grade 2	Grade 2	Grade 2
Hypertension	Grade 2	Grade1		Grade 1	Grade 2
Hand Foot syndrome	Grade 1				
Diarrhea	Grade 3				
Fatigue	Grade 3	Grade 2	Grade 2		Grade 1
Anorexia	Grade 3	Grade 2	Grade 3		Grade 1
Proteinuria	Grade 2	Grade 1	Grade 1	Grade 1	Grade 1
Weight loss	Grade 3	Grade 2	Grade 2	Grade 3	