Advances in lenvatinib monotherapy and combination therapies in anaplastic thyroid cancer (Review)

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Abstract. Anaplastic thyroid cancer (ATC) is a highly malignant and aggressive endocrine tumor with the poorest prognosis among all thyroid cancer (TC) subtypes. Although ATC is extremely rare, treatment remains a notable challenge, as traditional therapies have exhibited very limited efficacy. Targeted small-molecule inhibitors that disrupt molecular signaling pathways offer a potential therapeutic approach for patients with ATC. Lenvatinib, a tyrosine kinase inhibitor, has emerged as a promising therapeutic agent, which targets various factors involved in angiogenesis and tumor progression, including vascular endothelial growth factor receptor, platelet-derived growth factor receptor α, fibroblast growth factor receptor and mast/stem cell growth factor receptor. Preclinical and clinical trials have demonstrated the efficacy of lenvatinib, both as monotherapy and in combination with other targeted therapy, chemotherapy, immunotherapy, warranting a comprehensive review of these studies. However, lenvatinib monotherapy was associated with a high incidence of adverse events (including hypertension, anorexia and proteinuria) and certain limitations, particularly drug resistance, emphasizing the need for optimized therapeutic strategies. In the present review, the efficacy and safety of lenvatinib monotherapy and combination therapies in the treatment of ATC were examined. Furthermore, the feasibility and limitations of different combination therapies were analyzed and compared. The present review aimed to provide insights into potential lenvatinib-based regimens that could enhance survival outcomes and improve the quality of life for patients with ATC in the future.

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1. Introduction

Thyroid cancer (TC) is the most common type of malignant tumor in the endocrine system, which accounts for ~90% of all endocrine malignancies (1). Among the TC subtypes, anaplastic thyroid cancer (ATC) is extremely rare and represents only 1.7% of all TC cases (2). However, ATC is the most lethal TC subtype, with a high mortality rate (20-40%) and poor prognosis (3). The average survival time is ~6 months and the 1-year overall survival (OS) rate is only 20% (4), largely due to the high invasiveness and resistance to treatment (5). Clinically, ATC often presents with a rapidly enlarging neck mass, frequently accompanied by dysphagia, hoarseness, dyspnea and occasionally neck pain (6). Metastasis is observed in 50% of patients, with the lungs, brain and bones as the most common sites of distant spread (7).

The core pathogenesis of TC involves genetic and epigenetic alterations, which include gene mutations, amplifications, copy-number gains, aberrant methylation, gene translocations, decreased expression of the Na/I symporter and non-coding RNA imbalances (8). Key molecular pathways implicated in TC are the MAPK and PI3K-AKT pathways (Fig. 1). Mutations commonly involve oncogenes such as BRAF (~60%), Ras (~13%) and rearrangements of anaplastic lymphoma kinase, rearranged during transfection (RET) and neurotrophic tyrosine receptor kinase genes (~5%), as well as loss-of-function mutations in tumor suppressor genes, such as peroxisome proliferator-activated receptor γ, PTEN and TP53 (~10%) (9,10).

Notably, ATC displays distinct genetic profiles compared with differentiated TC (DTC). The prevalence of telomerase reverse transcriptase (TERT) promoter and TP53 mutations in ATC are markedly higher compared with mutations in BRAF and Ras, which are less frequent in ATC. TERT promoter mutations are common in both poorly DTC and ATC, but TP53

mutations are more common in ATC and may serve a key role in tumor aggressiveness. Mutations in PTEN, PIK3CA and immune-modulatory genes [for example, programmed death ligand (PD-L)-1; PD-L2 and Janus kinase 2] are also relatively common in ATC (9-11). The higher overall tumor mutation burden in ATC contributes to the invasiveness and resistance to conventional therapies, including chemotherapy, radiotherapy and single targeted therapy, which makes ATC treatment highly challenging.

Current treatments for ATC include surgery, chemotherapy, radiotherapy, immunotherapy and targeted therapy. For cases without distant metastasis, complete surgical resection is the primary treatment and has demonstrated efficacy in early-stage tumors (12). As with the most common type of TC-papillary thyroid carcinoma, early surgical treatment without lymph node dissection still results in an extremely low recurrence rate within 8 years (13,14). However, ~80% of ATC cases were diagnosed with invasion of surrounding tissues, lymph node involvement or distant metastases, where surgery alone has a poor prognosis (4). In such instances, adjuvant therapies such as chemotherapy or radiotherapy are typically required. Chemotherapy often includes doxorubicin, cisplatin and paclitaxel (or docetaxel), administered either alone or in combination (doxorubicin + docetaxel or cisplatin + paclitaxel) (15). While the American Thyroid Association recognizes the survival benefits of chemotherapy in ATC, the survival rate for late-stage ATC remains dismal, as the median survival was only 2.7-3 months (4). Additionally, the notable off-target toxicities of chemotherapy drugs frequently lead to dose reductions or treatment discontinuation, which severely affect the quality of life in patients (16). Common adverse effects include cardiotoxicity from doxorubicin (17), ototoxicity, neurotoxicity and nephrotoxicity from cisplatin (17), peripheral neuropathy, gastrointestinal disturbances and hematologic toxicities from paclitaxel, with elderly patients being particularly vulnerable compared with younger patients (18). ATC is also generally unresponsive to radioactive iodine (RAI) therapy. Previous studies have reported that BRAF and TERT promoter mutations, which are prevalent in ATC (9,19), were associated with the loss of RAI avidity and impaired expression of thyroid-specific genes (20). These findings highlight the need for alternative therapeutic approaches.

Targeted therapy has become a promising area of research when conventional therapeutic approaches fail. Lenvatinib (E7080), a tyrosine kinase inhibitor (TKI) approved by the US Food and Drug Administration (FDA) and European Medicines Agency for progressive, RAI-refractory DTC, has demonstrated efficacy in the treatment of ATC (21,22). However, lenvatinib monotherapy has notable limitations, which include a high incidence of adverse events (AE) (23).

In the present review, the efficacy and safety of lenvatinib monotherapy and combination therapies for ATC were analyzed. The present review aimed to provide insights into the feasibility of various therapeutic combinations to improve survival outcomes and quality of life for patients with ATC.

2. Database search strategy

The following search words were used for data mining in PubMed (https://pubmed.ncbi.nlm.nih.gov/.) and Web of Science (https://www.webofscience.com/) databases: {'lenvatinib' or all its synonyms [4-(3-chloro-4-((cyclopropylaminocarbonyl) amino)phenoxy)-7-methoxy-6-quinolinecarboxamide, E7080, Lenvima] in the Mesh database (Title/Abstract)} and ['anaplastic thyroid cancer' or all its synonyms (anaplastic thyroid carcinoma, anaplastic thyroid carcinomas, anaplastic thyroid cancers) in the Mesh database (Title/Abstract)]. Publications dated from 1st January 2024 to 7th February 2024 were imported into EndNote X9. After automatic elimination of duplicate documents, a total of 138 papers were obtained.

Inclusion criteria were as follows: i) Clinical trials of lenvatinib on ATC; ii) preclinical trials of lenvatinib on ATC; iii) clinical trial of lenvatinib combined with other drugs; and iv) preclinical trials of lenvatinib combined with other drugs on ATC. Exclusion criteria were as follows: i) Repeated literature and research; ii) irrelevant articles; iii) clinical trials of other TC types excluding ATC; and iv) preclinical trials of other types of TC excluding ATC.

Based on the aforementioned criteria, 42 studies were rejected (Fig. 2). The remaining 96 studies were examined and relevant materials were analyzed to extract the information and data required for the present review. After integrated analysis, the clinical efficacy and safety of lenvatinib and the combination with chemotherapy, radiotherapy, targeted therapy, immunotherapy and histone deacetylase inhibitors (HDACIs) on ATC were summarized. For the combination drugs that have not been clinically studied, the pre-clinical experiments were analyzed to assess their potential.

3. Lenvatinib

Lenvatinib is an oral, multi-target TKI that suppresses several key signaling pathways involved in tumor growth and angiogenesis. Lenvatinib targets include vascular endothelial growth factor receptor (VEGFR)1, VEGFR2 and VEGFR3, platelet-derived growth factor receptor (PDGFR)α, fibroblast growth factor receptor (FGFR)1, FGFR2, FGFR3 and FGFR4, mast/stem cell growth factor receptor, RET and the tumor angiogenesis-related proto-oncogene, receptor tyrosine kinase (c-KIT) signaling network, among others (24).

VEGF is a key cytokine in tumor neovascularization, which promotes tumor growth and cell proliferation. Upregulation of VEGFR was associated with increased tumor invasiveness and reduced recurrence-free survival. Among VEGFRs, VEGFR-2 served a pivotal role in tumor angiogenesis, while VEGFR-3 was key for lymph angiogenesis (27,28). By inhibition of the tyrosine kinase domain of VEGFR, lenvatinib disrupted intracellular signaling, which thereby suppressed tumor growth and migration (25-27).

PDGFR complements VEGFR in the mediation of angiogenesis. The PDGFRα signaling pathway has been identified as essential for cell migration and lenvatinib targets the PDGFRα pathway to impede tumor progression (28).

The FGFR family is upregulated in TC and regulates processes such as tumor cell proliferation, differentiation and survival (29). Lenvatinib exhibits notable potency against FGFR-1 by inhibition of the downstream effector, fibroblast growth factor receptor substrate 2 phosphorylation, which sets lenvatinib apart from other anti-angiogenic TKIs (imatinib, sorafenib), this ability may help overcome resistance to

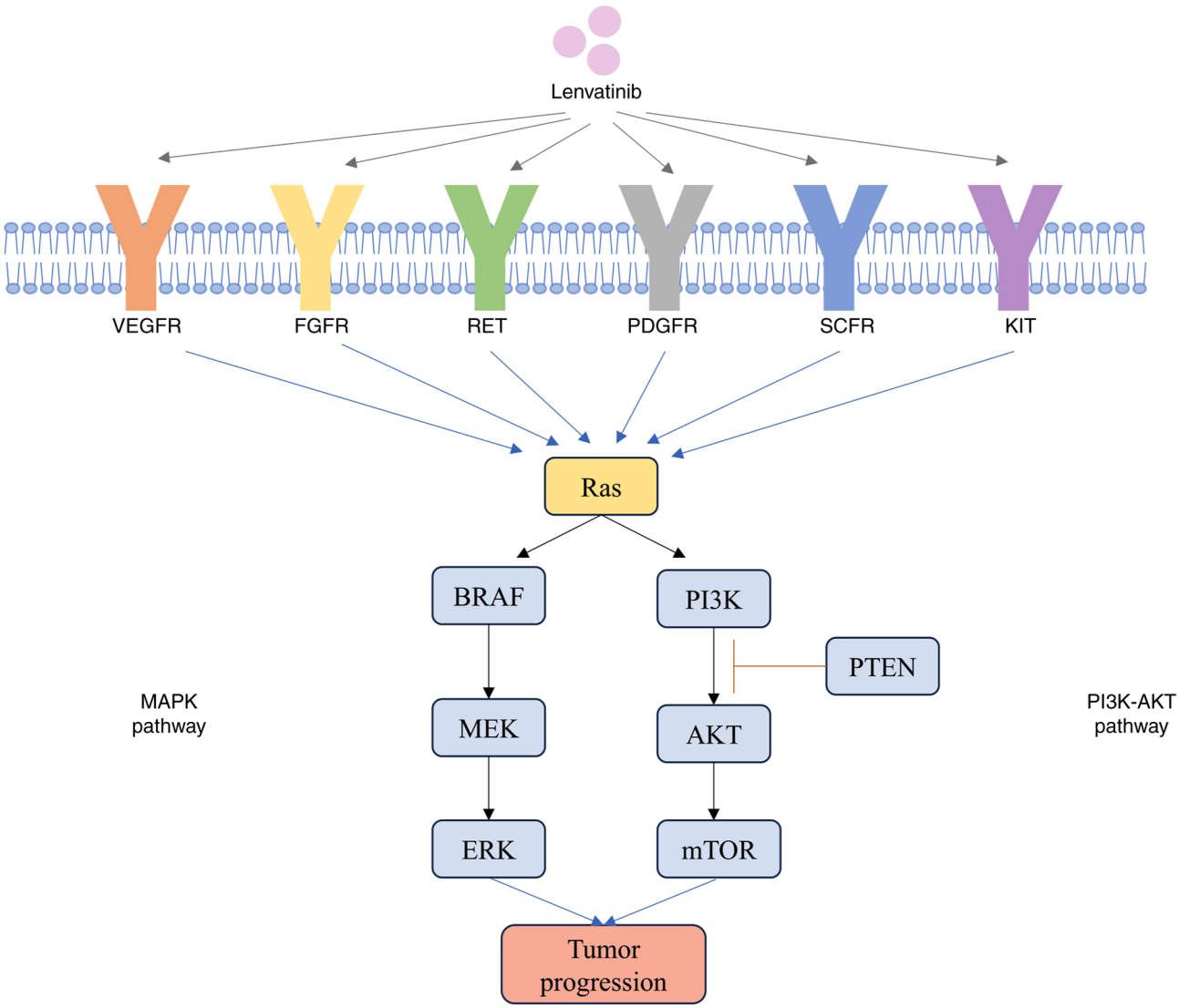

Figure 1. Regulatory mechanisms involved in thyroid tumor progression and related targets of lenvatinib. FGFR, fibroblast growth factor receptor; RET, rearranged during transfection; PDGR, platelet-derived growth factor receptor; SCFR, stem cell growth factor receptor; KIT, receptor tyrosine kinase type III.

other angiogenesis inhibitors (30). FGFR-2 is the only FGFR detected in normal thyroid tissues and FGFR-2 expression is reduced in TC tissues (29). FGFR-3 was more highly upregulated in less aggressive TC types, whereas FGFR-4 was highly upregulated in more aggressive primary thyroid tumors, including ATC and PDTC, FGFR-4 was not upregulated in well-differentiated, less aggressive TC types (31). Thus, the FGFR family may be able to serve as a prognostic factor for patients with TC (32).

RET gene fusions are frequently observed in TC (33). Lenvatinib demonstrated antitumor activity in RET gene fusion-driven tumor models by blocking oncogenic signaling (34). The c-KIT receptor is suggested to serve a role in thyroid epithelial cell proliferation, but this function may be lost during malignant transformation. Lenvatinib inhibited tumor progression by targeting this pathway (Fig. 1) as well (34).

Lenvatinib has demonstrated efficacy in the treatment of various solid tumors, including liver cancer, renal cell carcinoma and adenoid cystic carcinoma. The role of lenvatinib in TC, particularly in ATC, involves disrupting tumor angiogenesis and growth through the aforementioned mechanisms. The present review focused on the development of lenvatinib and the effectiveness in managing ATC (35).

4. Lenvatinib monotherapy in ATC

Preclinical studies. Tohyama *et al* (30) evaluated the antiproliferative effects of lenvatinib by comparing the half-maximal inhibitory concentration (IC_{50}) values in TC cell lines and Nthy-ori 3-1 cells (human thyroid follicular epithelial cells). Among 11 TC cell lines, only RO82-W-1 and TT cells demonstrated notable antiproliferative activity *in vitro*. However, in five ATC xenograft models, lenvatinib markedly reduced tumor micro vessel density, which suggested that the antitumor effects of lenvatinib in TC were primarily driven by antivascular activity.

Ferrari *et al* (36) investigated the effects of lenvatinib on primary ATC cells, 8305C cells and an ATC cell line (AF). Dose-dependent pro-apoptotic, anti-proliferative and inhibitory effects on migration and invasion were observed in primary ATC cells. Similar effects were seen in 8305C and AF cells, which attributed to the inhibition of EGFR, AKT and ERK1/2 phosphorylation. Lenvatinib also downregulated

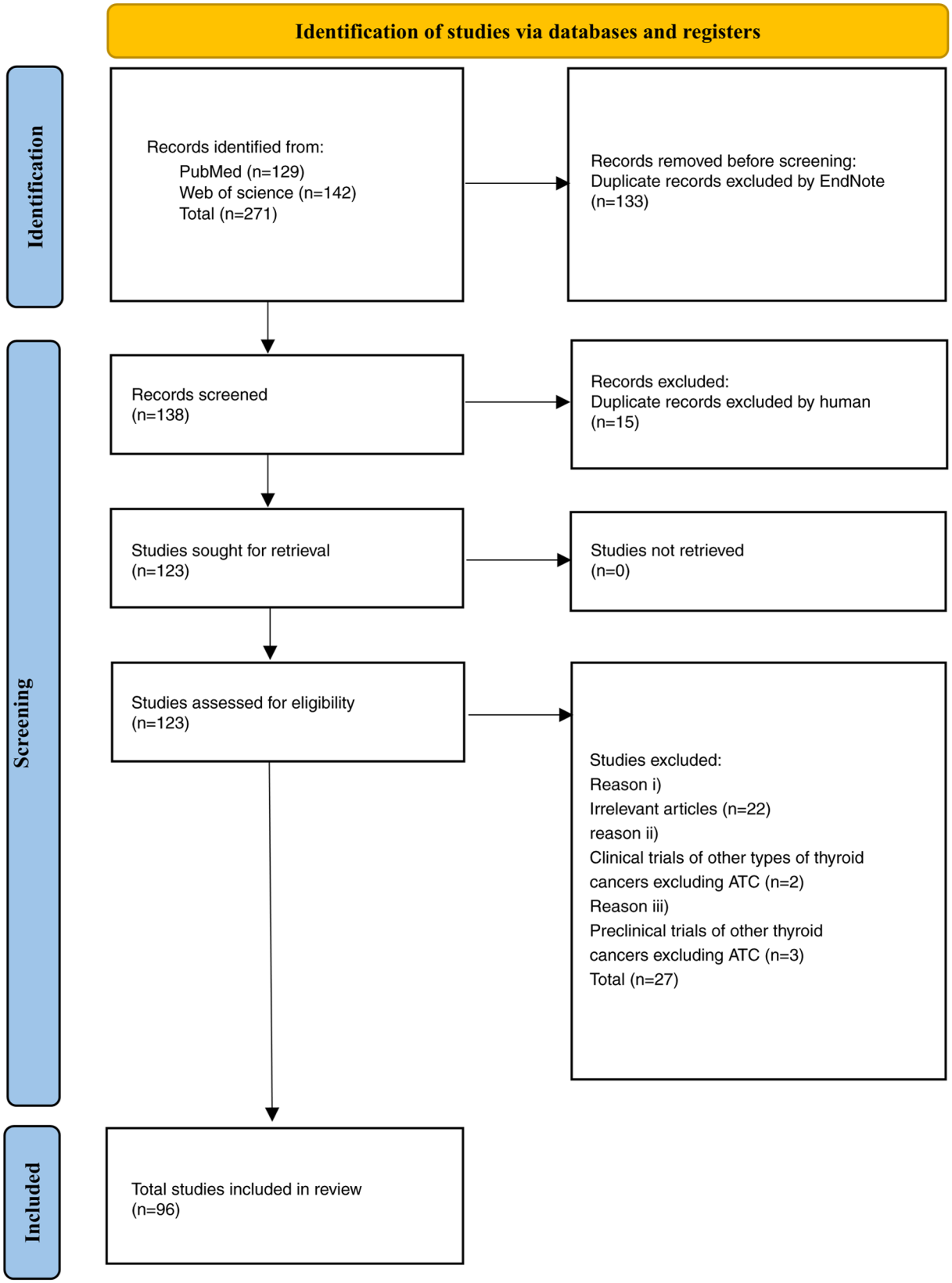

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram for the identification, screening and inclusion of studies in the present review. Adapted from Page *et al* (90). ATC, anaplastic thyroid cancer.

cyclin D1, a key regulator of cell cycle progression in ATC, which thereby suppressed tumor cell proliferation.

In vivo, lenvatinib reduced tumor growth, VEGF-A expression and blood vessel density in AF xenograft mice without affecting body weight. Additionally, while both lenvatinib and sorafenib inhibited subcutaneous ATC tumor growth, lenvatinib uniquely crossed the blood-brain barrier, which enabled intracranial tumor inhibition (37).

Clinical studies. Preclinical findings have been corroborated by clinical studies, which demonstrated the efficacy of lenvatinib in patients with ATC. In total, two Phase II trials (28,29) that included 54 and 17 patients with ATC, respectively, evaluated lenvatinib at an initial dose of 24 mg/day (adjusted based on patient tolerance). In the first trial, 20 patients failed to meet the minimum overall response rate (ORR) threshold of 15%, which led to early termination of treatment for those participants. Among the remaining 34 patients, 1 patient (2.9%) achieved partial response (PR), 17 patients (50%) had stable disease (SD) and the disease control rate (DCR) reached 90%. Median OS and progression-free survival (PFS) were 3.2 and 2.6 months, respectively. In the second trial, 4 patients (24%) achieved PR, 12 patients (71%) had SD, with a DCR of 94.1%. Median OS was 10.6 months and median PFS was 7.4 months.

Differences in clinical efficacy between the two Phase II clinical trials could be attributed to patient demographics. The first trial primarily included White and Black patients (88%), while the second study enrolled Japanese patients. Additionally, 9% of participants in the first trial received treatment with monoclonal antibodies or protein kinase inhibitors prior to lenvatinib, which potentially influenced patient outcomes.

Retrospective studies have further supported the benefits of lenvatinib in prolonging survival for patients with ATC (Table I). Murayama *et al* (38) reported that lenvatinib-induced pulmonary cavitation, observed in 46.2% of patients diagnosed with ATC with lung metastases, was associated with markedly longer OS (186 vs. 89 days for patients without cavitation). Another previous study (39) reported that 7 out of 10 patients with TC, who developed lung cavitation during treatment with lenvatinib or sorafenib were in the lenvatinib group, which suggested the potential efficacy of lenvatinib in the management of ATC with lung metastases.

The neutrophil-lymphocyte ratio (NLR) of patients with ATC was higher compared with that of radioiodine-refractory (RR)-DTC patients and NLR was also a diagnostic marker for distinguishing ATC from RR-DTC (40). In addition, NLR has also emerged as a prognostic marker for lenvatinib-treated patients with ATC. Fukuda *et al* (41) demonstrated that patients with low NLR had higher ORR (33.3%), longer median PFS (4.0 months) and longer median OS (10.2 months) compared with patients with high NLR. The study by Fukuda *et al* (41) was a single-center and small-sample retrospective study. The clinical stages of the experimental individuals were different and patients had undergone different degrees of radiotherapy, chemotherapy and surgical treatment before inclusion in the trial, which had an impact on the basic level of NLR. Another previous study (42) ruled out inflammatory interference and the statistical results indicated that NLR did not affect the therapeutic effect of lenvatinib. Nonetheless, monitoring dynamic changes in NLR before and after lenvatinib treatment could provide some prognostic insight for patients with ATC. Another previous study (43) on TKI treatment in ATC reported a notable increase in NLR levels at three key points: Before TKI initiation, after TKI initiation and at the time of death. However, current studies are influenced by numerous confounding factors such as prior treatments, recurrence or metastasis, infections, glucocorticoid use and physiological stress. Therefore, NLR requires validation through large-scale, multi-center prospective trials with stricter patient inclusion criteria.

Safety. Previous studies on lenvatinib in ATC reported at least 1 AE per patient, wherein hypertension, reduced appetite, fatigue and proteinuria were the most common AEs (23,27,44,45). These AEs were linked to the inhibition of VEGFR by lenvatinib (46). While the incidence of AEs is high, severe AEs (SAEs) associated with lenvatinib are rare and treatment discontinuation due to AEs is uncommon.

In a previous study conducted in Japan (47), of 124 patients with ATC (mean age, 73 years), 76.6% experienced grade ≥3 AEs, primarily hypertension (46.8%) and thrombocytopenia (12.9%). The high rate of severe AEs may be attributed to the advanced age of participants and the use of a 24 mg/day dose, which may be excessive for Asian populations (48).

Another study conducted in Korea on 14 patients with ATC, who were administered an initial dose of 20 mg/day reported 100% incidence of AEs, with 50% classified as grade ≥3 (49). At a maintenance dose of 13 mg/day, DCR reached 93% and median OS was 6.73 months. These findings suggested that lower starting doses may improve tolerability and efficacy in Asian populations despite differences in participant numbers between the studies.

5. Lenvatinib combination therapy in ATC

Preclinical studies

Lenvatinib and other targeted inhibitors. i) MEK inhibitors. Enomoto *et al* (50) investigated the combination of lenvatinib with MEK inhibitors (U0126 and selumetinib) in ATC. Lenvatinib inhibited AKT signaling but not MAPK signaling, which prompted the use of MEK inhibitors to complement its effects. *In vitro* assays demonstrated that a combination of 5 μM lenvatinib and 5 μM U0126 demonstrated synergistic antiproliferative effects in ATC cell lines (8505C and TCO1). The antiproliferative rate increased significantly compared with lenvatinib alone (8505C, 32 to 66%; TCO1, 58 to 72%), The present review concluded that lenvatinib suppressed AKT phosphorylation, while U0126 suppressed ERK phosphorylation and cell cycle protein D1 expression. *In vivo* assays demonstrated that mice treated with lenvatinib (30 mg/kg/day) and selumetinib (30 mg/kg/day) experienced significantly larger tumor volume reduction compared with tumor volumes in monotherapy groups. Tumor cell apoptosis increased via caspase-3 activation, while toxicity levels remained manageable.

The aforementioned results highlight the potential of lenvatinib and MEK inhibitors as a synergistic therapy for ATC, which targets both AKT and MAPK signaling pathways effectively.

ii) BRAF inhibitors. In a previous study, lenvatinib was combined with vemurafenib, a BRAF inhibitor, to treat BRAF-mutated (8505C) and non-BRAF-mutated (HTh7) ATC cell lines (51).

The results demonstrated that under low concentrations (0.25 μM) of vemurafenib, the proliferation of BRAF mutated 8505C cells was significantly inhibited, whereas the HTh7 cell line exhibited resistance to vemurafenib by 4 μM. Lenvatinib

Table I. Summary of clinical trials on the efficacy of lenvatinib in the treatment of patients with ATC.

First author, year	Study type	Initial dose, mg/day	Patients, n	Group	Median survival, (days/months)	Responses, n (%)	DCR[a], n (%)	Observations	(Refs.)
Murayama *et al*, 2022	Retrospective	24	26	Total (all patients)	OS, 128 d; PFS, NA	CR, 0 (0); PR, 6 (23.1); SD, 17 (65.4); PD, 2 (7.7); NE, 1 (3.8)	23 (88.5)	Nearly half of the patients developed LC, which demonstrated improved clinical outcomes compared with patients without LC.	(38)
			12	LC (+)	OS, 186 d; PFS, NA	CR, 0 (0); PR, 2 (16.7); SD, 8 (66.7); PD, 2, (16.7); NE, 0 (0)	10 (83.3)		
			14	LC (-)	OS, 89 d; PFS, NA	CR, 0 (0); PR, 4 (28.6); SD, 9 (64.3), PD, 0 (0); NE, 1 (7.1)	13 (92.9)		
Wirth *et al*, 2021	Phase II prospective	24	34	IAS	OS, 2.9 m; PFS, 2.6 m	CR, 0 (0); PR, 1 (5); SD, 9 (45); PD, 5 (25); NE, 5 (25)	10 (29.4)	Lenvatinib monotherapy might not have been an effective treatment for ATC.	(45)
			20	FAS	OS, 3.2 m; PFS, 2.6 m	CR, 0, (0); PR, 1 (2.9); SD, 17 (50); PD, 9 (26.5); NE, 7 (20.6)	18 (90)		
Iwasaki *et al*, 2021	Retrospective	24	32		Total, 3.2 m	CR, 6 (18.8); PR, 8 (25); SD, 6 (18.8); PD, 12 (37.5); NE, 0 (0)	20 (62.5)	Dose reduction or discontinuation of lenvatinib monotherapy was frequently required due to SAEs.	(23)
Yamazaki *et al*, 2020	Phase II prospective	10-24	12		OS, NA; PFS, 5 m	CR, 0 (0); PR, 4 (33.3); SD, 3 (25); PD, 0 (0); NE, 5 (41.7)	7 (58.3)	FGFR4 may have served as a prognostic predictor for lenvatinib treatment response.	(86)
Takahashi *et al*, 2020	Retrospective	24	124		OS, 101 d; PFS, NA	CR, 3 (2.9); PR, 43 (41); SD, 34 (32.4); PD, 25 (23.8); NE, 0 (0)	80 (64.5)	The safety profile of lenvatinib in ATC was confirmed to be favorable.	(47)
Kim *et al*, 2021	Retrospective	20-23	14		OS, 6.7 m; PFS, 5.7 m	CR, 0 (0); PR, 4 (29); SD, 9 (64); PD, 1 (7); NE, 0 (0)	13 (92.9)	The therapeutic benefits of lenvatinib remained modest in advanced ATC cases.	(49)
Fukuda *et al*, 2020	Retrospective	24	13	Total	OS, 10.2 m; PFS, 3.8 m	CR, 0 (0); PR, 3 (23); SD, 6 (46.2); PD, 4 (30.8); NE, 0 (0)	9 (69.2)	NLR may have served as a potential prognostic biomarker for lenvatinib treatment response.	(41)
			9	NLR <8	OS, 10.2 m; PFS, NA	CR, 0 (0); PR, 3 (33.3); SD, 5 (55.6); PD, 1 (11.1); NE, 0 (0)	8 (88.9)		
			4	NLR ≥8	Total OS, 3.8 m	CR, 0 (0); PR, 0 (0); SD, 1 (25); PD, 3 (75); NE, 0 (0)	1 (25)		

Table I. Continued.

First author, year	Study type	Initial dose, mg/day	Patients, n	Group	Median survival, (days/months)	Responses, n (%)	DCR[a], n (%)	Observations	(Refs.)
Iwasaki *et al*, 2020	Phase II prospective	10-24	16		OS, 4.2 m; PFS, NA	CR, 0 (0); PR, 7 (43.75); SD, 5 (31.3); PD, 4 (25); NE, 0 (0)	12 (75)	Judicious dose reduction of lenvatinib represented a necessary therapeutic strategy.	(87)
Iwasaki *et al*, 2018	Retrospective	20-24	23		OS, 166 d; PFS, NA	CR, 0 (0); PR, 4 (17.4); SD, 6 (26.1); PD, 7 (30.4); NE, 6 (26.1)	10 (43.5)	Lenvatinib exhibited clinical activity in patients with chemotherapy refractory ATC.	(91)
Tahara *et al*, 2017	Phase II prospective	24	17		OS, 10.6 m; PFS, 7.4 m	CR, 0 (0); PR, 4 (24); SD, 12 (71); PD, 1 (6); NE, 0 (0)	16 (94.1)	Lenvatinib demonstrated clinical benefits with manageable toxicity.	(44)
Koyama *et al*, 2018	Retrospective	24	5		Total OS, 165 d	CR, 0 (0); PR, 3 (60); SD, 2 (40); PD, 0 (0); NE, 0 (0)	5 (100)	Lenvatinib improved survival in patients with unresectable ATC.	(92)
Iyer *et al*, 2018	Retrospective	24	8		OS, 3.9 m; PFS, 2.6 m	CR, 0 (0); PR, 3 (37.5); SD, 0 (0); PD, 5 (62.5); NE, 0 (0)	3 (37.5)	Lenvatinib demonstrated therapeutic efficacy in patients with ATC who were ineligible for clinical trials.	(93)

[a]CR+PR+SD. -, negative; +, positive; OS, overall survival; PFS, progression-free survival; NA, not applicable; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; DCR, disease control rate; LC, lung cavitation; IAS, interim analysis set; FAS, full analysis set; NLR, neutrophil-to-lymphocyte ratio; m, months; d, days; ATC, anaplastic thyroid cancer; SAE, severe adverse event; FGFR, fibroblast growth factor receptor.

inhibited 8505C cell proliferation in a dose-dependent manner, whereas HTh7 cells did not exhibit an antiproliferative pattern compared with that of 8505C until lenvatinib reached 12. 5 μM and cell viability of HTh7 and 8505C did not differ statistically until 25 μM. HTh7 cells demonstrated only additive cytotoxic effects when combined treatment with lenvatinib and vemurafenib. Vemurafenib effectively inhibited the proliferation of 8505C cells but vemurafenib was less effective in HTh7 cells. The combination of lenvatinib and vemurafenib demonstrated cooperative cytotoxic effects in BRAF-mutated cells, which induced apoptosis through poly(ADP-ribose) polymerase cleavage.

In addition, combined BRAF and MEK inhibitors increased sodium/iodide symporter expression and RAI uptake in BRAF-mutated TC types (52,53), which offered a potential strategy for BRAF-mutated ATC. Further clinical trials are required to establish safety and optimal dosing for BRAF and MEK inhibitors combination therapy.

Lenvatinib and chemotherapeutic agents. i) Lenvatinib and doxorubicin. Doxorubicin, an approved chemotherapy for ATC, cannot improve the OS rate of advanced ATC and has strong cardiotoxicity as monotherapy. A preclinical study (54) combining lenvatinib (1 μM) and doxorubicin (10 nM) demonstrated synergistic effects in ATC cell lines (8305C, C643 and 8505C), which inhibited cell proliferation, migration, invasion and colony formation. *In vivo* assays demonstrated that the combination therapy group exhibited lighter tumor weights and lower Ki-67 levels compared with both the lenvatinib monotherapy and doxorubicin monotherapy groups. The mechanism may be to inhibit ERK phosphorylation and induce cell cycle arrest. The MAPK pathway has a notable effect on DNA repair in reaction to DNA damage and lenvatinib can impair DNA repair capacity by suppressing receptor tyrosine kinases and the downstream.

The lenvatinib and doxorubicin combination therapy may further enhance the damage of doxorubicin to DNA and thereby exert a synergistic anticancer effect (55,56) without added toxicity, which highlights the clinical potential of lenvatinib and doxorubicin.

ii) Lenvatinib and paclitaxel. The combination of lenvatinib and paclitaxel demonstrated similar cooperative effects to lenvatinib and doxorubicin, which includes inhibition of tumor cell growth, colony formation, increase of the proportion of G_2/M phase and induction of apoptosis in ATC cells. The effects were dose-dependent, which supports the potential for combination therapy (5).

iii) Lenvatinib and vinorelbine. Vinorelbine is a microtubule-targeting drug, which induces tumor cell death via apoptosis (57). The drug has also been demonstrated to block angiogenesis (58). *In vitro* assays demonstrated that lenvatinib in combination with vinorelbine has synergistic anti-proliferative activity, whereas sorafenib in combination with vinorelbine did not exhibit synergistic effects (59).

As an efflux pump, the ATP-binding cassette subfamily (ABC) transporter can excrete TKIs, which may increase tumor resistance to lenvatinib and vinorelbine (60). Lenvatinib reduced ABCB1 expression, which increased intracellular drug concentrations and overcame resistance (59). Wide permeation of tumor associated macrophages (TAMs) was observed in 95% of patients with ATC (61). The colony-stimulating factor-1 receptor (CSF-1R) gene, as a TAMs-related gene, was associated with low survival and was markedly upregulated in ATC (59). CSF-1 can also induce the generation of VEGF (62). However, both lenvatinib monotherapy and the combination with vinorelbine can inhibit the expression of CSF-1 mRNA, wherein lenvatinib combined with vinorelbine is more effective (63). This combination regimen might serve as an option to mitigate TKI resistance in patients with ATC. *In vivo* findings: Combination therapy reduced tumor volume, mitotic activity and Ki-67 levels, while increasing apoptosis markers such as caspase-3 (59). Lenvatinib combined with vinorelbine may mitigate resistance to TKIs in patients with ATC.

Lenvatinib and immunotherapy. Immunotherapy, particularly anti-programmed death-1 (PD-1)/PD-L1 agents, is a major research focus in ATC. ATC markedly upregulates PD-L1 compared with DTC (64). Gunda *et al* (3) reported that lenvatinib combined with anti-PD-1/PD-L1 therapy reduced tumor size and improved survival. ATC cells treated with lenvatinib alone did not affect PD-L1 expression but increased TAMs, $CD8^+$ T cells, regulatory T cells and polymorphonuclear myeloid derived suppressor cells (PMN-MDSCs). The lenvatinib treatment group also demonstrated an increase in granulocyte-CSF levels in tumor lysis fluid, which may drive the proliferation of MDSCs. T-cell defection and natural killer cell toxicity were linked to the increase in these cells, which had a negative effect on the efficacy of lenvatinib (65-67). The effect of lenvatinib to increase PMN-MDSCs was also demonstrated in patients with ATC and only the lenvatinib combined with anti-PD-1 group exhibited reduced PMN-MDSCs (3). Combining lenvatinib with therapies targeting PMN-MDSCs or TAMs, such as CSF-1R blockade, may enhance therapeutic efficacy and overcome immune evasion in ATC.

Lenvatinib and HDACIs. Histone deacetylase (HNHA) is a HDACI that removes acetyl groups from histone lysine residues. This process is called deacetylation, which suppresses cellular transcription and stalls tumor growth, polarization and apoptosis. In addition, it can sensitize tumor cells to radiation, which increases the uptake of RAI and the accumulation of RAI in tumors (68). A previous study (69) reported that the combination of HNHA and lenvatinib has a strong anti-proliferative effect, which increased apoptosis in GSA2 (first patient-derived ATC cells) and GSA1 (second patient-derived ATC cells) cell lines by increasing p53 and p21 levels, reduced cyclin D1 and CDK4 and induced cell cycle arrest. In the mouse xenograft model, both the monotherapy group and the HNHA combined with sorafenib group did not significantly suppress the development of GSA1 and GSA2 cell xenografts. However, HNHA combined with lenvatinib could significantly inhibit tumor growth.

Previous studies have suggested that drug resistance in poorly differentiated cancer stem cells is associated with epithelial mesenchymal transition (EMT) and the FGFR signaling pathway is involved in this process (70,71). A previous study reported that the expression of the FGFR signaling pathway and EMT markers in ATC cell lines is higher compared with that in DTC (69). Therefore, when combined lenvatinib with HNHA in GSA2 and GSA1 cell lines, lenvatinib combined with HNHA group had a stronger inhibitory effect on the FGFR signaling pathway compared with other groups. In addition, the EMT marker, β-catenin, is

important in EMT nuclear positioning induction in late-stage TC cells. Other studies have demonstrated that downregulating zinc finger E-box binding homeobox 1 (ZEB1) expression can restore drug sensitivity (72,73), which blocks β-catenin and downregulation of ZEB1, which may potentially be novel methods for the treatment of ATC resistance in the future. These findings suggest that combining lenvatinib with HDACIs could potentially be a promising strategy to overcome drug resistance in ATC.

Clinical studies. Although research is limited, clinical trials that investigated lenvatinib in combination with other agents for ATC have demonstrated promising efficacy.

Pembrolizumab, a monoclonal antibody targeting the PD-1 receptor, was approved by the US FDA for the treatment of several types of cancer, including non-small cell lung cancer, biliary tract cancer and ATC (64,74). ATC tumors exhibit diffuse expression of PD-L1, which makes this combination a rational therapeutic approach (31). Lenvatinib in combination with pembrolizumab has been evaluated in patients with ATC in two studies, with an initial lenvatinib dose of 24 mg/day and pembrolizumab at 200 mg every 3 weeks (31,64).

The first study (64) initially used with lenvatinib monotherapy and later introduced pembrolizumab upon ATC progression. Among 5 patients, 3 patients (60%) achieved PR, 1 patient (20%) achieved SD and the DCR was 83%. The median OS was 8.25 months. While the lack of a control group for continuous lenvatinib monotherapy limits direct comparisons, the median survival time for lenvatinib monotherapy before pembrolizumab addition was 10.4 months, which suggested an improvement in survival with combination therapy.

In the second study (31), 6 patients were treated with the combination therapy from the outset. Complete response (CR) was achieved in 4 patients (66.7%), 1 patient (16.7%) achieved SD and the DCR was 66%. The median OS was 17.3 months and the median PFS was 16.8 months. Treatment was well-tolerated, with a maximum treatment duration of 40 months and 3 patients (50%) were still receiving therapy at the time of data cut-off.

Another previous study reported that pembrolizumab is only partially effective in patients with prior resistance to TKIs, which resulted in a PFS of just 2.96 months (69). These findings underscore the importance of timing in adding pembrolizumab to TKI therapy. Previous studies have suggested that early addition of pembrolizumab may provide greater benefit compared with sequential therapy, though the optimal timing requires further investigation (64,75).

Another previous study (76) evaluated a combination regimen involving paclitaxel, intensity-modulated radiotherapy and lenvatinib. Patients began with one cycle of paclitaxel and IMRT. After 6 weeks, imaging determined the suitability for surgery. Patients, who were ineligible for surgery continued chemotherapy and radiotherapy, with lenvatinib (10 mg/day) added upon disease progression. Among 18 patients, the median OS was 230 days, with 6-month and 1-year survival rates of 61.1 and 22.2%, respectively. Notably, 3 patients (16.7%) survived beyond 1 year. While this study demonstrated a survival benefit, the optimal timing for the introduction of lenvatinib during radiotherapy remained unclear due to the absence of a control group initiating paclitaxel, radiotherapy and lenvatinib simultaneously. Furthermore, the toxicity profile of the three-drug combination requires additional investigation through larger sample sizes and more comprehensive clinical studies.

Lenvatinib combined with pembrolizumab or traditional chemoradiotherapy has demonstrated positive results for patients with ATC, particularly in improving survival outcomes (64,75,76). However, the timing of lenvatinib initiation and the role of lenvatinib in combination regimens require further clinical exploration. The aforementioned studies lay a foundation for future research aimed at the optimization of lenvatinib-based therapies for ATC.

6. Discussion

Clinical studies have demonstrated that lenvatinib monotherapy offers notable efficacy in the treatment of ATC, with PR rates ranging from 2.9 to 60%, DCR ranging from 25 to 100% and median OS ranging from 2.9 to 10.6 months. The difference in the PR, DCR and median OS rates may stem from the predominance of retrospective studies, which carry a high risk of selection bias, such as differences in enrollment criteria, sample sizes, prior treatments and demographic characteristics. For example: i) Age, poorer prognosis in trials with predominantly elderly participants (47); ii) sex; and iii) ethnicity, the initial recommended dose of lenvatinib (based on a phase III trial for RR-DTC) may not be optimal for Asian populations (77). Second, the external validity of retrospective studies is also questionable, as participants are often recruited from large single-center hospitals with more complex conditions. To address the aforementioned issues, it is essential to establish a standardized inclusion framework, recruit volunteers across multiple centers, dynamically adjust exclusion criteria and explore the optimal monotherapy dose under varying conditions. Third, the lack of predictive markers for ATC prognosis and lenvatinib efficacy. Previous studies have identified potential prognostic indicators, such as acute symptoms, white blood cell count, tumor diameter (≥5 cm), distant metastases, NLR, age >70 years and extra-thyroidal infiltration (T4b), which were associated with poor prognosis (78-80). Furthermore, a low NLR was associated with improved outcomes for lenvatinib-treated patients. Another potential predictive factor includes the presence of hand-foot syndrome, which was associated with improved a 24-month OS rate (81), and lower FGFR4 expression, which has been linked to better lenvatinib response (82). However, the lack of standardized detection methods, incomplete data collection and common selection biases require key interpretation of these results. Future research may employ more rigorous trial designs to validate these prognostic factors, which potentially leverage existing data to screen candidate biomarkers, establish uniform detection and enrollment criteria and conduct multi-center prospective validation trials.

Combination therapies including lenvatinib have demonstrated increased efficacy. For instance, in two studies investigating lenvatinib combined with pembrolizumab (64,75), the first study reported a DCR of 80% and a median OS of 18.65 months, while the second reported a DCR of 66% and a median OS of 17.3 months-substantial improvements compared with lenvatinib monotherapy. Additionally, a previous study that

examined lenvatinib combined with paclitaxel and radiotherapy observed a median OS of 230 days, although the efficacy was lower compared with that of pembrolizumab combinations. Notably, conventional chemotherapeutic agents combined with lenvatinib yielded less favorable results (76), likely due to the late introduction of targeted therapies. Nevertheless, the combination of lenvatinib and pembrolizumab demonstrated robust potential. A recent consensus supported the effectiveness of lenvatinib and pembrolizumab combination therapy in patients with ATC with BRAF mutations (83). According to the Thyroid Neck Morbidity Complexity (TNMC) Scoring System (84), current guidelines (4,85) recommend surgery as the first-line treatment for patients with stage IVB BRAFv-ATC (TNMC, 0) with resectable primary tumors, followed by adjuvant radiotherapy and chemotherapy. The consensus recommended first-line use of BRAF/MEK inhibitors [dabrafenib-trametinib (DT)] for patients with stage IVB BRAFv-ATC or patients with unresectable or advanced disease (TNMC ≥1), followed by surgery. The consensus also advised combining the regimen with pembrolizumab from the outset or adding pembrolizumab upon disease progression. If surgery is not feasible after 6 months of neoadjuvant treatment, radiotherapy and chemotherapy should be considered. Similar to lenvatinib, combination therapy with pembrolizumab demonstrates survival benefits in patients with ATC. However, a previous study (69) indicated that prior resistance to TKI inhibitors notably limits the efficacy of pembrolizumab, while the consensus suggested that the limited effectiveness of adding pembrolizumab midway was due to the delayed onset of action. Additionally, combining pembrolizumab with immune checkpoint inhibitors increased treatment toxicity (64). Therefore, clinical decisions should be individualized based on the condition of the patient. For patients with stage IVC BRAFv-ATC, both the guidelines and consensus recommended routine DT plus pembrolizumab (DTP), with reassessment after 2-3 months. If surgery is not possible or recurrence risk is high, DTP should be continued. If surgery is resectable, DTP should continue postoperatively and discontinuation of pembrolizumab after 1 year may offer enhanced survival benefits.

Targeted therapy combined with immunotherapy is a promising direction for the future treatment of ATC. However, several clinical studies (44,45,86,87) on combination therapies are single-arm phase II trials with low levels of evidence, which potentially overestimate treatment efficacy. Future studies should incorporate control groups for causal inference, avoid selecting only patients with favorable baseline characteristics and extend follow-up duration to improve long-term safety data collection.

ATC remains one of the most challenging malignancies in TC, with limited benefits from traditional treatments (16,17,86-93). Targeted therapies such as lenvatinib represent a vital avenue for improving patient outcomes (Table I) (23,38,41,44,45,47,49,86,87,91-93). The present review highlighted the efficacy and safety of lenvatinib as both a monotherapy and in combination regimens. There are still several directions worth exploring in the future. Notably, lenvatinib has exhibited superiority to sorafenib in preclinical models of ATC brain metastases and has provided notable survival benefits in patients with ATC lung metastases (37,39). Combination regimens have also proven effective in mitigating toxicity, with specific combinations that demonstrate sensitivity in certain ATC subgroups. For example, lenvatinib combined with the BRAF inhibitor vemurafenib or HDACIs increased RAI sensitivity and lenvatinib combined with vinorelbine or HDACIs reduced drug resistance (52,68). However, relevant studies remain scarce, with most evidence derived solely from animal models and lacking clinical validation. Future research is warranted to verify the aforementioned hypotheses and provide improved therapeutic options for specific ATC subgroups.

The findings from the aforementioned studies highlight promising directions for future clinical trials, aimed at optimizing lenvatinib combinations to enhance DCRs, minimize toxic side effects and improve survival outcomes for patients with ATC. The present review serves as a foundation for future research and clinical trial design, with the ultimate goal of developing individualized therapies to meet the diverse needs of patients with ATC.

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Authors' contributions

LX conceptualized the present review. YW, YX, and KY conducted the literature search, preliminary screening, and data collection. LX and QL performed the data analysis and prepared the original draft. WZ and XW reviewed and edited the manuscript. XW acquired funding and supervised the present review. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2017. CA Cancer J Clin 67: 7-30, 2017.
2. Fugazzola L, Elisei R, Fuhrer D, Jarzab B, Leboulleux S, Newbold K and Smit J: 2019 European thyroid association guidelines for the treatment and follow-up of advanced radioiodine-refractory thyroid cancer. Eur Thyroid J 8: 227-245, 2019.

3. Gunda V, Gigliotti B, Ashry T, Ndishabandi D, McCarthy M, Zhou Z, Amin S, Lee KE, Stork T, Wirth L, *et al*: Anti-PD-1/PD-L1 therapy augments lenvatinib's efficacy by favorably altering the immune microenvironment of murine anaplastic thyroid cancer. Int J Cancer 144: 2266-2278, 2019.
4. Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ Jr, Di Cristofano A, Foote R, Giordano T, Kasperbauer J, *et al*: 2021 American thyroid association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 31: 337-386, 2021.
5. Duan H, Li Y, Hu P, Gao J, Ying J, Xu W, Zhao D, Wang Z, Ye J, Lizaso A, *et al*: Mutational profiling of poorly differentiated and anaplastic thyroid carcinoma by the use of targeted next-generation sequencing. Histopathology 75: 890-899, 2019.
6. Ferrari SM, Elia G, Ragusa F, Ruffilli I, La Motta C, Paparo SR, Patrizio A, Vita R, Benvenga S, Materazzi G, *et al*: Novel treatments for anaplastic thyroid carcinoma. Gland Surg 9 (Suppl 1): S28-S42, 2020.
7. Ragazzi M, Ciarrocchi A, Sancisi V, Gandolfi G, Bisagni A and Piana S: Update on anaplastic thyroid carcinoma: morphological, molecular, and genetic features of the most aggressive thyroid cancer. Int J Endocrinol 2014: 790834, 2014.
8. Xing M: Molecular pathogenesis and mechanisms of thyroid cancer. Nat Rev Cancer 13: 184-199, 2013.
9. Landa I, Ibrahimpasic T, Boucai L, Sinha R, Knauf JA, Shah RH, Dogan S, Ricarte-Filho JC, Krishnamoorthy GP, Xu B, *et al*: Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers. J Clin Invest 126: 1052-1066, 2016.
10. Pozdeyev N, Gay LM, Sokol ES, Hartmaier R, Deaver KE, Davis S, French JD, Borre PV, LaBarbera DV, Tan AC, *et al*: Genetic analysis of 779 advanced differentiated and anaplastic thyroid cancers. Clin Cancer Res 24: 3059-3068, 2018.
11. Romei C, Tacito A, Molinaro E, Piaggi P, Cappagli V, Pieruzzi L, Matrone A, Viola D, Agate L, Torregrossa L, *et al*: Clinical, pathological and genetic features of anaplastic and poorly differentiated thyroid cancer: A single institute experience. Oncol Lett 15: 9174-9182, 2018.
12. Sacks D, Baxter B, Campbell BCV, Carpenter JS, Cognard C, Dippel D, Eesa M, Fischer U, Hausegger K, Hirsch JA, *et al*: Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke: From the American association of neurological surgeons (AANS), American society of neuroradiology (ASNR), cardiovascular and interventional radiology society of Europe (CIRSE), Canadian Interventional Radiology Association (CIRA), Congress of Neurological Surgeons (CNS), European society of minimally invasive neurological therapy (ESMINT), European society of neuroradiology (ESNR), European stroke organization (ESO), Society for Cardiovascular Angiography and Interventions (SCAI), Society of Interventional Radiology (SIR), Society of NeuroInterventional Surgery (SNIS), and World stroke organization (WSO). J Vasc Interv Radiol 29: 441-453, 2018.
13. Conzo G, Docimo G, Mauriello C, Gambardella C, Esposito D, Cavallo F, Tartaglia E, Napolitano S and Santini L: The current status of lymph node dissection in the treatment of papillary thyroid cancer. A literature review. Clin Ter 164: e343-e346, 2013.
14. Conzo G, Mauriello C, Docimo G, Gambardella C, Thomas G, Cavallo F, Tartaglia E, Napolitano S, Varriale R, Rossetti G, *et al*: Clinicopathological pattern of lymph node recurrence of papillary thyroid cancer. Implications for surgery. Int J Surg 12 (Suppl 1): S194-S197, 2014.
15. Laetitia G, Sven S and Fabrice J: Combinatorial therapies in thyroid cancer: An overview of preclinical and clinical progresses. Cells 9: 830, 2020.
16. Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ Jr, Di Cristofano A, Foote R, Giordano T, Kasperbauer J, *et al*: 2021 American Thyroid association guidelines for management of patients with anaplastic thyroid cancer: American thyroid association anaplastic thyroid cancer guidelines task force by bible. Thyroid 31: 337-386, 2021.
17. Trendowski MR, El Charif O, Dinh PC Jr, Travis LB and Dolan ME: Genetic and modifiable risk factors contributing to cisplatin-induced toxicities. Clin Cancer Res 25: 1147-1155, 2019.
18. Frederiks CN, Lam SW, Guchelaar HJ and Boven E: Genetic polymorphisms and paclitaxel- or docetaxel-induced toxicities: A systematic review. Cancer Treat Rev 41: 935-950, 2015.
19. Tirrò E, Martorana F, Romano C, Vitale SR, Motta G, Di Gregorio S, Massimino M, Pennisi MS, Stella S, Puma A, *et al*: Molecular alterations in thyroid cancer: From bench to clinical practice. Genes (Basel) 10: 709, 2019.
20. Liu J, Liu R, Shen X, Zhu G, Li B and Xing M: The genetic duet of BRAF V600E and TERT promoter mutations robustly predicts loss of radioiodine avidity in recurrent papillary thyroid cancer. J Nucl Med 61: 177-182, 2020.
21. Hussein Z, Mizuo H, Hayato S, Namiki M and Shumaker R: Clinical pharmacokinetic and pharmacodynamic profile of lenvatinib, an orally active, small-molecule, multitargeted tyrosine kinase inhibitor. Eur J Drug Metab Pharmacokinet 42: 903-914, 2017.
22. Nair A, Lemery SJ, Yang J, Marathe A, Zhao L, Zhao H, Jiang X, He K, Ladouceur G, Mitra AK, *et al*: FDA approval summary: lenvatinib for progressive, radio-iodine-refractory differentiated thyroid cancer. Clin Cancer Res 21: 5205-5208, 2015.
23. Iwasaki H, Toda S, Murayama D, Kato S and Matsui A: Relationship between adverse events associated with lenvatinib treatment for thyroid cancer and patient prognosis. Mol Clin Oncol 14: 28, 2021.
24. Cabanillas ME and Habra MA: Lenvatinib: Role in thyroid cancer and other solid tumors. Cancer Treat Rev 42: 47-55, 2016.
25. Zeng H, Dvorak HF and Mukhopadhyay D: Vascular permeability factor (VPF)/vascular endothelial growth factor (VEGF) peceptor-1 down-modulates VPF/VEGF receptor-2-mediated endothelial cell proliferation, but not migration, through phosphatidylinositol 3-kinase-dependent pathways. J Biol Chem 276: 26969-26979, 2001.
26. Barnhart BJ and Cox SH: DNA replication of induced prophage in Haemophilus influenzae. J Virol 12: 165-176, 1973.
27. Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, *et al*: ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 62: 4645-4655, 2002.
28. Glen H, Mason S, Patel H, Macleod K and Brunton VG: E7080, a multi-targeted tyrosine kinase inhibitor suppresses tumor cell migration and invasion. BMC Cancer 11: 309, 2011.
29. Wesche J, Haglund K and Haugsten EM: Fibroblast growth factors and their receptors in cancer. Biochem J 437: 199-213, 2011.
30. Tohyama O, Matsui J, Kodama K, Hata-Sugi N, Kimura T, Okamoto K, Minoshima Y, Iwata M and Funahashi Y: Antitumor activity of lenvatinib (e7080): An angiogenesis inhibitor that targets multiple receptor tyrosine kinases in preclinical human thyroid cancer models. J Thyroid Res 2014: 638747, 2014.
31. Adam P, Kircher S, Sbiera I, Koehler VF, Berg E, Knösel T, Sandner B, Fenske WK, Bläker H, Smaxwil C, *et al*: FGF-Receptors and PD-L1 in Anaplastic and Poorly Differentiated Thyroid Cancer: Evaluation of the Preclinical Rationale. Front Endocrinol (Lausanne) 12: 712107, 2021.
32. Okamoto K, Kodama K, Takase K, Sugi NH, Yamamoto Y, Iwata M and Tsuruoka A: Antitumor activities of the targeted multi-tyrosine kinase inhibitor lenvatinib (E7080) against RET gene fusion-driven tumor models. Cancer Lett 340: 97-103, 2013.
33. Santoro M, Melillo RM and Fusco A: RET/PTC activation in papillary thyroid carcinoma: European Journal of Endocrinology Prize Lecture. Eur J Endocrinol 155: 645-653, 2006.
34. Mazeh H, Mizrahi I, Halle D, Ilyayev N, Stojadinovic A, Trink B, Mitrani-Rosenbaum S, Roistacher M, Ariel I, Eid A, *et al*: Development of a microRNA-based molecular assay for the detection of papillary thyroid carcinoma in aspiration biopsy samples. Thyroid 21: 111-118, 2011.
35. Hao Z and Wang P: Lenvatinib in management of solid tumors. Oncologist 25: e302-e310, 2020.
36. Ferrari SM, Bocci G, Di Desidero T, Elia G, Ruffilli I, Ragusa F, Orlandi P, Paparo SR, Patrizio A, Piaggi S, *et al*: Lenvatinib exhibits antineoplastic activity in anaplastic thyroid cancer in vitro and in vivo. Oncol Rep 39: 2225-2234, 2018.
37. Wang R, Yamada T, Arai S, Fukuda K, Taniguchi H, Tanimoto A, Nishiyama A, Takeuchi S, Yamashita K, Ohtsubo K, *et al*: Distribution and activity of lenvatinib in brain tumor models of human anaplastic thyroid cancer cells in severe combined immune deficient mice. Mol Cancer Ther 18: 947-956, 2019.
38. Murayama D, Yamamoto Y, Matsui A, Yasukawa M, Okamoto S, Toda S and Iwasaki H: Lung cavitation in patients with anaplastic thyroid cancer treated with lenvatinib. Gland Surg 11: 963-969, 2022.
39. Datar S, Cabanillas M, Dadu R, Ost D and Grosu HB: Pulmonary cavitation in patients with thyroid cancer receiving antiangiogenic agents. BMC Cancer 20: 1181, 2020.
40. Cho JS, Park MH, Ryu YJ and Yoon JH: The neutrophil to lymphocyte ratio can discriminate anaplastic thyroid cancer against poorly or well differentiated cancer. Ann Surg Treat Res 88: 187-192, 2015.

41. Fukuda N, Toda K, Fujiwara YU, Wang X, Ohmoto A, Urasaki T, Hayashi N, Sato Y, Nakano K, Yunokawa M, *et al*: Neutrophil-to-lymphocyte ratio as a prognostic marker for anaplastic thyroid cancer treated with lenvatinib. In Vivo 34: 2859-2864, 2020.
42. Yamazaki H, Iwasaki H, Suganuma N, Toda S, Masudo K, Nakayama H, Rino Y and Masuda M: Inflammatory biomarkers and dynamics of neutrophil-to-lymphocyte ratio in lenvatinib treatment for anaplastic thyroid carcinoma. Gland Surg 10: 852-860, 2021.
43. Tomoda C, Sugino K, Kitagawa W, Nagahama M and Ito K: The time series behavior of neutrophil-to-lymphocyte ratio in thyroid cancer patients on tyrosine kinase inhibitor therapy. ORL J Otorhinolaryngol Relat Spec 83: 347-353, 2021.
44. Tahara M, Kiyota N, Yamazaki T, Chayahara N, Nakano K, Inagaki L, Toda K, Enokida T, Minami H, Imamura Y, *et al*: Lenvatinib for anaplastic thyroid cancer. Front Oncol 7: 25, 2017.
45. Wirth LJ, Brose MS, Sherman EJ, Licitra L, Schlumberger M, Sherman SI, Bible KC, Robinson B, Rodien P, Godbert Y, *et al*: Open-label, single-arm, multicenter, phase II trial of lenvatinib for the treatment of patients with anaplastic thyroid cancer. J Clin Oncol 39: 2359-2366, 2021.
46. Eskens FA and Verweij J: The clinical toxicity profile of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) targeting angiogenesis inhibitors; a review. Eur J Cancer 42: 3127-3139, 2006.
47. Takahashi S, Tahara M, Ito K, Tori M, Kiyota N, Yoshida K, Sakata Y and Yoshida A: Safety and effectiveness of lenvatinib in 594 patients with unresectable thyroid cancer in an all-case post-marketing observational study in Japan. Adv Ther 37: 3850-3862, 2020.
48. Yamada K, Yamamoto N, Yamada Y, Nokihara H, Fujiwara Y, Hirata T, Koizumi F, Nishio K, Koyama N and Tamura T: Phase I dose-escalation study and biomarker analysis of E7080 in patients with advanced solid tumors. Clin Cancer Res 17: 2528-2537, 2011.
49. Kim M, Ahn J, Song DE, Yoon JH, Kang HC, Lim DJ, Kim WG, Kim TY, Kim WB, Shong YK, *et al*: Real-world experience of lenvatinib in patients with advanced anaplastic thyroid cancer. Endocrine 71: 427-433, 2021.
50. Enomoto K, Hirayama S, Kumashiro N, Jing X, Kimura T, Tamagawa S, Matsuzaki I, Murata SI and Hotomi M: Synergistic effects of lenvatinib (E7080) and MEK inhibitors against anaplastic thyroid cancer in preclinical models. Cancers (Basel) 13: 862, 2021.
51. Hong CM, Oh JM, Gangadaran P, Rajendran RL and Ahn BC: treatment effect of combining lenvatinib and vemurafenib for BRAF mutated anaplastic thyroid cancer. Int J Thyroidol 14: 127-134, 2021.
52. Zhang H and Chen D: Synergistic inhibition of MEK/ERK and BRAF V600E with PD98059 and PLX4032 induces sodium/iodide symporter (NIS) expression and radioiodine uptake in BRAF mutated papillary thyroid cancer cells. Thyroid Res 11: 13, 2018.
53. Song H, Zhang J, Ning L, Zhang H, Chen D, Jiao X and Zhang K: The MEK1/2 Inhibitor AZD6244 Sensitizes BRAF-mutant thyroid cancer to vemurafenib. Med Sci Monit 24: 3002-3010, 2018.
54. Su X, Liu J, Zhang H, Gu Q, Zhou X, Ji M and Yao D: Lenvatinib promotes the antitumor effect of doxorubicin in anaplastic thyroid cancer. Onco Targets Ther 13: 11183-11192, 2020.
55. Ulm R, Revenkova E, di Sansebastiano GP, Bechtold N and Paszkowski J: Mitogen-activated protein kinase phosphatase is required for genotoxic stress relief in Arabidopsis. Genes Dev 15: 699-709, 2001.
56. Wood CD, Thornton TM, Sabio G, Davis RA and Rincon M: Nuclear localization of p38 MAPK in response to DNA damage. Int J Biol Sci 5: 428-437, 2009.
57. Martino E, Casamassima G, Castiglione S, Cellupica E, Pantalone S, Papagni F, Rui M, Siciliano AM and Collina S: Vinca alkaloids and analogues as anti-cancer agents: Looking back, peering ahead. Bioorg Med Chem Lett 28: 2816-2826, 2018.
58. Shaked Y, Emmenegger U, Man S, Cervi D, Bertolini F, Ben-David Y and Kerbel RS: Optimal biologic dose of metronomic chemotherapy regimens is associated with maximum antiangiogenic activity. Blood 106: 3058-3061, 2005.
59. Di Desidero T, Orlandi P, Gentile D, Banchi M, Alì G, Kusmic C, Armanetti P, Cayme GJ, Menichetti L, Fontanini G, *et al*: Pharmacological effects of vinorelbine in combination with lenvatinib in anaplastic thyroid cancer. Pharmacol Res 158: 104920, 2020.
60. Wu S and Fu L: Tyrosine kinase inhibitors enhanced the efficacy of conventional chemotherapeutic agent in multidrug resistant cancer cells. Mol Cancer 17: 25, 2018.
61. Ryder M, Ghossein RA, Ricarte-Filho JC, Knauf JA and Fagin JA: Increased density of tumor-associated macrophages is associated with decreased survival in advanced thyroid cancer. Endocr Relat Cancer 15: 1069-1074, 2008.
62. Eubank TD, Galloway M, Montague CM, Waldman WJ and Marsh CB: M-CSF induces vascular endothelial growth factor production and angiogenic activity from human monocytes. J Immunol 171: 2637-2643, 2003.
63. Abbasifarid E, Sajjadi-Jazi SM, Beheshtian M, Samimi H, Larijani B and Haghpanah V: The role of ATP-binding cassette transporters in the chemoresistance of anaplastic thyroid cancer: A systematic review. Endocrinology 160: 2015-2023, 2019.
64. Iyer PC, Dadu R, Gule-Monroe M, Busaidy NL, Ferrarotto R, Habra MA, Zafereo M, Williams MD, Gunn GB, Grosu H, *et al*: Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma. J Immunother Cancer 6: 68, 2018.
65. French JD, Bible K, Spitzweg C, Haugen BR and Ryder M: Leveraging the immune system to treat advanced thyroid cancers. Lancet Diabetes Endocrinol 5: 469-481, 2017.
66. Suzuki S, Shibata M, Gonda K, Kanke Y, Ashizawa M, Ujiie D, Suzushino S, Nakano K, Fukushima T, Sakurai K, *et al*: Immunosuppression involving increased myeloid-derived suppressor cell levels, systemic inflammation and hypoalbuminemia are present in patients with anaplastic thyroid cancer. Mol Clin Oncol 1: 959-964, 2013.
67. Galdiero MR, Varricchi G and Marone G: The immune network in thyroid cancer. Oncoimmunology 5: e1168556, 2016.
68. Woyach JA, Kloos RT, Ringel MD, Arbogast D, Collamore M, Zwiebel JA, Grever M, Villalona-Calero M and Shah MH: Lack of therapeutic effect of the histone deacetylase inhibitor vorinostat in patients with metastatic radioiodine-refractory thyroid carcinoma. J Clin Endocrinol Metab 94: 164-170, 2009.
69. Lee YS, Kim SM, Kim BW, Chang HJ, Kim SY, Park CS, Park KC and Chang HS: Anti-cancer effects of HNHA and lenvatinib by the suppression of EMT-mediated drug resistance in cancer stem cells. Neoplasia 20: 197-206, 2018.
70. Brown WS, Akhand SS and Wendt MK: FGFR signaling maintains a drug persistent cell population following epithelial-mesenchymal transition. Oncotarget 7: 83424-83436, 2016.
71. Shibue T and Weinberg RA: EMT, CSCs, and drug resistance: The mechanistic link and clinical implications. Nat Rev Clin Oncol 14: 611-629, 2017.
72. Meidhof S, Brabletz S, Lehmann W, Preca BT, Mock K, Ruh M, Schüler J, Berthold M, Weber A, Burk U, *et al*: ZEB1-associated drug resistance in cancer cells is reversed by the class I HDAC inhibitor mocetinostat. EMBO Mol Med 7: 831-847, 2015.
73. Zhou G, Zhang F, Guo Y, Huang J, Xie Y, Yue S, Chen M, Jiang H and Li M: miR-200c enhances sensitivity of drug-resistant non-small cell lung cancer to gefitinib by suppression of PI3K/Akt signaling pathway and inhibites cell migration via targeting ZEB1. Biomed Pharmacother 85: 113-119, 2017.
74. Kwok G, Yau TC, Chiu JW, Tse E and Kwong YL: Pembrolizumab (Keytruda). Hum Vaccin Immunother 12: 2777-2789, 2016.
75. Dierks C, Seufert J, Aumann K, Ruf J, Klein C, Kiefer S, Rassner M, Boerries M, Zielke A, la Rosee P, *et al*: Combination of lenvatinib and pembrolizumab is an effective treatment option for anaplastic and poorly differentiated thyroid carcinoma. Thyroid 31: 1076-1085, 2021.
76. Kim SY, Kim SM, Kim JW, Lee IJ, Jeon TJ, Chang H, Kim BW, Lee YS, Chang HS and Park CS: Survival with lenvatinib for the treatment of progressive anaplastic thyroid cancer: A single-center, retrospective analysis. Front Endocrinol (Lausanne) 11: 599, 2020.
77. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, *et al*: Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 372: 621-630, 2015.
78. Are C and Shaha AR: Anaplastic thyroid carcinoma: Biology, pathogenesis, prognostic factors, and treatment approaches. Ann Surg Oncol 13: 453-464, 2006.
79. Kebebew E, Greenspan FS, Clark OH, Woeber KA and McMillan A: Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer 103: 1330-1335, 2005.

80. Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A and Suzuki S: Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC research consortium of Japan cohort study of 677 patients. World J Surg 36: 1247-1254, 2012.
81. Liu L, Wang E, Li L, Chen D, Peng K, Wang M and Han G: As clinical markers, hand-foot-skin reaction and diarrhea can predict better outcomes for hepatocellular carcinoma patients receiving transarterial chemoembolization plus sorafenib. Can J Gastroenterol Hepatol 2019: 2576349, 2019.
82. Robinson B, Schlumberger M, Wirth LJ, Dutcus CE, Song J, Taylor MH, Kim SB, Krzyzanowska MK, Capdevila J, Sherman SI and Tahara M: Characterization of tumor size changes over time from the phase 3 study of lenvatinib in thyroid cancer. J Clin Endocrinol Metab 101: 4103-4109, 2016.
83. Hamidi S, Dadu R, Zafereo ME, Ferrarotto R, Wang JR, Maniakas A, Gunn GB, Lee A, Spiotto MT, Iyer PC, *et al*: Initial management of BRAF V600E-variant anaplastic thyroid cancer: The FAST multidisciplinary group consensus statement. JAMA Oncol 10: 1264-1271, 2024.
84. Zhao X, Wang JR, Dadu R, Busaidy NL, Xu L, Learned KO, Chasen NN, Vu T, Maniakas A, Eguia AA, *et al*: Surgery after BRAF-directed therapy is associated with improved survival in BRAF(V600E) mutant anaplastic thyroid cancer: A single-center retrospective cohort study. Thyroid 33: 484-491, 2023.
85. Cabanillas ME, Williams MD, Gunn GB, Weitzman SP, Burke L, Busaidy NL, Ying AK, Yiin YH, William WN, Lu C and Lai SY: Facilitating anaplastic thyroid cancer specialized treatment: A model for improving access to multidisciplinary care for patients with anaplastic thyroid cancer. Head Neck 39: 1291-1295, 2017.
86. Yamazaki H, Yokose T, Hayashi H, Iwasaki H, Osanai S, Suganuma N, Nakayama H, Masudo K, Rino Y and Masuda M: Expression of fibroblast growth factor receptor 4 and clinical response to lenvatinib in patients with anaplastic thyroid carcinoma: A pilot study. Eur J Clin Pharmacol 76: 703-709, 2020.
87. Iwasaki H, Toda S, Suganuma N, Murayama D, Nakayama H and Masudo K: Lenvatinib vs. palliative therapy for stage IVC anaplastic thyroid cancer. Mol Clin Oncol 12: 138-143, 2020.
88. Yang J and Barletta JA: Anaplastic thyroid carcinoma. Semin Diagn Pathol 37: 248-256, 2020.
89. Hu S, Helman SN, Hanly E and Likhterov I: The role of surgery in anaplastic thyroid cancer: A systematic review. Am J Otolaryngol 38: 337-350, 2017.
90. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 372: n71, 2021.
91. Iwasaki H, Yamazaki H, Takasaki H, Suganuma N, Nakayama H, Toda S and Masudo K: Lenvatinib as a novel treatment for anaplastic thyroid cancer: A retrospective study. Oncol Lett 16: 7271-7277, 2018.
92. Koyama S, Miyake N, Fujiwara K, Morisaki T, Fukuhara T, Kitano H and Takeuchi H: Lenvatinib for anaplastic thyroid cancer and lenvatinib-induced thyroid dysfunction. Eur Thyroid J 7: 139-144, 2018.
93. Iyer PC, Dadu R, Ferrarotto R, Busaidy NL, Habra MA, Zafereo M, Gross N, Hess KR, Gule-Monroe M, Williams MD and Cabanillas ME: Real-world experience with targeted therapy for the treatment of anaplastic thyroid carcinoma. Thyroid 28: 79-87, 2018.