Systematic Review and Meta-Analysis

Medicine

OPEN

The efficacy and safety of antiangiogenesis tyrosine kinase inhibitors in patients with advanced anaplastic thyroid cancer

A meta-analysis of prospective studies

Ru-Bo Cao, MS[a], Yao Ge, MS[b], Wen-Xuan Zhang, MS[a], Guo-He Lin, MD[c], Bo-Hua Kuang, MD[a], Bi-Cheng Wang, MD[a,*]

Abstract

Background: The poor prognosis of anaplastic thyroid cancer (ATC) patients is associated with limited effective therapeutic strategies. Multiple antiangiogenesis tyrosine kinase inhibitors (TKIs) have been applied in later-line treatment of ATC; however, the results reported in clinical trials were controversial. In this study, we reconstructed the patient-level data to pooled-analyze the survival data, responses, and adverse events.

Methods: Online databases (PubMed, Web of Science, Embase, and Cochrane CENTRAL) were searched on September 03, 2023. R software combined with the "metaSurvival" and "meta" packages were used to reconstruct the survival curves and summarize the response rates. The primary endpoints were progression-free survival (PFS) and overall survival (OS). The secondary endpoints were survival rate, objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events.

Results: Six prospective clinical trials involving 140 ATC patients were enrolled. Four types of TKIs (imatinib, pazopanib, sorafenib, and lenvatinib) were included. When advanced ATC patients were treated with the TKIs, the median OS was 4.8 months and the median PFS was 2.6 months. The pooled ORR and DCR were 9% and 53%. Hypertension, decreased appetite, rash, and lymphopenia were the most common grade ≥ 3 treatment-related adverse events.

Conclusion: Mono-anitangiogenesis TKI therapy showed limited improvements in treating advanced ATC patients. Combining antiangiogenesis TKI therapy with chemotherapy, radiotherapy, or immunotherapy could be the direction of future studies.

Abbreviations: ATC = anaplastic thyroid cancer, DCR = disease control rate, NGS = next-generation sequencing, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, TKI = tyrosine kinase inhibitor.

Keywords: anaplastic thyroid cancer, reconstructed patient-level analysis, responses, survival outcomes, tyrosine kinase inhibitor

1. Introduction

Notably, anaplastic thyroid cancer (ATC) is a type of aggressive malignant solid tumor with an extremely poor prognosis. Front-line therapeutic strategies include surgery, radiotherapy, and chemotherapy (anthracyclines, taxanes, and platinum compounds).[1] However, survival time remains critically short due to the rapid disease progression. How to prolong the survival of patients with advanced ATC becomes an emergency issue, even if the incidence rate is low.

Numerous efforts, like in vitro and in vivo studies, have greatly contributed to the treatment of ATC. Disrupting or cutting MAPK, PI3K/AKT/mTOR, JAK/STAT3/NF-κB, RAF-MEK-ERK, and Wnt/β-catenin signaling pathways could be the main directions of targeted therapy for ATC.[2–6] Almost all the basic research exhibited promising data on suppressing the proliferation and invasion of ATC cells and showed readers potentially novel therapeutic strategies for patients with ATC. However, before these ideas can be applied in clinical practice, there is a long way to go.

R-BC and YG contributed equally to this work.

This study was supported by the National Natural Science Foundation of China (No. 82302956 to Bi-Cheng Wang).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

[a] Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [b] Wuhan Mental Health Center, Wuhan, China, [c] Department of Oncology, the Second Affiliated Hospital of Anhui Medical University, Hefei, China.

** Correspondence: Bi-Cheng Wang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan 430022, China (e-mail: bcsnowell@163.com).*

How to cite this article: Cao R-B, Ge Y, Zhang W-X, Lin G-H, Kuang B-H, Wang B-C. The efficacy and safety of antiangiogenesis tyrosine kinase inhibitors in patients with advanced anaplastic thyroid cancer: A meta-analysis of prospective studies. Medicine 2024;103:31(e38679).

Received: 1 January 2024 / Received in final form: 8 May 2024 / Accepted: 31 May 2024

http://dx.doi.org/10.1097/MD.0000000000038679

Multiple tyrosine kinase inhibitors (TKIs) have been applied to advanced ATC patients to elevate survival and response rates. For instance, BRAF/MEK inhibitors,[7,8] NTRK inhibitors,[9] RET inhibitors,[10] mTOR inhibitors,[11] antiangiogenesis TKIs,[12] and CDK 4/6 inhibitors.[13] Among these TKIs, antiangiogenic drugs (e.g., sorafenib, lenvatinib, regorafenib, imatinib, cabozantinib, donafenib, and apatinib) were most widely administrated. Nevertheless, the benefits of antiangiogenesis TKIs for advanced ATC patients remain controversial.

Although we have reviewed and shown the benefits of TKIs in real-world clinical practice,[14] it is necessary for us to collect the efficacy and safety data published in prospective clinical trials and reconstruct the survival outcomes to comprehensively display the application of antiangiogenesis TKIs in advanced ATC patients.

2. Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline.[15] Since the data used in the analysis were based on published clinical studies with ethical approvals and not original raw data, ethical approval for this analysis was unnecessary.

2.1. Literature search

A systematic literature search was performed to identify prospective clinical studies eligible for pooled analysis. This search was conducted in PubMed, Web of Science, Embase, and Cochrane CENTRAL databases on September 3, 2023. The search terms included "anaplastic thyroid cancer or anaplastic thyroid carcinoma," "tyrosine kinase inhibitor or sorafenib or lenvatinib or regorafenib or imatinib or cabozantinib or donafenib or apatinib," and "trial or study."

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: advanced ATC patients; patients receiving antiangiogenesis TKI treatment; available efficacy and safety data; prospective clinical studies published in English. Meeting abstracts and case reports were excluded.

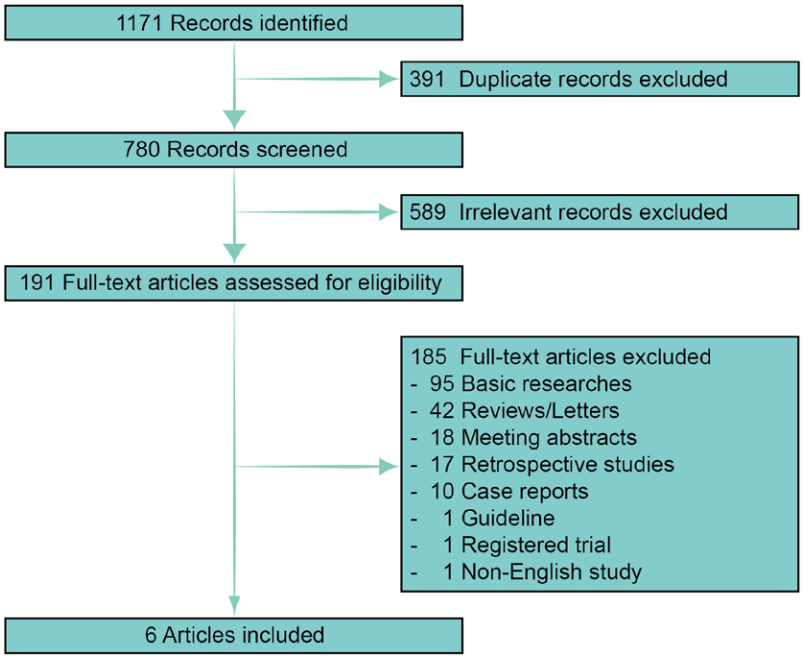

Figure 1. Flowchart of the searching and selecting process.

Table 1

Basic characteristics of enrolled clinical trials.

First author	Period	Design	No. patients	Median age (range)	Drug	Dose	Median PFS	Median OS
Huan T. Ha[16]	2004–2007	Phase 2 trial	11	65 (53–79)	Imatinib	400 mg orally twice daily	\	\
Keith C. Bible[17]	2008–2011	Multi-center single-arm phase 2 trial	16	66 (45–77)	Pazopanib	800 mg orally once daily	62 d	111 d
Panayiotis Savvides[18]	2005–2011	Multi-center phase 2 trial	20	59 (28–79)	Sorafenib	400 mg orally twice daily	1.9 mo (1.3–3.6)	3.9 mo (2.2–7.1)
Makoto Tahara[19]	2012–2015	Multi-center single-arm open-label phase 2 trial	17	65	Lenvatinib	24 mg orally once daily	7.4 mo (1.7–12.9)	10.6 mo (3.8–19.8)
Lori J. Wirth[20]	2016–2018	Multi-center open-label phase 2 trial	34	\	Lenvatinib	24 mg orally once daily	2.6 mo (1.4–2.8)	3.2 mo (2.8–8.2)
Takuya Higashiyama[21]	2016–2018	Multi-center single-arm open-label phase 2 trial	42	73 (39–89)	Lenvatinib	24 mg orally once daily	\	\

\ = not available, mo = months, OS = overall survival, PFS = progression-free survival.

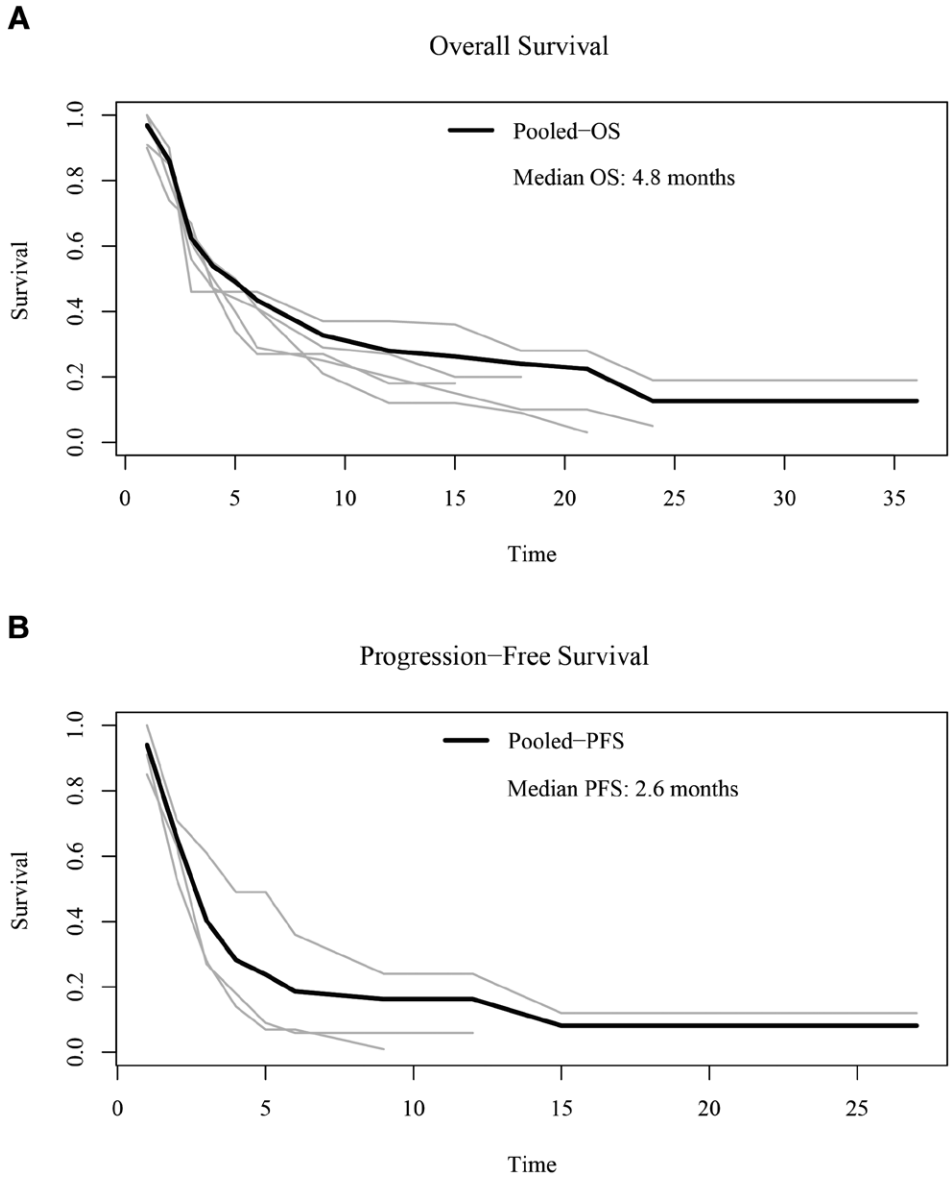

Figure 2. Reconstructed overall survival (OS, A) and progression-free survival (PFS, B) curves.

Table 2

Reconstructed survival rates of antiangiogenesis TKIs in ATC patients.

Survival rates (%)	OS	PFS
3 mo	62.46	40.38
6 mo	43.45	18.64
9 mo	32.71	16.30
12 mo	27.96	16.30
15 mo	26.24	8.15
18 mo	24.03	8.15
21 mo	22.45	8.15
24 mo	12.61	8.15

OS = overall survival, PFS = progression-free survival.

2.3. Data extraction

The detailed study design, number of patients, median age, therapeutic strategies, survival outcomes, responses, and treatment-related adverse events were collected. Kaplan–Meier curves were captured from the published papers and digitized using the Scanlt software (version 2.0.8.0).

2.4. Risk assessment

Funnel plots and Egger tests were applied to evaluate the publication bias.

2.5. Statistical analysis

R software (version 4.2.2) was used to conduct the analyses. Time-to-event data were reconstructed and analyzed by running the "metaSurvival" package. Odds ratios (OR) for response rates were calculated by running the "meta" package. A random-effects model was executed to reduce the heterogeneity.

3. Results

In this study, we identified 1171 records. In the first step, 780 records remained after 391 duplicate records were excluded. In the second step, 589 irrelevant records were excluded after screening the titles and abstracts. In the third step, 95 basic researches, 42 reviews/letters, 18 meeting abstracts, 17 retrospective studies, 10 case reports, 1 guideline, 1 registered trial, and 1 non-English study failed to meet the inclusion criteria.

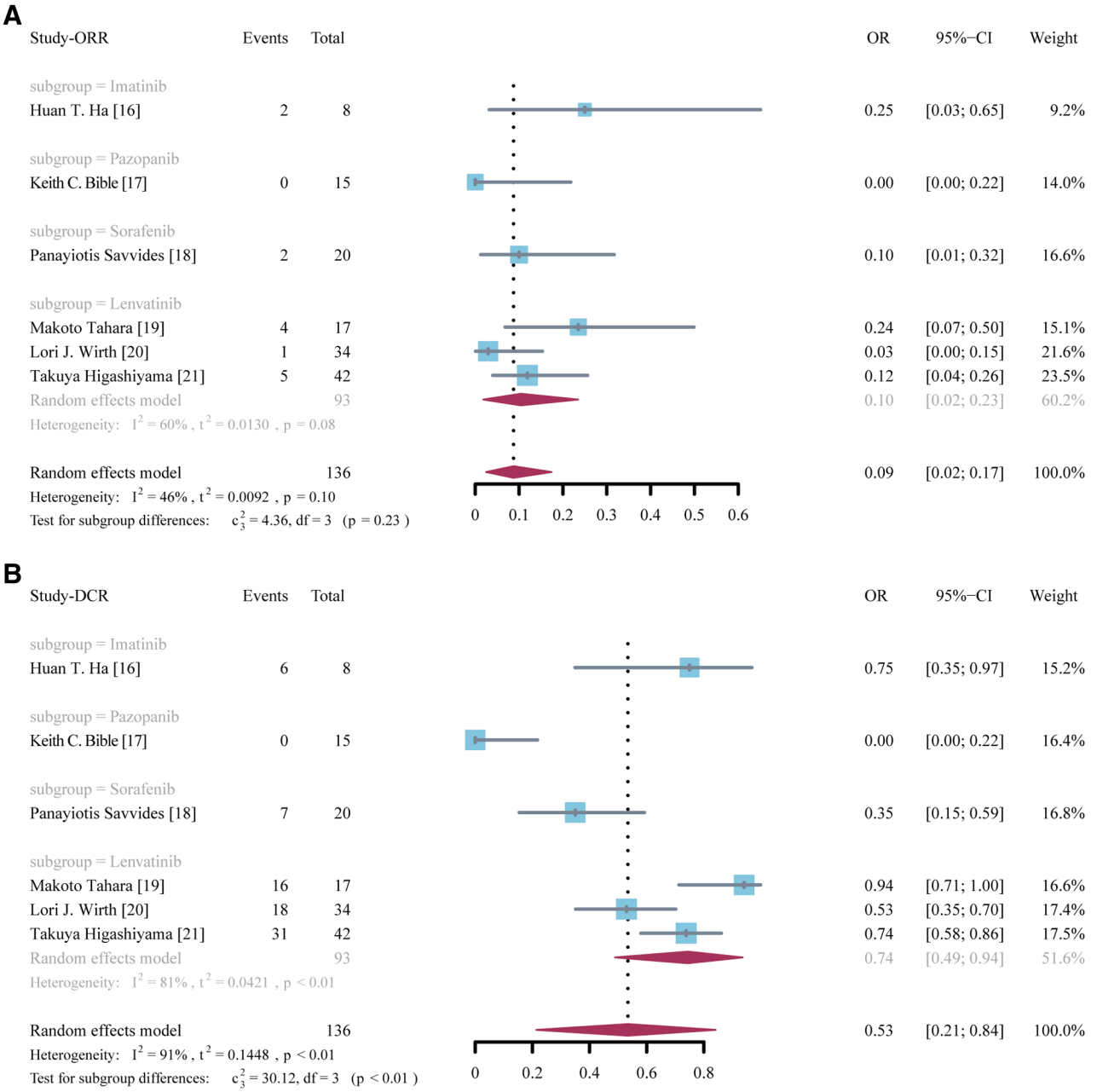

Figure 3. Forest plots of the pooled objective response rate (ORR, A) and disease control rate (DCR, B).

Finally, 6 full-text prospective clinical studies[16–21] were eligible for our analysis (Fig. 1).

All enrolled studies were phase 2 clinical trials involving 140 patients with advanced ATC. All enrolled patients were advanced ATC patients, and the TNM stage of the patients at the time of TKI therapy included 4A, 4B, and 4C. However, only 2 trials reported the stage distribution of the study participants. In addition, all of the eligible patients had received previous chemotherapy, radiotherapy, or surgery. In these studies, patients received imatinib, pazopanib, sorafenib, and lenvatinib, respectively. Detailed drug doses are displayed in Table 1. An important issue was that 4 of the 6 trials were halted. The main reasons comprised poor accrual, triggering the stopping rule, and an unmet response threshold.

Based on published data, we reconstructed patient-level data to exhibit the efficacy of TKIs in advanced ATC comprehensively. The median overall survival (OS) was 4.8 months (95% CI 2.74–8.84) (Fig. 2A), and 1 year OS rate was 27.96%. The median progression-free survival (PFS) was 2.62 months (95% CI unavailable) (Fig. 2B), and 1 year PFS rate was 16.30%. Table 2 lists the detailed survival rates of TKIs in treating patients with advanced ATC.

In Figure 3, forest plots showed that the objective response rate (ORR) and disease control rate (DCR) of TKIs were 9% (95% CI 2–17) and 53% (95% CI 21–84). Funnel plots and Egger tests did not find any publication bias.

The top 6 grades ≥ 3 treatment-related adverse events were collected and displayed in Table 3. The most common grade ≥ 3 treatment-related adverse events included hypertension, decreased appetite, rash, and lymphopenia. In addition, pharyngolaryngeal pain, fatigue, and proteinuria deserve our attention in clinical practice.

4. Discussion

In this reconstructed patient-level data analysis, TKIs showed a 2.6-month PFS and a 4.8-month OS in patients with advanced ATC, with an ORR of 9% and a DCR of 53%. As for the

Table 3

Top 6 grade ≥ 3 treatment-related adverse events.

Study	Drug	1	2	3	4	5	6
Huan T. Ha[16]	Imatinib	Lymphopenia 5/11	Edema 3/11	Anemia 2/11	Nausea/vomiting 2/11	Electrolyte abnormality 2/11	Syncope 2/11
Keith C. Bible[17]	Pazopanib	Hypertension 2/15	Pharyngo laryngeal pain 2/15				
Panayiotis Savvides[18]	Sorafenib	Rash/desquamation 3/20	Hyponatremia 2/20	Hypophosphatemia 2/20			
Makoto Tahara[19]	Lenvatinib	Hypertension 5/17	Decreased appetite 3/17	Thrombocytopenia 3/17			
Lori J. Wirth[20]	Lenvatinib	Hypertension 8/34	Asthenia 3/34	Proteinuria 2/34	Gamma-glutamyl transferase increased 2/34		
Takuya Higashiyama[21]	Lenvatinib	Decreased appetite 8/50	Fatigue 5/50	Hypertension 5/50	Proteinuria 4/50	Dyspnea 3/50	Aspiration pneumonia 3/50

disappointing PFS and ORR results, whether ATC patients may benefit from antiangiogenesis TKI therapy is warranted to explore.

In patients with BRAF V600E-mutant, dabrafenib plus trametinib achieved an excellent 56% ORR, with a median PFS of 6.7 months and a median OS of 14.5 months. Comparatively, most ATC patients are insensitive to the antiangiogenesis TKI treatment. Finding the accurate subgroup population who could benefit from each drug should be one of the future tasks. The next-generation sequencing (NGS) technique may help clinicians classify ATC patients and compare the differences between effective and ineffective patients who received TKIs.[22] Therefore, we encourage ATC patients to have an NGS detection at the beginning of disease diagnosis.

Combination therapy can be another therapeutic direction for ATC patients. Combining antiangiogenesis TKI therapy with chemotherapy, immunotherapy, or radiotherapy may further elevate the response rates and prolong survival time. For example, in the ATLEP trial,[23] 27 ATC patients were treated with lenvatinib plus pembrolizumab. The ORR and DCR were 51.9% and 96.3%. And the median PFS and OS were 9.5 months and 10.25 months. Although 25.9% (7/27) of the ATC patients were recorded to survive more than 2 years, an extremely short time between median PFS and OS meant that patients died quickly after disease progression. In a pilot study,[24] 13 ATC patients received tremelimumab plus durvalumab with stereotactic body radiotherapy. However, only 1 patient had stable disease, and the median OS was 14.5 weeks, indicating that dual immunotherapy plus radiotherapy failed to improve survival outcomes and responses. In an in vivo and in vitro study,[25] lenvatinib plus paclitaxel synergistically inhibited the proliferation of ATC cell lines and xenografts compared to lenvatinib or paclitaxel monotherapy. Thus, targeted therapy combined with chemotherapy may be a promising candidate therapeutic strategy for patients with advanced ATC.

The tolerability of TKIs in ATC patients should be another crucial challenge. For imatinib, the treatment was discontinued in 1 patient due to disease progression (progressive dysphagia).[16] For pazopanib, the discontinuation was mainly attributed to disease progression (12 patients) and treatment-related adverse events (hemorrhage [1 patient], hypertension [1 patient], and radiation recall tracheitis [1 patient]).[17] For lenvatinib, 15 patients discontinued due to treatment-related adverse events (detailed adverse events were unavailable).[19–21]

Several limitations existed in this study. Due to the rare incidence of ATC, the number of patients enrolled in each trial was limited, which might increase the bias of endpoints. All eligible studies were single-arm phase 2 trials, whereas randomized clinical trials may more effectively uncover the efficacy of TKIs in ATC patients. Four types of TKIs were analyzed in our study, and more data reported from other TKIs in future explorations may help complement our results.

Imatinib, pazopanib, sorafenib, and lenvatinib therapy did not show strong improvements in survival outcomes and responses in advanced ATC patients. More efforts are needed to break the bottleneck in treating ATC.

Acknowledgments

We thank Wang group for providing statistical support and for editing the manuscript.

Author contributions

Conceptualization: Guo-He Lin, Bi-Cheng Wang.
Data curation: Ru-Bo Cao, Yao Ge, Guo-He Lin, Bi-Cheng Wang.
Formal analysis: Yao Ge, Bi-Cheng Wang.
Funding acquisition: Bi-Cheng Wang.
Investigation: Yao Ge, Bi-Cheng Wang.
Methodology: Ru-Bo Cao, Yao Ge, Guo-He Lin, Bo-Hua Kuang, Bi-Cheng Wang.
Project administration: Ru-Bo Cao, Bo-Hua Kuang, Bi-Cheng Wang.
Resources: Ru-Bo Cao, Bo-Hua Kuang, Bi-Cheng Wang.
Software: Bo-Hua Kuang, Bi-Cheng Wang.
Supervision: Bo-Hua Kuang, Bi-Cheng Wang.
Validation: Bi-Cheng Wang.
Writing – original draft: Ru-Bo Cao, Yao Ge, Wen-Xuan Zhang, Guo-He Lin, Bo-Hua Kuang, Bi-Cheng Wang.
Writing – review & editing: Ru-Bo Cao, Yao Ge, Wen-Xuan Zhang, Guo-He Lin, Bo-Hua Kuang, Bi-Cheng Wang.

References

[1] Yuan J, Guo Y. Targeted therapy for anaplastic thyroid carcinoma: advances and management. Cancers (Basel). 2022;15:179.
[2] Petrulea MS, Plantinga TS, Smit JW, et al. PI3K/Akt/mTOR: a promising therapeutic target for non-medullary thyroid carcinoma. Cancer Treat Rev. 2015;41:707–13.
[3] Davidson CD, Bolf EL, Gillis NE, et al. Thyroid Hormone Receptor Beta Inhibits PI3K-Akt-mTOR signaling axis in anaplastic thyroid cancer via genomic mechanisms. J Endocr Soc. 2021;5:bvab102.

[4] Santarpia L, Lippman SM, El-Naggar AK. Targeting the MAPK-RAS-RAF signaling pathway in cancer therapy. Expert Opin Ther Targets. 2012;16:103–19.
[5] Yu W, Imoto I, Inoue J, et al. A novel amplification target, DUSP26, promotes anaplastic thyroid cancer cell growth by inhibiting p38 MAPK activity. Oncogene. 2007;26:1178–87.
[6] Liu D, Xing J, Trink B, et al. BRAF mutation-selective inhibition of thyroid cancer cells by the novel MEK inhibitor RDEA119 and genetic-potentiated synergism with the mTOR inhibitor temsirolimus. Int J Cancer. 2010;127:2965–73.
[7] Jeon YK, Jung HA, Park S, et al. 1655P Dabrafenib and trametinib in patients with metastatic BRAFV600E-mutated thyroid cancer. Ann Oncol. 2022;33:S1299.
[8] Choi Y-S, Kwon H, You M-H, et al. Effects of dabrafenib and erlotinib combination on treatment on anaplastic thyroid carcinoma. Endocr Relat Cancer. 2022;29:307–19.
[9] Waguespack SG, Drilon A, Lin JJ, et al. Efficacy and safety of larotrectinib in patients with TRK fusion-positive thyroid carcinoma. Eur J Endocrinol. 2022;186:631–43.
[10] Dias-Santagata D, Lennerz JK, Sadow PM, et al. Response to RET-specific therapy in RET fusion-positive anaplastic thyroid carcinoma. Thyroid. 2020;30:1384–9.
[11] Hanna GJ, Busaidy NL, Chau NG, et al. Genomic correlates of response to everolimus in aggressive radioiodine-refractory thyroid cancer: a phase II Study. Clin Cancer Res. 2018;24:1546–53.
[12] Huang D, Zhang J, Zheng X, et al. Efficacy and safety of lenvatinib in anaplastic thyroid carcinoma: a meta-analysis. Front Endocrinol (Lausanne). 2022;13:920857.
[13] Wong K, Di Cristofano F, Ranieri M, et al. PI3K/mTOR inhibition potentiates and extends palbociclib activity in anaplastic thyroid cancer. Endocr Relat Cancer. 2019;26:425–36.
[14] Kuang BH, Zhang WX, Lin GH, et al. Tyrosine kinase inhibitors in patients with advanced anaplastic thyroid cancer: an effective analysis based on real-world retrospective studies. Front Endocrinol (Lausanne). 2024;15:1345203.
[15] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj. 2015;350:g7647.
[16] Ha HT, Lee JS, Urba S, et al. A phase II study of imatinib in patients with advanced anaplastic thyroid cancer. Thyroid. 2010;20:975–80.
[17] Bible KC, Suman VJ, Menefee ME, et al. A multi-institutional phase 2 trial of pazopanib monotherapy in advanced anaplastic thyroid cancer. J Clin Endocrinol Metab. 2012;97:3179–84.
[18] Savvides P, Nagaiah G, Lavertu P, et al. Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. Thyroid. 2013;23:600–4.
[19] Tahara M, Kiyota N, Yamazaki T, et al. Lenvatinib for anaplastic thyroid cancer. Front Oncol. 2017;7:25.
[20] Wirth LJ, Brose MS, Sherman EJ, et al. Open-label, single-arm, multicenter, phase II trial of lenvatinib for the treatment of patients with anaplastic thyroid cancer. J Clin Oncol. 2021;39:2359–66.
[21] Higashiyama T, Sugino K, Hara H, et al. Phase II study of the efficacy and safety of lenvatinib for anaplastic thyroid cancer (HOPE). Eur J Cancer (Oxford, England : 1990). 2022;173:210–8.
[22] Singh A, Ham J, Po JW, et al. The genomic landscape of thyroid cancer tumourigenesis and implications for immunotherapy. Cells. 2021;10:1082.
[23] Dierks C, Ruf J, Seufert J, et al. Phase II ATLEP trial: Final results for lenvatinib/pembrolizumab in metastasized anaplastic and poorly differentiated thyroid carcinoma. Ann Oncol. 2022;33:S1295–S1295.
[24] Lee NY, Riaz N, Wu V, et al. A Pilot Study of Durvalumab (MEDI4736) with tremelimumab in combination with image-guided stereotactic body radiotherapy in the treatment of metastatic anaplastic thyroid cancer. Thyroid. 2022;32:799–806.
[25] Jing C, Gao Z, Wang R, et al. Lenvatinib enhances the antitumor effects of paclitaxel in anaplastic thyroid cancer. Am J Cancer Res. 2017;7:903–12.