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TARGETED THERAPIES VS. STANDARD TYROSINE KINASE INHIBITORS IN ADVANCED THYROID CANCER: A COMPARATIVE REVIEW OF UPDATED FDA APPROVALS AND NCCN GUIDELINES

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ABSTRACT

Background: Advanced thyroid cancer, including radioiodine-refractory differentiated thyroid cancer (RR-DTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC), has historically been associated with poor outcomes due to limited treatment options. The advent of tyrosine kinase inhibitors (TKIs) has revolutionized the systemic therapy landscape for these aggressive malignancies. **Objective:** This narrative review aims to compare the efficacy, safety, and clinical utility of standard multikinase inhibitors (MKIs) with newer, highly selective targeted therapies in the management of advanced thyroid cancer. It provides a critical synthesis of updated FDA approvals and the latest NCCN Clinical Practice Guidelines. **Methods:** A comprehensive literature search was conducted in PubMed, focusing on peer-reviewed articles, clinical trials, and systematic reviews published between 2020 and 2025. Key search terms included "advanced thyroid cancer," "targeted therapy," "tyrosine kinase inhibitors," "FDA approval," and "NCCN guidelines." **Key Findings:** The review confirms that MKIs like lenvatinib and sorafenib remain the standard first-line therapy for RR-DTC due to robust progression-free survival (PFS) benefits, albeit with significant toxicity. However, the treatment paradigm is shifting toward precision medicine. Highly selective inhibitors targeting specific driver mutations—such as selpercatinib and pralsetinib for RET-altered tumors, dabrafenib/trametinib for BRAF V600E-mutant ATC, and larotrectinib for NTRK fusions—demonstrate superior response rates and more favorable tolerability profiles. Consequently, NCCN guidelines have increasingly prioritized these biomarker-driven therapies. **Conclusion:** While standard MKIs continue to play a crucial role, the future of advanced thyroid cancer treatment lies in highly selective targeted therapies guided by comprehensive molecular profiling. This shift promises improved clinical outcomes and quality of life, though challenges such as acquired resistance and equitable access to molecular testing and novel agents remain.

KEYWORDS: Advanced thyroid cancer, Radioiodine-refractory differentiated thyroid cancer (RR-DTC), Medullary thyroid cancer (MTC).

1. INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, with a steadily increasing global incidence over recent decades.[1] While the majority of patients present with well-differentiated histotypes (e.g., papillary thyroid cancer) that have an excellent prognosis, a clinically significant subset—approximately 5–10%—develops advanced, metastatic disease that becomes refractory to standard treatments such as surgery and radioactive iodine (RAI).[2] These aggressive forms, including radioiodine-refractory differentiated thyroid cancer (RR-DTC), medullary thyroid cancer (MTC), and the highly lethal anaplastic thyroid cancer (ATC), have historically been associated with very poor outcomes and limited therapeutic options.[3]

Until the last decade, the systemic treatment landscape for these patients was sparse, relying on conventional cytotoxic chemotherapy with modest efficacy.[4] The breakthrough came with the development of tyrosine kinase inhibitors (TKIs), which target multiple pathways involved in tumor growth and angiogenesis.[5] Multikinase inhibitors (MKIs) such as sorafenib and lenvatinib were among the first to demonstrate significant improvements in progression-free survival (PFS) in pivotal phase III trials, thereby establishing targeted therapy as a viable option for RR-DTC.[6]

More recently, the treatment paradigm has undergone another profound shift with the advent of precision medicine.[7] Deep genomic characterization of thyroid tumors has revealed several actionable driver mutations, including BRAF V600E, RET alterations, and NTRK fusions.[8] This molecular understanding has led to the development of highly selective inhibitors that precisely target these oncogenic drivers.[9] Agents like selpercatinib, pralsetinib, dabrafenib, and trametinib have shown remarkable efficacy in mutation-selected patient populations, often with more favorable safety profiles than their multi-targeted predecessors.[10]

Consequently, clinical decision-making has become increasingly complex.[11] Oncologists must now navigate a growing armamentarium of drugs, comparing the robust but less specific efficacy of standard MKIs against the high response rates of newer, mutation-specific therapies.[12] The National Comprehensive Cancer Network (NCCN) guidelines have evolved to incorporate these advances, recommending biomarker testing to guide therapy.[13] This narrative review aims to provide a comparative analysis of standard TKIs and newer targeted agents in advanced thyroid cancer, focusing on their efficacy, safety, and positioning within updated FDA approvals and NCCN guidelines. By synthesizing current evidence, this review seeks to inform clinical practice and highlight future directions in the management of this challenging disease.

2. METHODOLOGY

This narrative review was conducted through a systematic search of the PubMed database, focusing on literature published between 2020 and April 2026. The search strategy employed a combination of MeSH terms and keywords, including “advanced thyroid cancer,” “targeted therapy,” “tyrosine kinase inhibitors,” “multikinase inhibitors,” “radioiodine-refractory differentiated thyroid cancer,” “medullary thyroid cancer,” “anaplastic thyroid cancer,” “FDA approval,” and “NCCN guidelines.” Only peer-reviewed articles, phase II/III clinical trials, systematic reviews, meta-analyses, and official guideline documents were considered. Additionally, the reference lists of retrieved articles were manually screened to identify further relevant studies. Data extraction focused on comparative measures of efficacy (e.g., progression-free survival, objective response rate), safety profiles (adverse events), and guideline recommendations. Given the narrative nature of this review, the synthesis of evidence is qualitative, providing a comprehensive overview and critical analysis of the current literature.

3. DISCUSSION

3.1. Standard Multikinase Inhibitors: The Established Cornerstone

For over a decade, multikinase inhibitors (MKIs) have served as the foundational systemic therapy for advanced thyroid cancer.[14] The two most prominent agents, lenvatinib and sorafenib, are approved for RR-DTC and have demonstrated unequivocal efficacy in landmark phase III trials.[15] The SELECT trial, which established lenvatinib as a category 1 preferred first-line option in the NCCN guidelines, showed a remarkable improvement in median PFS compared to placebo (18.3 vs. 3.6 months), with an objective response rate (ORR) of 65%.[16] Sorafenib, based on the DECISION trial, also showed a PFS benefit (10.8 vs. 5.8 months), though with a lower ORR of 12.2%.[6] In the second-line setting, cabozantinib has been approved for RR-DTC based on the COSMIC-311 trial, offering a PFS of 11 months for patients who progress on prior MKI therapy.[17] A recent Bayesian network meta-analysis reaffirmed that lenvatinib ranks first among all evaluated TKIs for both PFS and ORR in RAIR-DTC, confirming its position as a highly potent agent.[3] For MTC, vandetanib and cabozantinib are established MKIs that have significantly improved outcomes in this patient population.[5] While highly effective, the broad target spectrum of MKIs is a double-edged sword, contributing to a high incidence of grade ≥3 adverse events, which is a major limitation of this class.[11]

3.2. Selective RET Inhibitors: A Precision Paradigm for RET-Driven Cancers

The identification of RET mutations (in MTC) and RET fusions (in DTC) as key oncogenic drivers has led to a transformative shift in treatment.[9] The highly selective RET inhibitors selpercatinib and pralsetinib are now the only FDA-approved drugs specifically targeting RET-

altered thyroid cancers.[18] Clinical trials, most notably LIBRETTO-001 and LIBRETTO-531, have demonstrated superior efficacy, safety, and tolerability compared to the less specific MKIs, with overall response rates exceeding 84% in treatment-naïve RET-mutant MTC and reaching 95% in RET fusion-positive DTC.[5] A systematic review and meta-analysis of four studies (560 patients) confirmed this remarkable activity, showing a 1-year PFS of 84%, an ORR of 69%, and a disease control rate (DCR) of 93%.[6] Based on this compelling data, selpercatinib is now recommended as a first-line therapy for advanced RET-mutant MTC and as a second-line option for RAIR DTC by both the FDA and the European Medicines Agency (EMA).[18] The recent FDA clearance of pralsetinib for RET-mutant thyroid cancer further expands these options.[7] The high potency and improved tolerability of these agents have made them the preferred choice for patients with actionable RET alterations, representing a major success for precision oncology in thyroid cancer.

3.3. BRAF and MEK Inhibition in BRAF V600E-Mutant Disease

The BRAF V600E mutation is the most common actionable alteration in thyroid cancer, present in 40% to 60% of DTC and frequently enriched in RAIR tumors.[2] The combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib has shown remarkable efficacy in this molecular subset, particularly in the context of ATC, one of the most lethal human malignancies.[10] In the phase II ROAR basket study, the combination achieved an ORR of 63% in patients with BRAF V600E-mutant ATC, transforming the prognosis for this previously treatment-refractory population.[8] This led to a tumor-agnostic FDA approval in 2022 for BRAF V600E-mutant solid tumors, including thyroid cancer.[10] In the context of DTC, the use of dabrafenib/trametinib is an area of active investigation and evolving clinical practice.[2] Many physicians are transitioning from lenvatinib to frontline BRAF-targeted therapy based on a general preference for targeted therapy and a more tolerable toxicity profile.[2] Ongoing research is focused on determining the optimal sequencing of these agents, particularly whether they should be used as first-line therapy or reserved for patients who progress on MKIs.[19]

3.4. Comparative Efficacy: PFS, ORR, and OS

When comparing the efficacy of standard MKIs versus selective inhibitors, a nuanced picture emerges.[3] For unselected RR-DTC populations, lenvatinib offers a significant PFS advantage (median of 18.3 months) and a high ORR (65%).[16] However, in biomarker-selected populations, selective inhibitors achieve even more impressive response rates.[5] For instance, selpercatinib yields an ORR of up to 95% in RET fusion-positive DTC, and dabrafenib/trametinib shows an ORR of 63% in BRAF V600E-mutant ATC, a disease where standard MKIs have limited activity.[8,18] It is important to note that no targeted therapy, including MKIs, has yet demonstrated a statistically significant improvement in overall survival (OS) in phase III trials for RAIR-DTC.[4] While this may be attributed to crossover effects and the prolonged post-progression survival of these patients, it remains a critical point.[15] The primary endpoints for regulatory approval and clinical decision-making in this space remain PFS, ORR, and quality of life.[12] Future trials with longer follow-up and appropriate statistical designs are needed to definitively determine if the high ORRs achieved with selective agents translate into an OS benefit.[17]

3.5. Safety and Tolerability: A Critical Trade-Off

The safety profiles of TKIs represent a critical factor in treatment selection and patient management.[11] Standard MKIs, due to their multi-targeted nature, particularly against VEGFR, are associated with a high burden of toxicity.[14] In the SELECT trial, 76% of patients experienced grade ≥3 treatment-related adverse events (AEs), most commonly hypertension, diarrhea, and fatigue.[16] Hypertension of any grade, for example, has been reported in 70% to 75% of patients in clinical trials of lenvatinib.[11] These toxicities often require aggressive supportive care and frequent dose reductions or interruptions, which can impact treatment efficacy and patient quality of life.[4]

In contrast, highly selective inhibitors are designed to have a more favorable tolerability profile by sparing off-target effects.[9] The meta-analysis of RET inhibitors reported lower rates of grade ≥3 AEs, with hypertension (16%), diarrhea (3%), and increased ALT (11%).[6] Similarly, the dabrafenib/trametinib combination is generally well-tolerated.[8] This improved tolerability translates to fewer dose interruptions, better patient adherence, and a higher likelihood of maintaining dose intensity, which is crucial for durable disease control.[19] For many patients, the superior safety profile of selective agents is a decisive factor, particularly when comparing a highly toxic but effective MKI against a highly effective and well-tolerated targeted therapy.[12] The clinical challenge lies in balancing the broad efficacy of MKIs in unselected populations against the precision and tolerability of newer agents in mutation-selected patients.[2]

3.6. Mechanisms of Acquired Resistance

Despite the high initial response rates to both MKIs and selective inhibitors, acquired resistance inevitably develops, curtailing long-term disease control.[13] Understanding these mechanisms is crucial for developing next-generation therapies and rational combination strategies.[17] In the context of selective RET inhibitors, resistance often arises through on-target mutations in the RET kinase domain, such as solvent front mutations (e.g., G810R/S/C) that sterically hinder drug binding.[12] Off-target resistance mechanisms, such as the activation of bypass signaling pathways (e.g., MET amplification), have also been identified.[18] For BRAF/MEK inhibition, resistance can occur through the

induction of RAS mutations, which reactivate the MAPK pathway, or through the upregulation of alternative signaling cascades like the PI3K/AKT pathway.[8]

For MKIs, which target multiple kinases, resistance is more complex and less well-defined, but it is thought to involve the upregulation of alternative angiogenic pathways and changes in the tumor microenvironment.[14] The identification of specific resistance mechanisms is increasingly guiding post-progression therapy.[13] For example, the development of second- and third-generation RET inhibitors (e.g., LOXO-260, enbezotinib) is underway to overcome on-target resistance mutations.[18] Similarly, combination therapies that simultaneously target the primary driver and a bypass pathway are being investigated.[17] Routine molecular profiling of resistant tumors, through liquid or tissue biopsy, is becoming an essential clinical tool to inform these therapeutic pivots and optimize sequential treatment strategies.[19]

4. Future Directions and Recommendations

The future of advanced thyroid cancer management lies in further refining precision medicine and overcoming current limitations. First, the development and clinical validation of next-generation TKIs that can overcome common acquired resistance mutations are of paramount importance. Several next-generation RET inhibitors are already in early-phase clinical trials.[18] Second, exploring rational combination therapies will be key to enhancing efficacy and preventing or delaying resistance. Promising strategies include combining selective inhibitors with immunotherapy (e.g., anti-PD-1 antibodies), which has shown synergistic potential in early studies, and pairing them with redifferentiation agents to restore RAI avidity.[20] Third, expanding the reach of precision medicine requires universal access to comprehensive molecular testing, such as next-generation sequencing (NGS), to identify all patients who could benefit from targeted therapies.[9] Fourth, investigating the neoadjuvant use of potent targeted therapies to downstage locally advanced tumors and facilitate R0/R1 resection is a promising area of clinical research.[2] Finally, future clinical trial design must evolve to include biomarker-enriched populations and incorporate patient-reported outcomes to better capture the impact of therapies on quality of life.[12]

5. CONCLUSION

The treatment landscape for advanced thyroid cancer has been revolutionized by the development of targeted therapies. Standard multikinase inhibitors like lenvatinib and sorafenib have established themselves as effective first-line options for RR-DTC, providing significant PFS benefits. However, their use is often limited by a high burden of toxicity. The advent of highly selective inhibitors targeting specific driver mutations, including RET and BRAF V600E, has ushered in a new era of precision oncology. These agents, such as selpercatinib and dabrafenib/trametinib, offer superior response rates, improved tolerability, and better quality of life for patients with actionable alterations. NCCN guidelines have adapted to this paradigm shift, increasingly recommending biomarker-driven therapy. The primary clinical challenge has thus moved from a lack of effective drugs to the optimal sequencing and selection of therapies for individual patients. Despite these advances, acquired resistance and inequitable access to molecular testing and novel agents remain significant hurdles. Future efforts must focus on developing next-generation inhibitors to combat resistance, exploring rational drug combinations, and ensuring that all patients can benefit from the promise of precision medicine. The future of advanced thyroid cancer treatment is undoubtedly personalized, and continued research and innovation will be essential to further improve outcomes and ultimately, cure more patients.

Ethical statement

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.

Disclaimer

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