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EDITORIAL

Anaplastic thyroid cancer: Unveiling advances in diagnosis and management

Treshita Dey, Budhi Singh Yadav

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Abstract

The review article by Pavlidis *et al* published in *World J Clin Oncol* provides a meticulous analysis of the intricacies surrounding anaplastic carcinoma of the thyroid. Thyroid carcinoma encompasses a spectrum of diseases, each characterized by distinct behaviors and outcomes. Diagnostic approaches encompass a diverse array of tools. Surgery remains the pivotal treatment for anaplastic thyroid carcinoma. Radiotherapy and chemotherapy offer the best overall survival in aggressive disease. Combinations of immunotherapy with targeted therapies, such as dabrafenib-trametinib, demonstrate potential for enhanced effectiveness and improved survival outcomes. Multifaceted approach fuelled by precision medicine and interdisciplinary collaboration is imperative in charting a course toward improved outcomes in this formidable malignancy.

Key Words: Anaplastic thyroid cancer; Surgery; Radiotherapy; Chemotherapy; Targeted therapy; Immunotherapy

Core Tip: Anaplastic thyroid cancer is an aggressive disease. Surgery is the main treatment. Combination of radiotherapy and chemotherapy help to further improve the outcome of patients with this malignancy. Immunotherapy, targeted therapies, and molecular insights herald a new dawn for a patient cohort hitherto consigned to bleak prognoses.

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INTRODUCTION

The review article by Pavlidis *et al*[1] published in *World J Clin Oncol* provides a meticulous analysis of the intricacies surrounding anaplastic carcinoma of the thyroid[1]. Thyroid carcinoma encompasses a spectrum of diseases, each characterized by distinct behaviors and outcomes. While well-differentiated thyroid carcinomas typically has a favorable prognosis, constituting a 5-year survival rate exceeding 95%, anaplastic thyroid cancer, a rarity accounting for less than 0.2%, stands as an ominous exception[2]. This aggressive variant, often observed among the elderly, presents with rapid growth and lamentable prognosis, resulting in a median survival of 9.5 months, accompanied by a profound deterioration in quality of life[3].

The urgency of early diagnosis and staging cannot be undermined in confronting anaplastic thyroid cancer. Diagnostic approaches encompass a diverse array of tools, ranging from conventional biopsy techniques-fine needle aspiration (FNA), core needle biopsy (CNB), and open surgery-to sophisticated imaging modalities like high-resolution ultrasound (US), computed tomography (CT), magnetic resonance imaging, 18-fluoro-D-glucose positron emission tomography/CT, liquid biopsy, and microRNAs[4]. In cases of rapidly enlarging neck nodules, initial high-resolution US imaging is essential. Although FNA cytology under US guidance has been commonly used, its high false-negative rates do not support its use, and CNB has shown superior accuracy. Contrary to earlier guidelines, CNB is now recommended as the primary diagnostic method, avoiding unnecessary delays caused by inconclusive FNAs[5]. CNB is safe, rarely causing bleeding or hematoma. Incision/open surgery biopsies, once used, are now replaced by CNB. Liquid biopsy, a non-invasive genotyping method detecting malignant cells in serum and tumor DNA, offers valuable diagnostic, prognostic, and treatment response insights. Molecular investigations often unearth the presence of the *BRAF* gene, notably BRAF-V600E and BRAF wild type, alongside other implicated genes like *RET*, *KRAS*, *HRAS*, and *NRAS*, or genes implicated in the WNT and NOTCH signaling pathways, delineating possible options pivotal for personalized therapeutic interventions[6].

MANAGEMENT OF ANAPLASTIC THYROID CARCINOMA

Surgery remains the pivotal treatment for anaplastic thyroid carcinoma, with a spectrum ranging from palliative thyroidectomy to complete thyroidectomy and neck node dissection. Radical surgery, often combined with adjuvant chemotherapy, can yield occasional long-term survival over 5 years, especially in earlier disease stages and can improve locoregional disease control and quality of life. Studies have identified surgery and radiotherapy as independent factors predicting increased overall survival. But extreme radical resections like laryngectomy or extensive neck dissections lack substantial oncological benefits[7,8]. National Comprehensive Cancer Network and American Thyroid Association (ATA) guidelines recommend surgical resection, and lymphadenectomy for stage-IVA and IVB, and even for locally resectable stage-IVC tumors. Locally unresectable cases might respond to neoadjuvant therapies, becoming eligible for surgical excision. For inoperable cases, palliative surgeries aim to alleviate symptoms and prevent life-threatening events[9]. Although aggressive surgery, radiotherapy and chemotherapy offer the best overall survival, their use should be weighed against patient comfort and quality of life, and radiotherapy and chemotherapy are favored for unresectable cases.

Complementary to surgery, chemotherapy with agents like cisplatin or doxorubicin including taxanes (paclitaxel, docetaxel, cabazitaxel), radiotherapy in adjuvant or definitive settings, targeted biological agents, and the promising immunotherapy constitute the pillars of contemporary management paradigms and recommended by ATA guidelines [10]. Adjuvant chemotherapy enhances median survival, and newer strategies combine chemotherapy with targeted biological agents like dabrafenib and trametinib for *BRAF/MEK* gene mutations or immunotherapy for unmutated cases. Combining chemotherapy with radiation improves survival in resected and unresected cases. Food and Drug Administration (FDA)-approved anlotinib, combined with paclitaxel, capecitabine, or carboplatin, demonstrates safety and efficacy as a first-line therapy for advanced thyroid carcinoma[11].

Immunotherapy, specifically employing anti-programmed death-ligand 1 (PD-L1) antibodies, tailored stem cell therapies, advancements in nanotechnology, and the integration of artificial intelligence, have emerged as optimistic alternatives. Combinations of immunotherapy with targeted therapies like dabrafenib-trametinib demonstrate potential for enhanced effectiveness and improved survival outcomes. Recent developments in targeted PD-L1 and programmed cell death 1 (PD-1) interactions *via* monoclonal antibodies including pembrolizumab, atezolizumab and spartalizumab provide increasing adoption, particularly in cases with high PD-1/PD-L1 expression and without BRAF mutations[12]. Atezolizumab, specifically, exhibits encouraging outcomes in combination with radiation therapy. Spartalizumab and pembrolizumab, targeting PD-1, demonstrate promise in phase II studies for locally advanced or metastatic cases, showing notable survival rates but accompanied by side effects like diarrhea, pruritus, fever, and fatigue. These modalities demonstrate potential in reshaping the landscape of treatment outcomes for a patient cohort traditionally consigned to dismal prognoses.

Crucially, the treatment trajectory is increasingly influenced by the genomic profile, delineating molecular pathways, and thereby guiding novel therapeutic strategies. Strategies targeting specific mutations-anti-epidermal growth factor receptor (EGFR), anti-vascular endothelial growth factor-A (VEGF-A), and anti-BRAF-have emerged as a more tailored and effective approach. Notably, the combination therapy of the MEK inhibitor trametinib and the BRAF inhibitor dabrafenib has been approved by the FDA for cases featuring *BRAF-V600E* gene mutations. Drugs targeting various gene mutations include angiogenesis (lenvatinib, sorafenib), BRAF (dabrafenib, vemurafenib), MEK (trametinib, cobimetinib) and EGFR (docetaxel, gefitinib). Dabrafenib combined with trametinib is more effective than individual drugs. Vandetanib, sunitinib, and lenvatinib exhibit potent anti-cancer effects. Carfilzomib and suberoylanilide hydroxamic acid

show promise, affecting cell proliferation and promoting apoptosis. Lenvatinib, targeting VEGFRs, proves effective, extending survival in unresectable cases. Glutaminolysis inhibition by tyrosine kinase inhibitors enhances conventional chemotherapy efficiency. Several targets like ICAM1, CTHRC1, and fibronectin depletion show potential in overcoming resistance to inhibitors. Additionally, targeting EZH2 complex and one-carbon metabolism holds promise, offering potential therapeutic strategies for anaplastic thyroid carcinoma. These diverse approaches represent a broad spectrum of targeted therapies with potential implications for future treatments[13].

Radiation therapy stands as a crucial element in managing this malignancy, halting tumor progression, and preventing recurrence pre- and post-surgery. Utilized as neoadjuvant or adjuvant therapy, external beam radiation therapy (EBRT) significantly improves median survival rates in multimodal treatment, along with surgery, chemotherapy, targeted therapy, and immunotherapy. Optimal EBRT doses (45-70 Gy) and subsequent hypofractionation (> 5 Gy) reduce local recurrence and mortality. Furthermore, radiation therapy may synergize with immunotherapy, although its efficacy remains limited alongside targeted therapy like Lenvatinib[14].

Prognostic factors, such as younger age, earlier tumor stage, and the judicious incorporation of radiation therapy, have been identified as pivotal determinants for improved outcomes. An indispensable facet of confronting anaplastic thyroid cancer lies in adopting a multidisciplinary approach, tailoring therapeutic plans to individualized patient profiles based on insights gleaned from surveillance and epidemiology end results.

CONCLUSION

The contemporary vista of anaplastic thyroid cancer management signifies a departure from the erstwhile despondent landscape, offering rays of hope buoyed by innovative therapeutic avenues. The synergy between conventional interventions and burgeoning advancements in immunotherapy, targeted therapies, and molecular insights heralds a new dawn for a patient cohort hitherto consigned to bleak prognoses. Embracing this multifaceted approach, fuelled by precision medicine and interdisciplinary collaboration, is imperative in charting a course toward improved outcomes and enhanced quality of life for those afflicted by this formidable malignancy.

FOOTNOTES

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