EDITORIAL

Treatment horizons for advanced radioiodine refractory thyroid cancer: recent developments

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ABSTRACT

Novel targeted therapies tailored to the molecular profile of tumors have revolutionized the treatment landscape for advanced radioiodine-refractory differentiated thyroid cancer, showcasing notable progression-free survival rates. These emerging therapies, leveraging kinase inhibitors, exhibit a remarkable capacity to restore iodide uptake in RAI-R thyroid cancer cells. However, successful implementation relies on crucial factors like adopting a multidisciplinary team approach and timely initiation of targeted therapies.

Keywords: Multidisciplinary team, progression-free survival, targeted therapies, thyroid cancer.

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Radioactive iodine I-131 (RAI) is a crucial adjuvant in the management of high-risk differentiated thyroid cancer (DTC). However, 5% to 15% of DTCs and 50% of their metastases are radioiodine-refractory (RAI-R). Patients with RAI-R thyroid cancer have poor outcomes. The five-year disease-specific survival rate for RAI-R DTC is only 60% to 70%. It is even worse for RAI-R metastatic thyroid cancer, which is only about 10%. Resensitizing RAI-R tumors can potentially improve survival for patients with DTC [1].

The following criteria define RAI refractoriness: 1) no radioiodine uptake at the time of initial diagnosis; 2) absence or progressive loss of radioiodine uptake in post-therapy scans performed several days after RAI therapy; 3) multiple metastatic lesions with at least one lesion not exhibiting radioiodine uptake in post-therapy scans; 4) structural progression of tumors 12-16 months after RAI therapy despite iodine uptake in post-therapy scans; 5) tumors in patients who have received a cumulative dose of 600 mCi or 22.2 Gigabecquerel of RAI without remission; and 6) paradoxical significant uptake seen in 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography integrated with computed tomography (F-18 FDG PET/CT) scans [2].

Metastatic radioiodine refractory thyroid cancers (RAI-R) may remain symptom-free for a considerable time [3]. Patients with asymptomatic disease, minimal tumor growth, or low tumor burden can opt for active surveillance alongside thyroid-stimulating hormone (TSH) suppression. Following RAI therapy, small, symptom-free metastatic lymph nodes, and pulmonary nodules can undergo prolonged monitoring using neck ultrasonography and axial imaging. Additional diagnostic methods such as F-18 FDG PET/CT scans and regular thyroglobulin level assessments in TSH-suppressed patients can aid in tracking disease progression [1].

Local therapy is still the most common treatment for locoregional diseases. To preserve unaffected vital structures, compartmental central or lateral neck dissection may be used. External beam radiation therapy (EBRT) is a commonly used treatment modality, either alone or in combination with surgery, especially for thyroid cancers that have metastasized to the bone and central nervous system. Studies show that combining surgery with EBRT, which usually delivers doses between 40 and 50 Gy, improves locoregional control and prognosis, especially in patients 45 years of age and above [1]. For lymph node metastasis or regional relapse, percutaneous interventional methods such as cryoablation, ethanol ablation, and radiofrequency ablation can be applied. Furthermore, for metastases in the liver, trans-arterial chemoembolization or radioembolization may be used. Effective disease control can be achieved by combining these interventions with the systemic targeted therapies mentioned below [4].

RAI refractoriness frequently arises from the absence of thyroid differentiation characteristics, specifically the malfunction of the sodium/iodide symporter (NIS). The resistance to radioactive iodine is mainly caused by genetic and epigenetic changes in the RTK/BRAF/mitogen-activated protein kinase (MAPK)/ERK and PI3K-AKT-mTOR pathways. These modifications encompass acquired somatic mutations, chromosomal rearrangements, and aberrant gene methylation. The BRAFV600E mutation, which is present in approximately 50% of DTCs, inhibits the expression of NIS through two mechanisms: First, it triggers TGFβ/Smad3 signaling, which prevents the binding of the thyroid-specific transcription factor PAX8 to the NIS promoter in follicular cells. In addition, it causes histone deacetylation of H3 and H4 lysine residues on the NIS promoter, thereby directly impeding its transcription [1].

Over the past decade, targeted therapies employing tyrosine kinase inhibitors (TKIs) have seen significant development, particularly for the treatment of advanced RAI-R DTC. Numerous phase II and III trials have tested various agents in this context, showcasing improved progression-free survival rates; however, documenting an overall survival benefit in these trials has proven challenging.

Sorafenib and Lenvatinib, validated through extensive clinical trials involving multi-TKIs, have obtained approval from both the United States Food and Drug Administration (FDA) and European Medicines Agency for the treatment of advanced RAI-R thyroid cancer. This approval is based on the outcomes of pivotal phase three clinical trials, namely DECISION and SELECT [5]. Lenvatinib has demonstrated an overall survival benefit, especially in selected patients over 65 years old with RAI-R DTCs. While TKIs have revolutionized targeted therapy for RAI-R DTC patients, their administration is typically lifelong and comes with various drawbacks associated with long-term use. Therefore, the decision to initiate therapy should take into account factors such as access, adherence to close monitoring, continuous assessment of adverse effects, and the patient's quality of life. In cases where patients have previously received treatment with lenvatinib or sorafenib, and are confronted with aggressive disease without an available standard of care, cabozantinib (a RET, VEGFR2, c-MET, and KIT inhibitor) has proven to significantly extend progression-free survival [5].

Thyroid cancers often become RAI-R by co-opting RAF (rapidly accelerated fibrosarcoma) and RAS (Rat Sarcoma) signaling, repressing NIS and RAI uptake. Targeted therapies like BRAF inhibitors (dabrafenib and vemurafenib) have shown some success in resensitizing tumors to RAI, but these tumors often escape RAI sensitivity via aberrations in complementary pathways. In patients with documented responses to targeted therapies, the tumor escapes after several months, often due to the overactivation of alternative pathways. Combining adjuvant therapies with targetTKIs has the potential to eliminate or delay the escape effect and result in longer progression-free survival [1].

One distinctive mechanism contributing to the resistance of thyroid cancer to RAI treatment could involve the upregulation of the human epidermal receptor (HER) family of receptor tyrosine kinases. This alteration is observed in more than one-third of thyroid cancers and is associated with increased local tumor invasiveness. The overexpression of HER2 and HER3 may facilitate RAI-resistant tumor evasion in BRAF mutant cells treated with the BRAF inhibitor vemurafenib. Combining the HER2 inhibitor trastuzumab with vemurafenib treatment might enable patients with RAI-resistant tumors to counteract the escape phenomenon, potentially leading to a more sustained response to targeted therapy [1].

For patients unresponsive to approved TKIs or unable to tolerate treatment-related adverse events (AEs), novel targeted therapies can be used based on the tumor's molecular signature. Recent findings reveal that 2.2% of BRAF-WT (wild type) aggressive papillary thyroid cancers, associated with younger age and more severe disease at presentation, exhibit anaplastic lymphoma kinase (ALK) translocations [5]. ALK fusion proteins are recognized for their ability to activate multiple signaling pathways including the PI3K/AKT pathway and the MAPK pathways, and aberrant activation of these ALK fusion proteins promotes proliferation and survival in cancer cells. ALK-EML4 and various other ALK translocations have also been identified in RAI-R DTCs [5]. Pairing tailored ALK inhibitors like crizotinib with conventional adjuvant treatments could potentially yield a lasting response in patients diagnosed with ALK-positive tumors.

Emerging therapies employing kinase inhibitors (KIs) have demonstrated the ability to restore iodide uptake in RAI-R thyroid cancer cells. Changes in the PI3K/AKT/mTOR pathway are extensively observed in the development of thyroid cancer. Blocking mTOR encourages the redifferentiation of thyroid cancer cells by enhancing the expression of NIS mRNA and protein, leading to increased iodine uptake through upregulated transcription mediated by thyroid transcription factor-1 (TTF1) [6]. The reciprocal correlation exists between the activation of platelet-derived growth factor receptor-alpha (PDGFR-α) and the transcriptional activity of TTF1, whereby inhibiting PDGFR-α reinstates NIS expression.

Second-generation KIs fall into two categories: RET inhibitors (selpercatinib and pralsetinib) and TRK inhibitors (larotrectinib and entrectinib) [4]. Thyroid cancers, particularly in children, may involve NTRK (neurotrophic-tropomyosin receptor kinase) fusions in NTRK1, NTRK2, and NTRK3 genes. Larotrectinib and entrectinib are highly selective TRK inhibitors approved for

TRK-positive thyroid cancers. Larotrectinib demonstrated significant efficacy in phase 1 and 2 trials, with a 75% objective response rate. Entrectinib, targeting TRK, ALK, and ROS1 TKs, showed promise in phase 1 and ongoing phase 2 trials, achieving a 57% overall objective response rate. Selpercatinib gained FDA approval in May 2020 for RET-fusion positive thyroid cancer, with a remarkable 79% objective response rate and a 1-year progression-free survival of 64%. Drug-related adverse events (AEs) were primarily grade 1-2, with only 2% of patients discontinuing due to toxicity and 42% requiring dosage interruptions. Pralsetinib, another selective RET inhibitor, received approval in December 2020 for RET-fusion positive RAI-R DTC. In the ARROW trial, the objective response rate for this subgroup was an impressive 89%, with sustained responses for at least 6 months [5].

Combining a HER inhibitor with a BRAF/MEK inhibitor has been observed to enhance the sensitivity of BRAF-V600E-positive PTC to BRAF/MEK inhibitors by preventing MAPK rebound and augmenting NIS expression. The MEK 1/2 inhibitor selumetinib has shown promise in reversing refractoriness to RAI in patients with advanced or metastatic DTC. Lapatinib, HER3 inhibitor, has been identified to counteract MAPK rebound and sensitize BRAF-V600E-positive thyroid cancer cells to RAF or MAP/ERK inhibitors [6].

DTC has traditionally been considered poorly immunogenic due to its low tumor mutation burden. Various immune cells infiltrate DTC and express CTLA-4 and PD-L1. PD-L1 positivity is associated with poor prognosis in thyroid cancer patients, providing a rationale for targeting the PD-1/PD-L1 pathway in DTC [3]. Ongoing trials are evaluating the role of TKIs in advanced RAI-R thyroid cancer, either alone or in combination with immune checkpoint inhibitors (ICIs) or RAI therapy. In the phase Ib KEYNOTE-028 study (NCT02054806), the response rate to Pembrolizumab was 9%. Patients with follicular thyroid cancer and PTC exhibited a stable disease rate of 57%-60%, respectively, with a median progression-free survival of 7 months [7]. Significant uncertainties persist around the optimal utilization of ICIs for the treatment of advanced thyroid cancer. Questions regarding the appropriate timing in the treatment algorithm, methods for assessing treatment response, and the potential for combination therapy with Multikinase inhibitors remain unanswered.

Phase II trials on chemotherapy agents for recurrent and metastatic DTC, often using doxorubicin, have been documented. However, there is no consensus on the best cytotoxic regimen for radioactive iodine-resistant (RAI-R) disease, highlighting the need for clinical trials on cytotoxic chemotherapy, TKIs, and other targeted therapies for RAI-R patients.

Managing progressive radioactive iodine-refractory (RAI-R) thyroid cancer requires evaluating tumor burden, patient age, symptoms, metastasis location, and genetic profile. A multidisciplinary approach is standard, with the timely initiation of targeted therapies being crucial. The American Thyroid Association guidelines recommend high-risk metastatic progressive RAI-R DTC not amenable to conventional therapies be considered for TKIs in specialized centers. Delaying treatment can increase tumor dedifferentiation, reducing drug efficacy. Decisions must balance treatment benefits against risks, despite many patients showing gradual disease progression.

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