Radioiodine-Refractory Thyroid Cancer

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Recurrent, metastatic disease represents the most frequent cause of death for patients with thyroid cancer, and radioactive iodine (RAI) remains a mainstay of therapy for these patients. Unfortunately, many thyroid cancer patients have tumors that no longer trap iodine, and hence are refractory to RAI, heralding a poor prognosis. RAI-refractory (RAI-R) cancer cells result from the loss of thyroid differentiation features, such as iodide uptake and organification. This loss of differentiation features correlates with the degree of mitogen-activated protein kinase (MAPK) activation, which is higher in tumors with BRAF (B-Raf proto-oncogene) mutations than in those with RTK (receptor tyrosine kinase) or RAS (rat sarcoma) mutations. Hence, inhibition of the mitogen-activated protein kinase kinase-1 and -2 (MEK-1 and -2) downstream of RAF (rapidly accelerated fibrosarcoma) could sensitize RAI refractivity in thyroid cancer. However, a significant hurdle is the development of secondary tumor resistance (escape mechanisms) to these drugs through upregulation of tyrosine kinase receptors or another alternative signaling pathway. The sodium iodide symporter (NIS) is a plasma membrane glycoprotein, a member of solute carrier family 5A (SLC5A5), located on the basolateral surfaces of the thyroid follicular epithelial cells, which mediates active iodide transport into thyroid follicular cells.

radioactive iodine-refractory | differentiated thyroid cancer | papillary thyroid cancer | tyrosine kinase inhibitor | sodium/iodide symporter | braf

1. Introduction

Radioactive iodine I-131 (RAI) is a cornerstone in the routine adjuvant management in patients with high-risk differentiated thyroid cancer (DTC) [1]; however, 5% to 15% of DTC and 50% of metastatic DTCs are refractory to RAI treatment [2][3][4]. Patients with RAI-refractory (RAI-R) thyroid cancer have poor outcomes, with 5-year disease-specific survival rates of 60% to 70% [5]. Those with RAI-R metastatic thyroid cancer have the worst outcomes, with a 10-year survival rate of 10% [6]. Hence, resensitizing RAI-R tumors to RAI can potentially improve survival for patients with DTC.

With recent advances and developments in understanding of the oncogenic pathways involved in the development of thyroid cancers and the molecular basis of RAI refractoriness, targeted therapies are being developed and are showing promising results [7][8][9][10]. Here, we review the molecular mechanisms underlying RAI refractoriness, describe targeted therapies that may overcome these mechanisms, and explore promising therapeutic regimens to improve outcomes in RAI-R thyroid cancers.

2. Definition of RAI-R Tumors

A major obstacle to standardizing the approach to RAI-R tumors is the lack of a consistent definition for RAI-R. The following definitions for RAI-R tumors are used in the literature [11][12][13]:

i. Absence of RAI uptake at initial diagnosis of locoregional recurrence or distant metastasis;

ii. Absence or progressive loss of radioiodine uptake in the post-therapy scan several days after RAI therapy;

iii. Presence of more than 1 metastatic lesion with at least one lesion without RAI uptake in the post-therapy scan;

iv. Structural progression of tumors 12 to 16 months after RAI therapy despite the presence of iodine uptake in the post-therapy scan;

v. Tumors in patients who have received 600 millicurie (mCi)/22.2 gigabecquerel (GBq) or more of RAI cumulatively without signs of remission;

vi Significant uptake on 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography integrated with computed tomography (F-18 FDG PET/CT).

None of the above criterion alone portends that a tumor is RAI-R, rather it predicts the likelihood that a tumor will be RAI-refractory and should be used together for risk stratification of the tumors in assessing for refractoriness. It is important for the RAI uptake scan to be standardized and an optimal approach is required for patient preparation and choice of imaging modality [14].

Aggressive or poorly differentiated tumors on histology or tumors exhibiting aggressive genetic profiles (such as *BRAF* and telomerase reverse transcriptase (*TERT*) promoter mutation) can also be included for risk stratification of patients [15].

3. Management of RAI-R Thyroid Cancers

3.1. Monitoring and Watchful Waiting

RAI-R metastatic DTCs can be asymptomatic for several years [16]. Active surveillance and watchful waiting with TSH suppression can be employed in patients with asymptomatic disease, low tumor burden or tumor size less than 1 cm, and minimally progressive tumors [12][13][17][18]. Presence of small (<8 mm) and asymptomatic metastatic lymph nodes after RAI therapy with previous neck compartmental dissection and small (<1 cm) metastatic pulmonary nodules can be followed up for years with neck ultrasonography and axial imaging for the pulmonary nodules. Other imaging modalities, such as F-18 FDG PET/CT, and thyroglobulin levels in TSH-suppressed patients can also be used to assess disease progression [12][13][19][20][21]; these are used in conjunction with axial imaging when growth of lesions is suspected [22].

3.2. Local Therapy

In locoregional relapse, surgery is still the most commonly used therapeutic approach, with therapeutic compartmental central or lateral neck dissection to spare uninvolved vital structures, or a more limited surgery in cases of prior comprehensive neck dissection [12][13]. External-beam radiation therapy (EBRT) is commonly used alone or in combination with surgery in bone and central nervous system (CNS) metastasis of thyroid cancers [23][24]. Some studies have demonstrated benefit in locoregional control and good prognosis with surgery combined with EBRT in doses of 40 to 50 Gy in patients 45 years and older [25]. Limited outcome data are available on other locoregional therapies, such as radiofrequency ablation, and ethanol ablation or embolization [13]. It is of note that symptomatic patients with metastatic lung nodules or bone lesions are usually considered for local therapies before systemic therapies [26].

3.3. Targeted Therapies Using Tyrosine Kinase Inhibitors

Targeted treatments for thyroid cancer have been increasingly developed over the last decade along with increasing knowledge about the disease's underlying molecular alterations. Most agents that were tested in phase II and III trials were developed for treatment of advanced RAI-R thyroid cancer.

Cellular dedifferentiation in thyroid cancers causes tumor progression in the form of more aggressive growth, metastasis, loss of iodide uptake, or unresponsiveness to RAI therapy, and correlates with the degree of MAPK activation. Tyrosine kinases are involved in the MAPK signaling pathway through phosphorylation/dephosphorylation of several intracellular proteins, which underlies the rationale for the use of tyrosine kinase inhibitors (TKIs) in the treatment of thyroid cancer [27][28].

TKIs have been shown to significantly improve progression-free survival rates in advanced RAI-R DTCs. Overall survival has been difficult to document in these trials, likely because patients cross over to the drug arm once disease progression is documented in the control group [9][10]. An overall survival benefit was observed with the use of lenvatinib in selected patients > 65 years of age with RAI-R DTCs [29]. Two TKIs, lenvatinib and sorafenib, are currently used for the treatment of RAI-R DTC (**Table 1**), and two others, vandetanib (NCT01876784) and cabozantinib (NCT03690388), are under investigation in phase III trials for patients with progressive RAI-R DTCs and advanced RAI-R DTCs unresponsive to previous VEGFR therapy, respectively [30][31].

Table 1. Completed Phase III Clinical Trials of Agents Approved for the Treatment of Differentiated Thyroid Cancer by the U.S. Food and Drug Administration [9][10].

Parameters	**DECISION Trial: Sorafenib**	**SELECT Trial: Lenvatinib**
Drug targets	Specific target: RAF Other targets: VEGFR, c-Kit, RET, PDGFR, FLT3	Specific target: FGFR Other targets: VEGFR, c-Kit, RET, PDGFR, RET-KIF5B, CCDC6-RET, NcoA4-RET rearrangement

Parameters	DECISION Trial: Sorafenib	SELECT Trial: Lenvatinib
Patient population	*N* = 417, randomized 1:1 dose: 800 mg daily	*N* = 392, randomized 2:1 dose: 24 mg daily
Median progression-free survival (months)	10.8 vs. 5.8 ($p < 0.0001$)	18.3 vs. 3.6 ($p < 0.001$)
Complete response	0% vs. 0%	1.5% vs. 0%
Partial response	12.2% vs. 0.5%	63.2% vs. 1.5%
Stable disease > 23 weeks	41.8% vs. 33.2%	15.3% vs. 29.8%
Grade 3 and 4 adverse effects	Overall: 37.2% vs. 26.3%	Overall: 75.9% vs. 9.9%
	Hand-foot syndrome: 20.3%	Hypertension: 42%
	Hypertension: 9.7%	Proteinuria: 10%
	Hypocalcemia: 5.8%	Thromboembolic effects: 6.5% (arterial vs. venous: 2.7% vs. 3.8%)
	Weight loss: 5.8%	Acute Renal failure: 1.9%
	Diarrhea, fatigue: 5.3%	QT prolongation: 1.5%
	Rash/desquamation: 4.8%	Hepatic failure: 0.4%
	Shortness of breath: 4.8%	
Dose reduction	64.3%	67%
Treatment discontinuation	19%	14%

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treatment initiation. Also, a resistance to the treatment, also called "escape", can develop; hence, access and adherence to close monitoring with a continuous assessment of adverse effects and the patient's quality of life should be considered in the decision to start the therapy [32]. In clinical settings with no preselection of patients, lenvatinib has been shown to be useful in the management of RAI-R DTCs with implementation of good and specified management protocols for toxicities and adverse events [33][34].

Potential targets are also transcriptional factors such as vascular endothelial growth factor (VEGF). In response to intratumoral hypoxia, hypoxia inducible factor-1 alpha (HIF-1α) is activated and induces VEGF transcription together with co-stimulation by growth factor signaling pathways, such as the PI3K/AKT and MAPK pathways [35][36]. VEGF is a promoter of angiogenesis and is an attractive target for therapy. Another target for HIF-1α is the MET oncogene, which is overexpressed in thyroid cancers, especially medullary thyroid cancer (MTC), thereby promoting angiogenesis, cellular motility, invasion, and metastasis [37][38].

3.4. Tumoral Escape Mechanisms from Targeted Therapies

As discussed above, thyroid cancers often become RAI-R by co-opting RAF and RAS signaling, thereby repressing NIS and RAI uptake. Although targeted therapies such as BRAF inhibitors have shown some success in resensitizing tumors to RAI, these tumors often escape RAI sensitivity via aberrations in complementary pathways. In patients with documented response to targeted therapies, after several months, the tumor escapes (i.e., it ceases to respond and starts growing again). Several hypotheses and suggested mechanisms have been proposed to explain such escape, most of which involve overactivation of alternative pathways to overcome the drug's effect [39][40].

Combining adjuvant therapies with TKIs has the potential to eliminate or delay the escape effect (i.e., resistance) and result in longer progression-free survival. Numerous genetic and signal transduction alterations have been observed in RAI-R or advanced papillary thyroid cancer (PTC) [15][27][41], and simultaneous targeting of these alterations might allow more durable tumor control when combined with current TKIs.

One unique mechanism by which thyroid cancer drives RAI resistance may be via upregulation of the human epidermal receptor (HER) family of receptor tyrosine kinases, which is present in more than one-third of thyroid cancers and is positively correlated with local tumor invasiveness [42]. HER2 and HER3 are key players upstream of extracellular signal-regulated kinase (ERK) and AKT, and HER2 and HER3 activate these signaling pathways. Interestingly, overexpression of HER2 and HER3 may provide a mechanism of RAI-R tumor escape for *BRAF* mutant cells treated with the BRAF inhibitor vemurafenib [43]. Therefore, the addition of the HER2 inhibitor trastuzumab to vemurafenib treatment may enable patients with RAI-R tumors to overcome the escape phenomenon and experience a more durable effect from the targeted therapy [44].

Anaplastic lymphoma kinase (ALK) is a recently identified kinase with the potential to contribute to aggressive disease in non-small-cell lung cancers. This kinase can undergo rearrangements—the most common is EML4-ALK fusion with echinoderm microtubule–associated protein-like 4 (*EML4*) gene—that were described in a subset of patients, who tend to be younger with more aggressive disease [45]. ALK fusion proteins are known to activate various signaling pathways, such as the PI3K/AKT pathway and the MAPK pathways [46][47], and aberrant activation of these ALK fusion proteins promotes proliferation and survival in cancer cells [48]. ALK fusion has been demonstrated in medullary thyroid cancer and anaplastic carcinoma [49]. In RAI-R DTC, EML4-ALK fusion and several other ALK translocations were identified by whole genome sequencing [50]. A study of the translocation profile of ALK in DTC found ALK translocations in 11 of 498 papillary thyroid cancers (PTCs) (2.2%) and 3 of 23 diffuse sclerosing variant PTCs (13%). Combining specific ALK inhibitors such as crizotinib with standard adjuvant therapies might offer durable response in patients with ALK-positive tumors [51].

Alterations in the PI3K/AKT/mTOR cascade are well documented in thyroid cancer tumorigenesis (**Figure 1**). The inhibition of mTOR promotes redifferentiation of thyroid cancer cells by upregulating NIS mRNA and protein expression, resulting in elevated iodine uptake through increased transcription at the level of thyroid transcription factor-1 (TTF1), which indicates TTF1 dependence for NIS expression [52][53]. There is an inverse relationship between platelet-derived growth factor receptor-alpha (PDGFR-α) activation and transcriptional activity of TTF1, with PDGFR-α blockade restoring NIS expression [54]. Another important positive regulator of NIS expression is

PTEN, which is suppressed by oncogenic miR-21; antisense-miR-21 increases NIS expression [55]. Some clinical trials have evaluated the mTOR inhibitor everolimus and the combination of sorafenib and the mTOR inhibitor temsirolimus in the treatment of RAI-R thyroid cancer. However, these studies were not designed to evaluate the change in RAI uptake or the effectiveness of combined RAI therapy with the drugs [56][57]. Further clinical trials are needed to elucidate the role of mTOR inhibition in inducing radioiodine avidity.

Downstream mechanisms in the signaling pathways involved in RAI refractoriness affect the posttranslational modifications or shuttling of the transcribed NIS. Pituitary tumor transforming gene 1 (PTTG1) and PTTG-1 binding factor overexpression in thyroid cancers results in decreased NIS levels [58], likely through its retention in clathrin-coated vesicles or by repressing NIS mRNA transcription [59]. PI3K-AKT pathway activation in thyroid carcinoma leads to suppression of NIS glycosylation and surface translocation [60]. In a novel mechanism recently described by our group, decreased expression of ribosomal machinery subunits (i.e., phosphatidylinositol glycan anchor biosynthesis class U) resulted in improper NIS post-translational processing and deregulated trafficking of the protein to the plasma membrane, resulting in increased RAI refractoriness in thyroid cancer cells [61].

3.5. Other Systemic Therapies

Phase II trials of the efficacy of various chemotherapy agents for recurrent and metastatic DTC have been reported; in these, doxorubicin was the most frequently used agent [62]. No consensus has been reached for the use of a specific cytotoxic regimen in RAI-R disease, and clinical trials of cytotoxic chemotherapy, in addition to TKIs and other targeted therapies, are needed in patients with RAI-R disease [1].

3.6. Targeted Therapies and Tumor Immune Microenvironment in RAI-R Thyroid Cancer

Characterizing the immune landscape following TKI treatment in various tumor types, including thyroid cancer, has demonstrated dynamic alterations in the tumor immune microenvironment [63][64]. Using a TKI that targets the Vascular endothelial growth factor-A/Vascular Endothelial Growth Factor Receptor (VEGF-A/VEGFR) axis affects regulatory T cell percentages and seems to increase PD-1 (Programmed cell death protein 1) expression, which leads to inhibition of cytotoxic T cells [63]. Immune profiling of *BRAF-V600E*-positive DTC revealed high levels of PD-L1 (Programmed death-ligand 1) (53% vs. 12.5%) and human leukocyte antigen G (41% vs. 12.5%) compared with *BRAF* wild-type tumors. Furthermore, *BRAF-V600E*-positive tumors had a high level of suppressive T cell and macrophage components [64]. These results show the inhibitory effects of the aberrant tyrosine kinases on the immune system, indicating the potential of TKIs to reverse them, with the combination of TKIs and immune checkpoint inhibitors seemingly an attractive regimen for patients with RAI-R DTC.

Ongoing trials are evaluating the role of TKIs in advanced RAI-R thyroid cancer, either alone or in combination with immune checkpoint inhibitors or RAI therapy [65]. Sulfatinib is an oral TKI targeting VEGFR, FGFR-1 (Fibroblast growth factor receptor 1), and CSF1R (colony-stimulating factor 1 receptor); therefore, it might play a dual antiangiogenic and immunomodulatory role. The early results of NCT02614495, an open label, two-cohort, phase I and II trial of sulfatinib in RAI-R DTC, were presented in 2017. In this trial, patients were assigned to sulfatinib. Partial responses were confirmed in 3 of 12 patients with DTC; all others achieved stable disease [66]. An ongoing

phase IB/II trial (NCT02501096), is assessing the maximum tolerated dose of lenvatinib combined with the PD-1 inhibitor pembrolizumab in patients with solid tumors, including thyroid cancer [67]. Another ongoing trial, NCT01988896, is evaluating the PD-L1 inhibitor atezolizumab combined with the MAPK inhibitor cobimetinib in patients with locally advanced or metastatic solid tumors [68].

3.7. Current Recommendations for Treatment of Symptomatic RAI-R Thyroid Cancer

Current American Thyroid Association (ATA) guidelines recommend high-risk metastatic progressive (i.e., at least 20% increase in sum of longest diameter of lesions) RAI-R-DTCs not amenable to conventional therapies be considered for TKIs in specialized centers. Since immunotherapies and re-sensitization therapies are currently in the phase of clinical trials, the ATA recommends admittance into these trials if RAI-R DTCs are progressive after use of approved TKIs, such as lenvatinib or sorafenib. Molecular characterization of these lesions can help to identify and select the appropriate clinical trials. The ATA endorses the use of EBRT or radiofrequency ablation or cryoablation over surgery for symptomatic distant metastatic lesions or lesions with high risk of local complications prior to initiation of TKIs. It also advocates their use for single or multiple progressive lesions while on TKIs or other novel therapies [1].

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