Standard and Emerging Therapies for Metastatic Differentiated Thyroid Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the role and limitations of traditional treatments for metastatic differentiated thyroid cancer.
2. Discuss the molecular basis of and clinical evidence for novel and emerging treatments for metastatic differentiated thyroid cancer.
3. Identify suitable candidates for clinical trials among your patients with radioactive iodine refractory, metastatic differentiated thyroid cancer and enroll them.

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ABSTRACT

Differentiated thyroid cancer accounts for >90% of cases of thyroid cancer, with most patients having an excellent prognosis. Distant metastases occur in 10%–15% of patients, decreasing the overall 10-year survival rate in this group to 40%. Radioactive iodine has been the mainstay of treatment for distant metastases, with good results when lesions retain the ability to take up iodine. For patients with metastatic disease resistant to radioactive iodine, treatment options are few and survival is poor. Chemotherapy and external beam radio-

therapy have been used in these patients, but with disappointing results. In recent years, our understanding of the molecular pathways involved in thyroid cancer has increased and a number of molecular targets have been identified. These targets include the proto-oncogenes *BRAF* and *RET*, known to be common mutations in thyroid cancer; vascular endothelial growth factor receptor and platelet-derived growth factor receptor, associated with angiogenesis; and the sodium-iodide symporter, with the aim of restoring its

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expression and hence radioactive iodine uptake. There are now multiple trials of tyrosine kinase inhibitors, angiogenesis inhibitors, and other novel agents available to patients with metastatic thyroid cancer. This review dis-

cusses both traditional and novel treatments for metastatic differentiated thyroid cancer with a particular focus on emerging treatments for patients with radioactive iodine-refractory disease. *The Oncologist* 2010;15:146–156

INTRODUCTION

Differentiated thyroid cancer (DTC) includes both papillary and follicular subtypes and accounts for >90% of cases of thyroid cancer [1]. The incidence of thyroid cancer is increasing worldwide, particularly because of a rise in papillary cancer, the most common form of DTC [2–4]. Standard treatment of thyroid cancer includes total thyroidectomy, radioactive iodine (RAI) ablation, and thyroxine replacement (dosed at levels sufficient to suppress thyroid-stimulating hormone [TSH]) [5, 6]. The overall prognosis for patients with DTC is good, with a 10-year disease-specific survival rate of 85% [7]. Approximately 10%–15% of patients with DTC present with or subsequently develop distant metastases. In this group of patients, the 10-year disease-specific survival rate drops to 40%.

The lung is the most common site of metastasis (70%), with other sites including bone (20%), mediastinum, brain, adrenal, skin, and liver. Multiple sites (most commonly lung and bone) are involved in 10%–20% of patients at diagnosis [8]. Survival of patients with metastatic DTC varies greatly, with poor prognostic factors including advancing age, aggressive histological features of the primary tumor, aggressive variants of thyroid cancer, metastases without RAI uptake, and extrapulmonary or multiple site metastases [8–11]. RAI has been the mainstay of treatment for patients with distant metastases, with young patients having iodine-avid pulmonary micrometastases achieving remission rates of 90% at 10 years [8, 12]. However, for patients with metastatic disease for which the ability to uptake RAI is lost, survival is poor (10-year survival, 10%) [8]. Conventional chemotherapeutic agents and external beam radiotherapy (EBRT) have been used in this group, but with disappointing results [13–15]. Thus, there is a need for new and effective treatments for these advanced thyroid cancers.

During recent years, our understanding of the molecular biology of thyroid cancer has increased and a number of molecular targets have been identified [16–18]. These molecular targets include tyrosine kinases, angiogenesis pathways, and the sodium-iodide symporter. This review discusses the therapeutic options available to patients with metastatic DTC, with a particular focus on the role and limitations of traditional treatments, the molecular basis and

clinical evidence for emerging treatments, and the selection of patients to be enrolled into ongoing clinical trials.

RAI

RAI remnant ablation is recommended after total thyroidectomy for the majority of patients with DTC (particularly those with tumors with aggressive histopathological features) [5]. Postablation whole-body iodine scans are performed 3–7 days after administration of a therapeutic dose of RAI and are much more sensitive for functioning metastases, identifying metastatic deposits in an additional 10%–26% of patients, compared with diagnostic whole-body iodine scans [19–21]. Post-therapy scanning is also superior for functioning metastases and may identify metastatic disease when conventional anatomic imaging techniques (computed tomography [CT], magnetic resonance imaging [MRI], and ultrasound) are negative [10]. For patients with iodine-avid metastatic disease, RAI continues to be the initial treatment of choice [10, 22].

Multiple retrospective studies have suggested that the use of RAI in those with iodine-avid distant metastases confers a survival benefit [23–28]. Those with pulmonary micrometastases (especially lesions below the resolution of CT) have the best prognosis, with high rates of complete remission with RAI repeated at 6- to 12-month intervals while disease is responsive [12, 23, 25, 29, 30]. A 10-year survival rate of 92% has been reported in those with metastatic disease who attain a negative whole-body iodine scan after RAI treatment [8]. For those with pulmonary, macronodular (>1 cm) metastases or bone metastases that are iodine avid, RAI treatment has been associated with longer survival, but complete remission rates are low [23, 25, 27, 31–33]. Overall, treatment with RAI improves the disease-specific survival rate of those with iodine-avid metastases (10-year survival, 30%–55%). In contrast, survival in those with metastatic disease that does not concentrate iodine remains poor (10-year survival, 10%–18%) [25, 34–36].

Cumulative doses of RAI are associated with lacrimal and salivary gland dysfunction, pulmonary fibrosis, cancer, and leukemia. These effects are dose dependent and increase with cumulative activity. In 2003, Rubino et al. [37] reported that cumulative doses of RAI (>600 MCi, 22 GBq) are associated with a higher risk for leukemia. A greater risk for other secondary malignancies has also been

reported [38, 39]. Thus, the use of RAI should be individualized to balance the risks against the therapeutic benefit.

For patients with noniodine-avid disease, the detection of metastases may be delayed. Identification of metastases in this setting relies upon symptoms related to the metastasis or investigation following the detection of a rising serum thyroglobulin level. Anatomic imaging (CT, MRI, or ultrasound) is often used, with ^{18}F -fluoro-deoxyglucose positron emission tomography (PET) being increasingly used [10]. Wang et al. [40] reported a sensitivity of 79.3% for PET in patients with a negative iodine scan, compared with only 18.6% sensitivity in those with positive iodine scans. Patients with higher volumes of disease on PET scans are less likely to respond to RAI and have a higher mortality rate [41].

The use of RAI in patients with a positive serum thyroglobulin and a negative radioiodine scan remains controversial and evidence is scant [42]. There are reports of therapeutic responses to RAI in patients with negative diagnostic iodine scans; however, metastases were visualized on the post-therapeutic iodine scan [43, 44]. In such patients, the higher dose of RAI has assisted in the detection of metastatic disease, and hence RAI may still be of some benefit [45]. Those with no uptake even with higher-dose RAI have true refractory disease, and treatment with RAI produces little benefit [46]. It is this group of patients with refractory thyroid cancer for whom alternative treatments are required. For such patients, conventional chemotherapy has been used; and now trials investigating novel targeted molecular therapies and treatments aimed at restoring RAI uptake are in progress. The rationale and evidence for these treatments are discussed below.

CYTOTOXIC CHEMOTHERAPY

There is a lack of evidence to support the use of conventional chemotherapy for metastatic DTC. Most trials have recruited only small numbers of patients, and few of these have been prospective. Doxorubicin (Adriamycin®; Bedford Laboratories, Bedford, OH) is the most studied agent. However, at best, a partial response or disease stabilization is reported, and any response is generally not sustained for more than a few months [14, 47–49]. One of the earliest studies of doxorubicin, published in 1974, reported a partial response in 11 (37%) of 30 patients with refractory thyroid cancer of differing histological types [48]. Matuszczyk et al. [50] found, in their series of 22 patients treated with doxorubicin, that 5% had partial regression over 6 months and 42% had stable disease at 7 months. The remaining 53% of patients had progressive disease over 5 months.

The only randomized controlled trial of chemotherapy in refractory thyroid cancer was performed by Shimaoka et

al. [13], who compared treatment with doxorubicin alone with that of doxorubicin and cisplatin in combination. Although there was no statistically significant difference in the combined (partial and complete) response rate between the two groups (26% in the doxorubicin and cisplatin group, compared with 17% in the doxorubicin alone group; $p = .1$), the addition of cisplatin did improve the rate of complete response (12% compared with 0%). This higher response rate was, however, associated with greater toxicity, with life-threatening toxicity experienced in 12% of the combined chemotherapy group, compared with 5% of the doxorubicin alone group. Other trials assessing the combination of doxorubicin and cisplatin have reported partial responses at best, with a short duration of response and significant toxicity [14, 47].

Ongoing trials are available investigating chemotherapeutic agents in DTC, with one recent trial examining the combination of irifolven (an alkylating agent) and capecitabine. Although that trial is complete, no results are yet reported [51]. Overall, the use of conventional chemotherapy in patients with metastatic thyroid cancer is disappointing, with most likely to derive only a modest benefit. Thus, much research is now being directed away from conventional chemotherapy and toward novel targeted treatments. Response rates to conventional chemotherapy have been sufficiently poor that the current American Thyroid Association guidelines suggest that, prior to undergoing chemotherapy, “patients with progressive disease should first be considered for clinical trials” [5].

THYROXINE SUPPRESSION

TSH plays a role in upregulating thyroid cell proliferation. Thus, the therapeutic rationale for suppressing TSH levels by administering sufficiently high doses of thyroxine is to slow the growth of TSH-dependent tumors. In patients with high-risk thyroid cancer (stage III and stage IV), suppression of TSH (maintaining $\text{TSH} < 0.1 \text{ mIU/L}$) has been shown to decrease recurrence rates, progression, and cancer-related mortality [52, 53]. Aggressive TSH suppression confers a state of subclinical thyrotoxicosis, and may not be tolerated by some patients. Atrial fibrillation and bone loss are particular risks associated with TSH suppression, and patients should be monitored for these complications. The management of these complications includes the use of cardioselective β -blockers or bisphosphonates as appropriate [54].

EBRT

The literature examining EBRT for distant metastatic disease is sparse, with most studies assessing the benefits of local control only. Radiation is recommended in the man-

agement of disease that is not amenable to surgical resection, including gross residual cervical disease and bone and cerebral metastases [5]. The most frequent use of EBRT in DTC has been for locoregional control of thyroid cancer when there is residual or recurrent disease. Small series have reported rates of local control at 4–5 years of 72%–81% after the use of EBRT [55, 56].

The use of radiotherapy in bone metastases has focused on the palliation of bone pain and control of critical bony structures, such as the vertebral column, to prevent neurological compression [27, 57]. Complete or partial symptomatic relief can be achieved in >80% of patients, with at least half of these having a durable response of >6 months [31]. Patients with high-risk bone metastases should receive moderately high doses of radiation treatments (maximum, 40–50 Gy, given in 2-Gy fractions) [57]. There have additionally been some reports of benefit with the combination of EBRT and RAI with regard to tumor recurrence and symptomatic relief [58].

For cerebral metastases, surgery remains the preferred modality of treatment; however, EBRT is used in the setting of unresectable cerebral metastases or as adjuvant therapy following resection. There are few reports of such patients in the literature; however, some series suggest a small survival benefit with the use of EBRT in this setting [59, 60].

Radiotherapy is rarely used for pulmonary metastases because of the high incidence of complications, including pulmonary fibrosis and pneumonitis. There are, however, specific circumstances in which radiotherapy has been beneficial for pulmonary metastases, particularly with dominant lung lesions causing hemoptysis or bronchial obstruction [57].

SURGICAL RESECTION

Surgical resection of metastatic DTC has been associated with longer survival in selected patients. For bony metastases, surgical intervention should be considered for patients with symptomatic tumors (either with pain or neural compression) or when the uptake of RAI is poor [31]. Improvement in survival and quality of life have been reported after surgical excision of up to five bone metastases [27, 33]. Patients considered for surgical intervention should be carefully selected, with poor prognostic indicators including the presence of visceral metastases, multiple bony metastases, aggressive histological subtypes, and a short time interval between diagnosis of the primary tumor and metastases [61, 62].

The role of surgery is less well established for extraskelletal metastases in DTC patients. Cerebral metastases are associated with a poorer prognosis than other sites of metastasis; however, when feasible, surgery is the treat-

ment of choice. Although evidence in this area is scant, two series have reported longer survival with the resection of cerebral metastases [59, 60]. For patients with pulmonary metastases that are large or nonresponsive to RAI, surgical resection can be considered [63, 64]. One series of patients who underwent resection of pulmonary metastases reported a disease-free survival rate of 25% and overall 5-year survival rate of 33% [63].

POTENTIAL MOLECULAR TARGETS

Patients with distant metastatic disease who are resistant to the above treatments (particularly, those resistant to RAI) have a poor prognosis, and there is now much research activity directed at the development of novel therapies for this group of patients [65]. The majority of these therapies target specific molecules that are known to be involved in the tumorigenesis and progression of thyroid cancer. Such therapies are now transitioning from studies in thyroid cancer cell lines into phase I and phase II clinical trials in patients with advanced thyroid cancer [17, 66–68].

Somatic mutations are very common in both papillary and follicular thyroid cancer. In papillary thyroid cancer (PTC), the three more common mutations are usually mutually exclusive. Mutations of the B isoform of RAF kinase (*BRAF* mutations) are found in approximately 45% of cases, *Ras* mutations are found in 15% of cases, and *RET/PTC* rearrangements are found in 20% of cases [69]. All these mutations potentially lead to upregulation of the Ras/BRAF/mitogen-activated protein kinase (MAPK)/extracellular signal-related kinase (ERK) kinase (MEK)/ERK or MAPK pathway that is involved in thyroid cancer tumorigenesis.

BRAF mutation is the most commonly detected mutation in PTC. In >90% of *BRAF* mutations, there is a T1799A point mutation that leads to a V600E amino acid substitution (valine-to-glutamine). This leads to constitutive activation of the BRAF kinase, and hence upregulation of downstream pathways [70, 71]. Although not all studies are consistent, this mutation has been associated with a more advanced stage at diagnosis and greater risks for recurrence and death [72, 73]. Additionally, there is evidence that *BRAF* mutation is associated with impairment of the sodium-iodide symporter (NIS), causing decreased iodine uptake by the thyrocyte and subsequent relative resistance to RAI [74–76].

Common mutations in follicular thyroid cancer include *Ras* mutations (45%), the *PAX8-PPAR-γ* genetic rearrangement (35%), and mutations involving the phosphatidylinositol 3-kinase (PI3K)–Akt pathway (10%) [69]. The PI3K–Akt pathway is an alternate pathway to the MAPK pathway, and in aggressive DTC and anaplastic thyroid

cancer mutations that upregulate both pathways are common [77, 78]. Thus, it is these pathways that represent the main targets for molecular therapies in thyroid cancer [79].

Novel therapies are being developed to target these specific mutations and pathways, and include tyrosine kinase inhibitors (TKIs), inhibitors of angiogenesis, and therapies targeting intranuclear modulators of gene regulation. Therapies that re-establish the ability to take up RAI are also being developed and trialed. The mechanisms of many of these agents overlap; for example, TKIs may also inhibit angiogenesis and improve iodine uptake. The greatest number of recent trials focus on TKIs, and a summary of published phase II clinical trials is presented in Table 1. Published trials of other novel therapies are presented in Table 2 and ongoing trials of novel agents in thyroid cancer are listed in Table 3.

Interpretation of the results of these trials must be made with some caution. In some trials, patients with differing thyroid cancer histologies were enrolled (i.e., medullary, anaplastic, and DTC). Patients recruited have either locally advanced or distant metastatic disease, but the rate of progression of disease prior to the commencement of the trial is not always clear. Additionally, because of the nature of phase II clinical trials, there is no control group for comparison. Endpoints in most studies are either assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) [80] or by changes in tumor volume, with partial responses or stable disease being the most common outcomes [18, 81–91].

TKIs

TKIs are small-molecule drugs that bind to the ATP pocket of the kinase, thus competing with cellular ATP. This binding site is very similar among the different tyrosine kinases such that, although a drug may target a certain tyrosine kinase, it is likely to have some inhibitory action on multiple tyrosine kinases [92]. Because the majority of cancers have multiple mutations with the upregulation of multiple molecular pathways, this high degree of crossreactivity of the TKIs may be clinically beneficial. The majority of the TKIs used in trials do inhibit multiple tyrosine kinases; most commonly, those involved in vascular proliferation (VEGF, PDGF), and such “broad-spectrum” TKIs are of increasing clinical interest. Each drug has a different half-maximal inhibitory concentration (IC_{50}) for each specific target, and these can be used to compare different TKIs. For example, motesanib has an IC_{50} of 2 nMol/l for VEGFR-1, 6 nMol/l for Kit, 59 nMol/l for RET, and 83 nMol/l for PDGFR [93]. Even with the use of these “broad-spectrum” TKIs, tumors may become resistant to TKIs by the activation of alternative tyrosine kinases or molecular pathways.

Thus, it has been suggested that combinations of TKIs with broader targets may inhibit a greater number of molecular pathways and prove to be more effective than the use of a single agent [92, 94].

In the last 2 years, at least six phase II clinical trials assessing TKIs in advanced thyroid cancer have been completed (including one study published only in abstract form thus far), with short-term responses to treatment summarized in Table 1 [84–88, 91]. In addition, there are at least seven ongoing phase II trials investigating the role of TKIs (Table 3) [51]. Longer follow-up has been reported in a series of two patients with metastatic DTC treated with sunitinib (inhibitor of VEGF, PDGFR, and RET), with a partial response in one and stable disease in the other at 4 years of follow-up [95].

The largest of the phase II clinical trials published so far investigated the role of motesanib (AMG 706, an inhibitor of VEGFR, PDGFR, Kit, and RET) in 93 patients with DTC [84]. Eligible patients had histologically confirmed locally advanced or metastatic DTC with resistance to standard therapy (surgery, EBRT, RAI) and evidence of disease progression within the 6 months prior to entry into the trial. Motesanib diphosphate was administered once daily for up to 48 weeks (and was ceased early because of either toxicity or disease progression), with trough plasma concentrations consistently >10 nMol/l—above the IC_{50} of VEGFR and Kit [93]. There were no complete responses (as defined by the RECIST). A partial response was achieved in 13 patients (14%) at a median of 15 weeks, with the median duration of response being 32 weeks. Stable disease was observed in 62 patients (67%) and progression of disease occurred in seven patients (8%). Eighty-seven (94%) patients had at least one treatment-related adverse event, with 12 patients (13%) discontinuing treatment as a result of adverse events. The most common adverse events were diarrhea, hypertension, fatigue, and weight loss. Grade 3 adverse events were reported in 55% of patients, grade 4 adverse events were reported in five patients (5%), and there were two treatment-related deaths, both in patients with progressive disease.

Objective responses were also observed in clinical trials of sorafenib and axitinib, with partial responses in 12%–30% of patients and stable disease in 35%–65% of patients [85, 86, 88, 91]. In a trial of gefitinib (an epidermal growth factor receptor inhibitor), no objective responses were seen [87]. Adverse events were common in all trials, but the majority were reversible. Temporary discontinuation of the drug with reintroduction at a lower dose was common in all trials. Severe toxicities were rare, with only one patient in these trials thought to have died as a direct result of study medication (hepatic failure with sorafenib that was not re-

Table 1. Trials of tyrosine kinase inhibitors for differentiated thyroid cancer. Outcome in all trials measure by the RECIST

Agent	Motesanib [84]	Gefitinib [87]	Axitinib [85]	Sorafenib [86]	Sorafenib [91]	Sorafenib [88] ^a
Target	VEGFR, PDGFR, Kit	EGFR	VEGFR, PDGFR, Kit	BRAF, VEGFR	BRAF, VEGFR	BRAF, VEGFR
<i>n</i> enrolled	93	27	60	30	56	31
Histology (DTC)	93	18	45	27	52	27
Median age (range), yrs	62 (36–81)	65	59 (26–84)	63 (31–89)	61 (27–90)	65
Female	47%	40%	42%	50%	45%	
Median progression-free survival	40 wks	3.7 mos	18 mos	79 wks	15 mos	47–69 wks
Outcome (RECIST)						
Complete response	0	0	0	0	0	0
Partial response	14%	0	30%	23%	12%	26%
Stable disease	67%	81%	38%	53%	65%	35%
Progressive disease	8%	19%	7%	3%	12%	19%

^aResults published in abstract form only, progression-free survival time of 47 weeks in patients with bone metastases and 69 weeks in patients without bone metastases.

Abbreviations: BRAF, B isoform of Raf kinase; DTC, differentiated thyroid cancer; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; RECIST, Response Evaluation Criteria in Solid Tumors; VEGFR, vascular endothelial growth factor receptor.

Table 2. Other targeted therapies in metastatic differentiated thyroid cancer

Agent	Celecoxib [82]	Thalidomide [81]	Lenalidomide [89] ^a	Vorinostat [83]	Bortezomib [90] ^a
Mechanism of action	COX-2 inhibitor	Antiangiogenesis	Antiangiogenesis	Histone deacetylase inhibitor	Proteasome inhibitor
<i>n</i> enrolled	32	36	25	19	10 (6 evaluated)
Histology (DTC)	32	29	25	16	10
Median age (range), yrs	65 (42–89)	57 (26–87)	(30–71)	62 (40–77)	58
Female	59%	33%	40%	69%	40%
Outcome	RECIST	Tumor volume	Tumor volume	RECIST	RECIST
Complete response	0	0	0	0	0
Partial response	3%	18%	22%	0	0
Stable disease	3%	32%	44%	56%	67%
Progressive disease	72%	50%	34%	44%	33%

^aPreliminary results published in abstract form only.

Abbreviations: DTC, differentiated thyroid cancer; COX, cyclo-oxygenase; RECIST, Response Evaluation Criteria in Solid Tumors.

versible after discontinuation of the drug) [86]. Studies in tumor cell lines continue to be promising, with sorafenib and vandetanib both inhibiting RET kinases with an IC₅₀ of <50 nM and 100 nM, respectively [96, 97].

TKIs may also improve the sensitivity of thyroid cancer to more traditional treatments. Although there are no clinical trials yet published on this effect, there are a number of in vitro studies suggesting that the use of TKIs increases iodine avidity and sensitivity to doxorubicin [98, 99]. Further investigation is also required into the simultaneous use of

multiple TKIs that may more effectively inhibit the multiple pathways involved in tumorigenesis [92, 94].

OTHER MOLECULAR TARGETED THERAPIES

Other agents that have been trialed in advanced thyroid cancer include histone deacetylase inhibitors, cyclo-oxygenase-2 inhibitors, angiogenesis inhibitors, proteasome inhibitors, and heat shock protein 90 inhibitors (Tables 2 and 3). Little therapeutic effect was seen with celecoxib or with vorinostat (histone deacetylase inhibitor) [82, 83].

Table 3. Open trials of therapeutic agents for advanced thyroid cancer

Agent (therapeutic target)	Trial status
Tyrosine kinase inhibitors	
Axinitib (VEGF, PDGF, Kit)	Recruiting (2 trials)
Motesanib (VEGF, PDGF, Kit, RET)	Ongoing, not recruiting
Vandetanib (VEGF, RET, EGFR)	Ongoing, not recruiting
Sunitinib (VEGF, PDGF, Kit, RET)	Recruiting (2 trials)
Sorafenib (BRAF, VEGF)	Recruiting
-E7080 (VEGF via KDR & Flt-1, PDGF, FGF)	Recruiting
Heat shock protein 90 inhibitor	
17-AAG	Recruiting
Histone deacetylase inhibitor	
Romidepsin (FR901228)	Recruiting
Demethylation	
Decitabine	Ongoing, not recruiting
Proteasome inhibitor	
Bortezomib	Recruiting
Angiogenesis inhibitor	
Lenalidomide	Ongoing, not recruiting
Antimetabolite and antimicrotubule	
Pemetrexed and paclitaxel	Recruiting
PPAR- γ agonist	
Rosiglitazone	Ongoing, not recruiting
The majority of these phase II clinical trials are listed with the National Institutes of Health Clinical Trials database, available at http://www.ClinicalTrials.gov . Abbreviations: 17-AAG, 17-allylamino-17-demethoxygeldanamycin; BRAF, B isoform of Raf kinase; EGFR, epidermal growth factor receptor; fgf, fibroblast growth factor; PDGF, platelet-derived growth factor; PPAR- γ , peroxisome proliferator-activated receptor γ ; VEGF, vascular endothelial growth factor.	

The antiangiogenic properties of thalidomide were investigated in a phase II clinical trial of advanced thyroid cancer by Ain et al. [81] published in 2007. Outcomes were measured in terms of tumor volume rather than with the RECIST. A partial response was defined as a >50% reduction in tumor volume. Twenty-eight patients were available for assessment, and partial responses were reported in 18% with stable disease in 32%. The majority of patients required dose modifications because of toxicity. This same group of investigators is undertaking a phase II clinical trial of lenalidomide, with an interim analysis suggesting similar response rates to thalidomide but with lesser toxicity [89].

Other specific inhibitors of molecules that are known to

be upregulated in thyroid cancer are also being developed. MEK inhibitors have been proposed to inhibit the upregulation of the MAPK pathway in PTC [70]. Phase I and phase II clinical trials of the MEK inhibitor CI-1040 in breast, colon, pancreatic, and non-small cell lung cancer revealed minimal antitumor effects [100, 101]. In vitro studies have suggested that MEK inhibitors suppress growth in PTC tumor cell lines [102, 103]. Furthermore, there may be inhibition of the PI3K-Akt pathway in addition to the MAPK pathway [103].

THERAPIES TO RESTORE RAI AVIDITY

Advanced thyroid cancers dedifferentiate, downgrading expression of the NIS, and hence lose the ability to take up RAI. At a cellular level, thyroid malignancies have been shown to be associated with low NIS messenger RNA and higher intracellular NIS protein expression. These results suggest that the downgraded expression of the NIS may not be a result of a defect in transcription but rather because of the failure of the NIS to be targeted to, or retained within, the basolateral cell membrane [104–106]. Additionally, this loss of NIS expression has been associated with *BRAF* mutation and may explain the low RAI uptake in this group [74, 107]. Agents are being developed that aim to redifferentiate thyroid cancer cells and thus restore the ability to take up iodine. The success of these agents would then facilitate the use of RAI in previously refractory tumors.

Lithium inhibits the release of iodine from the thyroid, and hence may increase the effective half-life of RAI. Small clinical trials in patients with metastatic iodine-avid DTC do show prolonged uptake of RAI; however, any therapeutic benefit remains unclear [108, 109]. A more recent small study reported no clinical benefit with lithium and also performed in vitro testing to assess any effect of lithium on the NIS. Lithium did not alter iodine uptake via the NIS [110]. Thus, the clinical benefit of lithium in those with iodine-avid metastases remains uncertain, but for those with iodine-resistant metastases there is unlikely to be any benefit.

Retinoic acid is the active metabolite of vitamin A and acts via retinoic acid receptors (RAR, RXR) to regulate cell differentiation and proliferation. In thyroid cancer cell lines, retinoic acid has been shown to lead to redifferentiation [111], including greater NIS expression and iodine uptake [112]. Initial clinical studies investigating 13-cis-retinoic acid did suggest some clinical benefit [113, 114]; however, this was not reproduced in more recent clinical trials [115, 116]. Patients with progressive disease despite RAI treatment were enrolled in a trial of beraxotene, an RXR agonist. Eight of 11 patients had an increase in RAI uptake; however, in the majority this increase was small, being detectable only with single photon emission com-

puted tomography, and hence may not be clinically relevant [117]. All-trans-retinoic acid was studied in 11 patients, with some partial increases in iodine uptake [118].

Rosiglitazone is a thiazolidinedione more commonly used in the management of type 2 diabetes mellitus. Its action as a peroxisome proliferator-activated receptor (PPAR)- γ agonist has led to the investigation of its role in the redifferentiation of malignant cells and ability to inhibit tumor growth [119]. In two independent clinical trials, rosiglitazone was administered to patients with proven metastatic DTC but negative total-body iodine scans. Uptake of RAI improved in four of 10 patients in one study [120] and in six of 23 patients in the other [121]. In both studies, tissue was tested for PPAR- γ expression; however, the results correlating PPAR- γ expression and response to rosiglitazone are conflicting [120, 121]. Further trials are being conducted on the effect of rosiglitazone in patients with locally advanced or metastatic DTC [51].

Gene treatment with cloning of the *NIS* gene and then injection into tumor cells has been trialed [122, 123]. Although gene treatment does increase the uptake of RAI, retention of the gene, and hence any increase in iodine uptake, is short [124]. Human clinical trials have not yet been performed. In addition, histone deacetylase inhibitors and the TKI gefitinib have been reported to increase NIS expression in PTC cell lines, and hence may restore iodine avidity in vivo [98, 125, 126]. Further trials of treatments in combination with RAI are needed to confirm any effect.

CONCLUSION

Despite the recent proliferation of clinical trials in thyroid cancer, treatment options for those with metastatic DTC resistant to RAI remain limited. With our improved understanding of the pathways of tumorigenesis of thyroid cancer, therapies targeting specific molecules are being developed and progressing to clinical trials. At present, these treatments produce partial responses at best, but with limiting toxicities. Further treatments are being developed and combination therapies may prove to be more effective. There is insufficient evidence at present for the routine use of any of these novel agents; however, clinicians should be encouraged to enroll patients with metastatic DTC into clinical trials.

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