Biochemical Pharmacology 80 (2010) 592–601

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Targeted therapy of thyroid cancer

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ARTICLE INFO

Article history:
Received 3 February 2010
Accepted 6 May 2010

Keywords:
Thyroid carcinoma
Antineoplastic agents
Angiogenesis inhibitors
Protein kinase inhibitors

ABSTRACT

Systemic chemotherapies for advanced or metastatic thyroid carcinomas have been of only limited effectiveness. For patients with differentiated or medullary carcinomas unresponsive to conventional treatments, novel therapies are needed to improve disease outcomes. Multiple novel therapies primarily targeting angiogenesis have entered clinical trials for metastatic thyroid carcinoma. Partial response rates up to 30% have been reported in single agent studies, but prolonged disease stabilization is more commonly seen. The most successful agents target the vascular endothelial growth factor receptors, with potential targets including the mutant kinases associated with papillary and medullary oncogenesis. Two drugs approved for other malignancies, sorafenib and sunitinib, have had promising preliminary results reported, and are being used selectively for patients who do not qualify for clinical trials. Additional agents targeting tumor vasculature, nuclear receptors, epigenetic abnormalities, and the immune response to neoplasia have also been investigated. Randomized trials for several agents are underway that may lead to eventual drug approval for thyroid cancer. Treatment for patients with metastatic or advanced thyroid carcinoma now emphasizes clinical trial opportunities for novel agents with considerable promise. Alternative options now exist for use of tyrosine kinase inhibitors that are well tolerated and may prove worthy of regulatory approval for this disease.

Contents

Abbreviations: Bcr-ABL, A fusion between the Breakpoint cluster region and the *Abl* genes; DTC, differentiated thyroid carcinoma; ERK, extracellular signal regulated kinase; FGFR, fibroblast growth factor receptor; FTC, follicular thyroid carcinoma; HDAC, histone deacetylase; MAPK, Mitogen activated protein kinase; PFS, progression-free survival; PDGFR, platelet derived growth factor receptor; PI3K, phospho inositide-3 kinase; PPAR, peroxisome proliferators activator receptor; PTC, papillary thyroid carcinoma; RECIST, response evaluation criteria in solid tumors; TSH, Thyroid stimulating hormone; VEGFR, vascular endothelial growth factor receptor.

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doi:10.1016/j.bcp.2010.05.003

1. Introduction

The treatment of most patients with differentiated thyroid carcinoma (both papillary [PTC] and follicular [FTC] histologies) is based on surgery, radioactive iodine, and thyroid hormone therapy [1]. When metastatic disease occurs, radioactive iodine can be curative in a minority of patients, and TSH-suppressive thyroid hormone therapy can help to slow the pace of the disease. However, for those patients with metastatic differentiated thyroid carcinoma (DTC) that progresses despite radioiodine and TSH-suppressive thyroid hormone therapy, treatment options have historically been limited. Treatment of patients with medullary thyroid carcinoma (MTC) is also based on surgery for primary and regional metastatic disease. Because the neuroendocrine-derived MTC is not responsive to either radioiodine or TSH suppression, these options are not available for treatment of progressive, metastatic MTC.

Cytotoxic systemic chemotherapies for advanced, metastatic thyroid carcinomas have limited effectiveness, with response rates typically 25% or less [2]. With such poor outcomes, results from few clinical trials of new therapies for thyroid carcinomas were published during the latter half of the 20th century [3]. Plaguing these early trials was the practice of lumping patients with all histologies of thyroid carcinoma, confounding interpretation of the results. The definitions of response used in these earlier studies varied as well, and none are comparable to the currently used standard methodology [4,5]. Thus, treatment with cytotoxic chemotherapy is generally limited to patients with symptomatic or rapidly progressive metastatic disease unresponsive to or unsuitable for surgery, radioiodine (for tumors derived from differentiated carcinomas), and external beam radiotherapy.

During the past decade, biologic discoveries have sparked trials testing novel, biologically targeted therapies for advanced thyroid carcinomas. Of prime importance has been recognition of key oncogenic mutations in PTC and MTC. *BRAF* and *RAS* genes code for kinases that activate signaling through the mitogen-activated protein kinase (MAPK) pathway, regulating growth and function in many cells both normal and neoplastic. Evidence from various tumor models support the contention that most PTCs may be driven in part through single activating somatic mutations in one of three genes: *BRAF, RAS*, and translocations producing *RET/PTC* oncogenes [6]. The resultant RET/PTC proteins signal upstream from RAS, thus activating the same MAPK pathway. For MTC, almost all familial forms of the disease arise due to inheritable germline activating mutations in *RET*, and identical somatic mutations occurring in C cells commonly cause sporadic disease. Activated RET mutant proteins also enhance MAPK signaling. Consistent with the "oncogene addiction" hypothesis, inhibition of these etiologic activating mutations leads to either tumor stabilization or regression. Therefore, interest arose in the therapeutic potential of target-specific kinase inhibitors for these diseases.

A second development was recognition of processes facilitating tumor growth, reflecting either normal (such as hypoxia-inducible angiogenesis) or abnormal (such as epigenetic modifications of chromosomal DNA and histones) adaptations. Angiogenesis plays a critical role to support tumor cell growth and metastasis, supplying nutrients and oxygen, removing waste products, and facilitating distant metastasis [7]. Of the identified proangiogenic factors, vascular endothelial growth factor (VEGF) is key, binding to 2 receptor tyrosine kinases, VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR) in the endothelial cells, leading to activation of MAPK signaling [8]. In PTC, the intensity of VEGF expression correlates with a higher risk of metastasis and recurrence, a shorter disease-free survival, and BRAF mutation status [9,10,11].

This review will focus on findings from key studies that reflect this new paradigm for research-driven treatment using targeted therapies for metastatic thyroid carcinoma [12].[1]

2. Targeting oncogenic kinases

Given the oncogenic roles of activated BRAF, RET, and RET/PTC kinases, it is theorized that specific targeting of these kinases could block tumor growth and induce senescence [13]. To date, only selective inhibitors of BRAF have entered clinical trials as a test of this hypothesis, as the agents available to target RET and RET/PTC generally also inhibit VEGFR and other kinases [14]. In contrast with the experience of treating gastrointestinal stromal tumors containing activating *c-KIT* mutations with the KIT-inhibitor imatinib, use of selective BRAF inhibitors has not yet yielded impressive results in *BRAF*-mutant PTC [15]. The emerging evidence of a high frequency of squamous cell neoplasms as an adverse event seen with all BRAF inhibitors may reveal a novel mechanism of oncogenesis.

2.1. PLX 4032

PLX 4032 is an orally available small molecule that has higher selectivity for the V600E mutant BRAF kinase over wild-type BRAF kinase [16]. In melanoma and colon carcinoma cell lines bearing the V600E *BRAF* mutation, the IC50s for inhibiting phosphorylation of ERK were 10–30 nM and for inhibiting cellular proliferation were 47–126 nM [16,17]. The *RET/PTC* mutant thyroid cancer cell line TPC1, however, was poorly inhibited, with an IC50 for cellular proliferation of 10 μM. In contrast, *BRAF*-mutant cell lines are effectively inhibited at concentrations less than 100 nM, inducing a cell cycle blockade but not leading to cell death [18]. Preliminary data from a phase I study of escalating doses of PLX 4032 described the outcomes of 3 patients with *BRAF*-mutant PTC [17]. One PTC patient experienced a partial response with shrinkage of lung metastases, whereas the other 2 patients had prolonged stable disease. Among the overall cohort of 55 patients with solid tumors (49 of whom had melanoma), the most common adverse events were skin rash, fatigue, pruritus, photosensitivity, and nausea. Although severe side effects were uncommon, 11% of the patients developed cutaneous squamous cell carcinomas.

2.2. XL 281

XL 281, an oral small molecule that inhibits both wild-type and mutant BRAF kinases at low nanomolar concentrations, is currently in phase I trial [19]. Preliminary data described stable

[1] Online databases that can be searched to identify clinical trials currently recruiting patients can be found at www.thyroid.org and www.clinicaltrials.gov.

disease in 5 PTC patients; of the 2 patients whose tumors were documented to contain BRAF mutations, both remained stable after more than 1 year of therapy, as did a third PTC patient whose mutation status was unknown. Additional 2 patients with Hurthle cell carcinomas also were treated with prolonged stable disease, but 1 patient with anaplastic carcinoma progressed despite treatment. No partial response was seen in any of the thyroid cancer patients. The most common side effect reported among all 48 solid tumor patients in the trial was fatigue in nearly half of patients, and other common toxicities included nausea, diarrhea, and vomiting, all of which were occasionally severe. Four patients were also described as having developed either cutaneous squamous cell carcinomas or premalignant keratoacanthomas.

3. Targeting signaling kinases

A wide variety of multitargeted kinase inhibitors have entered clinical trials for patients with advanced or progressing metastatic thyroid cancers. Most of these agents have had the common property of inhibiting VEGF receptors at nanomolar concentrations, and thus have targeted angiogenesis primarily. However, given the considerable structural similarity between RET and VEGFR kinases, most of these small molecule inhibitors are capable of affecting both kinases. Because of the targeting similarities of many of these agents, common toxicities exist among these agents, including hypertension, diarrhea, skin rashes, and fatigue.

3.1. Motesanib

Motesanib (AMG706) is an oral, tyrosine kinase inhibitor targeting the VEGF receptors 1, 2, and 3 [20]. In both *in vitro* and cell-based assays, nanomolar concentrations of motesanib inhibited autophosphorylation of both wild-type and mutant RET; growth of xenografts of TT cells bearing the C634W *RET* mutation was effectively inhibited [21]. In a phase I study, motesanib, demonstrated antitumor activity in patients with advanced solid malignancies, including 5 patients with differentiated thyroid carcinoma (DTC) and 1 with MTC; 3 thyroid patients experienced >30% reductions in tumor diameters, qualifying as partial responders [4,22]. The most common toxicities included fatigue, nausea, diarrhea, and hypertension, all typical of this class of drugs.

Based on this phase I experience, a multicenter, open-label phase II trial was initiated, testing the efficacy of motesanib in separate cohorts of patients with progressive DTC [23] and patients with progressive or symptomatic MTC [24], starting at 125 mg daily. The eligibility criterion of progression was based upon serial radiographic imaging studies within the preceding 6 months, applying RECIST response assessment [4]. Of 93 DTC patients who initiated therapy, one-third were still on drug after 48 weeks. Partial response was confirmed by subsequent imaging and independent radiologic review in 14% of the DTC patients, and another 35% of these previously progressive disease patients maintained stable disease for at least 24 weeks. The median progression-free survival was 40 weeks. Although the drug does not inhibit BRAF, patients with *BRAF* mutation-bearing tumors were less likely to progress while on drug, which may relate to higher dependence upon VEGF-mediated angiogenesis in such tumors [25]. Of 91 patients with progressive or symptomatic MTC who initiated therapy, only 2% had confirmed partial response but another 47% experienced stable disease for at least 24 weeks [24]. Unexpectedly, the maximum and trough plasma concentrations of the drug in MTC patients were lower than reported with other solid tumor patients, and these differing pharmacokinetics may have contributed to the lower response rate. Overall, the drug was well tolerated, with similar side effects as reported in the phase I trial. An unanticipated side effect of motesanib therapy was a 30% increase in the mean dosages of levothyroxine required to maintain TSH suppression or euthyroidism, respectively, in DTC and MTC cohorts, and 60–70% of patients experienced peak TSH concentrations out of the therapeutic ranges [26].

3.2. Sorafenib

Sorafenib (BAY 43-9006) is an oral, small molecule TKI targeting VEGF receptors 2 and 3, RET (including most mutant forms that have been examined), and BRAF [27]. In preclinical studies, sorafenib prevented the growth of the TPC1 and TT cell lines, which contain the *RET/PTC1* and *C634W* RET mutations, respectively [28]. In four phase I trials testing varying doses and administration schedules of sorafenib, the optimal therapeutic dose was found to be 400 mg twice daily [29]. The most common or significant toxicities included hand-foot syndrome, rash, fatigue, diarrhea and hypertension. Like other agents that inhibit BRAF, sorafenib also has been associated with development of cutaneous squamous cell carcinomas in up to 5% of treated patients, and a similar frequency of keratoacanthomas and other premalignant actinic lesions [30].

Although no thyroid cancer patients were reported in these phase I trials, tumor shrinkage was reported in 1 thyroid cancer patient included in a phase II trial for advanced solid tumors [31]. Subsequently, 3 phase II trials have been performed focusing on patients with metastatic DTC, collectively representing the largest cohort of thyroid cancer patients studied with any single chemotherapy agent.

- A phase II trial recruited 58 patients in a 10-month period [32]. Although RAI treatment failure was required, demonstration of tumor progression was not an entry requirement. Of 41 PTC patients, confirmed partial response was seen in 15% (with a median time to response of at least 1 year), and stable disease was described in another 61%. For the subgroup of PTC patients whose cancer had not previously been treated with chemotherapy, median progression-free survival (PFS) was 16 months. Another 11 patients had FTC or Hurthle cell carcinoma; no objective responses were seen, and median PFS was only 4.5 months.
- In a smaller phase II study, unconfirmed partial responses were reported in 4 of 15 (27%) evaluable patients with PTC and 3 of 7 with FTC (43%) [33]. Median PFS was 84 weeks. Updated follow-up data from this latter trial were recently presented, comprising a total of 55 patients (25 with PTC, 19 with FTC or HTC, 4 with MTC, and 5 with poorly differentiated or anaplastic carcinomas) [34]. Although the overall PFS remained 84 weeks, it was significantly shorter at 54 weeks in those patients whose tumors lacked the *BRAF* activating mutation.
- A phase II study aimed to evaluate the effect of 26 weeks of sorafenib therapy on radioiodine uptake and tumor response in 32 patients with progressive, radioiodine-negative DTC [35]. At study end, 8 (25%) patients had a partial response, 11 had stable disease (34%), 7 had progressive disease (22%), and 6 were non-evaluable. Median PFS was 58 weeks, although patients with bone metastases had worse median PFS than those without (47 weeks compared with 69 weeks, $P < 0.05$). Of 21 patients who underwent radioiodine imaging after 26 weeks of treatment, none had induction of uptake in metastatic lesions. The most commonly reported and serious adverse events included hand-foot syndrome, weight loss, hypertension, diarrhea, alopecia, rash, mucositis, and hypocalcemia. One patient experienced a myocardial infarction, and another congestive heart failure.

In a recent retrospective series, sorafenib therapy was associated with prolongation of median progression-free survival

by at least 1 year, compared with patients' rate of disease progression prior to initiation of therapy [36]. A randomized, placebo-controlled phase III study of sorafenib as first-line therapy for progressive metastatic DTC has been initiated.

Anticipating synergy between sorafenib's ability to inhibit MAPK signaling and the RAS-blocking effects of the farnesyltransferase inhibitor tipifarnib, a phase I trial was performed of the combination of these drugs [37]. The maximum tolerated doses of sorafenib and tipifarnib were 200 and 100 mg twice daily, respectively. In the 21 patients with DTC treated, median progression-free survival was 20 months.

The anti-RET activity of sorafenib makes MTC a potential therapeutic target for this drug as well [38]. In a small pilot study, 5 patients with metastatic MTC were treated with sorafenib, starting at 400 mg twice daily [39]. Responses were described in 2 (including one complete response) after 6 months of treatment and symptomatic improvement was seen in all, but most patients required dose reduction due to side effects. Preliminary results have been reported from larger, open-label phase II study in patients with metastatic MTC [40]. Although partial response was only seen in 6% of patients with sporadic MTC, stable disease lasting more than 6 months was reported in 62%. A high frequency of side effects was noted, including flushing, diarrhea, weight loss, alopecia, hand/foot syndrome, and rash. Severe adverse events included a pulmonary embolus, hypokalemia, hypertension, hyponatremia, joint pain, and thrombocytopenia. Partial responses were also reported in 4 of 9 evaluable MTC patients participating in the phase I study of the combination of sorafenib and tipifarnib [37].

In anaplastic carcinoma cell lines, preclinical models suggested potential efficacy of sorafenib to inhibit MAPK signaling [41]. Subsequently, a phase II trial was started, evaluating sorafenib therapy in patients who had progressed after previous cytotoxic chemotherapy [42]. Of 15 patients evaluated, 2 had experienced a partial response and 4 had stable disease as their best responses to treatment, but the overall median time to progression was only 1.5 months and duration of survival 3.5 months.

Sorafenib is approved by the U.S. Food and Drug Administration as treatment for advanced renal cell carcinoma and unresectable hepatocellular carcinoma. Although not specifically approved for thyroid carcinomas, sorafenib is being used in selected patients with progressive metastatic papillary and medullary thyroid carcinoma for whom clinical trials are not appropriate [43]. Compared with patients' rate of disease progression prior to initiation of therapy, sorafenib may prolong progression-free survival in DTC by at least 1 year [36]. The drug may also be appropriate in selected pediatric cases; in 1 report, treatment with sorafenib yielded a marked response in a child whose lung metastases from PTC were progressing despite radioiodine therapy [44]. As with other antiangiogenic therapies, pediatric usage may result in bony growth plate inhibition and growth abnormalities.

3.3. Sunitinib

Sunitinib (SU11248) is an oral, small molecule TKI of all 3 VEGF receptors, RET, and RET/PTC subtypes 1 and 3 [45]. Prolonged partial responses have been described in 3 patients (with PTC, FTC, and MTC, respectively) treated with sunitinib, 50 mg daily for 28 days followed by 14 days of no treatment per cycle [46,47]. FDG uptake by positron emission tomography imaging was markedly reduced in the DTC patients. Preliminary results from an open-label phase II trial in patients with progressive DTC or MTC report partial response in 13% of 31 DTC patients, and disease stabilization in 68% of DTC and 83% of MTC patients [48]. Common or severe adverse events include fatigue, diarrhea, palmar-plantar erythrodysesthesia, neutropenia, and hypertension. Interim analysis from a second open-label phase II trial reported partial responses or stable disease for greater than 12 weeks in 2 of 12 DTC and 3 of 8 MTC patients [49]. Recently, preliminary results from a third trial, using a lower dose of 37.5 mg daily but administered continuously, were reported [50]. Of 33 patients with FDG-PET avid metastatic thyroid cancer (26 with DTC, 7 with MTC), 29 were evaluable for response: 7% complete response (lasting at least 9 months), 25% partial response, and 48% stable disease. Like sorafenib, sunitinib is approved for treatment of renal cell carcinoma, and is therefore available for use in selected thyroid cancer patients with metastatic disease warranting therapy outside of clinical trials.

3.4. Vandetanib

Vandetanib (ZD 6474) is an oral, small molecule TKI that targets VEGF receptors 2 and 3, RET, and at higher concentrations, the EGF receptor [51,52]. One of the first small molecule inhibitors to be studied in thyroid cancer cell lines, vandetanib was shown to inhibit effectively *RET/PTC3* mutations found in some PTC and *M918T* RET mutations occurring in MEN2B-associated and some sporadic MTC [53]. Growth of cell lines containing *RET/PTC1* or *RET/PTC3* was inhibited. However, the drug was not able to block RET when a hydrophobic amino acid substitution occurs at V804, as in some inherited forms of MTC [54]. In a phase I trial in 77 patients with various solid carcinomas other than thyroid, doses up to 300 mg daily were tolerated with the most common dose-limiting side effects of diarrhea, hypertension, and skin rash [55].

On the basis of the preclinical demonstration that vandetanib inhibited most *RET* point mutations, a multicenter, open-label phase II trial studied the efficacy of the drug in patients with metastatic familial forms of MTC [56]. Thirty patients were enrolled, starting therapy with vandetanib, 300 mg daily. Confirmed partial response was reported in 21% of these patients, and unconfirmed responses in another 17%. Calcitonin levels dropped by more than 50% in most patients, but blocking RET may lead to a direct inhibition of calcitonin gene expression, independent of tumor volume changes [57]. The most commonly reported side effects included rash (particularly photosensitivity), diarrhea, fatigue, and nausea, whereas the most severe toxicities included asymptomatic QT interval prolongation, rash, and diarrhea. A second phase II trial in familial MTC, starting at 100 mg daily, reported similar preliminary results [58]. Ongoing studies with vandetanib include (1) a multicenter, randomized, placebo-controlled phase III trial in patients with metastatic MTC, either sporadic or inherited,(2) an open-label phase II trial in patients under the age of 18 with familial MTC (with partial responses described in several patients including those with aggressive tumors associated with germline M918T *RET* mutations) [59], and (3) a randomized placebo-controlled phase II trial in patients with metastatic DTC.

Of interest has also been potential synergistic combinations of vandetanib with other agents. Given the clinical evidence of vandetanib's efficacy in MTC, and *in vitro* evidence that bortezomib triggered caspase-dependent apoptosis in MTC cells, a phase I/II trial of the combination has been initiated, with enrollment targeting patients with advanced MTC as well as other solid tumors [60].

3.5. Axitinib

Axitinib (AG-013736) is an oral inhibitor that effectively blocks VEGF receptors at subnanomolar concentrations, but notably not the RET kinase [61]. In a phase I study of 36 patients with advanced solid malignancies, 1 of 5 thyroid cancer patients experienced tumor shrinkage, although none qualified as a partial response [62]. A multicenter, open-label phase II study examined the

efficacy of axitinib in advanced or metastatic thyroid carcinoma, starting at a dose of 5 mg twice daily [63]. Of the 60 patients who started therapy, 50% had PTC, 25% had FTC (including Hurthle cell variants), and 18% had MTC. Although response assessment was not possible in 25% of the patients, confirmed partial response rate was 30% by intent-to-treat analysis (31% in DTC; 18% in MTC; 1 patient with ATC). Responses were seen in patients despite previous treatments with a variety of chemotherapeutic regimens. Median progression-free survival was 18 months. Common adverse events included fatigue, stomatitis, proteinuria, diarrhea, hypertension, and nausea. Exploratory analyses of soluble biomarkers demonstrated increases in serum VEGF levels, a recognized phenomenon of effective angiogenesis inhibition [64]. Given the absence of inhibitory activity against RET or other mutated kinases that are oncogenic in thyroid carcinoma, the efficacy of axitinib suggests that VEGFR-mediated angiogenesis is likely the primary mechanism by which the other anti-VEGFR inhibitory agents function.

Currently ongoing is a multicenter, open-label phase II study to determine the efficacy of axitinib in patients with metastatic DTC refractory to doxorubicin, or for whom doxorubicin therapy is contraindicated. Study completion is anticipated in September, 2010.

3.6. Pazopanib

Pazopanib is a potent small molecule inhibitor of all VEGFR subtypes as well as PDGFR. Like axitinib, it has insignificant inhibitory activity against the oncogenic kinases RET, RET/PTC, or BRAF, and therefore its actions are expected to be primarily anti-angiogenic in thyroid carcinoma. Preliminary results were recently reported for 37 patients with rapidly progressing DTC treated in a phase II trial [65]. With a starting daily dose of 800 mg, 32% of patients had confirmed partial responses, and the 6 months progression-free survival was 71%. The most common side effects of therapy included hypertension in nearly half, elevated serum transaminases, headache, and mucositis. Preliminary results were also recently reported for 14 patients with rapidly progressing MTC treated in a phase II trial [65]. One patient (7%) experienced a partial response; at the time of the report, 8 (57%) were alive without progression, 2 (14%) were alive with progression, and 4 (29%) had died. The study has continued on to a second stage, enrolling up to 28 patients.

3.7. Imatinib

Imatinib (STI571), an oral, small molecule kinase inhibitor of BCR-ABL, PDGF receptor beta and c-KIT, inhibits RET autophosphorylation and RET-mediated cell growth [66,67,68]. Two small open-label phase II studies have been completed that examined a total of 24 patients with metastatic MTC treated with imatinib, starting at 600 mg daily [69,70]. No objective tumor responses were reported, and a minority of patients achieved stable disease as their best tumor response. Toxicities included diarrhea, laryngeal edema, rash, and nausea; increased thyroid hormone dosage requirements were reported in 9 of 15 patients in the larger trial [70]. No objective responses were seen in a phase I study of imatinib combined with dacarbazine and capecitabine that included 7 patients with MTC [71]. A phase II trial was recently reported of imatinib therapy, 400 mg twice daily, in patients with anaplastic thyroid carcinoma found to overexpress either PDGFR or BCR-ABL [72]. Although 2 of 8 patients were reported with partial responses, and another 4 had stable disease, 6 month progression-free and overall survival were still only 27 and 46%, and the trial was stopped prematurely due to difficulty recruiting patients.

3.8. Gefitinib

Gefitinib (ZD1839), an oral, small molecule inhibitor of the EGF receptor, was initially introduced for treatment of non-small cell lung carcinoma [73,74]. Because many papillary and anaplastic thyroid carcinomas display activated EGFR signaling, and inhibitors have had demonstrated efficacy in preclinical models, an open-label phase II study was initiated, examining the effectiveness of gefitinib in a mixed cohort of thyroid cancer patients [75]. The starting daily dose was 250 mg. Of 27 enrolled patients, 41% had PTC, 22% FTC, 19% had anaplastic carcinoma, and 15% had MTC. There were no complete or partial responses in the 25 evaluable patients, although 8 had tumor reduction that did not qualify as partial response. One patient with anaplastic carcinoma had stable disease beyond 12 months of therapy, similar to that reported in a phase I trial of gefitinib and docetaxel [76]. Overall, median progression-free survival was just under 4 months, and under 3 months in the MTC cohort.

In non-small cell lung carcinoma, the efficacy of anti-EGFR therapy is primarily seen in tumors bearing activating mutations in the kinase domains of the EGFR [74]. Generally, such mutations have not been reported in thyroid carcinomas despite a moderate frequency of anaplastic and poorly differentiated tumors expressing EGFR, perhaps underlying the overall lack of efficacy of gefitinib [77]. However, recently, a patient with anaplastic carcinoma was reported whose tumor contained 2 distinct somatic point mutations or polymorphisms in the EGFR kinase [78]. After initial local control was achieved, she developed local recurrence and distant metastases. Treatment with the EGFR inhibitor erlotinib was initiated, titrating up to 150 mg orally every day, and marked regression of tumor was noted clinically and radiographically, both locally and distantly. Unfortunately, therapy was discontinued due to the high cost of the drug, and she died several months later.

3.9. XL 184

XL 184 is an oral, small molecule inhibitor of VEGF receptors 1 and 2, C-MET, RET, C-KIT, FLT3, and Tie-2 [79]. The inhibitory activity against C-MET, the cognate receptor for the hepatocyte growth factor, may provide additional synergistic benefit in thyroid carcinomas, given the enhanced expression of the receptor seen in PTC and MTC [80,81,82]. An ongoing phase I dose-escalation study has examined the safety and pharmacokinetics of XL 184 in patients with metastatic solid malignancies, with an expansion cohort limited to MTC [83]. Fifteen MTC patients (44%) had achieved at least 30% reduction in tumor measurements, with 10 (29%) having confirmed partial responses. No correlation was seen between *RET* mutation status (either germline or somatic) and tumor response. A phase III trial, comparing XL184 with placebo, is now underway for patients with progressive, metastatic MTC.

4. Other approaches to targeting vasculature and angiogenesis

Beyond direct inhibitors of angiogenic kinases such as VEGFR, other drugs are capable of either inhibiting angiogenesis or disrupt existing tumor vasculature. Two of these agents, thalidomide and fosbretabulin (combretastatin A4 phosphate), have been of particular interest following reported responses in individual patients with anaplastic thyroid carcinoma.

4.1. Thalidomide and lenalidomide

Thalidomide was found to be an angiogenesis inhibitor decades after it achieved notoriety as a teratogenic cause of neonatal dysmelia [84]. However, the exact mechanism by which thalido-

mide exerts its antiangiogenic effects remains unknown. In the report that described the efficacy of paclitaxel for treatment of anaplastic thyroid carcinoma, 1 patient who had progressed on the taxane was subsequently stabilized for at least 6 months while taking thalidomide [85]. Building upon this experience, an open-label, phase II trial was initiated to examine the efficacy of thalidomide in patients with progressive, metastatic thyroid carcinoma of varying histologies [86]. Starting at 200 mg daily, the dose of drug was progressively increased as tolerated, with a median maximum daily dose of about 600 mg. Of 28 evaluable patients, 18% achieved a partial response and 32% had stable disease as their best response. Histology-specific partial response rates were not reported, but partial response or durable stable disease was seen in 3 PTC patients, 2 FTC patients, 3 Hurthle cell cancer patients, and 1 MTC patient, along with 4 patients with either tall cell or insular variants. Toxicities were dose limiting in the majority of patients, and the most common adverse events included somnolence, peripheral neuropathy, constipation, dizziness, and infection. Given the suggested efficacy but high rate of adverse events with thalidomide, a subsequent phase II study was initiated using the presumably less-toxic lenalidomide [87]. Eligibility was limited to DTC patients whose measured tumor volumes had increased by at least 30% in the past year. Of 18 evaluable patients, 7 (39%) were reported with partial responses measured by reductions in tumor volumes, with a median duration of 11 months, and another 9 (50%) were stable. However, median overall survival was less than 11 months, and 3 patients experienced pulmonary emboli.

4.2. Fosbretabulin

Fosbretabulin is a tubulin inhibitor whose dephosphorylated metabolite selectively inhibits growth of proliferating endothelial cells in tumors [88]. Of 4 phase I studies that were performed, 1 patient with anaplastic thyroid carcinoma was reported to have a complete response of more than 4 years duration. Subsequently, in cell lines purported to derive from anaplastic thyroid carcinomas, fosbretabulin demonstrated cytotoxicity comparable to paclitaxel, and the effects were additive in combination [89,90]; however, subsequent studies determined that these cell lines were not of thyroidal origin [91]. An open-label phase II trial of fosbretabulin in locally advanced or metastatic anaplastic carcinoma enrolled 26 patients who received the drug intravenously, 45 mg/m^2, on days 1, 8, and 15 of every 28-day cycle [92]. Median survival was 4.7 months, and the 6-month survival was 34%, results probably comparable with those reported in the paclitaxel phase II trial [85]. Median duration of stable disease in 7 patients was about 1 year. Toxicities were frequent but generally not severe; they included lymphopenia, headache, tumor pain, and QTc interval prolongation. A randomized phase III trial is now underway, comparing the survival of patients treated with fosbretabulin in addition to paclitaxel and carboplatin with that of patients treated with paclitaxel and carboplatin alone [93].

4.3. Celecoxib

Activation of cyclooxygenase-2 (COX-2), an enzyme overexpressed in many cancers, promotes tumor development and progression, in part through enhanced hypoxia-induced angiogenesis. Expression of COX-2 mRNA and protein levels are increased in thyroid cancer tissue compared with non-neoplastic and benign thyroid tissues, especially those expressing RET/PTC mutations, leading to the hypothesis that treatment with a COX-2 inhibitor could be therapeutically beneficial. A 2 center phase II trial was performed testing this hypothesis in 32 patients with progressive differentiated thyroid carcinoma, identified radiographically or by rising serum thyroglobulin levels [94]. One patient had a partial response, and 1 remained stable on therapy for >12 months, but most patients progressed despite treatment. The study was terminated as a result of lack of efficacy combined with increasing concern about cardiovascular toxicity from COX-2 inhibitors.

5. Targeting epigenetic mechanisms

DNA hypermethylation and histone deacetylation are 2 common epigenetic mechanisms that have been implicated in the progression of thyroid carcinoma, particularly the loss of radioiodine avidity [95,96]. In the laboratory, treatment with DNA methylation inhibitors as well as histone deacetylase (HDAC) inhibitors has been associated with enhanced radioiodine uptake by non-avid cell lines, along with other markers to suggest improved tumor cell differentiation, prompting clinical trials. Actual clinical experience, however, has been disappointing.

5.1. Romidepsin

The cyclic peptide romidepsin (previously known as depsipeptide) selectively inhibits four isotypes of histone deacetylases [97]. In a variety of poorly differentiated and anaplastic cell lines, treatment with romidepsin led to expression of the sodium-iodide symporter, thyroglobulin, and thyroid-specific transcription factors, although tumor xenografts did not shrink [98,99]. A phase I dose escalation trial included 9 patients with radioiodine-refractory thyroid cancer, of whom 6 had disease stabilization but none experienced restoration of radioiodine uptake on scanning [100]. Toxicities were primarily hematologic, nausea, and vomiting. Subsequently, a phase II trial was initiated in patients with radioiodine-unresponsive, progressive metastatic DTC [101]. Although the primary endpoint was RECIST response, restoration of radioiodine uptake was a secondary objective. Of 20 patients enrolled, no objective tumor responses were reported; 10 patients achieved stable disease. Two patients exhibited restoration of uptake permitting therapeutic radioiodine administration. Significant cardiac toxicities were seen, however, including sudden death in 1 patient, and a grade 4 pulmonary embolus also occurred.

5.2. Vorinostat and valproic acid

The orally available histone deacetylase (HDAC) inhibitor vorinostat, derived from hydroxamic acid, inhibits all known classes of HDAC enzymes. The drug is approved for the treatment of cutaneous T-cell lymphoma. For advanced thyroid cancer, vorinostat was studied in 16 patients; no objective responses were reported, and most patients discontinued therapy due to progressive disease or adverse events, including fatigue, dehydration, ataxia, pneumonia, bruises, deep vein thrombosis, and severe thrombocytopenia [102]. Restoration of radioiodine uptake was not evaluated.

Although only a weak inhibitor of several isotypes of HDAC enzymes, valproic acid (VPA) has been the object of numerous preclinical studies in thyroid cancers, particularly anaplastic [103]. Although treatment with VPA alone can induce apoptosis in anaplastic cell lines, combinations with doxorubicin, paclitaxel, or imatinib may be significantly more potent [104,105,106]. An ongoing phase II trial is evaluating the effect of monotherapy with VPA on tumor size and radioiodine uptake in patients with radioiodine-refractory advanced DTC. Epigenetic synergy may also be expected in combination with DNA methylation inhibitors to block unregulated gene expression, as has been demonstrated in hematologic malignancies [97]. In a phase I trial combining VPA with 5-azacytidine, 3 patients with advanced thyroid cancer were

among a total of 55 studied [107]. One PTC patient had prolonged stable disease beyond 1 year, but no objective responses were identified in any tumor type.

5.3. Azacytidine and decitabine

A broad array of tumor suppressor genes is hypermethylated in papillary and follicular thyroid carcinomas leading to their decreased expression, including *PTEN*, tissue inhibitor of metalloproteinase-3, and death-associated protein kinase [108]. In various cell lines, re-expression of these genes and enhanced tumor cell differentiation has been seen following treatment with the DNA methylase inhibitor 5-azacytidine [109,110]. A phase II trial of 5-azacytidine monotherapy to restore radioiodine uptake was initiated, but results were never reported. Given the greater potency and tolerance of the azacytidine derivative decitabine, a phase II trial of this latter agent has been underway, evaluating the ability to restore radioiodine uptake in radioiodine-non-avid metastases; results of this multicenter trial are expected shortly. One difficulty with these approaches to therapy, however, is that these agents depend upon active DNA synthesis to be capable of inhibiting the DNA methylase; in other words, they apparently do not demethylate existing hypermethylated sequence, which may limit their effectiveness in slowly replicating tumor cells like those found in most thyroid carcinomas [111]. Further research may identify approaches to combining these methylation inhibitors with other therapeutic pathways that could enhance their effectiveness [107,112,113].

6. Targeting nuclear receptors

The possible role of retinoid receptors to regulate iodine uptake by thyroid follicular cells was suggested by studies demonstrating that incubation of poorly differentiated thyroid cancer cells with 13 cis-retinoic acid could partially restore radioiodine uptake [114]. Subsequent clinical trials yielded conflicting results [115]. Recently, a synthetic agonist of the retinoid X receptor (RXR), bexarotene, was tested in a phase II trial in patients with radioiodine-unresponsive metastatic disease [116]. After 6 weeks of therapy with bexarotene, 300 mg daily, radioiodine uptake was partially restored in 8 of 11 patients, but a clinical response with measurable tumor reduction was lacking. The PPAR gamma agonist rosiglitazone was evaluated for the potential of restoring radioiodine uptake in 10 patients with unresponsive metastases [117]. In 4 patients, radioiodine uptake was visualized following 8 weeks of therapy with oral doses up to 8 mg daily, but clinical response was limited. The lack of major clinical effect of restoring radioiodine uptake may have multiple explanations, including the acquisition by tumor cells of radiation resistance. Evaluating tumor response to bexarotene therapy rather than radioiodine uptake, an ongoing phase II trial is underway in patients with progressive metastatic PTC.

7. Targeting with immunotherapy

Following reports that interferon-α was active in the treatment of neuroendocrine malignancies, several attempts were made to define the role of interferon as an immunomodulatory therapy for thyroid carcinoma. One early study described 1 of 7 patients with marked tumor regression following monotherapy with interferon α2a [118]. Combining interferon α2b with the long-acting somatostatin analog, lanreotide stabilized disease in 5 of 7 patients in a subsequent study, along with reduction in disease-related symptoms such as diarrhea and flushing, but no partial responses were reported [119].

Given that interferon-α can induce a destructive thyroiditis, and is synergistic in addition to doxorubicin in certain other solid tumors, a 2-stage phase II trial evaluated the combination in patients with advanced or metastatic, radioiodine-resistant thyroid carcinoma (other than medullary histologies) [120]. In the first stage, 17 patients were treated with interferon α2b, 12 million units/m^2 administered subcutaneously daily for 5 days (days 1–5) of each cycle and doxorubicin 40 mg/m^2 administered iv on day 3, repeated every 28 days. Only one (6%) partial response was recorded, and 10 patients (62.5%) achieved stable disease. However, all patients eventually progressed on therapy, with median time to progression of 6 months. Nearly three-fourths of patients developed grade 3 or 4 neutropenia, and the most common other grade 3 toxicities were fatigue, nausea/vomiting, anorexia, mucositis, and neurologic symptoms. Given the low response rate and high toxicity profile, the protocol was terminated without extending to stage 2.

A novel approach to targeted immunotherapy has been the use of tumor vaccines. Dendritic cells, which are derived from bone marrow antigen-presenting cells, are capable of presenting tumor-associated antigens, thereby generating cytotoxic T-cells targeting tumor cells. This strategy has suggested efficacy in treating metastatic MTC in 2 recent trials. In 1 study, dendritic cells were obtained from each of 7 patients, and stimulated in the presence of both calcitonin and carcinoembryonic antigen (CEA) [121]. Following periodic intracutaneous injections of the stimulated dendritic cells, 1 patient experienced a partial response, including complete regression of hepatic metastases associated with a 70% reduction in serum tumor markers. Two other patients had mixed responses. In the second study, dendritic cells were stimulated using lysates of each individual patient's surgically resected primary tumor [122]. Three of 10 patients had partial responses, including 1 with complete resolution of radiographic evidence of disease. Toxicities in both of these trials were minor, including low-grade fever and asymptomatic transient autoantibody development. Further small studies are underway, refining the procedures to enhance the potency of the dendritic cell vaccines [123,124].

The expression of CEA on MTC cells has led to the exploitation of radiolabeled anti-CEA monoclonal antibodies for radioimmunotherapy. In early trials, antitumor effects have been noted using anti-CEA/anti-diethylenetriamine pentaacetic acid (DTPA) -indium BsMAb, followed 4 days later by a ^{131}I-labeled bivalent hapten. In a report of a non-randomized trial in patients with progressive metastatic MTC (defined as a calcitonin doubling time of less than 2 years), median overall survival after administration of this therapy was 110 months [125]. This compared favorably with a contemporaneous untreated cohort's median survival of only 60 months. Significant toxicities included grade 4 neutropenia and thrombocytopenia, lasting up to 3 weeks, and 1 patient (who had received previous radiotherapies) developed myelodysplasia.

8. Summary

The successful development of targeted therapies for cancer requires several key factors: (1) identification of biologically validated targets critical to development and maintenance of the malignant phenotype; (2) development of potent inhibitors of the targets, with broad therapeutic index separating efficacy from toxicity; (3) recognition of patient and tumor characteristics that can optimize the selection of patients for therapy; (4) identification of biomarkers predictive of patient outcome and that permit optimization of drug dosing; and (5) recognition of opportunities for well-tolerated and more efficacious combinatorial treatments. As summarized in this review, such advances have been made in the past few years in the development of successful targeted therapies for thyroid cancers.

Compared with the dismal historical track record, the recent proliferation of clinical trials for thyroid cancer has been remarkable. Targeting angiogenesis (and specifically VEGF receptors) has produced the most impressive clinical responses to date in both DTC and MTC. Although most small molecule VEGF receptor antagonists also inhibit RET, the efficacy of axitinib and pazopanib to induce objective responses in the absence of any anti-RET activity suggests that RET may not be as important a target for therapy as VEGFR. Unfortunately, eventual progression despite antiangiogenic VEGFR blockade suggests emergence of alternate pathways to promote tumor growth and metastasis (including FGFR, C-MET, and angiopoietins) [126]. Further studies are necessary to explore the value of effective inhibition of the MAPK pathway downstream from oncogenic mutations, as well as other pathways stimulating tumor growth and metabolism such as PI3K-AKT-mTOR signaling. Studies of therapies targeting nuclear mechanisms of gene regulation indicate that reversal of epigenetic or nuclear receptor abnormalities can potentially re-establish the cellular capacity to take up radioiodine, but the clinical significance of such an effect appears limited. Immunotherapy, particularly dendritic cell vaccines, appears as a very promising approach.

The overall goal of developing new treatments is to extend the duration of life without unduly harming the quality of that life. Presently, no novel treatment has yet demonstrated improved survival for thyroid cancer patients. The experience with other malignancies treated with VEGFR inhibitors suggests that survival may be improved by only a few months despite these radiographic tumor responses, and the possibility that short term responses may be achieved at the cost of promoting greater tumor invasiveness and further metastases should be sobering [127]. Toxicities of many of these new therapies, although less life-threatening than cytotoxic chemotherapies, are common and can be dose-limiting, and clinicians must be familiar with recognizing and managing the side effects if they intend to use these agents. Finally, the low rate of partial response, the absence of complete responses, and emergence of resistance in all of the various monotherapy trials identify the need to develop either more effect single agents or to identify rational combinations of therapeutic targets (including cytotoxic chemotherapies) that have synergistic effectiveness without enhanced cross-toxicities.

Disclosure

The author reports the following financial affiliations:

Research support: Genzyme, Eisai, AstraZeneca, Amgen, V Foundation for Cancer Research, National Cancer Institute.

Consulting: Bayer, Exelixis, Plexxikon, Genzyme, Semafore, Eli Lilly, Oxigene, Celgene, Veracyte.

Honoraria: Genzyme, Exelixis.

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