S4-NEW TREATMENT ALGORITHMS FOR SYSTEMIC THERAPY IN MANAGING AGGRESSIVE THYROID CANCER

Joshua Klopper and Bryan Haugen
University of Colorado School of Medicine

An important subset of patients with well differentiated thyroid cancer (WDTC) will develop progressive local or metastatic disease that no longer responds to the best targeted therapy, radioiodine (RAI). It is important to remember that directed therapy may still be appropriate with patients with widely metastatic disease if only one or a few lesions are progressing or symptomatic but the majority of the disease is stable and asymptomatic. Additionally, with advances in molecular oncology and therapies targeted at oncoproteins, patients with advanced thyroid cancer have more options for therapy than at any other time(1).

For persistent disease in the neck, when surgery is not a viable option, other directed modalities can be considered. External beam radiotherapy to growing regional disease can be considered. Newer modalities include radiofrequency ablation (RFA) and percutaneous ethanol ablation (PEI). Radiofrequency ablation is still primarily used in referral centers and has not been adopted in widespread practice(2). PEI is used more commonly and is useful to treat loco-regional nodes/masses (3). Though the strategy can only be used for a small number of lesions at one time, it is minimally invasive and has rare morbidity(4). However, in the setting of distant, progressive metastases, the utility of targeting an isolated lesion is of questionable value and systemic therapy is likely more appropriate.

TYROSINE KINASE INHIBITOR TREATMENT

In the setting of progressive radioiodine refractory thyroid cancer metastases, the availability of multi-targeted tyrosine kinase inhibitors (TKIs) has allowed beneficial and generally well tolerated therapy. At this point, the only TKI with an FDA approved indication for radioiodine resistant metastatic thyroid cancer is sorafenib (marketed as Nexavar) which received approval in November 2013. However, there are numerous other TKIs approved for medullary thyroid cancer (MTC) as well as other solid tumors that have been studied as well. As has been described in the earlier chapters of this symposium, systemic therapy is appropriate to consider for patients with RAI resistant therapy that is progressive; where a “watch and wait” strategy is no longer acceptable. The verification of progression is important as these therapies tend to provide a tumorostatic response as opposed to a tumorcidal effect as will be shown by the clinical trials data. Even when thyroid cancer is RAI refractory, and occasionally even when positron emission tomography (PET) positive, metastatic disease can be quite stable for some time, even years. In the absence of progression, therefore a drug that does not cause measurable regression of disease is likely to have an unacceptably high side effect to benefit ratio.

TKI therapies target multiple oncoproteins and oncogenic signaling pathways. A detailed explanation of how each TKI targets individual receptors and pathways is beyond the scope of this chapter but has been recently reviewed(5). Briefly, TKIs may inhibit activation of the mitogen-activated protein kinase pathway (MAPK) as well as the PI3K-AKT pathway in tumor cells. Additionally, they can target vascular endothelial growth factor receptor (VEFGFR), endothelial growth factor receptor (EGFR) and mitogen activated protein kinase enzyme (MET) on vascular endothelial cells. Most TKIs target more than one of these pathways/receptors. Table 1 demonstrates some of the targets of the TKIs that have been studied in published.

Table 1- Phase II Thyroid cancer clinical trials

Target	RET RET/PTC	EGFR	MET	BRAF	MEK	FLT3	VEFGFR (1-3)	PDGFR	c-kit
Axitinib							X	x	X
Gefitinib		x							
Motesanib	x						X	x	X
Pazopanib							X		
Selumetenib					x				
Sorafenib	x			x			X	x	X
Sunitinib	x					x	X	x	X
Vandetanib	x	x					X		

Targets of TKIs studied in published, peer-reviewed phase II clinical trials for advanced DTC. Adapted from (5;28)

Other TKIs have been studied in advanced DTC and to date have only been presented in abstract form and therefore are not described in detail in this chapter. These include lenvatinib and cabozantanib. As of the writing of this chapter, only one phase III trial of a TKI in advanced DTC has been completed studying sorafenib (the DECISION trial). This trial led to FDA approval of DTC as an indication for use, yet has still only been presented in abstract form (6). Additionally, phase III trials of other TKIs in advanced thyroid cancer are ongoing. A synopsis of phase II trial outcomes is summarized in Table 2 and the trials are briefly described in more detail below.

Axitinib(7) – 60 subjects (30 papillary, 15 follicular, 11 medullary, 2 anaplastic and 2 other) were enrolled in a multicenter single arm open label study of patients with advanced thyroid cancer that were not amenable to surgery or radioiodine. Axitinib was initiated at 5mg orally twice daily BIDand response by RECIST criteria was the primary end point. 30% of patients had a partial response (PR) and 38% had stable disease (SD). Median progression free survival (PFS) was 18 months. Thirteen percent of subjects discontinued the trial drug due to adverse events.

Gefitinib(8) – 27 subjects (11 papillary, 6 follicular, 5 anaplastic, 4 medullary and 1 hürthle cell thyroid cancers) were enrolled in a multicenter single arm open label study of patients with advanced thyroid cancer not amenable to radioiodine therapy. Gefitinib was initiated at 250mg daily (QD) and response by RECIST criteria was the primary endpoint. There were no PR, but at 6 months 24% of subjects had SD. Median PFS was 3.7 months. Two patients discontinued therapy due to toxicity.

Motesanib (9) – 93 subjects (57 papillary, 36 follicular/hürthle cell thyroid cancers) were enrolled in a multi- institution, international open label study of patients with radioiodine resistant DTC. Motesanib 125mg orally (PO) QD was initiated and the primary end point was objective tumor response by RECIST criteria. 14% of patients had a PR and 67% had SD for 24 weeks or longer. Thirteen percent of patients discontinued treatment due to toxicity.

Pazopanib(10) – 37 subjects (15 papillary, 11 follicular, 11 hürthle cell thyroid cancers) were enrolled in a multi-institution open label study of patients with metastatic, progressive, radioiodine refractory DTC. Pazopanib 800mg PO QD was initiated and the primary end point was objective tumor response by RECIST criteria. 49% of patients had a PR. PFS at one year

was 47% with a median duration of PFS of 11.7 months. Only one patient requested withdrawal of treatment.

Selumetenib(11) – 20 subjects (5 papillary, 8 tall-cell variant papillary, 7 poorly differentiated thyroid cancers) were enrolled in a single-institution open label study of patients with radioiodine resistant metastatic thyroid cancer. Selumetenib 75mg PO BID was given for 4 weeks with the primary outcome being re-induction of RAI avidity. If clinically relevant uptake occurred, the patients were treated with a dose calculated to deliver 2000cGy of ^{131}I to susceptible lesions. Twelve of 20 patients had reinduction of RAI uptake in lesions with 8/12 reaching a threshold considered adequate for treatment. Of those treated, 5/8 had a PR and 3/8 had SD at 6 months of follow up. All patients completed the 4 week course of selumetenib.

Sunitinib(12) – 35 subjects (18 papillary, 5 hürthle cell, 4 follicular, 1 insular, 7 medullary thyroid cancers) were enrolled in a mult-institutional open label study of patients with metastatic radioiodine refractory thyroid cancer. Sunitinib 37.5mg PO QD was initiated and the primary end point was objective response by RECIST criteria. There was one complete remission (CR), 28% of patients had a PR and 46% had stable disease. Median PFS was 12.8 months. No patients went off treatment entirely, but 60% did require at least one 25mg dose reduction secondary to toxicity.

Vandetanib(13) – This was an international, multicenter placebo controlled trial studying the efficacy of vandetanib to increase PFS. 72 patients were randomized to vandetanib 300mg PO QD and 73 matched controls were randomized to placebo. All patients had locally advanced or metastatic radioiodine refractory disease. PFS on vandetanib was 11.1 months as compared to 5.9 months on placebo. No patients discontinued therapy due to adverse toxicity. 38% of patients had dose interruptions and reductions for an average of 18.5 days.

Sorafenib(14-17) – There have been 4 published phase II studies of sorafenib therapy in advanced thyroid cancer. The primary results of all 4 are summarized in Table 2. However, as the only TKI now with an approved indication for advanced DTC, we will go into some depth regarding the US clinical trial data. Sorafenib inhibits human VEGFR 1-3, platelet derived growth factor (PDGF) and RET. The first US trial occurred at the University of Pennsylvania where 30 patients were treated with a starting dose of 400mg BID for a minimum of 16 weeks (14). Twenty-three percent of patients had a partial response lasting more than 18 weeks and 53% of patients had stable disease for up to and beyond 89 weeks. The median progression free survival was 79 weeks. The most common grade 3 (severe but not life-threatening; hospitalization required; limitation of patient's ability to care for him/herself) and grade 4 (Life-threatening; urgent intervention required) toxicities were hypertension (13%), skin rashes (including hand/foot syndrome – a distinct localized cutaneous reaction characterized by erythema, numbness, tingling, and either dysesthesia or paresthesia (18)) (10%) and weight loss (10%). One patient died from acute liver failure that was felt to be treatment related. The second trial occurred at Ohio State University where 56 patients started therapy with 400mg twice daily of sorafenib(15). Patients with metastatic disease from papillary thyroid cancer (PTC) or other DTC histologic subtypes (including four patients with anaplastic thyroid cancer (ATC) were enrolled and had to have measureable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria along with radioiodine resistance or were deemed non-RAI candidates by their treating physician(19). Of 41 patients with PTC, 15% had a PR that had a median duration of 7.5 months. Stable disease was observed in 56% of patients for over 6 months. The overall median PFS was 15 months. Progressive disease was noted in 12% of PTC patients despite sorafenib therapy. There were no partial responses seen in patients with non-PTC tumors. Prior treatment with traditional cytotoxic chemotherapy did not yield a significant difference in PFS or overall survival (OS). Dose reduction was required to improve

tolerance in 52% of patients. The most common grade 3 adverse events were hand/foot pain (12%), arthralgia (11%) and fatigue (16%). More recently, as reported at the 2013 American Society of Clinical Oncology meeting, the phase III DECISION multi-center trial enrolled 417 patients with progressive DTC refractory to RAI in a randomized placebo controlled fashion (20). The duration of PFS was 10.8 months with sorafenib as compared to 5.8 months with placebo and 12% of patients on sorafenib therapy had a partial response as opposed to <1% of patients in the placebo arm. The study was not powered for overall survival. The occurrence and rates of adverse reactions were similar to previous sorafenib trials. Finally, a recent meta-analysis of trials with sorafenib therapy for advanced thyroid cancer provides broader overview of the benefits and risks of therapy. Overall, 22% of patients treated with Sorafenib achieved a partial response and 52% showed stable disease (with the vast majority of patients having progressive disease prior to enrollment in each trial). Median PFS was 12.4 months when on sorafenib therapy. The most common adverse events associated with sorafenib use were hand-foot syndrome, diarrhea, fatigue, rash, weight loss and hypertension(21).

Table 2

Drug	First Author, Year (Ref.)	N	%PR/%SD	PFS, months
Axitinib	Cohen, 2008 (7)	60	31%/42%	18.1
Gefitinib	Pennell, 2008 (8)	17	0/24%	3.7
Motesanib	Sherman, 2008 (29)	93	14%/67%	9.3
Pazopanib	Bible, 2010 (10)	37	49%/NR	11.7
Selumetenib	Ho, 2013(11)	20	63%/37%	NR
Sorafenib	Gupta-Abramson, 2008(14) Kloos, 2009(15) Hoftijzer, 2009(16) Ahmed, 2011(17)	30 41 31 19	23%/53% 15%/56% 15%/46% 16%/74%	21 15 14.5 16.5
Sunitinib	Carr, 2010 (12)	33	28%/46%	12.8
Vandetanib	Leboulleux, 2012(13)	145 (72 active rx)	8%/57% (on active rx)	11

Published phase II trials of TKI therapy in advanced thyroid cancer. NR= not reported. Adapted from (28) For RECIST criteria--
http://en.wikipedia.org/wiki/Response_Evaluation_Criteria_in_Solid_Tumors

USE IN CLINICAL PRACTICE

At the present time, there are no guidelines detailing how or when TKIs should be used in clinical practice. The most recent American Thyroid Association Thyroid Cancer Guidelines describe TKI use as a future area of research (though they most certainly they will have a more prominent place in the upcoming revised guidelines)(22). Additionally, the most current National Comprehensive Cancer Network guidelines only recommend consideration of TKIs for progressive RAI refractory disease (http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf). A recent review of the MD Anderson experience with TKIs and recommendations for use provides rationale guidance in the absence of a consensus multi-center guideline (23). As described in a previous chapter, the

selection of an appropriate candidate is likely the most important decision when initiating TKI therapy. Briefly, the current authors would recommend considering patients with at least RAI resistant, unresectable (usually metastatic) disease that is progressive by RECIST criteria for TKI treatment. As opposed to experience in the trials, however, the initiation of TKI therapy for patients with new brain or bone metastases who often were excluded from trials should be considered now that a TKI has been approved for DTC therapy. Practitioners should note, however, that bone metastases in general do not appear to respond as well as, for example, lung metastases (24). Recommendations for pre-initiation assessment include:

1. A detailed history and physical with assessment of the patient's functional status (for example using the Eastern Cooperative Oncology Group performance status (ECOG) (25). (http://en.wikipedia.org/wiki/Response_Evaluation_Criteria_in_Solid_Tumors) Patients with very poor functional status have generally been denied clinical trial enrollment so their response to therapy is unknown.
2. A comprehensive laboratory analysis assessing metabolic, cardiovascular, hepatic and renal function. Additionally, a baseline electrocardiogram (ECG) is appropriate as TKIs can cause QT prolongation and ECGs should be serially monitored based on the clinical risk (see Figure 1).
3. A detailed discussion with the patient about the expectations of therapy. It is critical to frame the expectations of the patient and physician given the current data ascribed to this class of drugs for the treatment of thyroid cancer. A complete response is extremely unlikely and a partial response can only be expected in 10-20% of patients. The vast majority of patients should expect stabilization of disease for approximately one year (though this may be longer).
4. A detailed explanation of potential side effects is important to help patients avoid unpleasant surprises and allow for earlier symptomatic intervention to attenuate side effects. The most common side effects include(23;26):
    a. Cardiovascular: hypertension, QT prolongation and CHF. All of these should be assessed and optimized prior to starting TKI therapy. Antihypertensive therapy should be individualized for efficacy, tolerance and cost. ECG should be monitored and significant QT interval prolongation should lead to drug dose reduction or cessation. Electrolytes should be monitored and stabilized as compounding factors and other drugs associated with QT prolongation should be stopped prior to therapy if possible. CHF is rare but patients should be monitored for signs and symptoms at each visit. Baseline cardiac echocardiogram is not unreasonable to have as a comparator for a later study if CHF symptoms present during therapy.
    b. Dermatologic manifestations: After diarrhea and fatigue, hand-foot syndrome and other rashes are the most common adverse reactions to TKIs. These usually present early on in therapy and can be treated with creams, emollients, dose reduction or interruption of therapy.
    c. Hematologic manifestations: Given the targeting of VEGFR, there is potential bleeding risk with TKIs. These have included issues with thrombocytopenia; poor wound healing and severe bleeding in radiation related fistulas(27).
    d. Hepatic manifestations: Side effects have ranged from transient mild transaminitis to fulminant liver failure; though fortunately this has been very rare. Intervention for rising transaminases to 2-3x ULN is generally therapy interruption or cessation.
    e. Renal manifestations: Proteinuria has been described with TKI therapy, thus baseline and periodic on treatment urinalyses are appropriate to monitor for this side effect. If significant proteinuria develops, drug cessation is likely necessary.

It is important for prescribing physicians to understand that most TKI trials start with a maximum tolerated dose and a significant subset of patients require dose reductions during the trials. The trial data reported includes those with dose reductions. The authors' experience has been that many patients will require a dose reduction to alleviate side effects, yet tumor responses are consistent with expected and reported outcomes. A common practice in our center is to hold TKI therapy after unacceptable side effects for at least one week or until the side effect resolves, and then reinitiate the medication at 50-75% of the dose depending on the patient and clinician comfort. Should intolerable side effects recur, a second medication hold with re-initiation of medication at 25% of the starting dose is reasonable as long as there is not progressive disease. If there is still intolerance at these dose levels, it is likely time to move on to another therapy. Patients should be reassured that dose reduction will not necessarily translate into a decrease in efficacy, but close observation is critical at lower therapeutic doses.

5. An exploration of costs/payments for these drugs is important as they usually cost thousands of dollars/month. The insurance coverage for sorafenib is likely still being worked out with individual insurers given its recent approval. One clear advantage to clinical trials is the provision of therapy at no cost to the patient. Finally, most manufacturers have patient assistance programs that should be investigated prior to starting TKI treatment.

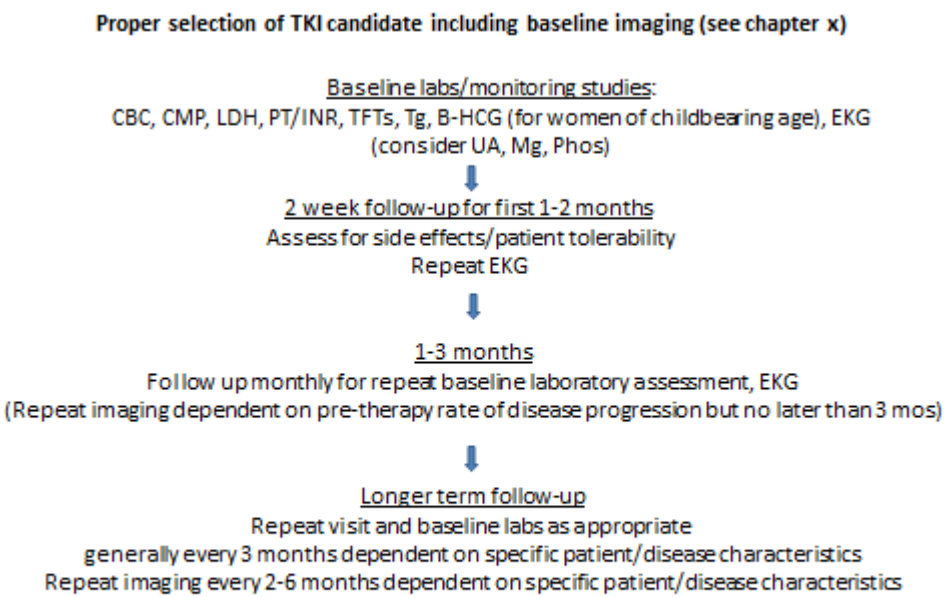

Fig.1

Fig 1
Adapted from
(23)

Given that sorafenib is the only approved TKI for metastatic differentiated thyroid cancer at this time, the authors suggest that this should be first line TKI therapy for appropriate candidates. If patients have previously failed sorafenib therapy with progressive disease or intolerance, evaluation of eligible clinical trials is likely the next best option. Finally, off label use of other TKIs with other indications is likely the next most reasonable approach. The TKIs that have been through phase II trials for advanced DTC and are FDA approved for other indications (primarily MTC and advanced renal cell carcinoma) are likely the next best choices. These

include vandetanib, sunitinib, pazopanib, axitinib, and gefitinib. Unfortunately, there is no clear correlation between oncoprotein expression (i.e. BRAF) or other molecular marker that can allow for a rationale prediction of one TKI providing more benefit over another based on clinical trial data. Additionally, there has been no trial of combination therapy of TKIs robust enough to lead to a recommendation of combination therapy. Increased toxicity is certainly a significant concern with multi-drug TKI treatment. The choice of TKI therapy after sorafenib may come down to availability, patient preference and comfort level of the treating physician based on their experience with a particular drug.

A very reasonable recommendation for monitoring has been outlined by Carhill et al(23). We believe that after initiation of TKI therapy, clinical and laboratory assessment should be performed at least monthly for the first 3 months along with imaging at 1-3 month intervals dependent on the rate of progression of disease prior to TKI initiation. Seeing a patient back every 2 weeks for the first month or two is reasonable to address concerns over side effects, tolerability and advising on management of side effects. Follow up evaluations should occur at least every 3 months if not more frequently based on the clinical response and tolerability of therapy thereafter. The specific drug package insert should always be checked for monitoring recommendations as post-marketing surveillance may alter such recommendations and drug specific recommendations may be made that do not apply broadly to all available TKIs. Though the typical duration of response will be approximately one year, patients should stay on prescribed therapy in the absence of progressive disease for as long as possible. It is important to note, progression at any point on one TKI does not necessarily predict failure of another TKI. This is likely attributable to the numerous targets and pathways these medications inhibit with different TKIs having overlapping and unique targets. When a patient has failed multiple TKI therapies (or not tolerated them), and there is rapid progression of disease, consideration of chemotherapy or phase I clinical trials is appropriate. An overall diagram of initiating and monitoring therapy is proposed in figure 1.

Finally, as described in the phase II trial data above, novel indications for TKI therapy in thyroid cancer are currently being investigated. The most exciting recent development has been the discovery that the TKI selumetenib appears to induce re-differentiation of RAI resistant thyroid cancers to be able to concentrate sufficient RAI for therapeutic benefit (11). There are now two multicenter studies studying the use of selumetenib in thyroid cancer. One is functionally an expansion of the aforementioned trial, while the other is a unique approach using selumetenib as a neo-adjuvant agent prior to initial 131I therapy in patients with aggressive localized disease.

In summary, the dissection of molecular pathways and events leading to the propagation of cancers of many types, including thyroid cancer, has led to a dramatic expansion of oral, targeted, generally well tolerated therapies for advanced malignancies. As opposed to cytotoxic chemotherapies that have historically had an unacceptable side effects and minimal therapeutic benefit in advanced DTC, TKIs have opened the door for at least bridge therapy for patients with progressive metastatic thyroid cancer while new therapeutic discoveries continue.

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