

Novel therapeutic options for aggressive thyroid cancer: Integrating information from the recent clinical trials into clinical practice

INTRODUCTION

The vast majority of thyroid cancer patients respond very well to our initial therapeutic interventions which usually include total thyroidectomy with appropriate lymph node dissection and selective use of radioactive iodine (^{131}I) ablation (1). In patients responding to this initial therapy, disease specific survival rates of more than 90 to 95% can be expected at 30 to 40 years of follow up (2; 3).

Unfortunately, there is a small cohort of thyroid cancer patients that have structurally progressive disease that is refractory to additional ^{131}I therapy and not amenable to further surgery or external beam irradiation. Most of these are older patients with either poorly differentiated thyroid cancer or one of the aggressive forms of differentiated thyroid cancer such as the tall cell, insular, or Hürthle cell variants. The most aggressive cases have disease that is markedly positive on ^{18}F FDG PET scanning (4). It is in this group of patients with ^{131}I -refractory, structurally progressive thyroid cancer that novel therapies are most urgently needed because without an effective systemic therapy, the 3 to 5-year survival rates can be less than 50% (5; 6).

TRADITIONAL APPROACH TO SYSTEMIC THERAPY IN THYROID CANCER

Currently, the only FDA approved drug for the treatment of ^{131}I -refractory thyroid cancer is doxorubicin (Adriamycin®). This approval was granted on the basis of several case series and relatively small uncontrolled trials in the 1970's and 1980's that demonstrated largely short term (usually less than a few months) partial response rates as high as 20 to 30% when doxorubicin was used either as a single agent or combined with other cytotoxic chemotherapy (7). None of these studies were done using the modern, standardized definitions of complete response, partial response, and disease progression (8) and therefore it is difficult to compare the clinical outcomes described in these older studies with the new phase 2 studies published over the last several years. However it is important to note that because of the toxicity profile and the lack of clinically meaningful durable responses, these agents are currently seldom used in clinical practice at major cancer centers and neither the American Thyroid Association (ATA) (9) nor the National Comprehensive Cancer Network (NCCN) guidelines (10) require patients to fail doxorubicin chemotherapy prior to enrollment in clinical trials.

WHAT ARE THE POTENTIAL TARGETS?

Over the last several years, our understanding of the pathophysiology of thyroid cancer has increased dramatically (11; 12). It is becoming increasingly apparent that the receptor tyrosine kinase/MAP kinase pathway is important in the initiation and progression of thyroid cancer. The descriptions of non-overlapping mutations in *ret/PTC*, *ras*, and *BRAF* in as many as 70% of differentiated thyroid cancers emphasize the central role of this pathway in the pathophysiology of differentiated thyroid cancer. Furthermore, angiogenesis appears to play a key role in

tumor growth making inhibition of the vascular endothelial growth factor tyrosine kinase receptor pathway an attractive target for many experimental therapies (13).

PHASE 2 CLINICAL TRIALS IN THYROID CANCER TRIAL DESIGN ISSUES

Over the last 10 years, at least nine Phase 2 clinical trials have been published that have examined the therapeutic effects of a wide variety of anti-neoplastic agents on structurally measurable disease in patients with ^{131}I -refractory differentiated thyroid cancer (15-23). Clinical trials designed primarily to evaluate re-differentiation therapy or medullary thyroid cancer therapies are not included in this review. In most phase 2 trials, a cohort of 20 to 100 patients with the same malignancy are treated with a selected dose of the drug in question. Usually these studies are non-randomized trials that do not include an untreated control group.

Table 1 presents a summary of the design of the 9 most recently published phase 2 clinical trials (15-23). Most of the trials enrolled primarily differentiated thyroid cancer patients (papillary thyroid cancer, follicular variants of papillary thyroid cancer, follicular thyroid cancers and other aggressive variants including poorly differentiated thyroid cancers) while often including an exploratory arm that allowed enrollment of patients with medullary thyroid cancer or anaplastic thyroid cancer. All of the trials required structurally identifiable disease, usually at least one lesion larger than 1 cm in diameter, but varied widely in the requirement (and definition) of disease progression prior to entry.

Structural responses to anti-neoplastic agents in modern clinical trials are most commonly reported using a standardized set of definitions commonly referred to as RECIST (response evaluation criteria in solid tumors) criteria (8). A defined set of "target" lesions is identified that will be carefully measured (usually with CT or MRI) prior to therapy and at specific intervals during the trial. Other visible lesions that are not part of this initial measurement set are referred to as non-target lesions. A complete response is defined as the disappearance of all target and non target lesions (these findings must be confirmed 4 weeks later to meet this definition) A partial response requires at least a 30% decrease in the longest diameter of a single tumor or the sum of longest diameters of multiple target lesions (also confirmed at 4 weeks). Progressive disease is defined as a greater than 20% increase in the longest diameter of a single tumor or the sum of longest diameters in multiple target lesions or the appearance of new lesions. By default, stable disease means that the patient did not meet criteria of complete response, partial response or progressive disease. It is important to note that an increase in longest diameter of up to 19% or a decrease as much 29% would be classified as "stable disease" using RECIST criteria. In most studies, a graph (waterfall plot) is presented showing the best response obtained during therapy (expressed as percent decrease or increase in the longest diameter) for each individual patient.

Table 1: Study Design

	Ain 2000	Mrozek 2006	Ain 2007	Woyach 2008	Argiris 2008	Pennell 2008	Sherman 2008	Cohen 2008	Gupta-Abramson 2008
Agent	Paclitaxel	Celecoxib	Thalidomide	Vorinostat	Doxorubicin and interferon alpha 2b	Gefitinib	Motesanib	Axitinib	Sorafenib
Target*	Anti-microtubule agent	Cox-2 inhibitor	Anti-angiogenesis	Histone deacetylase inhibitor	Cytotoxic + immune modulatory agent	EGFR	VEGFR, PDGFR, Kit	VEGFR	VEGFR, BRAF
Histology**	Anaplastic	DTC	DTC MTC	DTC MTC	DTC Anaplastic	DTC Anaplastic MTC	DTC	DTC MTC Anaplastic	DTC MTC Anaplastic
Entry Criteria	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Unresectable distant metastases	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease	Measureable locally advanced or metastatic disease
Progression requirement for entry	Identification of persistent, recurrent, or metastatic disease	Structural progression or rising thyroglobulin in previous year	30% increase in tumor volume in previous year	None specified	None specified	Not required, but 89% had radiographic evidence of disease progression in previous 6 months	Documented disease progression by RECIST within 6 months	None specified	Structural progression in previous year (93% had FDG PET positive disease)
Primary Endpoint***	2 week durable response	Objective response by RECIST	Tumor volume	Objective response by RECIST	Structural response (not RECIST)	Objective response by RECIST	Objective response by RECIST	Objective response by RECIST	Objective response by RECIST

* EGFR (Epidermal growth factor receptor), VEGFR (Vascular endothelial growth factor receptor), PDGFR (Platelet derived growth factor receptor)

** DTC includes PTC, FVPTC, FTC, all variants including poorly differentiated (excludes anaplastic and medullary thyroid cancers).

*** Objective response by RECIST (response evaluation criteria in solid tumors) includes either complete or partial response

PHASE 2 CLINICAL TRIALS IN THYROID CANCER OUTCOMES

As can be seen in Table 2, most of the phase 2 trials are relatively small and have enrolled primarily older patients (median age ranged from 57 to 69 yrs at the time of enrollment) with a disproportionate percentage of male patients compared to the usual 2:1 (female to male) distribution ratio seen at diagnosis (15-23). Only 1 complete response was seen in the 335 thyroid cancer patients enrolled in the 9 trials (15). Partial responses (as defined by RECIST) were more common, ranging from 3 to 30% (Table 2).

It is often difficult to determine if “stable disease” during a clinical trial represents an actual clinical benefit to the individual patient. Because of the relatively slow structural disease progression rate in many thyroid cancer patients, “stable disease” can only be considered a meaningful clinical endpoint if it can be documented that the patient would have reasonably been expected to progress over the time frame of the study based on documentation of disease progression prior to entry into the study, or possibly markedly positive 18FDG PET scanning at entry. If stable disease

is a primary study endpoint, the pre-study evaluation of disease progression should be done using the same imaging modality and time frame used during the study. Accordingly, because of the stricter entry criteria requiring documented structural disease progression in the 6 to 12 months prior to study entry, the relatively high stable disease best response rates reported with thalidomide (16), gefitinib (21), motesanib (22), and sorafenib (19) probably represent a true clinical benefit.

More clinically relevant than the best obtained response is an assessment of the duration of disease stabilization. To that end, Sherman et al. reported a durable stable disease rate (>24 weeks) of 35% of their cohort treated with motesanib yielding a clinical benefit of 49% (14% with partial response and 35% with durable stable disease) (22). Furthermore, a careful analysis of the waterfall plots (best obtained response expressed as percent change) demonstrate that most patients in the motesanib diphosphate (22), axitinib (18), and sorafenib (19) studies had some degree of tumor shrinkage as the best obtained response even though many did not reach the 30% decrease required for classification as a partial response.

While the precise rates of partial response and durable stable disease remains to be defined for each of these agents, it appears that these novel agents are more active than doxorubicin based cytotoxic chemotherapy. Unfortunately, it appears that these agents are more often cytostatic rather than tumoricidal since the rates of tumor stabilization far exceed the rates of partial or complete tumor responses. Therefore, the most common response that can be expected when patients are enrolled on these phase 2 trials is either stabilization of disease or minor decrease in tumor size that does not meet the RECIST definition of a partial response.

PHASE 2 CLINICAL TRIALS IN THYROID CANCER TOXICITIES

Even though the clinical outcomes in some of these phase 2 trials are very promising, they are not achieved without significant toxicities. In the sorafenib (19), axitinib (18), and motesanib trials (22), 13 to 20% of patients discontinued the drug because of intolerable side effects. The likelihood of discontinuing the drug secondary to unacceptable side effects appeared slightly higher in the vorinostat study (56%) (23) and in the thalidomide study (16) than in the other phase 2 studies.

Fortunately, the vast majority of the side effects were reversible with discontinuation of the drug and often were dose related. As such, temporary interruption of the drugs with re-institution at lower dose levels was not an uncommon event in most of the studies. While the side effects varied depending on the drug, the most common side effects were fatigue, diarrhea, rash, weight

loss, nausea, and hypertension. As would be expected, the vorinostat side effect profile included significant thrombocytopenia (23) and the doxorubicin/interferon-2b study had expected neutropenia, thrombocytopenia and cardiotoxicity (17). Although several patients died while on trial or shortly thereafter, only one death was thought to be possibly related to study medication (liver failure despite dose reduction and cessation of sorafenib) (19).

PHASE 2 CLINICAL TRIALS IN THYROID CANCER FINDING THE TRIALS

With the widespread use of the internet search engines, patients and health care professionals are becoming very adept at identifying available clinical trials. Both the ATA (<http://www.thyroidtrials.org>) and the National Cancer Institute (<http://www.cancer.gov/clinicaltrials>) have specific web sites that will identify most thyroid cancer clinical trials that are open and enrolling patients.

PHASE 2 CLINICAL TRIALS IN THYROID CANCER INTEGRATION INTO CLINICAL PRACTICE

When selecting patients for enrollment in clinical trials, it is of paramount importance that we differentiate those patients with stable, persistent disease from those that are having rapid structural disease progression (24). Because the most common clinical outcome in the phase 2 trials is stable disease, there seems to be little clinical benefit at this time in exposing patients that already have stable or very slowly progressive structural disease to the risks of experimental therapies. Likewise, patients

Table 2: Outcomes

	Ain 2000	Mrozek 2006	Ain 2007	Woyach 2008	Argiris 2008	Pennell 2008	Sherman 2008	Cohen 2008	Gupta-Abramson 2008
Agent	Paclitaxel	Celecoxib	Thalidomide	Vorinostat	Doxorubicin and interferon alpha 2b	Gefitinib	Motesanib	Axitinib	Sorafenib
Enrolled (n)	20	32	36	19	17	27	93	60	31
Histology*	20 ATC	32 DTC	29 DTC 7 MTC	16 DTC 3 MTC	15 DTC 2 ATC	18 DTC 5 ATC 4 MTC	93 DTC	46 DTC 12 MTC 2 ATC	27 DTC 1 MTC 2 ATC
Age at enrollment, median yrs (range)	58 (47-68)	65 (42-89)	57 (26-87)	62 (40-77)	69 (54-58)	65	62 (36-81)	59 (26-84)	63 (31-89)
Male Gender	65%	41%	67%	36%	47%	59%	53%	58%	50%
Outcome evaluable (n)	19	32	28	19	16	21	82	45	25
Best outcome**									
Complete response	5%	0	0	0	0	0	0	0	0
Partial response	47%	3%	18%	0	6%	0	14%	40%	23%
Stable Disease	5%	38%	32%	56%	63%	81%	67%	51%	53%
Progressive Disease	42%	59%	50%	44%	31%	19%	8%	9%	3%

*DTC includes PTC, FVPTC, FTC, all variants including poorly differentiated (excludes anaplastic (ATC) and medullary thyroid cancers).

** Best outcome as a percentage of the evaluable patients.

whose only evidence of progressive disease is a rising serum thyroglobulin in the absence of localizable disease are also not generally eligible for clinical trials in which the primary endpoints are the effect of the drug on structurally identifiable disease.

In our practice, we select patients for clinical trials that have refractory differentiated thyroid cancer with structurally progressive lesions that cannot be adequately treated with additional local measures (such as surgery or external beam irradiation). While not an absolute requirement for entry onto a clinical trial, most patients have 18FDG-avid disease and negative ¹³¹I diagnostic scans. Patients with metastatic disease that is either stable or very slowly progressive are followed with expectant observation and serial cross sectional imaging without additional treatments beyond TSH suppressive therapy.

In most cases, we define structurally progressive disease as a 20% or greater increase in size of the dominant lesion over a 6 month period, or as new metastatic lesions in the setting of at least one measurable lesion greater than 1 cm. Patients meeting these criteria would likely qualify for most clinical trials. However, the final decision about whether or not to begin a clinical trial (once these inclusion criteria are met) is based on the preferences of the patient, the rate of structural disease progression, other comorbidities, the sites of progressive disease, and toxicities of the proposed therapy.

Over the last several years we have often been in the position of helping our patients decide which one of several available clinical trials would be best for them. Unfortunately, this decision usually has to be made based on estimates of side effects and logistical issues (such as location of the trial, number of visits required, and potential impact on work/family) rather than a specific knowledge of clinical benefit (partial response or disease stabilization). While it is attractive to select specific agents on the basis of the specific molecular abnormalities in the patient's individual tumor (11), it remains unknown whether this approach will lead to better outcomes than using one of the multi-targeted tyrosine kinase agents currently in clinical trials. To address this important issue,

it is imperative that clinical trials include an assessment of clinical response based on the specific molecular profile of primary/metastatic tumor.

In keeping with the ATA and NCCN thyroid cancer guidelines, we offer Phase 2 clinical trials (and some Phase 1 clinical trials) as the preferred alternative to traditional doxorubicin based cytotoxic chemotherapy for patients with ¹³¹I-refractory, structurally progressive disease. Patients ineligible or unwilling to participate in clinical trials are offered either a cytotoxic chemotherapy regimen or off label use of sorafenib depending on the specific details of the patient involved.

As with most of solid tumor oncology, it is logical to assume that combination therapies will be required to produce clinically meaningful disease regression and cures. With the promising results seen in the recent trials of the multi-targeted tyrosine kinase inhibitors and the expanding understanding of the molecular pathophysiology of thyroid cancer, we anticipate clinical trials in the near future that combine agents that block several different key steps in these important pathways.

It is now readily apparent that thyroid cancer has much more in common with other human solid tumors than we previously appreciated. As such, many of the lessons learned in solid tumor biology can be translated into our understanding of the treatment of thyroid cancer. Given the complexity of the treatment choices available, effective care of these patients with rapidly progressive, ¹³¹I-refractory thyroid cancers require a multidisciplinary approach in which a wide variety of sub-specialty knowledge is brought to bear on the needs of an individual patient.

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