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Clinical Overview of Thyroid Cancer and Recent Advances in Treatment

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Abstract

Thyroid cancer represents a spectrum of biological and molecular activity. As such it can behave in a variety of ways. This makes metastatic thyroid cancer challenging to manage. In advanced rapidly progressive thyroid cancer new agents and multimodality care represent promising therapeutic options for patients. However, these agents are not without risk and clinicians must be judicious with their use, weighing toxicities, quality of life and likely benefits. We review the presentation, treatment and prognosis of thyroid cancer subtypes as well as the recent developments in targeted therapy for medullary thyroid cancer. We discuss the role of cytotoxic therapy in thyroid cancer and review recent trials of novel agents and currently recruiting trials.

Keywords: Thyroid cancer; prognosis; Cytotoxic therapy; Recruiting trials

Introduction and Overview of Thyroid Cancer Treatment

Thyroid cancer is rare, comprising less than 1% of all cancers diagnosed. The incidence is rising with a 2.4 fold increase over the last thirty years however mortality rates are stable [1]. Annually in Ireland 162 cases of thyroid cancer are recorded [2]. 68% present with localized disease 4% present with metastatic disease at diagnosis [3]. As Recurrence rates can be as high at 30%. Thyroid cancer arises from two main parenchymal cells of origin within the thyroid-the follicular and parafollicular cells [4]. These give rise to; well differentiated thyroid cancer, which includes follicular and papillary subtypes, and poorly differentiated thyroid cancer, which includes anaplastic and medullary subtypes. In terms of histologic presentation of thyroid cancer the majority present with well differentiated subtypes, papillary (80%) and, follicular (10%). Medullary (5-9%) and anaplastic (2%) histologic subtypes present less often. Previous radiation exposure is a risk factor for developing thyroid cancer. 5% of all differentiated thyroid cancers are associated with a familial syndrome and behave clinically more aggressively than sporadic thyroid cancers. These include Gardner syndrome, familial thyroid medullary cancer, familial adenomatous polyposis (FAP), multiple endocrine neoplasia (MEN) and Carney complex [5].

Most patients have an excellent prognosis however a small group of patients experience a more aggressive course that is refractory to treatment. Surgery is adequate treatment for the majority. Up to 90% of patients with thyroid cancer can be considered for treatment with radioactive iodine [6].

There are several novel agents for advanced thyroid cancer under review and future developments will likely include a multimodal, individualized approach based on specific genetic mutations and tumor biology. Here we present on overview of thyroid cancer treatment options.

Papillary Thyroid Cancer

The survival rate for papillary thyroid cancer is over 95% with appropriate treatment and prognosis improves with younger age at diagnosis. It is associated with previous radiation exposure and tends to invade the lymphatic system. Several genetic mutations have been identified in papillary thyroid cancer. Mutations involving RET proto-oncogene (RET/PTC), BRAF or RAS are present in over 70% of papillary thyroid cancers 5.20% of adults with sporadic papillary tumours have RET/PTC rearrangement. There is fusion of RET/PTC to the 5' portion of different genes [7]. 45% of those with papillary thyroid cancer carry an activating point mutation of BRAF. This can induce activation of mitogen-activated protein kinase (MAPK) signaling pathways and is associated with more advanced disease at diagnosis and independently predicts for recurrence. Most patients present with a solitary thyroid nodule that is either palpable or found incidentally [8,9]. This can lead to a delay in diagnosis. Most patients have an excellent prognosis however; certain features are associated with a higher risk of recurrence (Table 1).

Treatment for differentiated thyroid cancers involves resection of the primary tumour and radioactive iodine ablation (RAI) which can be repeated several times. RAI can be used for 1) thyroid tissue ablation, 2) high risk for residual disease following surgery and 3) for metastatic disease. Up to 35% will become refractory to RAI. Thyroid hormone replacement is required post-surgery to prevent hypothyroidism, aiming for a TSH between 0.1-0.5 mu/l. TSH suppression has been associated with improved progression free survival (PFS) in patients with papillary thyroid cancer with high risk features [10].

External beam radiation has been used to manage symptomatic local and distant disease. It is indicated for patients with 1) inoperable, residual disease post thyroidectomy 2) resected high risk disease where the likelihood of relapse is high and 3) as a palliative procedure to provide local control for unresectable, symptomatic disease [11,12]. In terms of systemic treatment options chemotherapy has minimal efficacy [13].

In recurrent disease which is localized, surgical resection is favored. If there is widespread involvement, palliative treatment options include; radioiodine ablation, external beam radiation, and local ablative techniques [14]. Palliative surgery for symptom control can also be offered [15].

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Patient Factors	
Age at diagnosis	Patients 20-45 years best prognosis [56]
Gender	Men have a more aggressive course [56]
Hereditary v sporadic	Familial thyroid cancer more aggressive subtype [57,58]
Tumour Features	
Histology	Columnar variant and diffuse sclerosing variant papillary thyroid cancer are associated with a worse prognosis [59,60]
Tumour size	Tumours>7 cm have a 50% 20 years mortality rate [60]
Local invasion	Differentiated thyroid cancers with local invasion have an increased risk of recurrence and 33% of patients die within a decade [61,62]
Vascular invasion	Associated with increased mortality [61]
BRAF V600 mutation	BRAF mutation is associated with more advanced stage at diagnosis, extra thyroidal invasion, lymph node involvement and tumour recurrence [61,62]
Metastatic at diagnosis	5 years survival 50-5% [37]

Table 1: Factors associated with Poor Prognosis in Differentiated Thyroid Cancer.

It is possible that new agents associated with improving the stability of the histone methyltransferases complex G9a/GLP might be a novel direction for the treatment of follicular thyroid carcinomas. This is based on preclinical data demonstrating, that fusion of paired box gene 8 (PAX8) to peroxisome proliferator-activated receptor gamma1 (PPARγ1) is essential for the occurrence of a subset of follicular thyroid carcinomas and that G9a negatively regulates the activity of oncogenic PPARγ1 [16].

Follicular Thyroid Cancer Overview

Follicular cancer is the second most common differentiated thyroid cancer. Its incidence is increased in iodine-sufficient areas. Microscopically, follicular cancer may demonstrate extension through the tumor capsule and vascular invasion and need to be differentiated from adenomas. Spread is haematogenous, however it is a slow growing cancer and metastatic disease is rare. Prognosis is favorable, with mortality rates between 1.4-1.5% [7]. Ras mutations are identified in 40% of follicular cancer and are associated with a more aggressive disease course and higher mortality rates [17,18]. Prognostic features are similar to those in papillary thyroid cancer. Features associated with adverse outcomes are older age and advanced stage at diagnosis (Table 2) [19,20].

The treatment is similar to that of all differentiated thyroid cancers and includes surgical resection, radioiodine ablation and thyroid stimulating hormone (TSH) suppression. For metastatic disease that is refractory to EBRT, RAI can be considered, as well as systemic treatment with cisplatin and doxorubicin [21].

Anaplastic Thyroid Carcinoma Overview

Anaplastic thyroid cancer is an undifferentiated thyroid cancer that arises from follicular epithelium. The mean age for diagnosis of anaplastic thyroid cancer is 65 years and the majority occur in women [22,23]. Patients with anaplastic thyroid cancer may present with a rapidly growing thyroid mass and symptoms such as dysphagia, hoarseness or hemoptysis due to local invasion of the trachea or larynx. Anaplastic thyroid cancer spreads rapidly and common sites of metastasis include lung, bone and brain. Over 50% of patients present with metastatic disease at diagnosis. Respiratory failure is a common cause of death [24]. Poor prognostic are similar to those seen in other types of differentiated thyroid cancers and include distant metastasis, large tumors, older age and dyspnea at presentation [25]. Anaplastic thyroid cancer often occurs on a background of previous thyroid pathology. Surgery is the mainstay of treatment for localized disease. During to the rapid nature of this disease early palliative input with use of palliative surgery and external beam radiotherapy (EBRT) for symptomatic management.

Combination radiation with doxorubicin and cisplatin is an appropriate initial treatment option for unresectable or metastatic anaplastic thyroid cancer. A study by Tennvall [26] demonstrated that multimodal treatment in patients with anaplastic thyroid cancer was well tolerated and provided local control. Thirty three patients were treated prospectively with a combination of pre and post-operative hyper fractionated radiotherapy, doxorubicin, and debulking surgery. Complete local remission was obtained in 48% of the patients. Anaplastic thyroid cancer has a poor prognosis with a median survival of one year and accounts for up to 40% of all deaths from thyroid cancer. The aggressive nature of anaplastic thyroid cancer has made clinical therapeutic trials challenging to perform. However, combretastatin A-4 phosphate (CA4P) ,a novel antitumor vascular targeting agent may have a role to play. A phase 1 trial in 25 patients with various advanced cancers resulted in one patient with anaplastic thyroid cancer having a complete response [27].

Medullary Thyroid Carcinoma Overview

Medullary thyroid cancer is an undifferentiated neuroendocrine tumor of parafollicualar cells which produce calcitonin. It makes up 5-9% of all thyroid cancers [2]. They are either sporadic (60-70%) [28] or hereditary in origin. Germline mutations in the RET proto-oncogene occur in virtually all patients with hereditary medullary thyroid cancer. All patients should be assessed for presence of MEN syndrome with screening for hyperparathyroidism and phaeochromocytoma. If presence of a familial syndrome is detected, family members should be sent for genetic counseling and consideration of a prophylactic thyroidectomy as the majority will have medullary thyroid cancer or c-cell hyperplasia at surgery [29].

Medullary thyroid cancer commonly presents as a solitary thyroid nodule and in most cases disease has metastasized at diagnosis. In localized disease surgery is the mainstay of treatment as medullary thyroid cancer doses not concentrate radioiodine. This form of thyroid cancer is relatively chemotherapy resistant [12]. Thyroglobulin suppression is not appropriate for this group as c-cells lack TSH receptors. TSH should be maintained within the normal range [6,7]. Post-operative radiation has not been adequately studied and is not widely used as adjuvant therapy [6,8,9]. Post –op surveillance guidelines recommend two-three weekly carcinoembryonic antigen (CEA) and Calcitonin levels [30]. Patients with raised serum tumor maker levels or symptoms suspicious for recurrence such as palpable neck mass or unresolving respiratory symptoms should have further imaging such as a CT neck, thorax, abdomen, pelvis and a bone scan. Management of symptoms due to excretion of hormonally active peptide may require the use of somatostatin analogues [31]. Common symptoms include Cushing's syndrome, flushing and diarrhea.

The five year survival rate for medullary thyroid cancer with local nodal involvement is 81% however if there is metastatic disease it decreases to 28% [32]. In sporadic medullary thyroid cancer, somatic mutations of codon 918 has been associated with a poorer prognosis [33,34]. Lack of calcitonin immunostaining, rising CEA levels and postoperative hypercalcitonmeia have all been associated with poorer outcomes [35,36].

Trial Citation	Phase of Trial	Thyroid cancer subtype	Intervention	Cohort number	Outcome
Robinson et al. [40]	Phase II	MTC	received 100 mg/d vandetanib. eligible patients postprogression treatment -300 mg/d vandetanib	19	ORR 16% (95% CI 3.4-39.6). DCR 68% (95% CI 43.4-87.4)
Wells et al. [41]	Phase II	MTC	vandetanib 300 mg od	30	20% PR 53% SD ≥ 6 months
Lam et al. [45]	Phase II	MTC	sorafenib 400 mg bd		PFS 17.9 month
Kurzrock et al. [63]	Phase I	Advanced solid tumours including 37 with MTC	oral cabozantinib	85 37 had MTC	15 (41%) of 37 patients with MTC had stable disease (SD) for at least ≥ 6 months partial response in 68% of patients with MTC.
Thornton et al. [64]	Phase III	MTC	vandetanib, 300 mg versus placebo	231 v100	The PFS (hazard ratio = 0.35; 95% confidence interval, 0.24-0.53; P < 0.0001) ORR 44% versus 1%
Elisei et al. [38]	Phase III	MTC	cabozantinib (140 mg per day) versus placebo	330	PFS 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio, 0.28; 95% CI, 0.19 to 0.40; P < .001). RR 28% for cabozantinib and 0% for placeb PFS 1 year are 47.3% for cabozantinib and 7.2% for placebo
Bible et al. [65]	Phase II	MTC	Pazopanib 800 mg od	35	14% PR (14.3%; 90% confidence interval 5.8%-27.7%) PFS 9.5 months OS 19.9 months

DCR: Disease Control Rate, ORR: Objective Response Rate, SD: Stable Disease, PR: Partial Response, PFS: Progression Free Survival

Table 2: Completed Trials in Medullary Thyroid Cancer.

Chemotherapy has a limited role and is not considered first line treatment in patients with metastatic medullary thyroid cancer. There are few long term responses and partial responses range from 10-20% [37]. Most chemotherapeutic regimens combine dacarbazine with 5-fluorouracil, cyclophosphamide, vincristine, streptozocin, or doxorubicin. Combination treatment with cyclophosphamide, vincristine and dacarbazine in one study resulted in 2/7 patients experiencing a durable partial response lasting over a year [38]. Another study reviewed alternating cycles of doxorubicin and streptozocin with 5-fluorouracil and dacarbazine. 15% had partial responses 50% had stable disease for over 8 months [39].

Tyrosine Kinase inhibitors can be considered in a select group of patients who have symptomatic, rapidly growing recurrent or persistent disease. Both Vendetanib and Cabozantanib are oral kinase inhibitors which have demonstrated improved progression free survival (PFS) in metastatic medullary thyroid cancer [40-43]. Vendatanib inhibits RET kinase, vascular endothelial growth factor receptor, and epidermal growth factor receptor signaling. A phase 3 trial of vandetanib versus placebo showed a statistically significant advantage for vandetanib, for PFS. Objective response rate, disease control rate, and biochemical response [44]. Boxed warnings include QT prolongation, torsade de pointes and sudden death. Of note, vendatanib can decrease calcitonin without a resulting decrease in disease burden. As such, it may not be a useful marker of disease activity in patients receiving RETS inhibitor therapy [43].

Cabazantinib is an oral tyrosine kinase inhibitor that targets MET, VEGF receptor 2 and RET. One phase III trial compared cabozantinib to placebo in 330 patients with metastatic MTC. PFS at 1 year was 47.3% for cabozantinib and 7.2% for placebo. Common side effects associated with cabazantinib included diarrhea, palmar-plantar erythrodysesthesia, decreased weight, appetite, nausea, and fatigue [45]. Rare side effects include severe hemorrhage, GI perforation and fistula [46]. Both Caboxanatnib and Vendetanib improve PFS however they have not shown on OS benefit and no head to head comparisons studies have been completed.

Other small molecular inhibitors can be considered. Sorafanib targets VEGFR 2, 3 and RET and has shown efficacy in reducing symptoms due hypercalcemia and metastasis [47]. A phase II trial of 16 patients with metastatic medullary thyroid carcinoma treated with sorafenib yielded a median progression-free survival of nearly 18 months [48]. In another study a significant clinical response was seen in 6 out of 8 patients treated with combination sorafenib and a farnesyitransferase inhibitor tipiforinib [49]. Sunitinib had been associated with clinical response in several case reports [50-52]. One case report describes a patient with locally aggressive, treatment resistant medullary thyroid cancer that was unrespectable at diagnosis. The patient had no response to chemotherapy but had a dramatic response to sunitinib becoming resectable. The patient underwent thyroidectomy and neck dissection and has no recurrence at follow up (14 months). In a phase II trial of 7 patients with a median follow up of 15.5 months 2 out of 7 patients with progressive refractory medullary thyroid cancer had disease stabilization and 3 out of 7 had a partial response (Table 3) [53-55].

Targeted therapy in combination with radioiodine ablation may represent a novel therapeutic option. The combination of a MEF inhibitor with RIA was used in radioiodine –refractory thyroid cancers with therapeutic benefit. Of the 12 patients who reached the dosimetry threshold for radioiodine therapy, 5 had partial responses and 3 had stable disease. This demonstrated the important potential role of combination treatment in overcoming treatment resistance [56-58].

Pazopanib is a TKI that targets the VEGF receptor that is clinically efficacious in patients with metastatic, rapidly progressive, and radioiodine-refractory differentiated thyroid cancers. A phase 3 study of 37 patients demonstrated a response rate of 49% (95% CI 35–68) lasting longer than 1 year in 66% of patients who responded [59-62].

Toxicities associated with all the VEGF-targeted TKIs include renal impairment, hyper or hypothyroidism, hepatotoxicity, muscle wasting, myelosuppression, thromboembolism, cardiotoxicity, hypertension, and cutaneous toxicity. There is ongoing development of targeted agents including tyrosine kinase, MEK and ALK inhibitors, a PARP-y agonist and combination Dabrafenib and Trametinib therapy [63-65]. Combinations studies targeted agents with systemic there pay or EBRT are areas are under development. There is also a trial of a vaccine targeting for medullary thyroid cancers targeting CEA producing cells (Table 2).

Trial Citation	Phase of Trial	Thyroid Subtype	Outcome
Safety and Efficacy of Sorafenib in Patients With Advanced Thyroid Cancer	Phase II	DTC	Primary; clinical activity and safety profile of sorafenib Secondary; PFS, adverse events a
A Study of MLN0128in Metastatic Anaplastic Thyroid Cancer (MTOR kinase)	Phase II	Anaplastic	Primary: PFS Secondary; ORR, OS, adverse events, identification of biomarkers predictive of response to therapy with MLN0128
Nintedanib (BIBF1120) in Thyroid Cancer (inhibits VEGF, FGF, PDGF receptors)	Phase II	DTC medullary	Primary; PFS Secondary; adverse events, RR, duration of response, biomarker study
Dabrafenib With or Without Trametinib in Treating Patients With Recurrent Thyroid cancer	Phase II	Follicular, Insular, Papillary	Primary; ORR Secondary; PFS,OS, adverse events, tolerability
Study of GI-6207in Patients With Recurrent Medullary Thyroid Cancer(vaccine targeting CEA producing cells)	Phase II	Medullary	Primary; calcitonin growth rate Secondary; CEA-specific T-cells at 3 months, time to progression
Study Comparing Complete Remission After Treatment With Selumetinib /Placebo in Patient With Differentiated Thyroid Cancer(MEK Kinase Inhibitor)	Phase III	DTC	Primary; complete remission rate in overall study population Secondary; RR, adverse events, Selumetinib concentration, CRR in sub-group positive for v-raf murine sarcoma viral oncogene homolog B1 or NRAS
Cabozantinib for the Treatment of Radioiodine -Refractory DTC in the First-line Setting	Phase II	DTC	Primary; adverse events
Enhancing Radioiodine (RAI) Incorporation Into BRAF Mutant, RAI-Refractory Thyroid Cancer with the BRAF Inhibitor Vemurafenib: A Pilot Study	Phase I	All?	Primary; Overall response, duration of overall response Secondary; objective response rate
Efatutazone (oral PPAR-γ agonist) With Paclitaxel Versus Paclitaxel Alone in Treating Patients With Advanced Anaplastic Thyroid Cancer	Phase II	Anaplastic	Primary; os Secondary ;RR, PFS, adverse events
Ceritinib (LDK378) in Mutation and Oncogene Directed Therapy in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer	Phases	Anaplastic	Primary; time to progression
A Study of Two Different Doses of Cabozantinib (XL184) in Progressive, Metastatic Medullary Thyroid Cancer (EXAMINER)	Phase IV	Medullary	Primary; PFS Secondary; ORR,
Phase II Study of the Optimal Scheme of Administration of Pazopanib in Thyroid Cancer	Phase II	DTC	Primary; Time to treatment failure Secondary; ORR, CR, PR, DCR, PFS, RR, OS, safety profile, QOL

DCR: Disease Control Rate, ORR: Objective Response Rate, SD: Stable Disease, PR: Partial Response, PFS: Progression Free Survival.

Table 3: A Selection of Trials currently recruiting in thyroid cancer taken from Clinical Trials.gov.

Palliative surgery or radiation can be used for symptomatic management of focal disease and bisphosphonate or denosumab can be added for patients with bone involvement.

In advanced rapidly progressive thyroid cancer new agents and multimodality care represent promising therapeutic options for patients. However, these agents are not without risk and clinicians must be judicious with their use, weighing toxicities, quality of life and likely benefits.

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