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Head and Neck Cancer (CP Rodriguez, Section Editor)

Contemporary Management of Anaplastic Thyroid Cancer

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Abbreviations *ATC* Anaplastic thyroid cancer · *DTC* Differentiated thyroid cancer · *PDTC* Poorly differentiated thyroid cancer

Opinion statement

Anaplastic thyroid cancer (ATC) is a rare but very aggressive form of undifferentiated thyroid cancer. Due to its rapid rate of progression and invasive nature, ATC poses significant risks of morbidity and mortality. The cornerstone in the management of ATC remains a prompt diagnosis of the disease and timely management of complications depending on the stage of disease. Surgery continues to offer a higher chance of a cure, although not all patients are candidates for surgical management. Patients with advanced disease may be considered for palliative surgery to reduce morbidity and complications from advanced disease. With the advent of new molecular testing and improved methods of diagnosis, novel therapeutic targets have been identified. Systemic therapy (chemotherapy and radiation therapy) as well as novel immunotherapy have shown some promise in patients with targetable genetic mutations. Patients should therefore have molecular testing of their tumor—if it is unresectable—and be tested for mutations that are targetable. Mutation-targeted therapy may be effective and may result in a significant response to allow surgical intervention for exceptional responders. Overall, patients who receive all three modalities of therapy (surgery, chemotherapy, and radiation therapy) have the highest overall survival.

Introduction

Anaplastic thyroid cancer (ATC) is a rare form of undifferentiated thyroid cancer representing approximately 2% of all thyroid cancers, but accounting for a majority of all thyroid cancer deaths [1]. The median overall survival of patients with ATC is approximately 3–6 months and less than 20% of affected patients are alive 1 year after diagnosis; thus, ATC is one of the most aggressive malignancies in humans [2, 3]. Approximately 30–40% of patients present with locoregional metastases and/or vocal cord paralysis, and 70% of patients have direct invasion of local tissue including the trachea, muscle, esophagus, and larynx [4]. Distant metastasis at the time of presentation is common and can involve multiple sites including the lungs (50–80%), bone, skin, and brain (6–12%) [4]. Mortality from ATC usually occurs as a result of persistent metastatic disease, despite aggressive treatment.

Treatment of ATC almost always involves surgical resection of the primary tumor (except when deemed unresectable), and a combination of external beam radiation (EBRT) and/or systemic chemotherapy which all have varying degrees of efficacy. Identification of various molecular targets has led to novel therapy and approaches to the care of patients diagnosed with ATC.

Risk factors for ATC

It has been a challenge to determine risk factors for ATC. This is because it is rare and the optimal study design to identify risk factors in a patient population is a case-control study, and case-control studies in the ATC patient population are scarce. The only case-control study was performed by Zivaljevic and colleagues, who performed a series of studies that showed low education level, type B blood group, first full-term pregnancy before age 19, family history of malignant tumors, and goiter to be independent risk factors for ATC [5]. Furthermore, several systematic reviews and meta-analyses have reported an association between patient body mass index (BMI) and the risk of thyroid cancer (and in some cases, ATC) [6–8]. Olson and colleagues, in a recent retrospective, population-based study conducted using the National Cancer Database from 2000 to 2013, found that the increase in ATC was largely, in part, due to an increased rate of detection of papillary thyroid cancers and that age > 60 years and medullary/anaplastic histology were associated with a significantly higher incidence of Stage IV thyroid cancer [9]. Other significant characteristics were a lower level of education, lower income, male sex, increased number of comorbidities, further distance from a treatment facility, and Medicare insurance [9].

Differentiated thyroid cancer (DTC) is a risk factor for the development of ATC. Several studies have suggested that ATC develops from DTC based on (1) the presence of a histologic focus of ATC in DTC, (2) the occurrence of DTC and ATC in the same patient, and (3) genetic mutations present in DTC being present in ATC which also has additional mutations. Based on genetic studies, ATC is thought to develop in a stepwise fashion from DTC to poorly differentiated thyroid cancer (PDTC), then to ATC. Mutations in *BRAF* and *RAS* are present in DTC, PDTC, and ATC, with additional mutation in *TP53* and promoter mutations in *TERT* being present in ATC and PDTC, supporting a stepwise cumulative genetic alteration developing in DTC to PDTC and ATC [10–

12,13••,14]. Most recently, alterations in the PI3/AKT/mTOR pathway and alterations within the SWI/SNF complex (*ARI1D1A*/*ARID1B*/*SMARCB1*/*PBRM1*/*ATRAX*), histone methyltransferase pathway mutations (*KMT2A*/*KMT2C*/*KMT2D*/*SETD2*), loss of function mutations in DNA repair genes (*MSH2*/*MSH6*/*MLH1*/*BRCA1*/*BRCA2*/*ATM*), and, to a lesser extent, alterations in tumor suppressor genes (*TP53*, *NF1/2*, *MEN1*) have been reported in PDTC and ATC [10, 15••]. Ravi and colleagues, in 14 ATC samples, found commonly mutated genes including *TP53*, *TERT*, and *ATM*, but also identified a high frequency of genomic amplifications including amplification of *CCNE1* and *CDK6*, both of which may be targetable by CDK inhibitors [16]. Jung and associates also showed that stem cell markers and epithelial mesenchymal transitions are overexpressed in ATC, in contrast to DTC [17].

Diagnosis of ATC

The incidence of ATC peaks around the seventh decade of life, and affects more women than men at a ratio of approximately 3:1 [18]. Accurate diagnosis of ATC requires a high degree of clinical suspicion and timely workup. A neck ultrasound is the first imaging modality to be obtained. This may demonstrate an irregular hypoechoic mass with or without any evidence of local invasion [12]. A fine needle aspiration (FNA) biopsy and cytologic examination may suggest ATC, but sometimes a core needle biopsy or open biopsy may be necessary. The differential diagnosis on cytologic examination in addition to ATC may include medullary thyroid cancer, PDTC, primary thyroid lymphoma, sarcoma, and metastasis to the thyroid gland. Immunohistochemical staining for specific protein markers (+keratin, +vimentin, −thyroglobulin, −calcitonin expression) and transcription factors (+*PAX8*, +*P53* expression) can be helpful in distinguishing ATC from other malignancies. Squamous or sarcomatoid subtypes of ATC may appear on histology, which increases the risk of misdiagnosis; however, the above immunohistochemical stainings (especially +PAX8 expression) can be used to differentiate these from thyroid sarcoma [19]. Of note, ATC may co-exist in a single specimen with as much as 50% admixed with DTC cells reported [20, 21]. FNA in combination with core needle cytologic examination for analysis of the above molecular markers and mutations may increase the diagnostic accuracy for ATC [22]. It is important to note that the sensitivity of core needle biopsy may be lowered due to the potentially large portions of necrotic or inflammatory tissue present in ATC. As such, if both FNA and core needle biopsy are non-diagnostic, an open biopsy should be performed to establish the definitive diagnosis on histology [23].

Liquid biopsy is a new technology that utilizes peripheral blood to test for circulating DNA and tumor cells to diagnose malignancy and identify early recurrence [24]. Circulating tumor cells have been shown to be present early, when tumors have spread to distant organs [25]. Diagnosis of ATC using liquid biopsy techniques has been reported [26]. The assay evaluates patient samples for circulating cell-free DNA using known gene mutation profiles present in ATC [26]. Liquid biopsy may also have utility in prognostication by identifying

specific mutations in the tumor, some of which (e.g., *BRAF V600E*) may be possible drug targets [24]. Limitations of liquid biopsy in ATC include the cost of mutational analysis and barriers to real-world utility/application, given that currently the process is time-consuming, expensive, and requires advanced skills for accurate interpretation [27].

Staging

Because of the aggressive nature of ATC, the American Joint Committee on Cancer (AJCC) designates all ATC as Stage IV thyroid cancer. The stage of ATC is further divided into Stage IVA, IVB, and IVC, based on the extent of disease at the time of diagnosis. Stage IVA (T1–T3a, N0, M0) represents tumors localized to the thyroid gland without lymph node involvement (N0) and distant metastasis (M0). Stage IVB is a primary tumor with gross extrathyroidal extension (T3b, T4) and/or involvement of locoregional lymph nodes (≥ N1), and Stage IVC (any T, any N, M1) is the presence of distant metastasis (M1) [28].

Prognosis

The median overall survival of patients with ATC is 3–10 months, with only 20% of patients surviving 1 year after diagnosis [2, 29]. However, the individual patient course may be highly variable and survival is also stage-dependent, with various multi-institutional retrospective studies suggesting an average overall survival of 9 months in patients with Stage IVA disease, 4.8 months in Stage IVB disease, and 3 months in Stage IVC disease [30, 31].

Several factors have been associated with prognosis. Some widely established favorable prognostic factors in patients with ATC include younger age at diagnosis, tumor size < 5 cm, local extent of disease, intrathyroidal primary tumor, and treatment with multimodal therapy [32–36]. Tumor characteristics such as tumor size > 5 cm, extrathyroidal extension, and distant metastases have been shown to negatively influence prognosis [37]. Symptomatic disease (hoarseness, neck pain, and vocal cord paralysis) has also been associated with worse prognosis, often indicating locally advanced disease that is unresectable. For instance, Tashima and colleagues found dyspnea to be an independent poor prognostic factor for patients with ATC (HR = 3.2, $p = 0.01$) [38].

Post-therapeutic prognostic factors including surgical vs non-surgical treatment, extent of resection (R0 vs R1/R2), and the amount/type of adjuvant therapy (chemotherapy, radiotherapy) have all been shown to be associated with prognosis, although these are more controversial [33–36]. Sugitani and colleagues suggested that these prognostic factors could be used to stratify which patients would benefit most from aggressive multimodal therapy [39]. Similarly, several investigators have developed and tested prognostic scoring systems to determine the extent of therapy for patients diagnosed with ATC [40, 41]. For example, Sun and colleagues performed a retrospective analysis to explore the use of a prognostic scoring system (using age > 55 years, leukocytosis ≥ 10×10^9/L, blood platelet count >300×10^9/L, and advanced clinical TNM stage as negative prognostic factors) to guide treatment in patients with

ATC. Patients with more than two negative risk factors were high risk and had lower overall survival at 1 year (90% vs 6.5%) and were less likely to benefit from post-surgical radiotherapy [41].

Management of ATC

Management of ATC requires a multidisciplinary team and multimodal treatment approaches based on the stage of disease (Fig. 1, Table 1) [42]. It is essential also to establish the goals of care with the patient. Given the extent of disease and high rate of disease progression, initial management of patients with ATC always begins with evaluation of the airway. Patients with very advanced disease are at high risk of airway obstruction and unstable respiratory status, which sometimes requires emergency tracheostomy. Once a stable airway is confirmed or established, workup for metastatic disease should be undertaken to ensure that the correct treatment pathway is followed (Stage IVA/B versus Stage IVC disease). This is important because up to 50% of all ATC patients present with metastatic disease at diagnosis, and these patients have a short time to treatment failure [43]. If metastatic disease is present, the next step in management usually depends on the "volume" or extent of metastatic disease. Patients with "small-volume" disease typically undergo intensity-modulated radiation therapy to ensure locoregional control, followed by definitive management with high-dose radiation and chemotherapy. "Large-volume" metastatic disease usually warrants palliation with a short course of

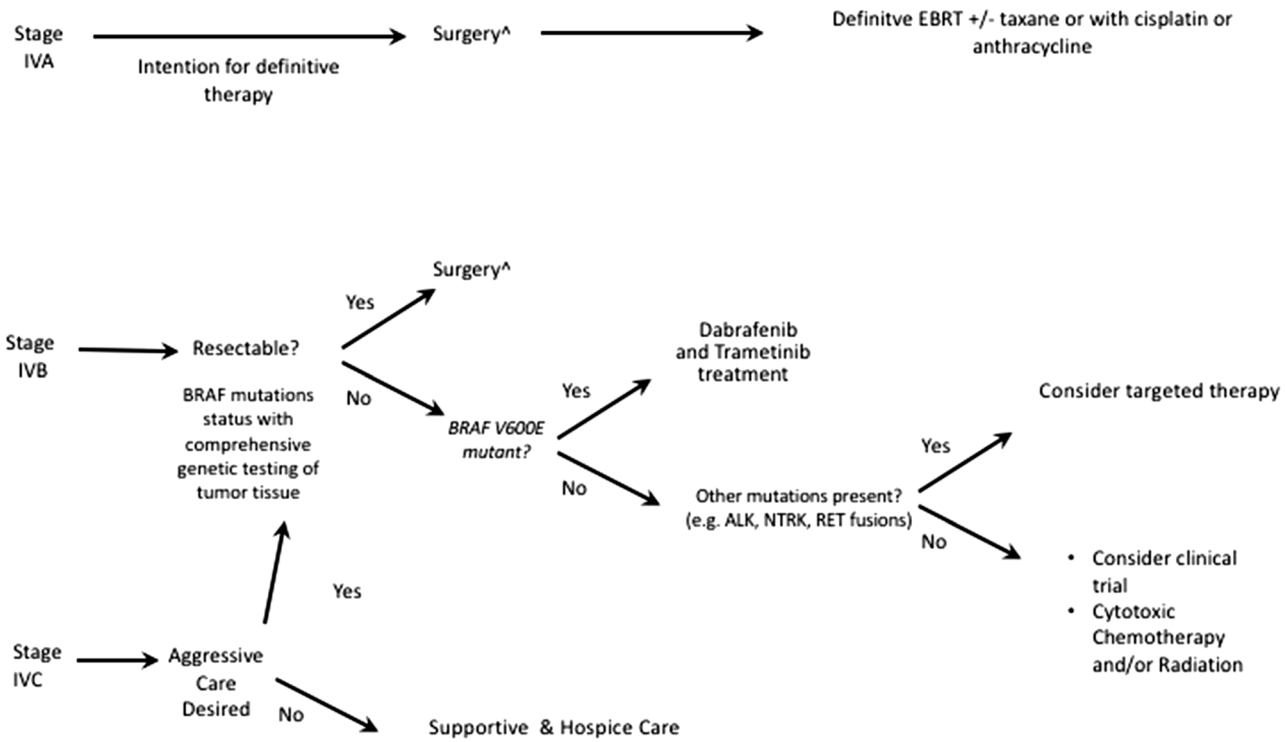

Figure 1. Evaluation and treatment decisions based on anaplastic thyroid cancer extent of disease

Table 1. Model for multidisciplinary care team and issues that need to be discussed between a patient with anaplastic thyroid cancer and the multidisciplinary care team

List of providers that should be involved in the management of patients with anaplastic thyroid cancer
• Endocrinologist/Endocrine Oncologist
•Medical Oncologist
•Bioethicist
•Pathologist/Cytopathologist
•Endocrine Surgeon
•Nuclear Medicine
•Radiation Oncology
Issues that need to be addressed
•Patient's goals of care
•Patient performance status/comorbidities
•Patient willingness to have treatment morbidity upfront for potential benefit later or no benefit?
•Assess patient support systems, geographic proximity to providers to administer therapy
•What are the medical and financial resources available to patient?
•Access to targeted therapy/clinical trials

radiation therapy followed by chemotherapy vs upfront chemotherapy for palliative intent, and consideration of clinical trials or no treatment intervention if that is the patient's goal of care.

If metastatic disease is ruled out, the primary tumor should then be evaluated for resectability. In contrast to the management of DTC and MTC where surgical resection is the initial step in management, surgical resection in ATC should only be performed in patients with good potential for complete resection (R0/R1). This is imperative because debulking of ATC has not been shown to be beneficial for patients with ATC and furthermore risks delaying radiation/systemic therapy that could be beneficial in some patients [23]. If deemed resectable, surgical resection is undertaken promptly, followed by radiation therapy approximately 2–4 weeks post-operatively. In a patient with an unresectable primary tumor without evidence of distant metastasis, definitive intensity-modulated radiation therapy (≥ 60 Gy) with adjuvant systemic chemotherapy can be considered [44]. Finally, *BRAF V600E* mutation status should be determined, as targeted therapy may be a good initial treatment option. Systemic therapy for *BRAF V600E* mutations is usually with combination BRAF and MEK inhibitors (dabrafenib and trametinib), or with only a BRAF kinase inhibitor (vemurafenib), both of which have shown efficacy in this patient population [29].

Initial evaluation

In patients with ATC, prompt preoperative evaluation should be obtained with an ultrasound of the neck and high-resolution intravenous contrast-enhanced

computed tomography (CT) of the neck and chest. In addition, a staging 18-FDG PET/CT of the chest, abdomen, and pelvis should be completed as well as an MRI or CT of the brain if neurologic symptoms are present or brain metastasis is suspected. The tumor should have molecular testing to determine treatment alternatives. In some cases, laryngoscopy, esophagostomy, and bronchoscopy are also needed to further delineate extent of disease, especially if the patient has locoregional symptoms. After preoperative workup is complete, the patient and a multidisciplinary team must engage in shared decision-making to determine the extent or aggressiveness of treatment (Fig. 1, Table 1). It is imperative that workup of disease is completed immediately prior to intervention, as ATC progresses rapidly and thus the stage of the patient's disease could change between workup and time of surgery.

Surgery

There is no widely accepted definition of "resectability," and indications for surgical intervention remain variable. The American Thyroid Association guideline recommends that only patients who present with locoregional disease (i.e., T4a/T4b disease) and have the potential for negative margin upon resection (R0/R1) should undergo surgical resection. However, resection of the primary tumor for palliation and/or prevention of future airway complications may be considered in patients with Stage IVC disease [23]. The recommended surgical approach for localized ATC is a total thyroidectomy with central neck dissection (level VI) given the propensity for ATC to spread rapidly both locally and systemically. Unilateral or bilateral modified radical neck dissection (levels II, III, IV, and sometimes V) may also be performed, if the lymph nodes involved are identified. Ipsilateral thyroid lobectomy is more controversial, given the risk of concomitant DTC in the contralateral thyroid lobe. In addition, thyroid lobectomy may also be considered in patients who may have pre-existing risk of or known injury to the contralateral recurrent laryngeal nerve or parathyroid glands, so as to reduce the morbidity related to bilateral laryngeal nerve injury and significant hypoparathyroidism from an unintended total parathyroidectomy. In either case, significant effort must be made to remove all apparent disease with a goal to achieve an R0/R1 resection.

Resectability of Stage IVB ATC depends upon the patient's tumor size, extrathyroidal extension, and involvement of adjacent structures [18]. These patients may require concomitant trachea, superior mediastinum, laryngopharynx, esophagus, and carotid artery resection, if these structures are grossly involved. Possible postoperative complications include recurrent laryngeal nerve injury, hemorrhage, wound dehiscence, hypoparathyroidism/hypocalcemia, fistula, infection, and vocal cord paralysis/hoarseness [45, 46]. Obviously, these are quite invasive procedures, so patients must be well informed regarding the significant postoperative morbidity associated with them and should only be considered if an R0/R1 resection can be achieved, recognizing the high risk of recurrent ATC.

Previous studies have demonstrated conflicting results on the benefit of surgical resection and neoadjuvant therapy, and the true benefit of each modality individually and in combination [30]. Surgical resection has more recently been independently associated with longer overall survival [37, 46, 47].

Akaishi and associates found, among 100 patients with ATC, that 1-year overall survival was 53% after complete resection, 16.5% after debulking, and 3.6% after no surgery [34]. Although surgery and multimodal therapy with surgery and chemotherapy and/or radiation have been reported to be associated with longer overall survival, one should be aware of the inherent selection bias associated with these studies, given that only those patients who have disease that can be treated and that can tolerate these interventions are selected for intervention [43, 48]. There have also been few reports of no significant improvement in overall survival among patients undergoing surgical resection [49–51]. Because of these conflicting reports, Hu and colleagues performed a systematic review of 40 studies ($n = 1683$) on the role of surgery in ATC and found that surgery is associated with a survival benefit with a median overall survival of 8 months compared with 3 months in patients who did not undergo surgical resection [46]. As such, the gold standard remains complete resection with negative margins (R0/R1), if possible. In cases of more advanced disease or an inability to obtain negative margins, debulking of disease with a goal of at least 90% disease resection has been associated with improved palliation and tolerance of adjuvant therapy [34].

External radiation therapy in ATC

External beam radiation therapy (EBRT) plays an important role in the management of local disease in patients with advanced ATC. It is commonly used as adjuvant therapy in patients with local disease. Although the presence of distant metastases does not preclude the use of EBRT for locoregional therapy, radiation therapy is used mostly for palliative intent in these patients with impending upper airway or esophageal compromise. Radiation therapy is effective for advanced disease given the rapid division of the tumor cells, and is effective in ATC cells which are typically resistant to radioiodine therapy. Studies have shown that a successful radiation therapy dose depends on the stage of tumor, with Stage IVA/IVB patients having a better survival benefit compared with Stage IVC patients [52]. The dose of radiation depends on the resectability of the primary tumor, with unresectable tumors requiring higher (60–75 Gy) vs lower (45–59.9 Gy) doses [53••]. Due to the side effects of high-dose radiation therapy, certain techniques are implemented to increase the efficacy of EBRT, such as the use of multiple smaller fractions administered more frequently in an accelerated fashion. This technique serves to reduce the treatment duration as well as to increase the total radiation dose delivered [54].

Pharmacologic treatment in ATC

Currently available FDA-approved drugs for advanced thyroid cancer can be divided into two groups based on their mechanism of action as follows: cytotoxic agents such as anti-angiogenic tyrosine kinase inhibitors (vandetanib, cabozantinib, sorafenib, and lenvatinib) and mutation-specific drugs such as dabrafenib/trametinib (for BRAF-mutated ATC) and larotrectinib (for NTRK fusion thyroid cancer).

Cytotoxic agents in ATC

Systemic chemotherapy may be considered in patients with Stage IVB/C ATC who desire aggressive initial therapy and are candidates for locoregional radiation therapy [23]. Concurrent use of EBRT with systemic chemotherapy has been studied in non-anaplastic thyroid carcinomas and has been shown to be effective [55]. Historically, radiation therapy was combined with doxorubicin. However, better results have been observed with the addition of taxane class drugs such as paclitaxel and docetaxel when combined with EBRT [56, 57]. For instance, Foote and colleagues reported a median overall survival of 60 months (overall survival at 1 and 2 years of 70% and 60%, respectively) following a chemoradiation regimen combining radiotherapy and combination of docetaxel plus doxorubicin [57]. Patients amenable to "tri-modal" therapy (surgery, EBRT, and chemotherapy) have been found to have longer survival of up to 22 months compared with 6.5 months in patients receiving dual therapy with EBRT and chemotherapy [43, 58].

The use of multi-kinase inhibitors in patients with advanced thyroid cancers has been evaluated in various phase II clinical trials without any obvious survival advantage or durable and dramatic objective response. Sorafenib, a multi-kinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and RAF was evaluated in a phase II clinical trial in 10 patients with ATC. Median overall survival in this patient cohort was only 5 months with no objective response to treatment [59]. Similar results were obtained in two other clinical trials evaluating the efficacy of sorafenib in patients with advanced and metastatic thyroid cancers [60, 61]. Similarly, pazopanib (a multi-kinase inhibitor) targeting VEGFR, PDGFR, and c-kit was studied in a phase II clinical trial in 15 patients with ATC. There were no RECIST responses and the median overall survival was 111 days [62]. Lenvatinib, a small-molecule VEGFR inhibitor, is currently FDA-approved for treatment of DTC. Its use in ATC was recently evaluated in an international phase II clinical trial involving 51 patients, 17 of which had ATC. The median progression-free survival in ATC patients was 7.4 months, with a median overall survival of 10.6 months [63].

Emerging data on the use of monoclonal antibodies for the treatment of ATC shows promise. Spartalizumab, a humanized IgG4 anti-PD1 antibody was recently reported to have clinical benefit among 26 patients with ATC in a phase II trial, with an overall disease control rate of approximately 30% [64]. More studies on immunotherapy in ATC are expected in the future, and a lot remains to be learned regarding their utility and efficacy in the management of these patients.

Mutation-directed therapy

The *BRAF V600E* mutation is the most common genetic alteration seen in papillary thyroid cancer [65], and is also commonly found in ATC. The *BRAF* gene encodes a protein that is essential in regulating cell division and differentiation. The *BRAF V600E* mutation results in constitutive catalytic activity that results in continuous phosphorylation of downstream target proteins [66]. In thyroid cancer, *BRAF V600E* mutations have been shown to play a role in aggressive clinicopathologic features, including extrathyroidal invasion, nodal and distant metastases, and inhibition of genes involved in iodine metabolism via the loss of Na-I symporter expression [65, 67].

The FDA-approved BRAF and MEK inhibitor combination therapy with dabrafenib and trametinib should be the first line of treatment in patients with *BRAF V600E* ATC. Dabrafenib, a selective mutant BRAF kinase inhibitor commonly used in the treatment of melanoma, was used and showed good promise in 14 patients with metastatic *BRAF V600E* mutant differentiated thyroid cancer [68]. A phase II trial was then undertaken using a combination of dabrafenib and the MEK inhibitor trametinib in 53 patients with *BRAF V600E*-mutated PTC, which also showed durable and good response [69]. A similarly positive response was reported in a phase II open-label trial of the combination regimen (dabrafenib and trametinib) among 16 patients with *BRAF V600E*-mutated ATC, with an overall response rate of 69% and overall survival of 80% at 12 months [70]. Of note, all 16 patients had received prior radiation treatment, surgery, or both. Finally, a case series of 6 consecutive patients with *BRAF V600E*-mutated ATC showed that neoadjuvant dabrafenib and trametinib combination therapy resulted in complete surgical resection, with a 12-month overall survival of 83% [71]. The combination drug therapy is thought to result in greater clinical efficacy than dabrafenib alone, via vertical inhibition of the RAF/MAP/ERK pathway and mitigation of potential mechanisms of resistance. Most recently, a case report of neoadjuvant therapy with dabrafenib, trametinib, and pembrolizumab in a patient with *BRAF V600E*-mutated ATC was shown to have impressive response despite having a previously unresectable tumor. This patient successfully underwent a total thyroidectomy, bilateral central compartment dissection, and bilateral lateral neck dissection after 3 months of the neoadjuvant combination therapy without the need for laryngectomy and/or tracheostomy [72••].

NTRK fusion mutations are rare in thyroid cancer [73••]. Larotrectinib, a highly selective inhibitor of TRKA, TRKB, and TRKC, is approved by the FDA for treatment of solid tumors with NTRK fusions [74, 75]. Entrectinib, another selective inhibitor of TRKA, TRKB, and TRKC, also inhibits ALK and ROS1 tyrosine kinases and has been shown to penetrate the blood–brain barrier, making it a therapeutic target for patients with brain metastasis from NTRK, ROS1, or ALK fusion [76, 77]. Both drugs have shown some promise in phase I and II clinical trials of patients with various cancers [76, 78–80] including a small proportion (9%) of thyroid cancer patients [78]. However, evidence of their efficacy in ATC specifically has not yet been reported.

Mammalian target of rapamycin (*mTOR*) mutations are a common genetic mutation in human cancers. *mTOR* regulates cellular functions including cell proliferation, growth, metabolism, and autophagy [81]. *mTOR* mutations have been implicated in some thyroid cancers including ATC [82]. Everolimus, an FDA-approved serine-threonine kinase inhibitor of *mTOR*, has been shown in multiple phase II clinical trials to be effective in increasing progression-free survival among patients with advanced and metastatic thyroid cancers [83–85]. The multi-institutional phase II trial of everolimus among 50 patients with aggressive thyroid cancer (including 7 with ATC) showed promising results among the ATC cohort—one patient with near-complete response, another with partial response and 17.9-month progression-free survival (PFS), and one with a 26-month PFS prior to death from congestive heart failure. Four patients had progressive disease within 3 months of enrollment in the study [83].

The recent systematic review of phase II clinical trials investigating targeted therapy in patients with ATC highlights the importance of molecular characterization of ATC [29]. As the identification of molecular targets increases and becomes more precise, molecular testing to select the optimal treatment for patients with ATC becomes very important because it has potential to increase both PFS and overall survival for these patients.

Conclusions

Given the poor prognosis of ATC, patients with ATC should have a goals of care discussion with a multidisciplinary team involved. Prompt diagnosis and surgical resection provide the best outcome in patients with Stage IVA/B ATC. EBRT may be palliative in patients with unresectable Stage IVA/B ATC, and adjuvant EBRT may be beneficial in patients who have R0/R1 surgical resection. All patients with ATC should have molecular testing of their tumor. Patients with Stage IVC ATC may benefit from mutation-targeted therapy. Multimodal therapy is associated with longer overall survival in patients with ATC.

Compliance with Ethical Standards

Conflict of Interest

None of the authors has any potential conflicts of interest to disclose.

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