Response to Targeted Therapy in BRAF Mutant Anaplastic Thyroid Cancer

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Abstract

Anaplastic thyroid cancer (ATC) is an aggressive uncommon malignancy with limited treatment. Traditional antineoplastic chemotherapy has not been successful in the management of metastatic ATC. As a result, the focus has shifted to the development of novel therapies for this disease. The availability of economical comprehensive genomic profiling (CGP) platforms with rapid turn-around to identify molecular aberrations in tumors that are potential therapeutic targets has increasingly changed the face of cancer therapy. Identification of targetable aberrations may help identify novel treatment options for ATC. Herein, we report our experience with a 47-year-old patient with metastatic ATC who experienced recurrent, progressive disease and rapid clinical deterioration despite surgery, radiation therapy, and treatment with 2 different chemotherapy regimens. She was found to have a BRAF V600E mutation on CGP, and was started on targeted therapy with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib. After 2 months of treatment, she showed a clinical and radiologic response. The patient remained on this combination for 9 months until evidence of disease progression. Discontinuation of these drugs was associated with rapid tumor growth. Through this case we want to emphasize the importance of early molecular sequencing and identification of genetic aberrations in patients with ATC, and using that information to develop therapies for ATC, an aggressive malignancy with limited therapy and a poor outcome.

Anaplastic thyroid cancer (ATC) is a rare, aggressive malignancy with an annual incidence of 1 to 2 cases per million in the United States.1 ATC accounts for 1.6% of all thyroid cancers but has a much higher mortality rate compared with other thyroid cancer histologies, with a dismal median survival of 5 months and a 1-year survival rate of only 20%.2 The benefit of systemic therapy in advanced metastatic ATC has yet to be proven in a controlled randomized clinical trial. Several cytotoxic chemotherapy agents, including bleomycin, carboplatin, cisplatin, docetaxel, doxorubicin, and paclitaxel, used in various combinations, have been reported to have palliative benefit in small nonrandomized trials, but little impact on survival.1,3,4 As a result of the poor outcome and lack of effective therapy, there is an urgent need for the development of novel agents for the treatment of ATC.

The availability of increasingly low-cost rapid comprehensive genomic profiling (CGP) and the elucidation of critical pathways in tumorigenesis have identified potentially targetable molecular mutations in a number of cancers. As a result, a number of studied targeted agents have demonstrated antitumor activity in preclinical models of thyroid cancer.5–7 Despite these encouraging results, the benefits of these novel agents have not been demonstrated in clinical trials. Two phase II trials using the multikinase inhibitors sorafenib and pazopanib failed to show significant benefit.8,9 However, anecdotal reports of benefit with a number of these agents in ATC are found in literature.8,10–12 This report presents a patient with advanced refractory metastatic ATC who was found to have a BRAF V600E mutation through CGP, was subsequently treated with dabrafenib and trametinib, and experienced a response.
**Case Report**

A 47-year-old woman with a history of moderately severe rheumatoid arthritis treated with infliximab and methotrexate presented with a 1-month history of a rapidly enlarging left neck mass associated with voice changes, sore throat, and difficulty swallowing. Ultrasound showed a 3.1-cm mass in the lower pole of the left lobe of the thyroid gland. Fine-needle aspiration biopsy showed pleomorphic cells with extensive necrosis that were positive for both CK5/6 and p40, but were negative for thyroglobulin and TTF-1, consistent with poorly differentiated carcinoma. A CT scan of the neck showed the large mass inferior to the left thyroid lobe with tracheal deviation. Flexible laryngoscopy demonstrated a paralyzed left vocal cord. The patient underwent an attempt at left thyroidectomy with tumor resection that also involved the esophagus and jugular vein, and a limited left neck dissection. Pathology was consistent with anaplastic (undifferentiated) carcinoma of thyroid, with lymphovascular and perineural invasion that also involved the adjoining esophagus and jugular vein; 1 of 3 lymph nodes was positive for metastatic carcinoma. Two separate papillary thyroid microcarcinomas, 0.4 and 0.1 cm, were also identified with the larger one demonstrating tall cell features. The patient was staged as IVB (pT4bN1M0). Postoperative PET/CT scan showed low-level fluorodeoxyglucose (FDG) uptake corresponding to the left thyroidectomy surgical bed. No distant metastatic site was seen. The patient received adjuvant concurrent chemotherapy and radiation with 6 cycles of weekly intravenous carboplatin (area under the curve, 2) and paclitaxel at 50 mg/m². Four weeks after surgery she received 63 Gy of radiation in 35 fractions of 1.8 Gy per fraction, using a 3-dimensional conformal technique.

The patient did well until 14 months after the thyroidectomy when her disease recurred, as evidenced by PET/CT imaging that showed increased uptake in the left thyroid bed and increased uptake in the right lower lobe of the lung. She underwent resection of a lung nodule that demonstrated metastatic ATC followed by an unsuccessful attempt at resection of the recurrent left neck mass, left neck dissection, and left carotid artery. Pathology was consistent with metastatic ATC (Figure 1). The tumor cells were positive for PAX-8, and negative for TTF-1, napsin, and CK20. Postsurgical scans showed worsening metastatic disease with increasing lung nodules and a new lytic lesion involving the L1 vertebral body. She was started on cisplatin, 60 mg/m² and doxorubicin, 60 mg/m², with growth factor support every 21 days. Imaging after 3 cycles of treatment demonstrated progressive disease. The patient also developed progressive dysphagia and spontaneous development of a malignant pharyngeal-cutaneous fistula necessitating placement of a gastrostomy tube. The resected lung specimen was sent for CGP, which identified BRAF V600E, TP53 V217G, and CBL C419W genetic alterations (Figure 2).

In the absence of an available clinical trial, targeted therapy was initiated against the BRAF V600E mutation with oral dabrafenib at 150 mg twice daily and trametinib at 2 mg daily. Because the patient was taking all of her nutrition through a gastrostomy tube, she would open the capsules and administer her medication through her feeding tube. After beginning treatment, the patient sustained a marked clinical improvement and healing of the fistula. Follow-up CT imaging after 2 months of therapy showed a

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**Figure 1.** Photomicrographs of a biopsied lung nodule demonstrating metastatic ATC. (A) Hematoxylin-eosin staining (original magnification x200; inset x400). Immunohistochemical staining showing tumor cells are (B) positive for PAX-8 (original magnification x200) and (C) negative for TTF-1 (original magnification x200), consistent with ATC. Abbreviation: ATC, anaplastic thyroid cancer.

**Figure 2.** Twenty-five of the most frequently altered genes in ATC of 135 total mutated genes identified in the MSKCC study. Mutations seen in our patient have been marked with an asterisk. The CBL mutation has not been previously reported in ATC. **Abbreviations:** ATC, anaplastic thyroid cancer; MSKCC, Memorial Sloan Kettering Cancer Center.
radiologic response of the lung nodules (Figure 3). The lytic lesion involving the L1 remained stable.

The patient continued to show clinical and radiologic response of the lung lesions at 6-month follow-up (Figure 3). During this follow-up, there was a concern for tumor along the posterior wall of the upper esophagus, and a biopsy was positive for ATC. It was not clear whether this was recurrent or residual disease. Because the patient was responding systemically, dabrafenib and trametinib were continued.

Subsequent scans demonstrated enlargement of a left paraesophageal mass. She was treated with a course of palliative radiation. Dabrafenib and trametinib were continued because the patient was not considered a candidate for systemic chemotherapy. Her condition slowly deteriorated, and dabrafenib and trametinib were discontinued after 9 months, after which the patient’s health then rapidly deteriorated and she died within 15 days. Chest CT performed 2 days before the patient died showed marked tumor progression compared with a CT obtained 2 weeks prior (Figure 4).

**Discussion**

ATC typically follows a clinically aggressive course and its 1-year mortality rate approaches 80%. Its rarity, aggressive nature, and limited therapy has made ATC a therapeutic challenge. As a result, the urgent need to identify new and novel therapies for advanced ATC cannot be overemphasized. Identification of molecular aberrations that drive tumor growth can help identify potential therapies that may have clinical merit.

ATC has been shown to harbor RAS, RET, PTEN, PI3KCA, TP53, and BRAF mutations. Recently, frameshift insertions in PTEN and TP53 has also been reported in metastatic brain lesions and primary tumors in patients with ATC. ALK gene rearrangements have also been reported, and a significant tumor response with 90% tumor shrinkage was reported in a patient treated with crizotinib. As seen in this patient, up to 30% to 35% patients with ATC have coexisting well-differentiated thyroid cancers, suggesting that ATC is the end result of “dedifferentiation” of an initially well-differentiated lesion. It has been suggested that the mutations in BRAF, which is present in both well-differentiated thyroid cancers and ATC, are the early event in the tumor development, and the accumulation of P53 mutations leads to dedifferentiation, which ultimately leads to progression to ATC.

Although P53 is one of the most common mutations found in human cancers, targeting of P53 has not been feasible. On the other hand, BRAF V600E mutations have been successfully targeted in the clinic. Patients with malignant melanoma and BRAF mutations have been treated with vemurafenib or dabrafenib either alone or in combination with the MEK inhibitor trametinib. BRAF mutations occurring in ATC are not well studied. In one report, vemurafenib treatment led to near complete response in a patient with BRAF V600E–mutated ATC. In another report of a BRAF-mutated thyroid cancer, one patient with ATC demonstrated a 66% shrinkage in target lesions, but simultaneously developed a new metastatic lesion. Hyman et al reported a phase II basket study of 122 patients with BRAF V600 mutation–positive cancers treated with vemurafenib, in which 2 patients with ATC...
experienced response. Preclinical studies in papillary thyroid cancer cells have identified a high copy number gain of MCL1 (chromosome 1q) and loss of CDKN2A (P16, chromosome 9p) as a resistance mechanism to vemurafenib, and have suggested the role of combination therapy with vemurafenib and pan-BCL2 inhibitors. Other preclinical studies have suggested that a combination of BRAF and MEK inhibitors may be active in ATC. Clinical responses to the combination of dabrafenib and trametinib were reported previously in one patient as a meeting abstract, and the follow-up information is not available.

Our patient also showed evidence of tumor flare when the combination was acutely discontinued after experiencing slowly progressive disease (Figure 4). Although there was evidence of local progression at 6 months of therapy, we continued the combination as she was clinically responding at all other sites. However, when systemic progression was clearly evident at 9 months, the combination therapy was discontinued. The patient then rapidly deteriorated after discontinuing the combination therapy and expired 15 days later. Tumor flare after discontinuation has been previously reported with other targeted therapy agents such as vemurafenib, erlotinib, gefitinib, and imatinib in other diseases. The possible mechanism underlying tumor flare involves rapid progression of chronically suppressed sensitive clones when drug suppression is removed. In a long-term outcome analysis of 48 patients with melanoma treated with vemurafenib, patients who discontinued vemurafenib after progressive disease had an overall survival of 11 months compared with 26 months in patients who continued vemurafenib after progression. These studies suggest the role of continuation of targeted therapies even in the face of disease progression. The outcome of our patient suggests that she may have experienced tumor flare after discontinuing therapy.

There are no uniform recommendations for management of patients with ATC with BRAF mutations. The prognostic or predictive significance of these mutations is not well established. CBL mutations as seen in our patient have not been reported in ATC and its significance is unknown. Because of the rarity of ATC, large-scale clinical trials evaluating the role of novel targeted therapies have been difficult to conduct. Results of a clinical trial evaluating response to pazopanib in combination with concurrent chemotherapy and radiation (ClinicalTrials.gov identifier: NCT01236547) in ATC is awaited. We recommend that patients with advanced metastatic ATC undergo theranostic genomic profiling early in the course of treatment and enroll in clinical trials. In the absence of a clinical trial, use of appropriate targeted agents should be considered.

References


