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Rechallenge with dabrafenib plus trametinib in anaplastic thyroid cancer: A case report and review of literature

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ABSTRACT

Introduction: Anaplastic thyroid carcinoma (ATC) is a highly aggressive, undifferentiated rare tumor. Median overall survival is usually between 8 and10 months, with a 1-year survival rate of 20%. Conventional anthracycline based chemotherapy regimens demonstrate low response rates with short duration. Novel therapeutic agents including BRAF and MEK inhibitors based on the molecular landscape of ATC have been investigated. *Case presentation:* We herein report the rechallenge of a 52-year-old ATC patient with BRAF V600E mutation with dabrafenib plus trametinib. She presented with recurrent and progressive disease despite surgery, radiation therapy, 3 different chemotherapy regimens, and combination of dabrafenib-trametinib in different settings. She was rechallenged with dabrafenib-trametinib, and had a good response. *Conclusion:* To our knowledge, this is the first ATC case who responded to dabrafenib-trametinib rechallenge, reported in the literature. We want to emphasize that combination of dabrafenib and trametinib might be a good choice for resistant locoregional and metastatic ATC patients with BRAF V600E mutation, particularly in whom rapid clinical response is urgently needed. Moreover, rechallenge with this combination should be kept in mind in selected cases.

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Introduction

Anaplastic thyroid carcinoma (ATC) is a rare, highly aggressive, undifferentiated tumor which comprises 1%-10% of all thyroid cancers.[1] Generally, patients are older and they present with rapidly growing mass. Almost half of them have distant metastatic disease at the time of diagnosis.[2] Median overall survival is 8-10 months.[3-6]

Multimodal treatment strategy (debulking surgery, followed by hyperfractionated accelerated external beam radiotherapy [EBRT], and chemotherapy with platinum compounds or anthracyclines) has been considered the most effective therapy of ATC. Conventional chemotherapy regimens unfortunately demonstrate low response rates and short duration of response.[7] Therefore, novel therapeutic agents have been investigated based on the molecular landscape of ATC.

V-raf murine sarcoma viral oncogene homolog B (BRAF) mutations are commonly identified in ATC. It is associated with worse prognosis when compared to wild type disease/tumors. Following highly promising results of a phase 2 trial on ATC, combination of dabrafenib (BRAF V600E inhibitor), and trametinib (MEK 1/2 inhibitor) was approved by Food and Drug Administration (FDA) on May 4, 2018.

Here we present a BRAF V600E mutant ATC patient refractory to multiple series including dabrafenib-trametinib, and had a good rapid response to dabrafenib-trametinib rechallenge.

Case

A 52-year-old woman presented with 1-month history of swelling on her neck. She had no other significant medical comorbidities. On physical examination, she only had palpable left cervical lymph nodes. Ultrasonography showed approximately 1 cm mass in left thyroid lobe and left conglomerated lymphadenopathies (LAPs) in levels III and IV, largest of which was 4.5 cm in diameter. Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET/CT) revealed high uptake (SUV_{max}: 3.7) in thyroid gland nodule and in enlarged lymph nodes (SUV_{max}: 4.5), while there were no distant metastases. Pathological diagnosis was reported as ATC in fine needle aspiration biopsy.

Total thyroidectomy and lymph node dissection was performed. Surgical pathology revealed $1.2 \times 1 \times 1$ cm papillary thyroid carcinoma (%60 conventional + %30 oncocytic + %10 clear cell variant) in thyroid gland and ATC metastasis in $8 \times 5 \times 4$ cm conglomerated cervical lymph nodes. Anaplastic component was positive on resection margins. Due to poor prognosis of ATC, primary therapy was planned to focus on anaplastic component. Concurrent chemoradiotherapy was administered as 5000 cGy to neck and 6000 cGy to tumor bed in 30 fractions with weekly cisplatin (20 mg/m^2) and doxorubicin (10 mg/m^2). Following chemoradiotherapy, 3 more cycles of cisplatin (50 mg/m^2) and doxorubicin (50 mg/m^2) were given every 3 weeks. At the end of this treatment, 10×7 mm LAP adjacent to the left submandibular gland was seen in magnetic resonance imaging (MRI) scans. Patient did not give consent to any intervention to rule out recurrence, and any other treatment.

After 6 months, she presented again with a growing neck mass. MRI demonstrated an enlarged left submandibular LAP of 37×28 mm. FDG-PET/CT showed an increased uptake in this LAP (SUV_{max} of 6.5), and there were also milimetric lung nodules with no pathologic FDG uptake. In multidisciplinary tumor board systemic therapy was considered as an appropriate option. Carboplatin (AUC 5) and paclitaxel (175 mg/m^2) were administered every 3 weeks, for 3

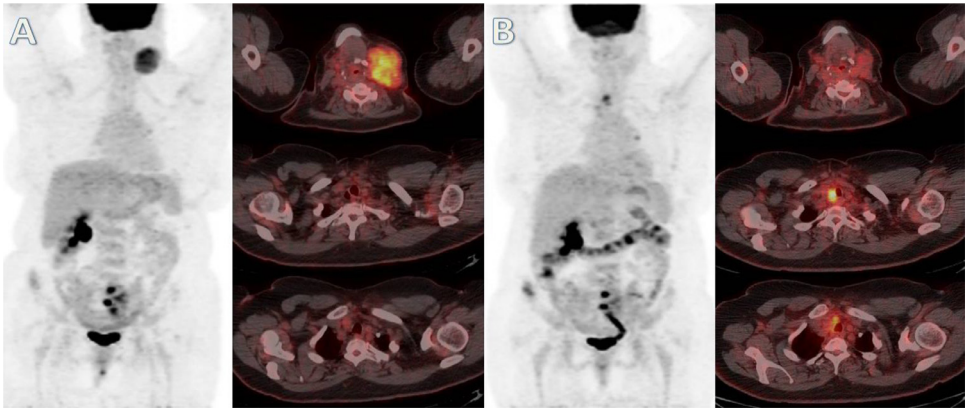


Fig. (A) Baseline FDG PET-CT. (B) FDG PET-CT done 12-weeks post dabrafenib-trametinib treatment.

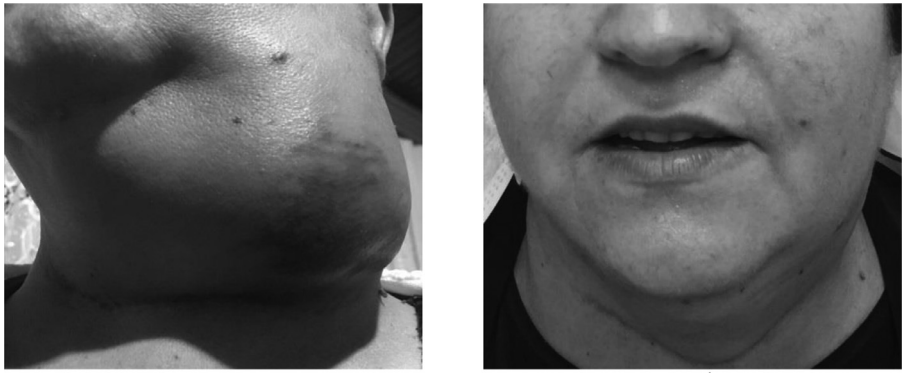
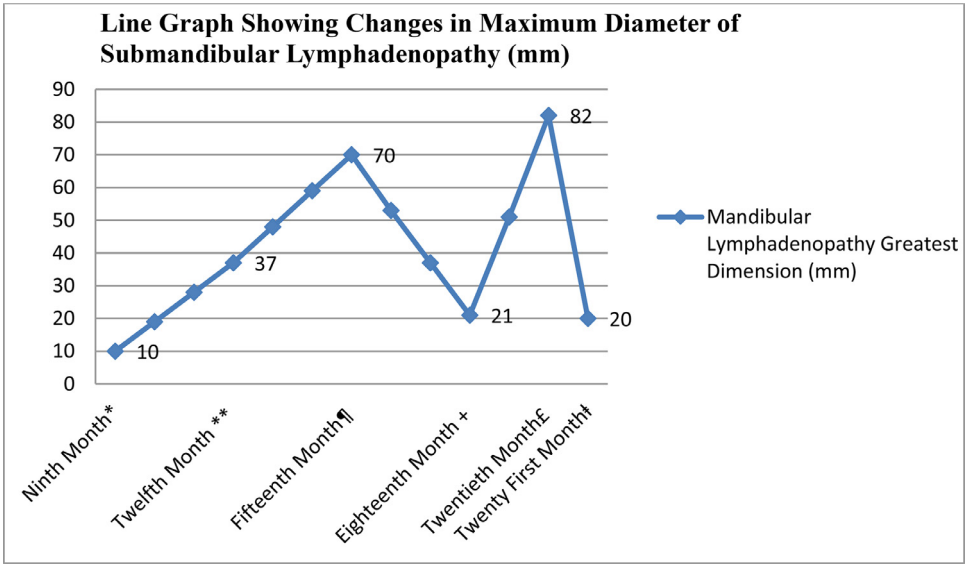


Fig. (C) First day of rechallenge. (D) 20th day of rechallenge.

months. Neck mass enlarged clinically during the last cycle, and MRI showed progression of left submandibular LAP measured as 7×4.5 cm. Lung nodules were stable and still there were no distant metastasis in FDG-PET/CT. Meanwhile surgical specimen analysis for BRAF mutation came back positive. Patient was started on dabrafenib (150 mg twice a day) and trametinib (2 mg once daily).

Patient noticed a dramatic relief of her neck stiffness/inflexibility in the first month of anti-BRAF therapy. After 2 months of therapy, neck mass shrunk markedly and was not detected any more on physical examination. This very rapid clinical response persisted until the end of third month. She tolerated the drugs well with no major side effects, except grade 1 anemia and fatigue. Although FDG-PET/CT demonstrated a favorable metabolic and anatomic response in the submandibular LAP (SUV_{max} decreased from 5.7 to 1.6 and maximal dimension from 73 to 21 mm), new lesions with increased uptake, one 2×1 cm mass located in the right thyroid lobe region (SUV_{max}: 6.3), and another 9-mm LAP in front of this new mass (SUV_{max}: 4.1) were reported. There were also two more new mediastinal LAPs in 2R and 3 (6 and 4 mm in diameter and SUVmax uptakes of 2.8 and 3.2, respectively) (Figure A and B). Patient was switched to albumin-bound paclitaxel (nab-paclitaxel) and gemcitabine.

After 2 courses of albumin-bound paclitaxel and gemcitabine, neck mass started to enlarge rapidly, and patient became symptomatic with severe pain and dyspnea. MRI showed left submandibular LAP measured as 8.2×5.5 cm and mass continued to enlargement fast until the patient evaluated. As she had limited treatment options, needed to palliate the neck mass ur-



Line Graph: Changes in size of submandibular LAP over time.
*Time of Recurrence
**Start of 1.Line Therapy (Carboplatin+Paclitaxel))
¶Start of 2.Line Therapy (Dabrafenib+Trametinib)
†Third Month of 2.Line Therapy
£Second Month of 3. Line Therapy (Gemcitabin+Nab-Paclitaxel)
‡20.Day of Rechallenge (Dabrafenib+Trametinib)

gently, and had a rapid response priorly, she was rechallenged with dabrafenib and trametinib. On the 20th day of rechallenge, neck mass shrank dramatically followed by resolution of both pain and dyspnea (Figure C and D). Patient is still being followed-up without symptoms at the third month of rechallenge and she is still alive after 23 months of diagnosis. Line graph shows the changes in maximum diameter of submandibular lymphadenopathy that causes morbidity over time.

Discussion

Most common BRAF mutation is the substitution of valine with glutamic acid at amino acid residue 600 (V600E), and is seen in 20%-25% of ATC patients.[8-10]

Dabrafenib downregulates MEK/ERK phosphorylation, and inhibits BRAF-mutated cell viability through G0/G1-arrest. Trametinib inhibits cellular viability by downregulating ERK phosphorylation. Dual blockade by both inhibitors showed cytostatic effects in four ATC cell lines.[11]

Phase I trial of single agent dabrafenib was done in 184 patients, 156 of whom with metastatic melanoma, 28 with BRAF-mutated non-melanoma solid tumors.[12] In this group 14 had metastatic radioiodine-refractory BRAF-mutated papillary thyroid cancer, and dabrafenib showed a 29% response rate in this subgroup, and two-thirds of patients achieved at least 10% reduction in tumor size.

Following this phase I study, dabrafenib monotherapy was also given to several ATC patients. In 2016, Lim et al reported 2 cases with BRAF V600E mutant ATC, treated with dabrafenib.[13] A 49-year-old woman operated with a T4bN1bM0 disease, had symptomatic metastatic disease 8 weeks after chemoradiotherapy. A complete response was shown by FDG-PET scan 1 month after the start of dabrafenib. Patient progressed in 3 months, and died 11 months after the diagnosis.

The second patient was a 67-year-old man, who was treated with dabrafenib for a T4aN1bM0 ATC, and tumor shrinkage was detected within 10 days. Disease was stable for 11 weeks, but patient died 11 months after the diagnosis with disease progression.

Different clinical trials for melanoma showed that resistance to dabrafenib mostly seen within 6-7 months. Flaherty et al emphasized that dabrafenib resistance could be prevented by combining dabrafenib with trametinib in melanoma patients.[14]

In 2016, Canabillas et al reported another case of an 81-year-old woman with BRAF V600E mutant ATC.[15] She underwent total thyroidectomy followed by EBRT. Four months after initial diagnosis, she presented with lung metastasis and recurrent neck mass. She received an additional 24 Gy of EBRT to the neck, and pazopanib was started. Neck and lung masses progressed rapidly on pazopanib, and treatment was changed to dabrafenib and trametinib combination. Symptomatic relief was observed within 2 weeks, and remarkable responses in both neck mass and lung metastasis were detected at the end of first month. She progressed in 6 months and stopped therapy.

Combination of dabrafenib and trametinib was investigated in a multicenter, open-label phase II study, which enrolled a total of 100 patients with BRAF V600E positive rare tumors, including 16 ATC patients.[16] Prior treatments of ATC patients were surgery (in %88), EBRT (in %81) and chemotherapy (in %38). Patients received dabrafenib (150 mg bid) and trametinib (2 mg qd) until unacceptable toxicity, disease progression, or death. Median follow-up was 47 weeks. Interim analysis of these 16 ATC patients was published in 2017. Overall response rate was 69% (95% CI: 41%-89%), with 1 complete response, 10 partial response (PR), 3 stable disease and 1 progressive disease. Confirmed responses in the ATC cohort were durable, with 7 of 11 responses were ongoing at the time of data cutoff. Most common adverse events of any grade were fatigue (44%), pyrexia (31%), and nausea (31%). Promising results of this trial led to approval of dabrafenib and trametinib combination by FDA for patients with locally advanced, unresectable, or metastatic BRAF V600E mutant ATC with no locoregional treatment options.

Real-world data of 16 BRAF mutant ATC patients who were treated with targeted therapy included 10 patients with lenvatinib, 6 with dabrafenib-trametinib combination.[17] PR was observed with combination therapy in 3 of 6 (50%) patients, stable disease in 2 (33%), and one patient progressed. No grade 4 or higher AEs were noted. This study showed that targeted therapies might still be a good option for patients who are not eligible for clinical trials.

Resistance to dabrafenib-tremetinib treatment is mostly studied in melanoma patients. Data indicates that resistance to anti-BRAF treatment is mediated by a number of different mechanisms. Shi et al detected RAS mutation in 70%, and activation of PI3K pathway in 22% of melanoma patients who progressed on anti-BRAF treatment.[18] Rizos et al reported that they could detect a resistance mechanism only in 58% of patients. AKT-1, NRAS, MEK, IGF-1R mutations, and BRAF amplification was shown as the reason for resistance, and BRAF splice variants was the most common one.[19] Activation of PI3K and MAPK pathways has also been shown to be associated with poor prognosis in ATC.[20,21]

Efficacy of dabrafenib and trametinib rechallenge have been demonstrated in several studies involving patients with melanoma. Schreuer et al reported 25 stage 3C or 4 melanoma patients who previously progressed under anti-BRAF treatment, and were rechallenged with dabrafenib and trametinib after a 12-month interval. They had 32% of tumor response to retreatment.[22] Valpione et al administered anti-BRAF retreatment in 116 metastatic melanoma patients, whose BRAF targeted treatments were terminated mostly due to resistance or progression. Of 83 patients who discontinued BRAF inhibitor due to disease progression, 31 (37.3%) responded (30 PR and 1 complete response) to retreatment. Median OS calculated from the beginning of retreatment was 9.8 months, and progression free survival was 5 months. [23]

Mechanism of achieving a rapid response with dabrafenib-trametinib rechallenge is an important issue. Resistance mechanisms may not be irreversible. Das Thakur et al emphasized clues coming from preclinical modals, showing BRAF inhibitor resistant clones might have a fitness disadvantage relative to those sensitive to BRAF inhibitor, and this selective growth advantage in the face of BRAF inhibitor therapy could be lost on discontinuation of targeted therapy.[24]

Our patient is the first case with ATC reported in the literature that was rechallenged with dabrafenib and trametinib. She had a rapid good response to rechallenged with dabrafenib and trametinib during the last 3 months, and is still alive 23 months after the first diagnosis. Even for now, this OS is much longer than reported in the literature. She developed resistance in a very short period of time in first usage. Heterogeneous primary tumor and different tumor clones could be responsible for this early resistance. Our patient did not give consent to any invasive procedures, therefore we could not test and prove any resistance mutations. ATC usually causes serious morbidities including the need for tracheostomy, reducing morbidity has great importance. Combination of dabrafenib and trametinib appears to be a good choice for resistant locoregional and metastatic ATC patients with BRAF mutations, particularly if rapid clinical response is urgently needed. Rechallenge of dabrafenib and trametinib should be kept in mind in selected cases, especially if the patient had a response previously. To support these findings, more studies with larger numbers of patients are needed.

Statement of ethics

All diagnostic and therapeutic procedures were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from the individual participant included in the report.

Declaration of competing interest

The authors have no conflict of interest.

References

1. NationalCancerInstitute: SEER Cancer Stat Facts: ThyroidCancer. https://seer.cancer.gov/statfacts/html/thyro.html.
2. Ranganath R, Shah MA, Shah AR. Anaplastic thyroid cancer. *Curr Opin Endocrinol Diabetes Obes*. 2015;22:387–391. doi:10.1097/MED.0000000000000189.
3. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: Pathogenesis and emerging therapies. *Clin Oncol*. 2010;22:486–497. doi:10.1016/j.clon.2010.03.013.
4. Nagaiah G, Hossain A, Mooney CJ, et al. Anaplastic thyroid cancer: A review of epidemiology, pathogenesis, and treatment. *J Oncol*. 2011;2011:1–13. doi:10.1155/2011/542358.
5. Brignardello E, Palestini N, Felicetti F, et al. Early surgery and survival of patients with anaplastic thyroid carcinoma: Analysis of a case series referred to a single institution between 1999 and 2012. *Thyroid*. 2014;24:1600–1606. doi:10.1089/thy.2014.0004.
6. Prasongsook N, Kumar A, Chintakuntlawar AV, et al. Survival in response to multimodal therapy in anaplastic thyroid cancer. *J Clin Endocrinol Metab*. 2017;102:4506–4514. doi:10.1210/jc.2017-01180.
7. Denaro N, Lo Nigro, Russi Eg, et al. The role of chemotherapy and latest emerging target therapies in anaplastic thyroid cancer. *Onco Targets Ther*. 2013;1231. doi:10.2147/OTT.S46545.
8. Kimura ET, Nikiforova MN, Zhu Z, et al. High prevalence of BRAF mutations in thyroid cancer: Genetic evidence for constitutive activation of the RET/PTC-RAS-BRAF signaling pathway in papillary thyroid carcinoma. *Cancer Res*. 2003;63:1454–1457. http://www.ncbi.nlm.nih.gov/pubmed/12670889.
9. Lee J-H, Lee E-S, Kim Y-S. Clinicopathologic significance ofBRAF V600E mutation in papillary carcinomas of the thyroid. *Cancer*. 2007;110:38–46. doi:10.1002/cncr.22754.
10. Santarpia L, El-Naggar AK, Cote GJ, et al. Phosphatidylinositol 3-kinase/akt and ras/raf-mitogen-activated protein kinase pathway mutations in anaplastic thyroid cancer. *J Clin Endocrinol Metab*. 2008;93:278–284. doi:10.1210/jc.2007-1076.
11. Fallahi P, Ruffilli I, Elia G, et al. Novel treatment options for anaplastic thyroid cancer. *Expert Rev Endocrinol Metab*. 2017;12:279–288. doi:10.1080/17446651.2017.1340155.
12. Falchook GS, Millward M, Hong D, et al. BRAF inhibitor dabrafenib in patients with metastatic BRAF -Mutant thyroid cancer. *Thyroid*. 2015;25:71–77. doi:10.1089/thy.2014.0123.
13. Lim AM, Taylor GR, Fellowes A, et al. BRAF inhibition in BRAF V600E -Positive anaplastic thyroid carcinoma. *J Natl Compr Cancer Netw*. 2016;14:249–254. doi:10.6004/jnccn.2016.0030.
14. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med*. 2012;367:1694–1703. doi:10.1056/NEJMoa1210093.
15. Cabanillas ME, Busaidy NL, Khan SA, et al. Molecular diagnostics and anaplastic thyroid carcinoma: The time has come to harvest the high hanging fruit. *Int J Endocr Oncol*. 2016;3:221–233. doi:10.2217/ije-2016-0007.

16. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600–Mutant anaplastic thyroid cancer. *J Clin Oncol*. 2018;36:7–13. doi:10.1200/JCO.2017.73.6785.
17. Iyer PC, Dadu R, Ferrarotto R, et al. Real-world experience with targeted therapy for the treatment of anaplastic thyroid carcinoma. *Thyroid*. 2018;28:79–87. doi:10.1089/thy.2017.0285.
18. Shi H, Hugo W, Kong X, et al. Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy. *Cancer Discov*. 2014;4:80–93. doi:10.1158/2159-8290.CD-13-0642.
19. Rizos H, Menzies AM, Pupo GM, et al. BRAF inhibitor resistance mechanisms in metastatic melanoma: Spectrum and clinical impact. *Clin Cancer Res*. 2014;20:1965–1977. doi:10.1158/1078-0432.CCR-13-3122.
20. Nikiforova MN, Nikiforov YE. Molecular genetics of thyroid cancer: Implications for diagnosis, treatment and prognosis. *Expert Rev Mol Diagn*. 2008;8:83–95. doi:10.1586/14737159.8.1.83.
21. Ruggeri RM, Campennì A, Baldari S, et al. What is new on thyroid cancer biomarkers. *Biomark Insights*. 2008;3 BMI.S669. doi:10.4137/BMI.S669.
22. Schreuer M, Jansen Y, Planken S, et al. Combination of dabrafenib plus trametinib for BRAF and MEK inhibitor pretreated patients with advanced BRAFV600-mutant melanoma: An open-label, single arm, dual-centre, phase 2 clinical trial. *Lancet Oncol*. 2017;18:464–472. doi:10.1016/S1470-2045(17)30171-7.
23. Valpione S, Carlino MS, Mangana J, et al. Rechallenge with BRAF-directed treatment in metastatic melanoma: A multi-institutional retrospective study. *Eur J Cancer*. 2018;91:116–124. doi:10.1016/j.ejca.2017.12.007.
24. Das Thakur M, Salangsang F, Landman AS, et al. Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. *Nature*. 2013;494:251–255. doi:10.1038/nature11814.