BANGLADESH JOURNAL OF
OTORHINOLARYNGOLOGY
DOI: https://doi.org/10.3329/bjo.v31i2.89000
www.banglajol.info

Article info
Received : 25.02.2024
Accepted : 07-09-2025
No. of Tables : 01
No. of Figure : 02
No. of References : 19

Case Report

Progression free survival by the treatment with Cabozantinib in a case of BRAF mutated Radioiodine refractory recurrent metastatic Papillary Carcinoma Thyroid

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Abstract:

Metastatic differentiated thyroid carcinoma that fails to respond to radioactive iodine (RAI) therapy carries a poor prognosis with frequent recurrence. Multikinase inhibitors may help slow disease progression, particularly in cases with BRAF mutations, where RAI refractoriness is common. Agents such as dabrafenib, trametinib, lenvatinib, and cabozantinib have shown therapeutic benefit. This report focuses on the clinical course of a 65 year old male with BRAF (V600E)–mutated, RAI refractory, recurrent metastatic papillary thyroid carcinoma (PTC) and his response to lenvatinib and cabozantinib.

The patient initially presented with a painless anterior neck swelling, diagnosed as PTC by FNAC. CT imaging revealed subcentimetric nodal involvement, and he underwent total thyroidectomy with central compartment clearance and selective neck dissection (stageT3N1Mx). Postoperative RAI ablation (150 mCi) showed no significant uptake, though the patient remained symptom free with normal thyroglobulin and TSH levels. One year later, follow up evaluations detected metastatic cervical lymph nodes. PET CT confirmed metabolically active disease in bilateral cervical nodes and pulmonary nodules. He subsequently underwent repeat neck dissection followed by RAI, but recurrence persisted due to aggressive tumor behavior.

Molecular analysis later identified a BRAF (V600E) mutation. Lenvatinib therapy was initiated to slow disease progression; however, despite partial response, the patient experienced hypertension and further nodal recurrence after multiple RAI exposures. Following additional surgery, cabozantinib was introduced, resulting in noticeable regression of metastatic neck nodes despite some adverse effects.

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This case highlights the aggressive nature of BRAF positive, RAI refractory PTC and underscores the therapeutic value of targeted multikinase inhibitors. Cabozantinib offered disease control in an otherwise rapidly progressive clinical scenario. This case emphasizes the importance of early molecular profiling and the role of alternative systemic therapies in managing advanced refractory thyroid carcinoma.

Key words: *Cabozantinib, Lenvatenib, Papillary carrcinoma, Debrafenib, Trametinib, radioiodine, BRAF (V600E), mutation, mek inhibitor.*

Cite the Article: Akter S, Hanif MA, Azad MA, Alam M, Sohan SA. Progression free survival by the treatment with Cabozatinib in a case of BRAF mutated Radioiodine refractory recurrent metastatic Papillary Carcinoma Thyroid. Bangladesh J Otorhinolaryngol 2025; 31(2): 86-94

Introduction:

Incidence of Thyroid Carcinoma is increasing day by day throughout the world. Also the picture of Bangladesh is alarming. Although 5 years overall survival rate for papillary thyroid carcinoma is nearly 98%[1], this may be reduced significantly in recurrent metastatic diseases. Most common treatment for Thyroid Carcinoma followed worldwide is Surgery following Post operative radioactive iodine therapy (I^{131}). Radioiodine therapy is helpful for preventing recurrence and improvement of overall survival. Some cases which are refractory to Radioiodine therapy show poor prognosis and frequent recurrences have occurred. Overall 10 year survival for metastatic diseases with RAI effective cases is about 56% and it can be reduced to 10% in radioiodine refractory cases[2]. Several types of genetic mutation have noticed in these refractory cases like RET- PTC, BRAF (V6OOE), and RAS etc. BRAF (V6OOE) gene mutation is usually identified in Papillary Carcinoma & some cases of Anaplastic Carcinoma. On the other hand RAS & RET genetic translocation can be noticed especially in Medullary and Follicular Carcinoma[3]. Despite genetic translocation over expression of VEGF (vascular endothelial derived growth factor) also play role in increasing aggressiveness of disease[3].

Significant advancement has achieved in the arena of treatment of recurrent metastatic cases. Multikinase Inhibitor is a recent invention in the field of treatment of Thyroid Carcinoma[4, 5]. Promising effect in reduction of disease progression and aggressiveness is noticed by use of Multikinase Inhibitor like Lenvatinib, Sorafenib, Dabrafenib,Trematinib, Cabozatinib etc. Several clinical trials have been done to ensure safety and these drugs are approved by FDA in progressive Diseases[5, 6]. Due to adverse effects some Patient cannot tolerate & became unable to maintain the continuation of the medication. So that their use can became limited.

Activated Mitogen Activated Protein Kinase (MAPK) reduces the expression of sodium-iodide symportar (NIS) results in reduction of iodide uptake, thus radioiodine therapy become unsuccessful[6, 7]. Mode of action of BRAF & MEK inhibitor is, to inhibit MAPK pathway to restore expression of NIS.

Several clinical trials had been placed to highlight the benefit of using combination of BRAF & MEK Inhibitor for reduction of disease progression in aggressive metastatic refractory cases[8-11]. In this case study we tried to represent a case of Papillary Carcinoma Thyroid which is BRAF (V600E) positive, refractory to RAI therapy and multiple recurrence has occurred.

In this case, treatment was switched to **Cabozantinib** as Dabrafenib & Trematinib were unavailable at that time in our country. This patient has experienced progressive reduction of the neck nodal burden, although some adverse effects were observed. The overall disease aggressiveness also appeared to decrease with this therapy. This case highlights the challenges of managing aggressive and RAI refractory PTC and emphasizes the potential role of oral anticancer agents such as Cabozantinib as alternative therapeutic options.

Case Description:

65 years old male patient with no significant co morbidities reported to Otolaryngology department on June 2019 for a painless progressively growing mass in front of the neck for approximately 5 years. Patient was euthyroid then. Initial investigations like USG of neck showed a solid mass which is confirmed as Papillary Carcinoma Thyroid by FNAC. Initial CT imaging noticed solid mass about 3 cm X 4.1cm X 3.1cm in size involving right lobe and part of isthmus of thyroid gland which is inseparable from sternocleidomastoid muscle in some places. Multiple tiny nodules also noticed in left lobe and subcetrimetric nodes were present bilaterally. He underwent Total thyroidectomy with central Compartment clearance with selective neck dissection on 26 June 2019. Tumor was well differentiated and no sign of perineural and lymphovascular invasion. Initial staging was stage-III ($T_3N_1M_X$). His post operative period was uneventful and no history of hypocalcaemia was noted and voice was normal. After operation he received radio iodine ablation therapy 150 mci on 18 September 2019. A large dose I^{131} scan was done then which showed two foci of RTC in thyroid bed which is shown in figure 1.

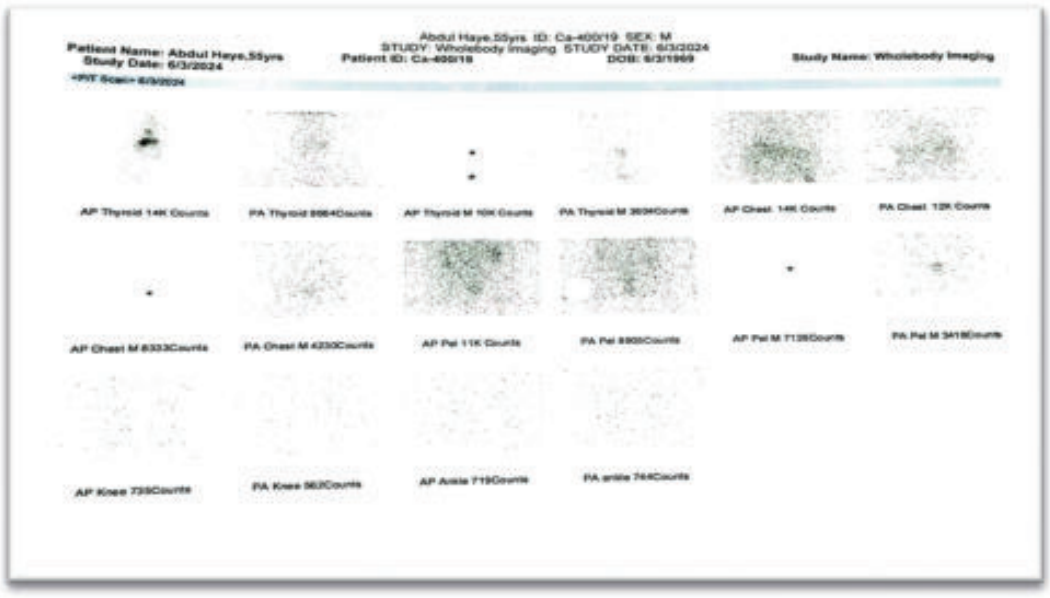

Figure 1: *I^{131} scan showing two foci of RTC in thyroid bed*

Initially after treatment patient was symptom free and all the tumor markers were initially within normal limit. Throughout the disease process his serum Thyroglobulin level, TSH level and all other hormonal level & tumor marker were within normal limit (shown in table 1). RAI-131 whole body scan resembled no significant uptake of RAI. But patient represent with positive neck node after one year and neck nodes were positive for metastatic Papillary Carcinoma. FDG-PET (Positron emission tomography) was then performed where recurrent metastatic disease was noted with hyper metabolism in the both sided cervical lymph nodes and also some nodules in lung. Then patient again went for surgery selective neck dissection bilateral for the 2nd time on 23 November 2020 & post operative RAI therapy Second dose 150 mci on 17 February 2021. Post operative calcium level normal and voice was normal. Histopathology mentioned metastatic papillary carcinoma thyroid and cells were well differentiated. But unfortunately again recurrence occurred after a small period of time. Patient presented with neck nodal enlargement & he went for selective neck dissection bilaterally for 3rd time on 23 June 2021. This time post operative calcium level and voice was also normal. On histopathology cells were well differentiated and extra nodal extension was present. In that time serum Thyroglobulin level, anti Tg antibody & TSH level were within normal limit, (shown in table 1) with a view to doctors decided not to give any further radioiodine therapy.

Then Molecular testing was done and came to know about BRAF (V600E) gene mutation and cellular differentiations also become changed from well differentiated to poorly differentiate. Patient was then treated with targeted therapy by Lenvatinib (20 mg) to hinder the disease process and continued for three months. In course of treatment with Lenvatinib patient was hypertensive as side effect. In spite of taking Lenvatinib again neck node metastasis occurred and patient had to go for 4th time surgical treatment selective neck dissection (II-V) Bilateral with IA on 09 January 2023. So far post operative calcium level was normal but voice changed due to damage of Left sided recurrent laryngeal nerve has occurred (shown in figure 2) as tumor extended to the carotid sheath. Subsequently patient had received 3rd dose of radio iodine therapy 150 mci on 31 May 2023.

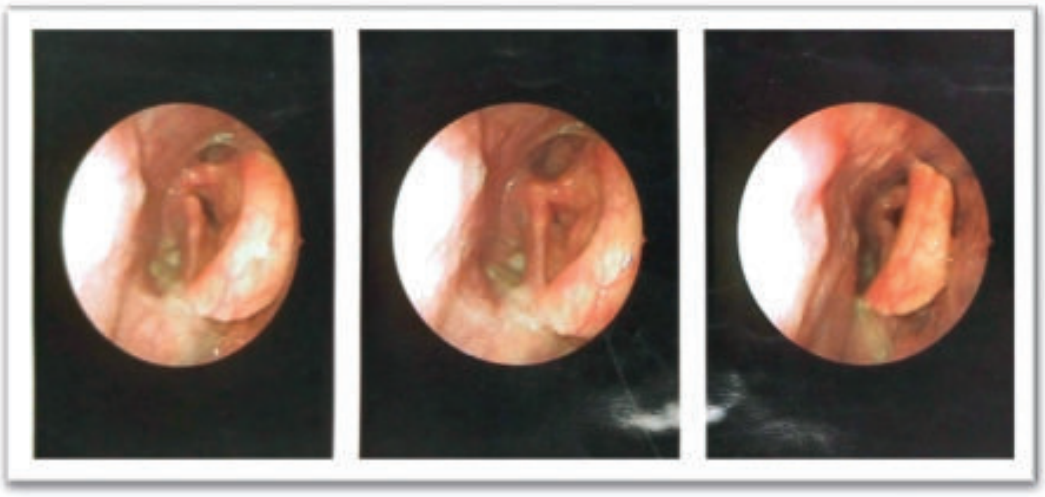

Figure 2: *Post operative Fiber optic laryngoscopy shows left sided vocal cord paralysis*

Table-I

Level of different hormone and tumor markers throughout the disease

	Serum Thyroglobulin	Serum TSH	FT3	FT4	Anti TgAb	Serum Calcium	Serum PTH
31.07.19 (1st postop with thyroxine withdrawal)	13.90 ng/ml	84.80 mIU/ml	4.5 pmol/L	10.3 pmol/L	75.30U/ml	9.15 mg/dl	20.10 pg/ml
23.12.19 (after 1st dose of RAI)	1.14 ng/ml	0.006 mIU/ml	5.4 pmol/L	31.0 pmol/L	<10.0 U/ml	9.04 mg/dl	
10.03.20	1.22 ng/ml	<0.005 mIU/ml	6.1 pmol/L	36.1 pmol/L	<10.0 U/ml	9.0 mg/dl	
08.12.20 (2nd postop with thyroxine withdrawal)	11.7 ng/ml	32.99 mIU/ml	6.9 pmol/L	12.3 pmol/L	25.9 U/ml	9.2 mg/dl	
15.07.21 (3rd postop with thyroxine withdrawal)	1.81 ng/ml	47.79 mIU/ml	1.5 pmol/L	6.7 pmol/L	1.02 U/ml	9.5 mg/dl	
03.10.21	1.11 ng/ml	<0.001 mIU/ml	7.0 pmol/L	36.2 pmol/L	25.00 U/ml	9.9 mg/dl	
02.08.22	0.43 ng/ml	0.18 mIU/ml	4.1 pmol/L	20.2 pmol/L	10.9 U/ml	9.4 mg/dl	
13.02.23	4.03 ng/ml	<0.001 mIU/ml	6.6 pmol/L	30.8 pmol/L	4.56 U/ml	9.7 mg/dl	
09.10.23	23.70 ng/ml	<0.005 mIU/ml	6.8 pmol/L	31.0 pmol/L	12.76 U/ml	9.1 mg/dl	
27.03.24	10.10 ng/ml	<0.001 mIU/ml	5.5 pmol/L	24.0 pmol/L	1.71 U/ml	8.8 mg/dl	
08.10.24	7.47 ng/ml	<0.001 mIU/ml	6.2 pmol/L	27.8 pmol/L	8.073 U/ml	9.1 mg/dl	
14.01.25	4.23 ng/ml	<0.001 mIU/ml	5.6 pmol/L	25.3 pmol/L	4.36 U/ml	8.5 mg/dl	36.00 pg/ml

Unfortunately with in a very short period of time recurrence occurred and neck node was removed locally for **5th** time. None of the treatment procedure was effective to decrease the tumor aggressiveness and continuation of disease progression occurred. By this time patient was experienced with distant metastasis. HRCT scan of chest showed bilateral pulmonary nodules with homogenous opacity (CANON BALL appearance). Finally doctors planned for empirical RAIT 150 mci on 29 may 2024. Empirical therapy remained failed and patient present with huge enlargement of neck node. Without finding any way 6th time surgical treatment was done on 12 January 2025. But patient was not fortunate enough that within one month of surgery again neck node appeared and also pulmonary nodules became larger than before. As the tumor was so aggressive that

results in frequent recurrence despite of expert hand surgery and post operative radioiodine therapy then tumor was classified as refractory case of radioiodine.

Medical board decided to start treatment with Dabrafenib as palliative care, but that time Dabrafenib was unavailable in our country. Then finally treatment starts with Cabozatinib (20 mg) 7 capsules daily (140 mg/day), which shows progressive regression of the neck nodes dramatically despite of some adverse effects like nausea, weight loss, anemia etc. due to adverse effects he couldn't be able to take the medicine in proper dose, which had to reduce to 60 mg per day and also couldn't be possible to continue for a period of time. Patient was abide to take the medicine for a short period like 15 days, then an interval for few days and then again for some days. In spite of this aggressiveness of the disease process was reduced with the use of the medicine. USG of neck revealed regression of tumor size and no new nodule was appeared in comparison to previous report. Patient is not completely disease free now but disease progression is reduced to some extent. By representing the case we tried to focus on alternatives way to treat aggressive refractory case of thyroid carcinoma by oral anticancer drugs like Cabozatinib.

Discussion:

As morbidity and mortality rate is higher in case of radioiodine-refractory cases of thyroid carcinoma, to decrease the sufferings of such patients we need a lot of research for developing newer agents which are effective in treating the radioiodine-refractory recurrent cases. We can observe a remarkable development in this field in last decade. These studies and research works have enlightened our understanding the underlying mechanisms at molecular level responsible for recurrence and radioiodine refractoriness. Such researches are showing the pathway for the invention of agents specifically designed for inhibit the mutated gene which play a significant role in radioiodine refractoriness.

Different genetic mutation had been identified in recurrent and refractory cases. BRAF genetic translocation is responsible for increased rate of lymph node metastasis, extra-thyroidal extension & recurrent papillary carcinoma thyroid. BRAF, a proto-oncogene encode the protein called cytoplasmic kinase that is a part of MAPK pathway which has a regulatory function for cell proliferation, differentiation and programmed cell death.[12] Point mutation on 15 axon of BRAF is most common in papillary carcinoma thyroid. BRAF (V600E) is stands for valine to glutamate substitution at codon 600. This mutation results in permanent activation of BRAF protein which is responsible for reduction expression of several genes like gene for thyroglobulin, gene for thyroperoxidase and gene for NIS (sodium iodide symporter)[13, 14]. Patients with altered gene have experienced aggressive behavior of tumor results in failure to the conventional treatment, followed by recurrence, local and distant metastasis.[15] Radio-iodine therapy remain ineffective due to reduction of iodine transport into the cell. In such situation when surgery and radioactive iodine therapy remain ineffective, targeted therapy can play an important role.

Lenvatinib, Sorafenib, Cabozantinib, Debrafenib, Trametenib are used for targeted therapy and also known as multikinase inhibitors, as they block several kinase proteins. These drugs execute their effects through two ways- they help to block angiogenesis (forming new blood vessels), and also block some targeted proteins that are produced by cancer cells, which are needed for tumor growth.

Lenvatinib and Sorafenib can be helpful to cease the cancer growth in patient with papillary or follicular thyroid carcinoma whose radioactive iodine treatment is no longer functioning. If these drugs didn't play definitive role, Dabrafenib & Cabozantinib may be an option.

BRAF, an intracellular kinase, is frequently mutated in thyroid, melanoma and lung cancers among others. The BRAF V600E mutation is known to be oncogenic. While the RAF-targeted inhibitor Dabrafenib in combination with the MEK1/2-targeted inhibitor Trametinib is approved by FDA for the treatment purpose of patients with BRAF V600E mutant anaplastic thyroid carcinoma, melanoma and non-small cell lung Cancer[8-11]. The clinical benefit of Dabrafenib in combination with Trametinib in patients with BRAF V6OOE mutant papillary thyroid cancer has yet to be determined. Wang, F et al. have denoted male sex as a poor prognostic factor for BRAF V60OE-mutated papillary thyroid carcinomas, but not for their counterparts with BRAF-wild type mutation. Different studies signified the association between the mutation of V600E variant and the aggressive features of the disease like lymph node metastases, invasion, and recurrence. Small phase clinical trials have demonstrated that BRAF inhibitors Dabrafenib and Vemurafenib, can stimulate radioactive iodine uptake in BRAFV600E-positive RAIR papillary thyroid cancer [16, 17]. With a view to the successful result of BRAF and MEK inhibitors in patient with BRAF-mutated melanoma, several studies were took place on the basis of their use in case of well-differentiated thyroid carcinoma for their potential for redifferentiation and restoration of radioactive iodine uptake. , Rothenburg et. al highlighted restoration of radioiodine uptake with Dabrafenib in six patient out of ten with BRAF-mutant papillary thyroid carcinoma[16] while Irvani et al. denoted the increased uptake of radioiodine with combined use of BRAF and MEK inhibition in all BRAFV600E mutated patients.[17] Ho et al. signified the use of Selumetinib, a MEK inhibitor by increasing radioiodine uptake in patients with radioiodine refractory papillary thyroid carcinoma resulting inhibition of the MAPK pathway. This effect was actually achieved in the patients with RAS-mutated tumors[18]. S Brose represents in an article about Cabozatinib, showing significant improvements in progression free survival by the use of Cabozatinib over placebo in cases with radioiodine refractory differentiated thyroid carcinoma previously treated with other targeted therapy[19].

All these drugs are taken orally. There are some usual adverse effects like fatigability, rashes all over the body, loss of appetite, nausea, occasionally vomiting, diarrhea, increased blood pressure, anemia and hand foot syndrome (redness, pain, swelling, or blisters on the palms of the hands or soles of the feet). Sometimes severe bleeding and intestinal perforation can also be observed. Unfortunately, due to treatment-related side effects doctors have to reduce the dose and in many patients have to discontinue the treatment either temporary or permanent that can potentially reduce long-term utilization.

Here we present a case of a patient who experienced regression of his disease, RAI-refractory recurrent metastatic papillary thyroid cancer after treatment with Cabozatinib. After failing with Lenvatinib, disease progression is finally reduced by the use of Cabozatinib. Due to significant adverse effect he couldn't continue the medicine for a long term and used to take the medicine for short phase within small time interval. As Dabrafenib is unavailable at that time and we don't use the medicine in our case, we couldn't specify effects of that. In spite of

adverse effect patient is now trying to adjust with the medicine and his quality of life has been improved. Patient is not free from the disease now but this medicine significantly reduces the disease progression. Treatment is ongoing and he is on our surveillance.

Conclusion:

Metastatic radioiodine refractory thyroid carcinoma associated genetic mutation show poor prognosis. Conventional treatment protocol for thyroid carcinoma like surgery and post operative radioiodine therapy cannot be effective to cure the patient. To reduce the sufferings of this kind of patient significant research efforts have been directed recently for the invention of newer therapeutic agents that can induce redifferentiation and also halting the disease progression in such patients. Targeted therapy by oral anti cancer drugs may be a good option for patient with recurrent treatment failure thyroid diseases. Our patient described in this case report may be an example for encouraging other patients with no hope as Cabozantinib significantly prolongs progression-free survival and might provide a new treatment option for the patients with radioiodine-refractory differentiated thyroid carcinoma who have no other available standard treatment option.

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