Brunei International Medical Journal

OFFICIAL PUBLICATION OF
THE MINISTRY OF HEALTH
AND
UNIVERSITI BRUNEI DARUSSALAM

Volume 18 20 May 2022 (19 Syawal 1443H)

THE RESPONSE TO ANAPLASTIC LYMPHOMA KINASE INHIBITOR IN METASTATIC ANAPLASTIC THYROID CARCINOMA.

Ab Muin NF[1], Ho GF[2].

[1]Radiotherapy & Oncology Department, Hospital Canselor Tuanku Muhriz, Faculty of Medicine, Universiti Kebangsaan Malaysia.
[2]Clinical Oncology Department, University of Malaya Medical Centre, Faculty of Medicine, University of Malaya.

ABSTRACT

Anaplastic thyroid carcinoma is an undifferentiated tumour and lethal. Conventional treatment has not demonstrated clear therapeutic efficacy in prolonging the survival in metastatic anaplastic thyroid carcinoma. We report a case of a 44-year-old woman who was diagnosed with stage IV anaplastic thyroid carcinoma with positive anaplastic lymphoma kinase-echinoderm microtubule-associated protein-like-4 mutation. She demonstrated a good response to anaplastic lymphoma kinase inhibitors therapy with stable disease status for more than six months. This case report shows clinical efficacy of anaplastic lymphoma kinase inhibitor in a patient with stage IVC anaplastic thyroid carcinoma with positive anaplastic lymphoma kinase mutation.

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Brunei Int Med J. *2022;18:84-88*

ISSN 1560 5876 Print
ISSN 2079 3146 Online

Online version of the journal is available at www.bimjonline.com

Brunei International Medical Journal (BIMJ)
Official Publication of
The Ministry of Health
and
Universiti Brunei Darussalam

ISSN 1560-5876 Print
ISSN 2079-3146 Online

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Acknowledgements

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ABSTRACT

Anaplastic thyroid carcinoma is an undifferentiated tumour and lethal. Conventional treatment has not demonstrated clear therapeutic efficacy in prolonging the survival in metastatic anaplastic thyroid carcinoma. We report a case of a 44-year-old woman who was diagnosed with stage IV anaplastic thyroid carcinoma with positive anaplastic lymphoma kinase-echinoderm microtubule-associated protein-like-4 mutation. She demonstrated a good response to anaplastic lymphoma kinase inhibitors therapy with stable disease status for more than six months. This case report shows clinical efficacy of anaplastic lymphoma kinase inhibitor in a patient with stage IVC anaplastic thyroid carcinoma with positive anaplastic lymphoma kinase mutation.

Keywords: Anaplastic Thyroid Carcinoma, ALK Inhibitor, Ceritinib, Alectinib, Tyrosine Kinase Inhibitor.

INTRODUCTION

Anaplastic Thyroid Carcinoma (ATC) is an aggressive cancer with median survival time of four months and a six-months overall survival of 35%. [1] All patients are stage IV according to the American Joint Committee on Cancer (AJCC) tumour, nodes, and metastases (TNM) staging system; stage IVA if the lesion is restricted to the thyroid gland; stage IVB with loco-regional lymph nodes involvement and stage IVC if there is distant metastasis. [2]

Up till now, there is no established optimal treatment for ATC. [3,4] Cytotoxic drugs alone for advanced ATC are poorly effective. Given the scarcity of established evidence in the management stage IV ATC, identifying actionable mutations is becoming more critical for this lethal disease. Targeted biological agents could be a viable therapeutic option, especially the tyrosine kinase inhibitors.[4]

We report a case of a 44-year-old woman who was diagnosed with stage IVC

Corresponding author: Nur Fa'izah Ab Muin, Oncology & Radiotherapy Department, Pusat Perubatan Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur.
Tel : +60128388054;
Email : faizah.muin@ummc.edu.my

ATC with positive anaplastic lymphoma kinase -echinoderm microtubule-associated protein-like-4 mutation, who responded well to a course of anaplastic lymphoma kinase inhibitors therapy with stable disease status for total of more than six months.

CASE REPORT

The patient was a 44-years-old Chinese woman who presented with the left neck swelling for two months that had progressed rapidly to involve both sides of her neck and her left axilla. She subsequently developed an episode of seizure which led to her admission and further investigations.

The computed tomography (CT) scan of the brain showed a focal enhancing brain lesion at the left frontal lobe measuring 25x18mm. The positron emission tomography (PET) scan demonstrated metabolic active diseases at the thyroid gland, left frontal lobe of cerebrum, left lower lobe of lung and multiple nodal metastasis. (Figure 1 & 2)

The histopathology of the right cervical lymph node biopsy showed metastatic carcinoma. Immunohistochemistry staining were positive for thyroid transcription factor-1 (TTF-1), p40, p63, and thyroglobulin but were negative for CD30, Napsin A, B-cell lymphoma-2 (BCL-2) and Epstein Barr virus-latent membrane protein-1 (EBV-LMP-1). Based on all the findings stage IVC ATC was diagnosed.

The patient underwent an urgent stereotactic radiosurgery to remove the brain lesion. An extended next generation sequencing panel showed positive result for anaplastic lymphoma kinase-echinoderm microtubule -associated protein-like-4 (ALK-EML4) mutation. She was started on 250mg twice a day (BD) of crizotinib, a first generation ALK-inhibitor, which led to a positive reduction in the size of the cervical lymph node swelling.

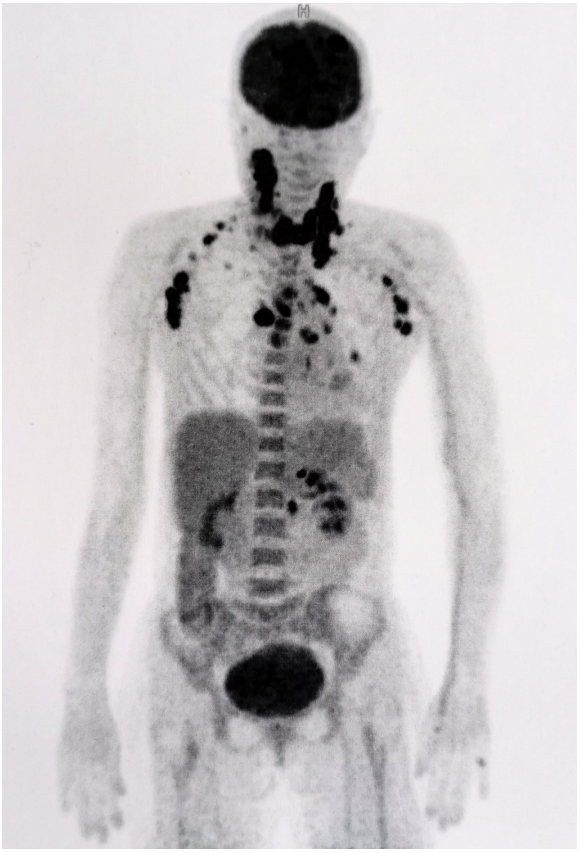

Figure 1: PET scan at diagnosis showing the extent of the disease. (Click to enlarge)

However, she unfortunately developed crizotinib-induced interstitial pneumonitis and as a result, the treatment was stopped.

She was then started on a second generation ALK-inhibitor, ceritinib, on the 9th November 2018. The cervical lymph node swelling became noticeably smaller after fourteen days. Her condition remained stable during the subsequent clinics follow-up.

A scheduled CT scan was performed at six months post-treatment which showed a new metastatic nodule (1.4cm) at right lower lobe of the lung with stable disease elsewhere (Figure 3). She had a radiofrequency ablation (RFA) to the right lower lung nodule, and ceritinib was subsequently switched to the third generation ALK-inhibitor alectinib at eight months post-treatment. The disease subsequently remained stable on alectinib for approximately four months. In April 2021,

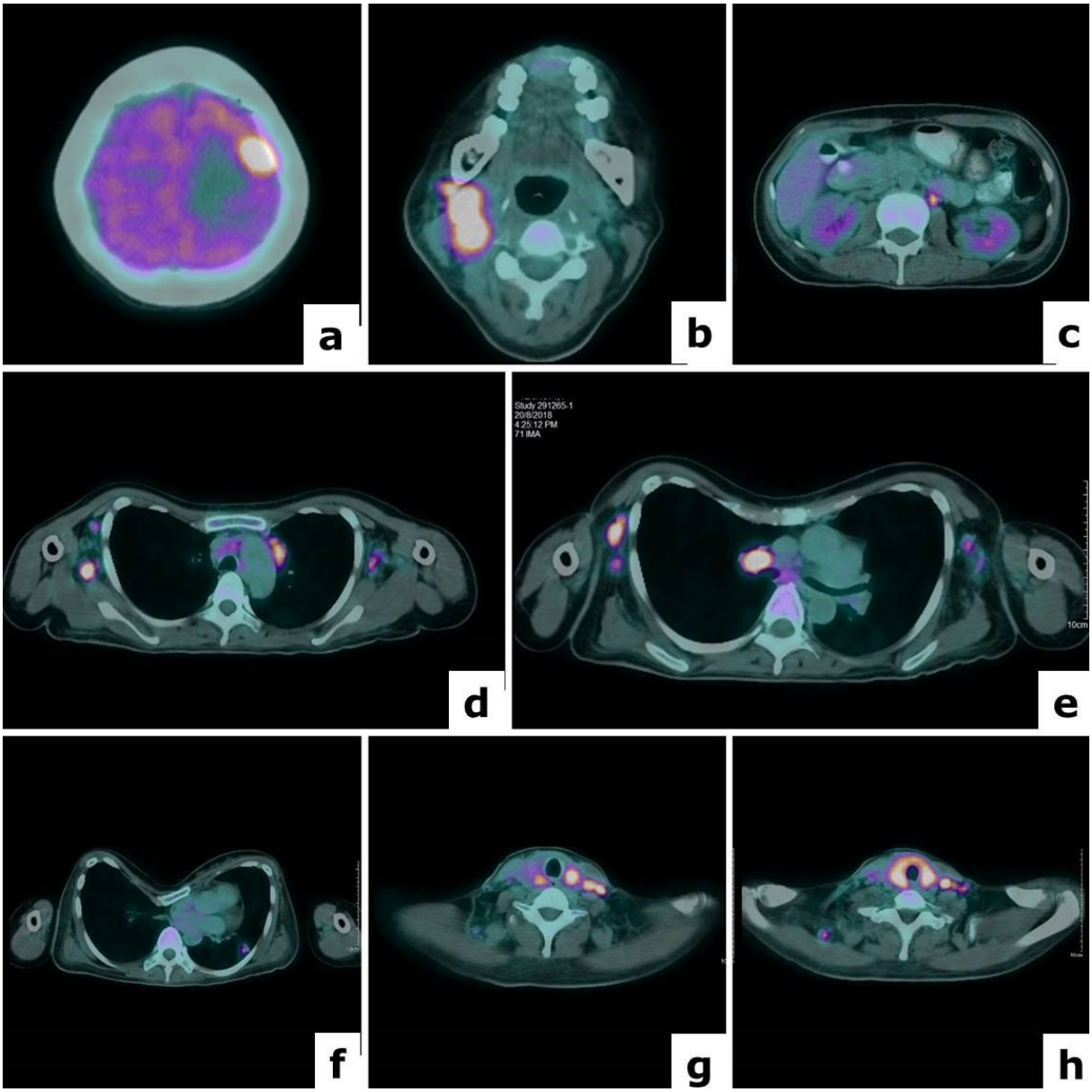

Figure 2: PET/CT showing uptake at (a)Left frontal lobe of cerebrum (b) Cervical nodes (c) Abdominal para-aortic node. (d) Mediastinal and bilateral axillary nodes (e) Hilar node (f) Left lower lobe of lung nodule (g) Bilateral cervical nodes (h) Thyroid gland. (Click to enlarge)

her treatment was switched to lorlatinib and the recent repeat CT brain/thorax/abdomen/pelvis scan showed new but small left adrenal metastasis measuring 1.5x1.0 cm but there was no recurrence elsewhere. She remains well with stable disease till today.

DISCUSSION

ATC is an undifferentiated tumour and lethal. Current conventional treatment has not shown clear therapeutic efficacy in prolonging survival in patients with stage IV metastatic ATC. There is growing interest in the new molecular targeted therapies, which may provide a better outlook in terms of overall survival time.

Several mutations have been identified in ATC with variable frequencies. Tumour protein p53 (TP53) mutations are the most common mutations found whereas v-raf murine sarcoma viral oncogene homolog B1 (BRAF), rat sarcoma (RAS) and phosphatidyl-

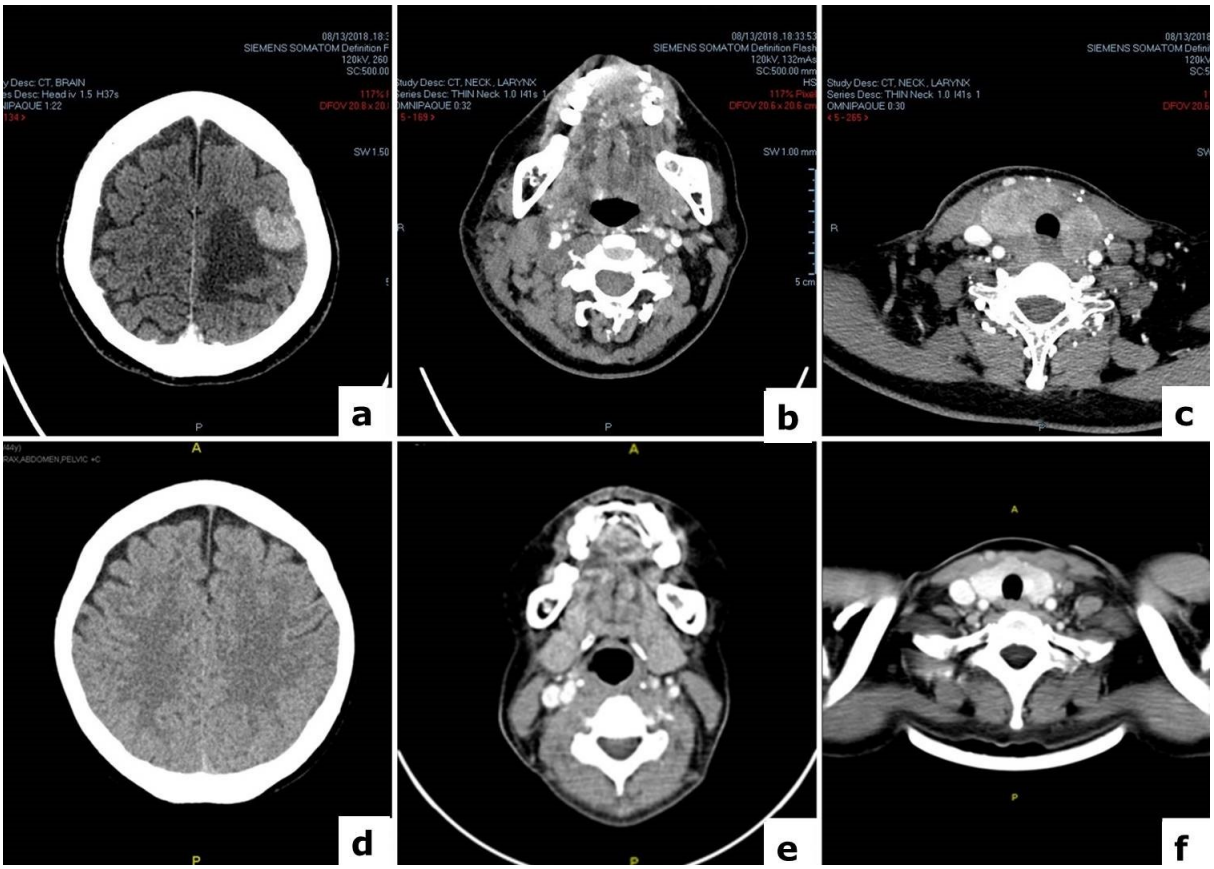

Figure 3: Contrast enhanced CT images comparing lesions at diagnosis (a-c) and at six months post ceritinib (d-f) showing (a) Left frontal lobe lesion (b) Right cervical lymph nodes (c) Enlarged thyroid gland which have regressed significantly post treatment (d-f). (Click to enlarge)

inositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations are seen in 25%, 28% and 13% of these tumours, respectively.[5]

For BRAF mutated ATC, US Food and Drug Administration has approved the combination of dabrafenib (a BRAF V600E inhibitor) and trametinib (a mitogen-activated protein kinase 1/2 (MEK1/2) inhibitor) on 4th May 2018 based on a multi-centre phase II trial.[6] It is approved for patients with BRAF V600E mutated ATC that is locally advanced, unresectable, or metastatic with no loco-regional treatment options.

ALK mutation is even rarer in ATC (4%) but there was a case report that demonstrated 90% shrinkage of targeted lesions that was sustained at six months follow-up, in a 71-year-old patient with stage IVC ATC that harboured an ALK mutation.[5,7] There is also an ongoing phase II clinical trial evaluating ALK-inhibitor ceritinib in ATC patients with ALK mutations (NCT02289144).

In the present case, the patient presented with stage IVC ATC and was symptomatic with limited site of brain metastasis. Therefore, she was first treated for the brain metastasis with stereotactic radiosurgery. Total resection of thyroid lesion was not performed given the distant metastasis and it was thought that the systemic therapy was the best strategy. The patient had a rather long and durable response to sequential ALK-inhibitors with approximately six months disease control with ceritinib and, subsequently remained in stable disease with the alectinib for four months.

CONCLUSION

This case report shows clinical efficacy of ALK inhibitor in a patient with stage IVC ATC with ALK mutation. This could add to the growing evidence of the efficacy of this agent and hopefully a definitive result of its efficacy will be validated in a larger randomised prospective trial soon.

CONFLICT OF INTEREST

The author reported no conflict of interest or financial liability.

INFORMED CONSENT

Informed consent has been obtained from the patient in regards to the pictures and details included in this report.

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