CASE REPORT

Uncommon response of cisplatin and etoposide for treatment of advanced medullary thyroid carcinoma

Nathamon Panomuppakarn1, Patamintita Witoonpanich2, Jariya Waisayaratt3, Chuleeporn Jiarpinitnun2, Touch Ativitava1 & Nuttapong Ngamphaiboon1

1Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
2Division of Radiation Oncology, Department of Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
3Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Correspondence
Nuttapong Ngamphaiboon, Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok, 10400, Thailand.
Tel: +66-2-201-1671;
Fax: +66-2-643-5648;
E-mail: Nuttapong.nga@mahidol.ac.th

Funding Information
No sources of funding were declared for this study.

Received: 22 May 2017; Revised: 7 July 2017; Accepted: 18 July 2017

Clinical Case Reports 2017; 5(10): 1628–1633
doi: 10.1002/ccr3.1123

Introduction

Medullary thyroid carcinoma (MTC) is a well-differentiated thyroid cancer, which originates from the neuroendocrine parafollicular cells (C cells) [1]. Total thyroidectomy with central and bilateral functional neck dissection is recommended as a standard of care for resectable MTC [2]. Despite adequate surgical resection, only 43% of patients attained normal biochemistry, defined by normalization of serum calcitonin and CEA [3]. Although radioactive iodine (RAI) is an effective treatment for differentiated thyroid cancer, RAI is ineffective for MTC as C cells do not accumulate iodine [4]. External-beam radiotherapy (EBRT) may be of use in locoregional control after surgical resection for high-risk patients [4]. Metastatic or recurrent disease in patients who are not suitable for further surgical operations eventually requires systemic therapy with palliative intent. Systemic treatment of MTC is currently limited to the use of a tyrosine kinase inhibitor (TKI) which had resulted in various response rates (RR) of 28–45% and progression-free survival (PFS) ranging between 11.2 and 30.5 months [5–10]. Several studies investigating the combination of cytotoxic chemotherapy for unresectable and/or metastatic MTC did not demonstrate any significant clinical benefits [4, 11–14]. Therefore, cytotoxic chemotherapy is not routinely recommended for advanced MTC in the earlier lines of treatment due to the lack of efficacy. In this report, we describe a patient with locally advanced MTC who had an uncommon response to cisplatin and etoposide.

Case

A 52-year-old man presenting with an enlarged left neck mass, which had been rapidly growing for 2 months (March 2014). He denied any history of malignancy in the family. Physical examination showed several matted enlarged left cervical lymphadenopathy at levels II-V, measuring about 6 x 6 cm and 7 x 8 cm, respectively.
Left thyroid nodule (3 × 3 cm) was also palpated. Other physical examinations were unremarkable. Computed tomography (CT) scan demonstrated multiple enlarged and matted lymph nodes (LN) with various sizes along the left cervical levels II-V, left supraclavicular region and left superior mediastinum, measuring about 1.3–5.8 cm. These enlarged LN partially encased the left common carotid artery. Multiple hypoechoic nodules were also found scattering in both lobes of thyroid gland, ranging between 0.5 and 2.9 cm, with the largest nodule containing cystic component situating at the lower pole of the left lobe (Fig. 1A and B). Panendoscopy was also performed but yielded unremarkable results and multiple random negative biopsies. Fine-needle aspiration (FNA) of the left thyroid nodule revealed nodular goiter, with no malignant changes detected. Left cervical LN FNA showed metastatic carcinoma, which was suspicious for neuroendocrine carcinoma. Incisional biopsy of the left cervical LN demonstrated metastatic carcinoma with suspicious neuroendocrine feature. Immunohistochemical analysis revealed that the tumor cells expressed chromogranin A, CD56, CK7, and TTF-1. No expression of CK20, p63, CK5/6, and synaptophysin was observed. Ki-67 labeling index was 10%. These findings were consistent with metastatic neuroendocrine carcinoma of unknown primary.

The patient was then started on cisplatin (75 mg/m² day 1) and etoposide (100 mg/m² day 1–3) every 3 weeks. After the 1st cycle, he had a dramatic response and achieved partial clinical response of the left cervical LN. He subsequently completed three cycles of cisplatin and etoposide. Following the chemotherapy, the MRI scan of the head and neck revealed markedly decrease in size of the left cervical and supraclavicular LN, with multiple stable thyroid nodules (Fig. 1C and D).

In September 2014, he underwent left modified radical neck dissection type III with left thyroid lobectomy. Pathology report of the left cervical LN showed metastatic MTC in 12 of 42 LN. A left thyroid lobectomy demonstrated MTC characterized by individual sheets, nests, trabeculae, and follicles of polygonal, round, spindle cells, separating by fibrous bands with variable degrees of amyloid deposition (Fig. 2A). Angiolymphatic invasion was identified. Scattered coarse calcifications

Figure 1. (A) Contrast CT scan of the neck; multiple hypoechoic nodules in both lobes of thyroid gland, with the largest nodules containing cystic component at lower pole of the left lobe (red arrow). (B) Multiple enlarged/matted lymph nodes (white arrow) of various sizes occupying along the left cervical level II-V, left supraclavicular region and left-sided superior mediastinum. (C) Postgadolinium axial T1FS after three-cycle chemotherapy; no significant change of thyroid nodules, the largest node at lower pole of the left lobe (red arrow) but (D) decreased size of the multiple enlarged matted lymph nodes (white arrow) along the left neck.
were also present. The tumor cells contained granular cytoplasm and uniform round/oval nuclei with punctate chromatin (Fig. 2B). Immunohistochemistry (IHC) stains confirmed the expression of calcitonin in tumor cells (Fig. 2C). Serum calcitonin postoperatively was undetectable. After a final diagnosis of MTC was confirmed, the patient underwent complete thyroidectomy with right modified radical neck dissection type III and central neck dissection. Pathology report showed no residual MTC in both thyroid and right cervical LNs seen. He remained in remission with disease-free interval for 13 months.

In November 2015, he had a recurrence of enlarged left cervical LNs level IV and supraclavicular lymphadenopathy (Fig. 3A and B). Serum calcitonin and CEA were also elevated (Fig. 4). FNA confirmed neoplastic cells with neuroendocrine feature. He achieved partial response with three cycles of cisplatin and etoposide and subsequently underwent salvage surgery of the left cervical lymphadenopathy (Fig. 3C and D). Pathology revealed

Figure 2. (A) Hematoxylin and eosin, 4X: Microscopic appearance of MTC. (B) Hematoxylin and eosin, 20X: Tumor cells show granular cytoplasm and uniform round/oval nuclei with punctate chromatin. (C) Immunohistochemistry stain, 4X: Diffuse and strong expression of calcitonin in tumor cells.

Figure 3. (A–B) Postcontrast CT scan with enlarged lymphadenopathy (white arrow) occupying along the left cervical level IV and left supraclavicular region. (C–D) After three cycles of cisplatin and etoposide, postgadolinium axial and coronal T1FS shows further decreased size of the enhancing lymphadenopathy (white arrow).
metastatic carcinoma with neuroendocrine feature (IHC: calcitonin-, chromogranin-, synaptophysin+), consistent with MTC. Postoperative radiation with a dose of 7000 cGy was given for 35 fractions. After treatment, he remained disease free with normalized serum CEA and undetectable calcitonin until the last follow-up on November 2016.

Discussion

Medullary thyroid carcinoma is less often associated with hereditary multiple endocrine neoplasia (MEN) type 2 syndromes (MEN2A and MEN2B), with the majority of MTC cases (approximately 75%) being sporadic [10]. RET proto-oncogene is the dominant oncogene in MTC. Activating germ line mutations of the RET proto-oncogene is associated with almost all patients with MEN2A and MEN2B. In sporadic MTC, somatic RET mutations are the most common driver in genetic alterations, followed by RAS mutations and RET or ALK fusions [10]. In addition, angiogenesis plays a significant role in tumor growth, proliferation and metastasis [4]. Thus, several tyrosine kinase inhibitors (TKIs) targeting RET and vascular endothelial growth factor (VEGF) pathways were evaluated in clinical studies, which led to the US FDA approval of vandetanib and cabozantinib for recurrent/metastatic MTC [10]. Vandetanib and cabozantinib significantly improved PFS from 19.3 to 30.5 months (HR 0.59: 95% CI: 0.31–0.69; P < 0.001), and 4.0–11.2 months (HR 0.28: 95% CI: 0.19–0.40; P < 0.001), respectively, when compared with a placebo [5, 8]. Other TKIs such as sorafenib and lenvatinib also demonstrated clinical activity in recurrent/metastatic MTC patients [6, 9].

Prior to the era of targeted therapy, cytotoxic chemotherapy was used for metastatic MTC in a palliative setting with limited antitumor activity [4]. Doxorubicin-based chemotherapy and dacarbazine-based chemotherapy were the most extensively studied regimens. In a small subset of prospective phase II study of doxorubicin for advanced thyroid cancer, 10 patients with MTC were treated with doxorubicin with or without cisplatin [11]. Three patients demonstrated partial response (PR). Another small phase II study of doxorubicin in combination with cisplatin and vincristine demonstrated PR in only one of 10 metastatic MTC patients [12].

Dacarbazine is an alkylating agent, which was evaluated in combination with cyclophosphamide and vincristine for treatment of advanced MTC [13]. Two of seven patients achieved PR and biochemical response for 14 and 29 months. In addition, combination of dacarbazine and 5-fluorouracil demonstrated PR in three of five metastatic MTC patients and lasted for 8–10 months [14]. Recently, a good response from a combination of capecitabine and temozolomide was reported in metastatic MTC patient, based on the efficacy of the combination of dacarbazine and 5-fluorouracil [15] Temozolomide and dacarbazine are prodrugs of the active alkylating agent 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide, which could be used alternatively. Similarly, capecitabine is a prodrug of 5-fluorouracil.
Here, we described an uncommon response to the combination of cisplatin and etoposide in advanced MTC patient, who was initially misdiagnosed as a neuroendocrine tumor (NET) of unknown primary. Cisplatin (75 mg/m² Day 1) and etoposide (100 mg/m² Day 1–3) regimens are routinely used as a standard treatment for advanced high-grade gastrointestinal NET and small-cell lung cancer (SCLC) [16]. Although MTC is considered as a neuroendocrine tumor of thyroid arising from C cells, the standard treatment of MTC is different from other NETs [10, 16]. NETs generally cover heterogeneous subtypes of tumor with a wide range of clinical behavior and genetic alterations [16]. Histopathological classification separates well-differentiated (grade 1/2) versus poorly differentiated NET to guide physicians for treatment selection. Well-differentiated NET may respond to targeted therapies involving the VEGF and mTOR pathways, whereas platinum-based chemotherapy is the mainstay treatment for poorly differentiated NET [16]. In this particular case, the patient presented with rapidly progressive bulky lymphadenopathy, which behaved like poorly differentiated NET or SCLC. We speculated that the response to chemotherapy in this case might be related to poorly differentiated NET component of the tumor. To our knowledge, this is the first report of clinical activity of the combination of cisplatin and etoposide in advanced MTC patient. As MTC is considered as a NET of thyroid, using platinum-based chemotherapy regimens for poorly differentiated NET might be of benefit for selected advanced MTC patients who failed standard targeted therapies.

Conclusion

In the current era of targeted therapy, uncommon response to cisplatin and etoposide as treatment for advanced MTC was observed in this report. Therefore, the benefits of platinum-based chemotherapy regimens used for poorly differentiated NETs or SCLC should be further explored in selected advanced MTC patients who had failed standard targeted therapy.

Acknowledgment

The authors would like to thank Tanapon Boonchuaysream for English editing and grammatical corrections. NN acknowledges the Talent Management Program, Mahidol University, and the Ramathibodi Grant for Research Development, Ramathibodi Hospital.

Authorship

NP: drafted the manuscript. PW and JW: provided imaging and edited and approved the manuscript. CJ: edited and approved the manuscript. TA: approved the manuscript. NN: edited and finally approved the manuscript.

Conflict of Interest

All authors declare no conflict of interest.

References

1. Wolfe, H. J., K. E. Melvin, S. J. Cervi-Skinner, A. A. Saadi, J. F. Juliar, C. E. Jackson, et al. 1973. C-cell hyperplasia preceding medullary thyroid carcinoma. N. Engl. J. Med. 289:437–441.
2. Moley, J. F., and M. K. DelBenedetti. 1999. Patterns of nodal metastases in palpable medullary thyroid carcinoma: recommendations for extent of node dissection. Ann. Surg. 229:880–887; discussion 887–888.
3. Modigliani, E., R. Cohen, J. M. Campos, et al. 1998. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: results in 899 patients. The GETC Study Group. Groupe d’etude des tumeurs a calcitonine. Clin. Endocrinol. (Oxf) 48:265–273.
4. Maxwell, J. E., S. K. Sherman, T. M. O’Dorisio, and J. R. Howe. 2014. Medical management of metastatic medullary thyroid cancer. Cancer 120:3287–3301.
5. Wells, S. A. Jr, B. G. Robinson, R. F. Gagel, et al. 2012. Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. J. Clin. Oncol. 30:134–141.
6. Brose, M. S., C. M. Nutting, S. I. Sherman, et al. 2011. Rationale and design of decision: a double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory differentiated thyroid cancer. BMC Cancer 11:349.
7. Sherman, S. L., D. O. Clary, R. Elisei, et al. 2016. Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib in patients with progressive, metastatic medullary thyroid cancer. Cancer 24:3856–3864.
8. Elisei, R., M. J. Schlumberger, S. P. Muller, et al. 2013. Cabozantinib in progressive medullary thyroid cancer. J. Clin. Oncol. 31:3639–3646.
9. Schlumberger, M., B. Jarzab, M. E. Cabanillas, et al. 2016. A phase II trial of the multitargeted tyrosine kinase inhibitor lenvatinib (E7080) in advanced medullary thyroid cancer. Clin. Cancer Res. 22:44–53.
10. Fagin, J. A., and S. A. Jr Wells. 2016. Biologic and clinical perspectives on thyroid cancer. N. Engl. J. Med. 375:1054–1067.
11. Shimaoka, K., D. A. Schoenfeld, W. D. DeWys, et al. 1985. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 56:2155–2160.
12. Scherubl, H., F. Raue, and R. Ziegler. 1990. Combination chemotherapy of advanced medullary and differentiated thyroid cancer. Phase II study. J. Cancer Res. Clin. Oncol. 116:21–23.
13. Wu, L. T., S. D. Averbuch, D. W. Ball, et al. 1994. Treatment of advanced medullary thyroid carcinoma with a combination of cyclophosphamide, vincristine, and dacarbazine. Cancer 73:432–436.
14. Orlandi, F., P. Caraci, A. Berruti, et al. 1994. Chemotherapy with dacarbazine and 5-fluorouracil in advanced medullary thyroid cancer. Ann. Oncol. 5:763–765.
15. Lacin, S., E. Esin, Y. Karakas, and S. Yalcin. 2015. Metastatic medullary thyroid cancer: a dramatic response to a systemic chemotherapy (temozolomide and capecitabine) regimen. Onco. Targets Ther. 8:1039–1042.
16. Bergsland, E. K. 2013. The evolving landscape of neuroendocrine tumors. Semin. Oncol. 40:4–22.