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Case Report

Lenvatinib Administration for Anaplastic Thyroid Carcinoma with Brain Metastasis

Atsuto Obayashi[a], Kazuma Aoki[a], Tadayoshi Wada[a], Hiromi Furuie[a], Kazuya Kuraoka[b], Takao Hamamoto[c]*, and Takaharu Tatsukawa[a]

Departments of [a]Otorhinolaryngology, [b]Diagnostic Pathology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, kure, Hiroshima 737-0023, Japan, [c]Department of Otorhinolaryngology, Head and Neck Surgery, Hiroshima University Hospital, Hiroshima 734-8551, Japan

We describe the use of the tyrosine kinase inhibitor lenvatinib in a patient with brain tumor metastases from anaplastic thyroid carcinoma (ATC). A 52-year-old Japanese male presented with consciousness loss. Imaging revealed a thyroid tumor and multiple brain lesions. After the brain tumor's resection, pathology results provided the diagnosis of ATC. Total thyroidectomy was performed, followed by whole-brain irradiation. Additional brain lesions later developed, and lenvatinib therapy was initiated with no remarkable complications. However, the treatment effects were limited, and the patient died 2 months after starting lenvatinib, 202 days after the initial brain surgery. Relevant literature is discussed.

Key words: anaplastic thyroid carcinoma, brain metastasis, lenvatinib

Anaplastic thyroid carcinoma (ATC), which accounts for 1-2% of all malignant thyroid tumors, is a highly aggressive tumor with a 1-year survival rate of 5-20% [1]. Although multimodal therapies have been introduced including radical surgery, radiotherapy, and chemotherapy, the survival times remain poor [2,3]. Clinically apparent brain metastases at presentation are relatively unusual in ATC, occurring in 1-5% of patients [4-6]. Lenvatinib, a new molecular-targeted anticancer drug, is a multi-targeted receptor tyrosine kinase inhibitor (TKI) approved by Japan's regulatory agency for the treatment of thyroid cancer, including ATC.

TKIs inhibit the activity of vascular endothelial growth factor (VEGF) receptors, fibroblast growth factor (FGF) receptors, platelet-derived growth factor (PDGF) receptors, and KIT and RET proteins. Although TKIs are associated with an increased risk of bleeding into brain metastases, we elected to use this therapy in patient with a a metastatic brain tumor of ATC that was not responding to initial treatment. We describe the rare clinical course of this patient, who was treated with multimodal therapy. We also briefly present findings from the relevant literature.

Case Report

A 52-year-old Japanese man with no previous diseases or allergies collapsed from loss of consciousness and was rushed to a nearby emergency hospital. After arrival, he regained consciousness without any cerebral neurological symptoms. Computed tomography (CT) was performed, and it revealed multiple low-density lesions in the patient's brain and a single thyroid tumor (Fig. 1A). The patient was referred to our institution for

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*Corresponding author. Phone: +81-82-257-5252; Fax: +81-82-257-5254
E-mail: takao0320@hiroshima-u.ac.jp (T. Hamamoto)

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further examination and treatment.

Cervical ultrasound revealed an irregularly-shaped, internally coarse mass formation in the right thyroid lobe (18×10×12 mm) without any lymph-node swelling, and fine-needle aspiration of the thyroid mass was suggestive of malignancy. Enhanced magnetic resonance imaging (MRI) demonstrated multiple ring-enhanced brain tumors (Fig. 1C, D), and positron emission tomography revealed local accumulation in the thyroid gland without accumulation in any cervical lymph nodes (Fig. 1B). No abnormal findings were detected in the patient's blood or by biochemical tests, including thyroid-related results.

Since the thyroid tumor was relatively small and did not appear to be a primary tumor that would result in brain metastasis, we decided to first remove the brain tumor from the right frontal lobe for both treatment and diagnosis. Postoperative pathological findings revealed that the tumor was a metastatic ATC brain tumor (Fig. 2A, B). At the time of surgery, the primary thyroid gland exhibited minimal change, and the progression of the remaining brain lesions was considered life-threatening; we therefore elected to prioritize whole-brain irradiation (total: 37.5, 2.5 Gy, 15 times). Post-radiation CT exhibited no significant change in the primary thyroid gland, and approx. 2 months after the patient's initial visit, a total thyroidectomy and bilateral neck dissection were performed. The pathological diagnosis was ATC (pT3bN0), and the surgical margin was negative (Fig. 2C, D).

At 2 weeks after the patient's thyroid surgery, brain MRI revealed no apparent recurrence in the resected area and no remarkable change in the cerebellar lesion; however, small new brain tumor lesions were observed (Fig. 3). As the risk of tumor hemorrhage was assumed to be low due to the small size of the lesions, and since no other appropriate treatment appeared effective, we initiated lenvatinib treatment (24 mg) with the consent of the patient and his family.

One month after the initiation of lenvatinib therapy, muscle weakness in the left upper and lower extremities began to develop. MRI revealed that the previous small

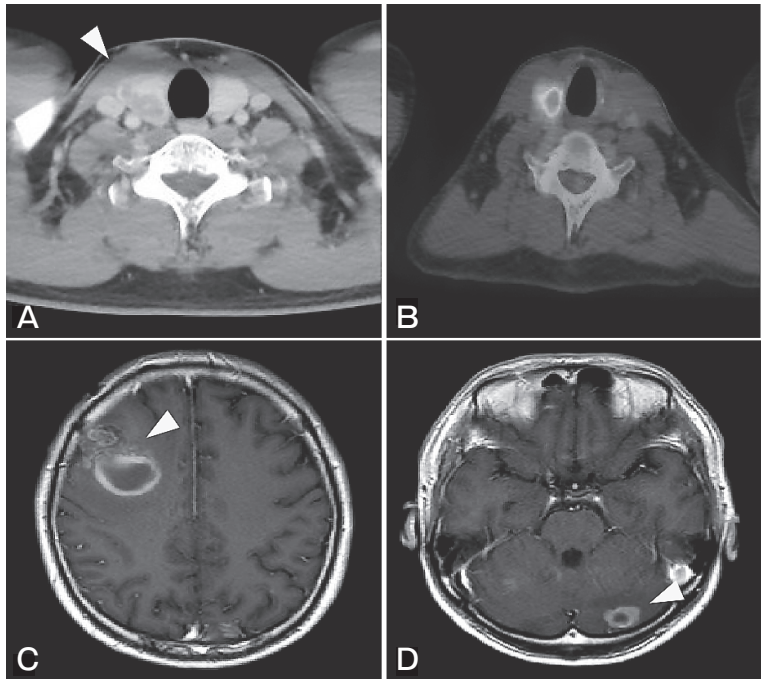

Fig. 1 Image findings at the initial examination of the patient, a 52-year-old male. **A**, Enhanced CT revealed a low-density area with indistinct borders in the right thyroid lobe (*arrowhead*); **B**, PET-CT revealed high accumulation in the right thyroid lobe without accumulation in any cervical lymph nodes; **C**, MRI (enhanced T1) detected a tumor exhibiting a ring-enhanced effect with partial hematoma change in the right frontal lobe (*arrowhead*); **D**, Mass shadows exhibiting a ring-enhanced effect in the cerebellar (*arrowhead*) were observed.

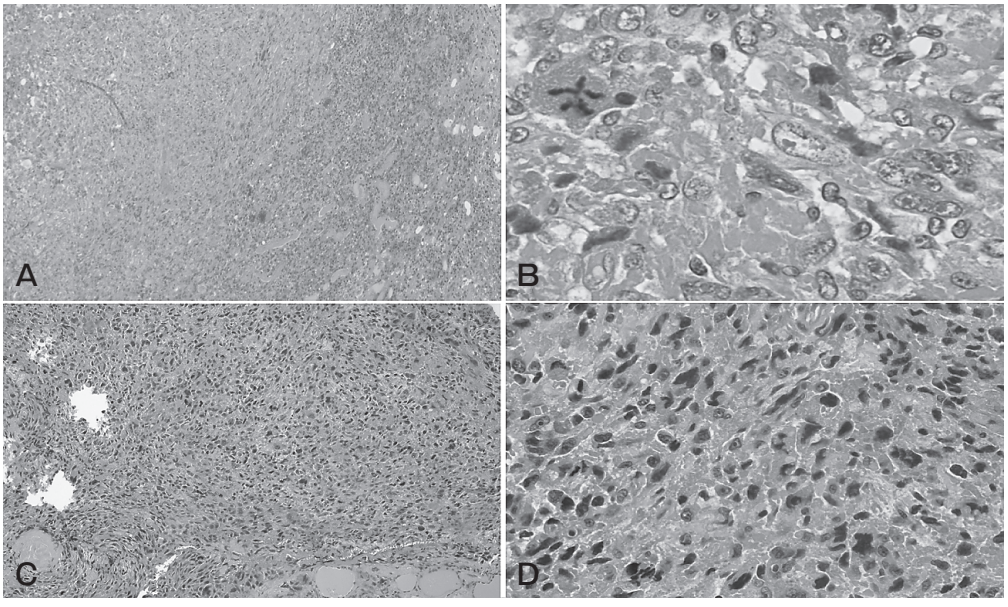

Fig. 2 Pathological thyroid findings (H&E staining) of (**A**, **B**) the brain tumor and (**C**, **D**) the thyroid tumor. **A**, Low-power view; **B**, High-power view: A dense growth of spindle-shaped or polymorphous tumor cells with hemorrhage and necrosis was observed in certain areas. Immunostaining demonstrated that CK, GFAP, vimentin, and S100a were partially positive, while EMA, PAX8, HMB45, Melan A, p63, and LCA were negative; **C**, Low-power view; **D**, High-power view: Hyperplasia of tumor cells with large polygonal or spindle-shaped atypical nuclei and broad acidophilic endoplasmic reticulum was observed in the thyroid gland. Diffuse infiltration was observed between thyroid follicles. Abnormal fission was observed in scattered areas.

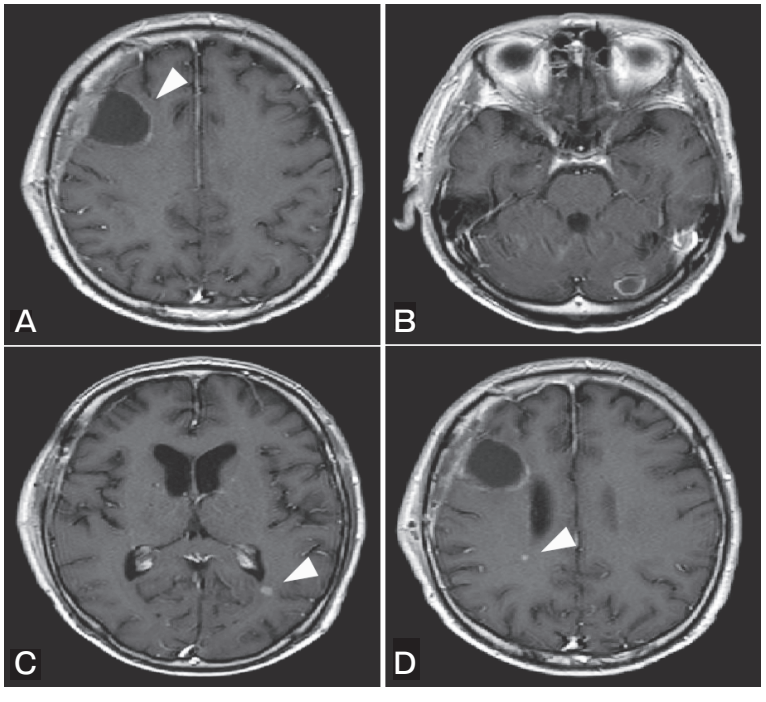

Fig. 3 MRI (enhanced T1) findings after the patient had undergone whole-brain irradiation and thyroidectomy. **A**, No apparent recurrence in the resected area of the frontal lobe (*arrowhead*); **B**, The cerebellar lesion showing no remarkable change (*arrowhead*); **C**, **D**, Small new lesions appeared (*arrowhead*).

new lesions had almost disappeared; however, a new lesion in the occipital lobe and multiple edematous changes were detected with enhancement (Fig. 4). During the same period, symptoms such as progressive paralysis, decreased oral intake, increased headache, and decreased level of consciousness also gradually appeared, which were attributed to an exacerbation of the brain metastasis. As the patient's general condition deteriorated, a palliative care response was elected based on the desires of the patient and his family. The patient died 2 months after the initial administration of lenvatinib, 202 days after the initial brain surgery.

Discussion

ATC is one of the most malignant solid tumors diagnosed in humans, and its prognosis is so poor that no effective treatment strategy is available. The estimated median time interval from the diagnosis of ATC to the diagnosis of brain metastasis is 0.7 years, with 1.3 months as the median interval from the diagnosis of brain lesions to death; disease-specific mortality is reportedly 100% [6]. In our present patient's case, metastatic brain tumors were detected after a thorough examination for the cause of his loss of consciousness, and a thyroid tumor was simultaneously discovered. As the thyroid tumor was small, had no cervical lymph-node metastases, and did not appear to be a lesion that could result in brain metastasis, a resection of the metastatic brain tumors was initially performed. Although the pathological findings of the excised specimen led to a diagnosis of brain metastasis of ATC, the postoperative imaging revealed no change in the thyroid lesion; therefore, whole-brain irradiation was performed prior to additional surgery to address the concerns regarding the residual brain lesions. The imaging re-evaluation after the patient's whole-brain irradiation again showed no significant change in the thyroid lesion. A planned total thyroidectomy was performed, and the histopathological diagnosis of the thyroid tumor remained that of ATC.

Salvati *et al.* reported solitary brain metastasis in five patients with ATC, all of whom were treated with surgical removal and postoperative radiotherapy [5]. Their

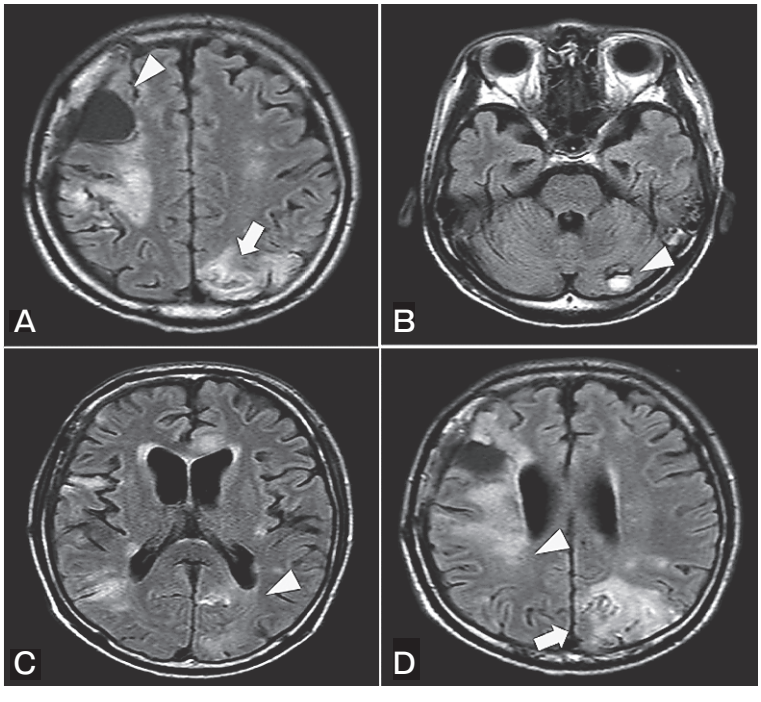

Fig. 4 MRI (FLAIR long TR) findings after lenvatinib initiation. **A**, No apparent recurrence in the resected area of the frontal lobe (*arrowhead*), but new lesions appeared in the occipital lobe (*arrow*); **B**, The cerebellar lesion showing no remarkable change (*arrowhead*); **C**, **D**, The small new lesions had almost disappeared (*arrowheads*), but multiple edematous changes appeared as a result of increased brain metastases (*arrow*).

study showed a statistically significant improvement in survival among patients with ATC who underwent the gross total removal of brain metastasis compared to patients who underwent a subtotal removal. Chiu *et al.* suggested the surgical resection of brain metastases in differentiated carcinoma [6]. However, they implied that there were insufficient data for making recommendations for or against radiotherapy versus surgical resection in ATC patients with brain metastases. The 2021 American Thyroid Association Guidelines for ATC suggest that a careful decision is required for ATC patients with brain metastases regarding whether to select aggressive treatment or palliative care with a consideration of the patient's goals [7].

Regarding systemic chemotherapy for ATC, there has been a transition from traditional chemotherapy to molecular-targeted therapy [8]. In 2014, phase III clinical trials demonstrated the effectiveness of multi-targeted tyrosine kinase inhibitors (TKIs) in thyroid cancer [9, 10]. Additionally, a phase II clinical trial of lenvatinib in Japan demonstrated the effect of TKIs on ATC [11]. In our patient's case, lenvatinib was selected as additional treatment because the regrowth of brain metastatic lesions appeared early after the total thyroidectomy. Although there is no published evidence that systemic therapy is effective in treating brain metastasis of ATC, there are some case reports of its efficacy in brain metastasis of differentiated thyroid cancer (DTC) without adverse events, such as brain hemorrhages [12, 13]. In a brain metastasis-mimicking model, Rong *et al.* demonstrated that lenvatinib suppressed ATC tumor growth via the inhibition of angiogenesis, which attests to the ability of lenvatinib to cross the blood-brain barrier [14].

In a study of 594 patients with unresectable thyroid cancer treated with lenvatinib, Takahashi *et al.* reported that 1.6% of DTC cases and 8.1% of ATC cases showed carotid artery hemorrhage, venous hemorrhage, or tumor hemorrhage associated with tumor shrinkage or necrosis [15]. Because the vaso-inhibitory effects of TKIs are associated with the risk of bleeding and vascular disruption due to local tumor disruption, the lenvatinib package insert states that TKIs should be administered with caution to patients with brain or liver metastases or lesions suspected to invade large blood vessels [16, 17].

Few studies have described the use of TKIs for ATC brain metastases, and reports concerning the treatment efficacy of TKIs and the risk of adverse events in such cases remain limited. However, reports on intratumoral hemorrhage and metastatic brain lesion bleeding in renal and liver cancers, where TKI use is also indicated, have been reviewed. A recent network meta-analysis revealed that neither lenvatinib nor sorafenib were associated with an increased bleeding incidence in patients with cancer [18]. Pang *et al.* reported that the bleeding rates in patients with hepatocellular carcinoma who never received TKIs and those who were taking TKIs were 70% and 61.5%, respectively, and they concluded that TKI use in patients with brain metastasis was a safe strategy [19].

The efficacy of systemic therapy for ATC brain metastases and the risk of tumor hemorrhage have not been fully documented. The present report is the first to describe the feasibility of lenvatinib therapy for ATC brain metastases without any complications. Since ATC is a tumor with a poor prognosis, even with multimodal treatment, it would be inappropriate to disregard possible treatment options because of concerns about complications. Although the present case did not demonstrate lenvatinib's efficacy, we hope that additional cases describing aggressive treatments of ATC with brain metastasis will generate evidence for new therapies.

Conclusion

We have described the case of a patient with metastatic brain tumors from ATC treated with lenvatinib. As there are few reports about the use of TKIs to treat brain metastases of ATC, further case studies are required to clarify the efficacy and risks of using TKIs for brain metastases.

References

1. Ferrari SM, Elia G, Ragusa F, Ruffilli I, La Motta C, Paparo SR, Patrizio A, Vita R, Benvenga S, Materazzi G, Fallahi P and Antonelli A: Novel treatments for anaplastic thyroid carcinoma. Gland Surg (2020) 9: S28–42.
2. Kebebew E, Greenspan FS, Clark OH, Woeber KA and McMillan A: Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer (2005) 103: 1330–1335.
3. Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A and Suzuki S: Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 667 patients. World J Surg (2012) 36: 1247–1254.
4. Venkatesh YS, Ordonez NG, Schultz PN, Hickey RC, Goepfert H

and Samaan NA: Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases. Cancer (1990) 66: 321–330.
5. Salvati M, Frati A, Rocchi G, Masciangelo R, Antonaci A, Gagliardi FM and Felfini R: Single brain metastasis from thyroid cancer: report of twelve cases and review of the literature. J Neurooncol (2001) 51: 33–40.
6. Chiu AC, Delpassand ES and Sherman SI: Prognosis and treatment of brain metastases in thyroid carcinoma. J Clin Endocrinol Metab (1997) 82: 3637–3642.
7. Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ Cristofano AD, Foote R, Giordano T, Kasperbauer J, Newbold K, Nikiforov Y, Randolph G, Rosenthal MS, Sawka AM, Shah M, Shaha A, Smallrigde R and Wong-Clark CK: 2021 American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid (2021) 31: 337–386.
8. Soares P, Lima J, Preto A, Castro P, Vinagre J, Celestino R, Vinagre J, Celestino R, Couto JP, Prazeres H, Eloy C, Maximo V and Sobrinho-Simoes M: Genetic alterations in poorly differentiated and undifferentiated thyroid carcinomas. Curr Genomics (2011) 12: 609–617.
9. Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, Bastholt L, Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman S, Smit JWA, Chung J, Kappeler C, Pena C, Molnar I, Schlumberger MJ and DECISION investigators: sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomized, double-blind, phase 3 trial. Lancet (2014) 384: 319–328.
10. Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, Heras N, Zhu J and Sherman SI: Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med (2015) 372: 621–630.
11. Takahashi S, Tahara M, Kiyota N, Yamazaki T, Chayahara N and Nakano K: Phase 2 study of lenvatinib, a multi-targeted tyrosine kinase inhibitor, in patients with all histologic subtypes of advanced thyroid cancer. Ann Oncol (2014) 25: iv343.
12. Yan Shen, Maomei Ruan, Quanyong Luo, Yongli Yu, Hankui Lu, Ruisen Zhu and Libo Chen: Brain metastasis from follicular thyroid carcinoma: treatment with sorafenib. Thyroid (2012) 22: 856–860.
13. Toshiro Shimo, Masayuki Tori, Kana Anno, Katsuhide Yoshidome, Hironao Yasuoka, Masahiko Tsujimoto, Ichiro Akiyama and Yoshiyuki Usui: A case report of long-term disease control by Sorafenib into brain metastases from thyroid papillary carcinoma. Official Journal of the Japan Association of Endocrine Surgeons and the Japanese Society of Thyroid Surgery (2018) 35: 219–222.
14. Wang R, Yamada T, Arai S, Fukuda K, Taniguchi H, Tanimoto A, Nishiyama A, Takeuchi S, Yamashita K, Ohtsubo K, Matsui J, Onoda N, Hirata E, Taira S and Yano S: Distribution and activity of lenvatinib in brain tumor models of human anaplastic thyroid cancer cells in severe combined immune deficient mice. Mol Cancer Ther (2019) 18: 947–956.
15. Shunji Takahashi, Makoto Tahara, Koichi Ito, Masayuki Tori, Naomi Kiyota, Katsutoshi Yoshida, Yukinori Sakata, and Akira Yoshida: Safety and effectiveness of lenvatinib in 594 patients with unresectable thyroid cancer in an all-case post marketing observational study in Japan. Advances in Therapy (2020) 37: 3850–862.
16. Pandey AK, Singhi EK, Arroyo JP, Ikizler TA, Gould ER, Brown J, Beckman JA, Harrison DG and Moslehi J: Mechanisms of VEGF (vascular endothelial growth factor) inhibitor-associated hypertension and vascular disease. Hypertension (2018) 71: e1–8.
17. Li Y, Gao ZH and Qu XJ: The adverse effects of sorafenib in patients with advanced cancers. Basic Clin Pharmacol Toxicol (2015) 116: 216–221.
18. Das A, Mahapatra S, Bandyopadhyay D, Samanta S, Chakraborty S, Philpotts LL, Jahangir E and Roy B: Bleeding with vascular endothelial growth factor tyrosine kinase inhibitor: A network meta-analysis. Crit Rev Oncol Hematol (2021) 157: 103186.
19. Pang-Shuo Permg, Yu-Hsuan Lai, Po-Hsuan Lee, Cin-Chen Huang, Hao-Hsiang Hsu and Jung-Shun Lee: Safety and Efficacy of Sorafenib and lenvatinib in patients who underwent surgery or whole-brain radiotherapy for brain metastasis of hepatocellular carcinoma. J Clin Med (2022) 11: 1536.