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Case Report of Anlotinib in Advanced Thymic Cancer

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Abstract: Thymoma is a rare mediastinal tumor that originates from thymic epithelial cells. The current treatment of thymoma depends on the benign and malignant degree of the tumor. Thymic carcinoma is very rare, it is invasive, the prognosis is poor, and the patient has a short survival time. At present, there is no standard treatment mode. Most scholars prefer comprehensive treatment. Anlotinib is a new type of small-molecule multi-target tyrosine kinase inhibitor independently developed by China. It has anti-tumor angiogenesis and inhibits tumor growth, and has good safety and tolerance. Anlotinib can be used for the treatment of advanced thymic cancer, or it can achieve the purpose of treatment. We report a case of patients with advanced thymic cancer who responded to anlotinib hydrochloride after failing third-line treatment. The patient was diagnosed with advanced thymic cancer (stage IVb) in our hospital on March 10, 2016. She was given cisplatin + paclitaxel for 4 cycles, followed by sequential chest and neck radiotherapy. The second line was given 6 cycles of cyclophosphamide + pirorubium Bistar + Nedaplatin chemotherapy; three lines of 4 cycles of gemcitabine + nedaplatin chemotherapy; four lines of anilotinib monotherapy, as of the latest review, the patient's progression-free survival reached 10 months. Rotini is light and safe and controllable. This is the first report of anlotinib hydrochloride in the treatment of advanced thymic cancer. More clinical studies are still needed to confirm the efficacy and safety of anlotinib in the treatment of thymic cancer.

1. Introduction

Thymic carcinoma is a collective name for a class of malignant tumors originating from thymic epithelial cells, including squamous epithelial cell carcinoma, basal cell-like carcinoma, mucoepidermoid carcinoma, lymphoepithelial neoplasia, clear cell carcinoma, sarcomatoid carcinoma, adenocarcinoma. Among them, squamous cell carcinoma is the most common, accounting for about 80% [1]. The cause of thymic cancer is unclear and clinically rare, accounting for only 12.9% of thymic epitheliomas [2]. Early clinical manifestations of the disease have no obvious specificity, and are mostly due to cough, sputum, chest tightness, chest pain, etc. Only when metastasis of lymph nodes or surrounding tissues occurs, physical examination can show

positive signs, which is very easy to be misdiagnosed and missed. However, its pathological manifestations are highly atypical and highly invasive, and are often accompanied by infiltration of surrounding tissues and organs. The prognosis is poor, and the 5-year survival rate of patients is about 55% [3].

In the past, thymic cancer has been considered as a malignant thymoma. In recent years, with the continuous exploration of many scholars and experts, it has been found that thymic cancer and thymoma have distinct histopathological characteristics and prognosis, and gradually distinguish thymic cancer from thymoma. In the World Health Organization (WHO) histological classification of thymic tumors in 2015, thymic cancer and thymoma were classified as subclasses of thymic epithelial tumors [4]. Thymic tumors have a higher incidence in current chest diseases, which will have a serious impact on the respiratory system, and as a highly malignant tumor, the prognosis is often low. Chemotherapy can achieve a certain degree of thymic cancer in patients. The effect of treatment and postoperative drug treatment are also very critical. There are few clinical studies on thymic cancer chemotherapy. In the past, traditional first- and second-generation chemotherapy drugs such as cyclophosphamide, doxorubicin, vinblastine, and etoposide were often selected. There are few related studies to study the effect of anlotinib in the treatment of advanced thymic cancer. This study will provide a new idea for the treatment of advanced thymic cancer.

This article reports a case of patients with advanced thymic cancer who had been treated with anlotinib until the latest review. The patient's progression-free survival reached 10 months. The adverse reactions during the use of anlotinib were mild and controllable. This is the first report of anlotinib hydrochloride in the treatment of advanced thymic cancer. More clinical studies are still needed to confirm the efficacy and safety of anlotinib in the treatment of thymic cancer.

2. Proposed Method

2.1. Mechanism of Anlotinib Antitumor Therapy

2.1.1. Antitumor Angiogenesis

Tumor angiogenesis plays a key role in the growth and metastasis of tumors, and is a necessary condition for tumor proliferation, invasion, metastasis and recurrence. Vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet derived growth factor (PDGF) and other angiogenic factors such as binding to the corresponding receptors mediate signaling pathways that regulate tumors plays a vital role in the process of angiogenesis. Studies have shown that compared with other anti-angiogenic drugs, anlotinib can inhibit VEGF / VEGFR-mediated signaling pathways, especially the strongest inhibitory activity on VEGFR2 and VEGFR3, with half inhibitory concentrations (IC50) of 0.2nmol, respectively. / L and 0.7nmol / L; in addition to VEGF / VEGFR-mediated signaling pathways, anlotinib can also effectively inhibit PDGF / PDGFR and FGF / FGFR-mediated signaling pathways. All three signaling pathways are blocked at the same time. Inhibit tumor angiogenesis. It is worth noting that the anti-angiogenesis effect of anlotinib is better than the three commonly used anti-angiogenesis drugs sunitinib, sorafenib, and nidanib. Further molecular dynamics simulations found that anlotinib can inhibit the phosphorylation of VEGFR2, PDGFR-β, and FGFR1 kinases in human umbilical vein endothelial cells in a nanomolar concentration-dependent manner, thereby blocking the transduction of downstream related signaling pathways and finally play a role in inhibiting angiogenesis. In vitro and in vivo experiments have shown that anlotinib can significantly inhibit the endothelial cell proliferation, migration, and ability to form lumens induced by VEGF / PDGF-BB / FGF-2. In the rat aortic ring experiment and chicken chorionic allantoic membrane experiment, it was also found that anlotinib can inhibit vascular germination and reduce microvessel density in tumors. Some scholars have found that

anlotinib can inhibit tumor angiogenesis by down-regulating the expression level of CC-type chemokine ligand 2 (CCL2) in a xenograft tumor model derived from human lung adenocarcinoma NCI-H1975 cells. . In addition, anlotinib is able to inhibit Januskinase 2 (Januskinase2, JAK2) / signal transduction and activator of transcription 3 (STAT3) / VEGFA signaling pathways in non-small cell lung cancer by autophagy, thereby enhancing anti-tumor blood vessels generate properties.

2.1.2. Inhibition of Tumor Growth

Studies have shown that when stem cell factors bind to their receptor c-Kit, they can activate downstream signaling pathways such as phosphatidylinositol 3-kinase / serine threoninekinase (PI3K / AKT), JAK / STAT and mitogen-activated proteinkinase (MAPK) activities, which affect the proliferation, invasion and migration of tumor cells. In vitro experiments show that anlotinib can specifically bind and inhibit c-Kit, block its downstream signal pathway transduction, thereby affecting tumor cell proliferation, invasion, and migration, in order to achieve the purpose of inhibiting tumor growth. Second, anlotinib can block the cell cycle in the G2 / M phase and induce tumor cell apoptosis in part by activating the TP53 signaling pathway. It is worth noting that anlotinib can also significantly inhibit distant lung metastasis of tumor cells.

2.1.3. Predictors of Anlotinib Efficacy

1) Activated CD-31 circulating endothelial cells (aC-ECs)

ACECs may be a predictor of the efficacy of anlotinib in anti-tumor angiogenesis. The aCECs count was detected by flow cytometry. According to the ratio of the minimum aCECs count to the baseline (pre-treatment) count <1 (= 35) or ⩾1 (= 14), 49 patients in the anlotinib group were divided into 2 groups. Through follow-up, it was found that patients with aCECs minimum count / baseline ratio <1 had significantly longer PFS than those with a ratio of ⩾1.Therefore, aCECs is a more sensitive biomarker for predicting the efficacy of anlotinib treatment. The decrease of its count indicates the prolongation of PFS under the treatment of arotinib.

2) Serum CCL2 level

CCL2 is another important therapeutic target to promote tumor angiogenesis. Anlotinib has been shown to have a significant anti-tumor angiogenesis effect by inhibiting the CCL2-MMP9 axis in vitro and in vivo. It is speculated that changes in serum CCL2 levels can predict and reflect the efficacy of anlotinib in the treatment of advanced NSCLC. In the ALTER0303 trial, the study subjects were 14 patients each with randomly selected anlotinib treated with PFS> 80d and ⩽80d, at baseline (BL), best response (BR), and disease progression (PD) 3. Blood samples from patients with PFS> 80d were collected at two time points, and blood samples from patients with PFS⩽80d were collected at BL and PD time points. Serum CCL2 levels were determined by ELISA. In the serum of 13 patients with PFS> 80d, it was found that the CCL2 level decreased significantly when the response to treatment was the best, but increased during PD. At the same time, in the serum of 11 patients with PFS⩽80d, the CCL2 level increased as the disease progressed. In addition, at BL, serum CCL2 levels were significantly higher in patients with PFS> 80d than in patients with PFS⩽ 80d . Therefore, serum CCL2 levels can predict the response of anlotinib as a third-line and above treatment for advanced NSCLC.

2.1.4. Resistance Mechanism of Anlotinib

In the ALTER0303 trial, the PFS and OS of the anlotinib group were prolonged by 3.3 months

and 4 months, respectively, compared with the control group. However, the resistance to anlotinib caused the disease progression in the later stage. The current resistance mechanism of anlotinib and treatment options for anlotinib resistance need to be further explored. CXCL2 is a cytokine associated with tumor metastasis, apoptosis, angiogenesis, and secondary resistance to anti-tumor drugs. In a previous Transwell test and scratch test, it was found that the administration of exogenous CXCL2 could offset the inhibitory effect of anlotinib on the migration and invasion of NCI-H1975 cells, revealing that CXCL2 may mediate the resistance of anlotinib. Autophagy is a catabolic process that degrades and recovers various cellular components. It occurs at a lower level in almost all cells, including tumor cells. When tumor cells lack nutrients or autophagy is activated under the pressure of chemoradiotherapy and targeted therapy. Studies have shown that the activation of protective autophagy is associated with acquired resistance to AZD9291. Anlotinib can induce protective autophagy in lung cancer cells in a time- and dose-dependent manner, which may be a potential drug resistance mechanism of anlotinib. Further research found that the combined use of autophagy-specific inhibitor chloroquine (CQ) and silencing autophagy-related genes Beclin-1 can significantly improve the antitumor activity of anlotinib, which is expected to be a solution to the problem of anlotinib resistance in advanced NSCLC Treatment strategy. In general, the specific resistance mechanism of anlotinib and the treatment after anlotinib resistance are still unclear, and it is worth further investigation.

2.2. Characteristics of Advanced Thymic Cancer

Patients with advanced thymic cancer have locally infiltrative growth and are tightly adhered to peripheral organs. The boundaries are difficult to distinguish. Some tumors invade the mediastinal pleura and cause local spread to the large blood vessels of the heart and the lung tissue on both sides. In severe cases, they envelop the heart and compress the heart and blood vessels, leading to surgery. Cannot be completely removed, some patients can undergo local palliative resection, but the recurrence rate is high. The literature reports that only 20% to 40% of patients can completely remove the tumor. The common invasion sites of thymic cancer are the pericardium, lung tissue, and large blood vessels of the heart. If it is invaded, the tumor and the tissue that may be invaded are removed according to the principle of tumor enblock. Due to the wide range of tumor invasion in palliative surgery, tumors cannot be removed radically. There are tumors remaining, but the tumor body is removed. A small number of tumors are huge and completely enclose the large blood vessels of the heart. The boundaries are difficult to distinguish. At the same time, the blood flow is very rich. The bleeding during the operation is fierce and the risk of the operation is huge. In the past, most surgeons thought that since surgery could not be radically removed, surgery was abandoned. After palliative surgery and exploration, it was found that palliative surgery can still improve the patient's prognosis and prolong the survival time of patients. Do your best to remove the tumor.

Finding out whether advanced thymic cancer tumors can be removed depends on the following aspects:

(1) The growth status of the tumor itself, those with abundant blood flow and dense adhesion are difficult to remove;

(2) The experience and technical level of the operator;

(3) Due to the high risk and long time, the technical support of the anesthesia and monitoring team is required.

Palliative surgery results in more bleeding in the visual field and slower postoperative recovery. Ultrasound can control bleeding well and is worth promoting. Whether the tumor can be completely removed is closely related to the clinical experience, technical level and surgical equipment of the

surgeon. There are many reports about the surgical approach. At present, due to the rapid development of thoracoscopy technology, many early thymic cancers can achieve good results through laparoscopic surgery. The late thymic cancer is densely adhered to the large blood vessels of the heart. Considering the risk of surgery, currently open thoracotomy is still recommended, and some skilled surgeons may still consider thoracoscopy. It is reported in the literature that the conventional claw approach is usually performed with the sternal split in the middle, because the sternal split can obtain a better surgical field and better control the bleeding during the operation. It can also remove the surrounding tissue invaded by the tumor to the greatest extent. The choice is mainly determined by the growth site of the tumor and the surgical habits of the operator during the operation. The anterior mediastinal giant thymic carcinoma should be considered as far as possible to the sternal split approach. Thymic carcinoma that partially invades bilateral lung tissue or bilateral pulmonary blood vessels can also be considered Transect the sternum. Although patients with advanced thymic cancer have a high risk of surgery and a slow recovery, they have accumulated a large amount of surgical experience and reported a success rate of more than 95%.

Advanced thymic cancer may invade the heart and large blood vessels. When tumors invade large blood vessels, in order to remove the tumor as much as possible, the application of artificial blood vessels will be considered. Some patients have a wide range of tumor invasion and need extracorporeal circulation to assist. When the scope of the resection is limited to the anterior wall of the blood vessel and the scope is small, the large blood vessel can be directly sutured, and the tumor is repaired with a pericardial slice. When tumors invade large blood vessels more widely, artificial blood vessel transplantation can be considered. Enlarged resection of the tumor may cause damage to the phrenic nerve and cause respiratory failure, so it is necessary to protect the phrenic nerve during surgery. Some patients with advanced thymic cancer have undergone radical resection, and a significant proportion of patients have recurrence. Radiotherapy is a treatment method for thymic cancer. At present, the conventional dose is 2250 ~ 7000cGy, and the corresponding therapeutic effect has been achieved in postoperative adjuvant radiotherapy. Foreign literature reported that a group of patients with advanced thymic cancer had a tumor recurrence rate of up to 70% in those who did not undergo postoperative radiotherapy, and the recurrence rate was reduced to 22% after adjuvant radiotherapy. Statistical analysis showed a significant difference between the two ($P < 0.05$), and the study found that postoperative radiotherapy is not only effective for patients after radical resection, but also effective for reducing the recurrence rate after palliative resection. At present, there are few reports on preoperative radiotherapy literature. Some studies have pointed out that preoperative radiotherapy can reduce tumor volume and increase the rate of radical resection. The effect of postoperative adjuvant chemotherapy is still controversial. The postoperative chemotherapy regimen for thymic cancer is mainly cAP (cyclophosphamide + doxorubicin + cisplatin) and ADOC (cyclophosphamide + doxorubicin + vincristine + cisplatin) as first-line chemotherapy. Cancer patients rarely survive 1 year after chemotherapy. By analyzing the prognosis of advanced thymic cancer surgical treatment and its influencing factors, it is found that radical surgical resection is the most effective treatment method for thymic cancer at present. When the tumor invades the heart and large blood vessels cause radical resection, the tumor should also be removed to the maximum extent possible. And postoperative radiotherapy. The dose of radiotherapy needs to be finalized according to the recovery status of patients after surgery. The current dose of radiotherapy is 4000 ~ 6000Gy. The traditional 379 chemotherapy regimen has no obvious effect in the treatment of thymic cancer and is not recommended. Whether new emerging chemotherapeutic drugs and gene-targeted drugs are effective for thymic cancer requires further research.

3. Experiment

3.1. Case Report

3.1.1. General Information

A 46-year-old female patient was admitted to the Department of Thoracic Surgery on March 8, 2016 due to "I found the left supraclavicular mass in January". She had no limb weakness, no cough, sputum, hemoptysis, no drooping eyelids, and blurred vision, Diplopia, strabismus, limb weakness and other discomforts. Admission physical examination: a mass of about 4.0 * 3.0 cm can be touched on the left clavicle, and it is hard, with good mobility, and clear from the surrounding tissues. Chest CT: A number of round, slightly high-density shadows can be seen in front of the large blood vessels of the heart, and a round mass of shadow can be seen in the left supraclavicular fossa with clear boundaries.

3.1.2. Results of Pathological Tests

On March 9, 2016, a left anterior mediastinal mass biopsy was performed under ultrasound guidance. Postoperative pathology showed pathological thymic carcinoma (lowly differentiated squamous cell carcinoma). Immunohistochemistry: CD5 (+), CK5 / 6 (+), Ki-67 (+, about 30%), P40 part (+) is shown in Figure 1.

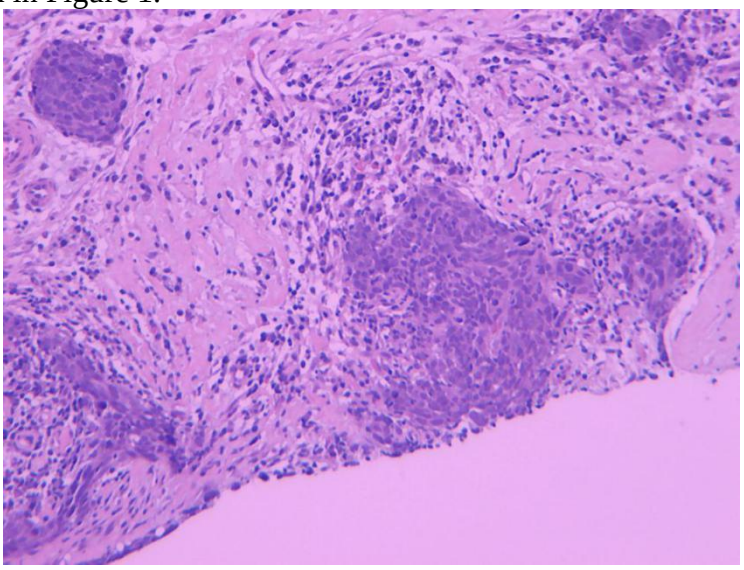

Figure 1. Left anterior mediastinal mass biopsy pathology-HE staining, magnification 200 ×

Whole body bone scan: no obvious abnormalities. A definite diagnosis of thymic squamous cell carcinoma with metastasis to the left supraclavicular lymph node (stage IVb) (Masaoka staging method) has been performed without indication of surgery.

3.1.3. Treatment Methods and Processes

On March 16, 2016, cisplatin 40 mg d1-d3 + paclitaxel 260 mg d1 was given as first-line chemotherapy. CT was reviewed after 2 cycles, and the response evaluation criteria for solid tumors were adopted (Response Evaluation Criteria in Solid Tumors, RECIST 1.1). SD, Sequential radiotherapy was performed in the Department of Radiotherapy of our hospital on June 14, 2016. A review of CT after radiotherapy revealed that the anterior mediastinum and left supraclavicular

fossa tumors were significantly reduced, and the effect evaluation reached PR. From August 17, 2016 to our hospital Thoracic surgery continued with the fourth cycle of chemotherapy, the same as before. Periodic review thereafter. On September 20, 2016, a review of CT revealed intrapulmonary metastases and disease progression. The 6-cycle CAP regimen was transferred to our department for second-line chemotherapy, specifically: cyclophosphamide 1.2g d1 + pirarubicin 80mg d1 + nedaplatin 40mg d1- 3. After regular review, the effect is stable. On March 19, 2018, an outpatient CT review in our hospital showed that the anterior mediastinal cancer and right upper lobe nodules did not change much compared with the previous one, but the metastasis of inferior vena cava lymph nodes appeared, and the effect was evaluated by PD. From March 30 to May 24, 2018, three-line and three-cycle gemcitabine + nedaplatin chemotherapy was used. Specific drugs and dosages: gemcitabine 1.8g d1, 1.6g d8 + nedaplatin 40mg d1-3. Curative effect after 2 cycles of chemotherapy Evaluation was SD. During the fourth cycle of chemotherapy on June 15, 2018, a review of blood routine showed 3 degrees of bone marrow suppression, and the patient could not tolerate the toxicity of chemotherapy and terminated chemotherapy. On October 22, 2018, a CT scan of the patient revealed left pleural effusion. At the same time, new lesions appeared in the left axillary and retroperitoneal lymph nodes, and the effect was evaluated by PD. At this time, the patient could not tolerate chemotherapy, and according to the relevant guidelines at the time, no fourth-line treatment plan could be used as a guide. To communicate with patients and their families, try anti-vascular survival drugs. After obtaining their written informed consent, the use of anlotinib 12mg qd began on October 23, 2018, and was reviewed regularly every 2 months thereafter.

4. Result

Anlotinib 12mg qd began to be used on October 23, 2018, and is reviewed regularly every 2 months thereafter. Efficacy evaluations were all SD, during which grade 2 hypertension, hypertriglyceridemia (TG highest value: 2.14mmol / L), thyroid dysfunction (TSH highest value: 31.35 uIU / ml) occurred, and all were treated symptomatically. It returned to normal and the patient's tumor status was in a long-term stable state.

5. Discussion

5.1. Analysis of Patient Treatment Process

The current treatment of advanced thymic cancer still lacks a standard treatment model. In the first-line clinical treatment of advanced thymic cancer, the most widely used chemotherapy regimen is cisplatin-anthracycline (CAP, cyclophosphamide + doxorubicin + cisplatin or ADOC, vinblastine + cyclophosphamide + doxorubicin + Cisplatin) or a combination of cisplatin and etoposide. However, retrospective studies have shown that the RR for thymic cancer treated with the above scheme is only about 40% [5]. Recent studies have found that platinum + paclitaxel is slightly less effective than ADOC, but has less side effects [6]. In the latest version (2019 v2) of the NCCN guidelines, it is still recommended as the first treatment for thymic cancer chemotherapy.

5.1.1. Analysis of First-line Treatment

In our case, the first-line treatment was given 4 cycles of cisplatin + paclitaxel and sequential radiotherapy. Due to intrapulmonary progression, the second-line protocol was changed to 6 cycles of CAP. After that, the lesions were re-examined in 1 year and the inferior vena cava occurred in March 2018. Paralymph node metastasis, third-line chemotherapy with gemcitabine + nedaplatin was started, and chemotherapy could not be tolerated at the fourth cycle, and chemotherapy was

terminated. The tumor progression in October 2018 is shown in Figure 2.

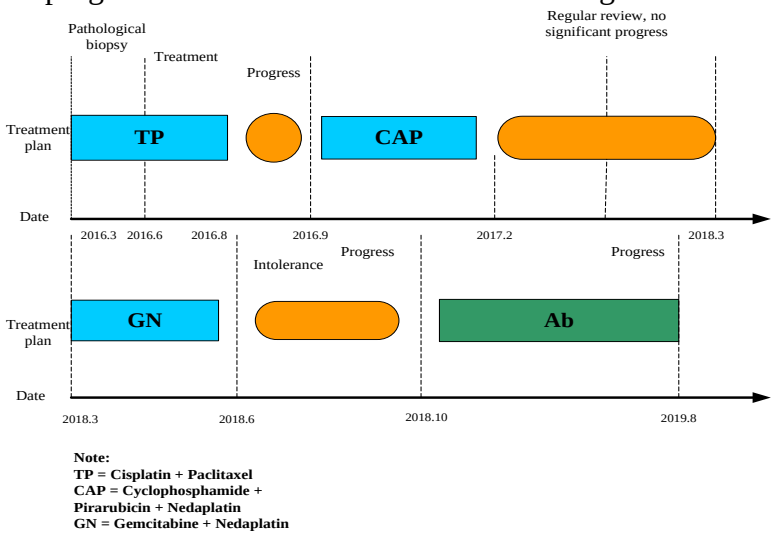

Figure 2. Summary of patient treatment time

A summary table of patient treatment time can be seen from Figure 2. The patient was given first-line chemotherapy with cisplatin 40 mg d1-d3 + paclitaxel 260 mg d1 on March 16, 2016. The pathological examination at this time is shown in Figure 3. CT was reviewed after 2 cycles, and the response evaluation criteria for solid tumors (RECIST 1.1) were adopted. The efficacy evaluation was SD.

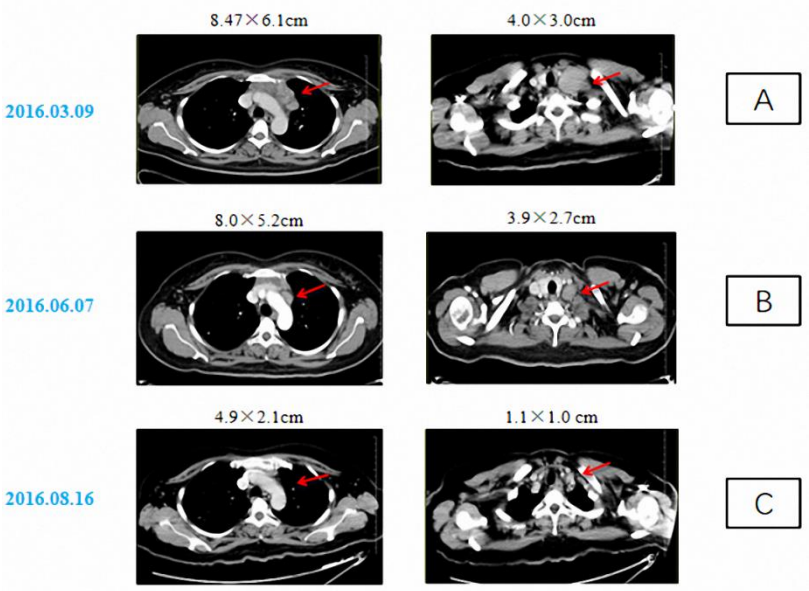

Figure 3. CT examination results of patients at baseline and first-line treatment

In Figure 3, AC is the first-line treatment stage, and A is the baseline. The soft tissue density shadow is seen in front of the large blood vessels of the heart, and the density of the mass is uneven. There may be multiple round-shaped slightly higher-density shadows, and a round shape in the left supraclavicular fossa. Tumor-shaped shadows; B and C are before and after radiotherapy, and the anterior mediastinal lesion and left supraclavicular lymph nodes were significantly smaller than before.

5.1.2. Analysis of Second-line Treatment

Sequential radiotherapy was performed in the Department of Radiotherapy of our hospital on June 14, 2016. A review of CT after radiotherapy revealed that the anterior mediastinum and left supraclavicular fossa tumors were significantly reduced. Continue the fourth cycle of chemotherapy, the same as before. Periodic review thereafter. On September 20, 2016, a review of CT revealed intrapulmonary metastases and disease progression. The 6-cycle CAP regimen was transferred to our department. Second-line chemotherapy is shown in Figure 4.

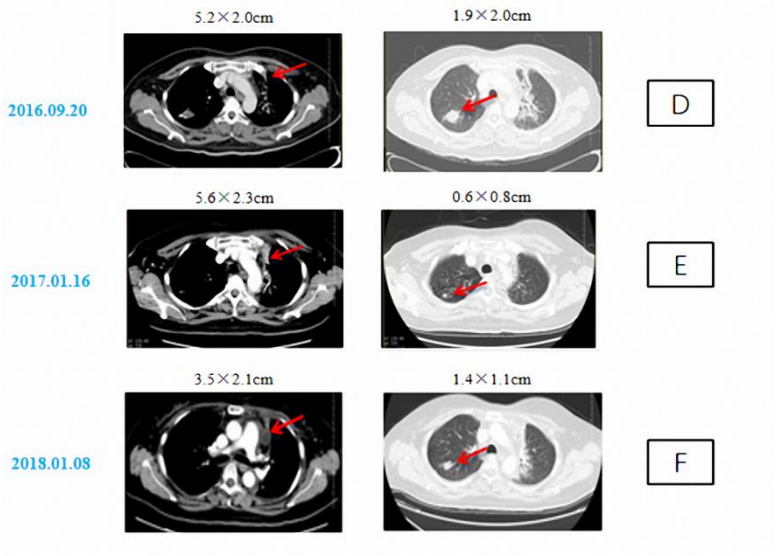

Figure 4. CT examination results of patients during second-line treatment

It can be seen from Figure 2 that the second-line treatment is specifically: cyclophosphamide 1.2 g d1 + pirarubicin 80 mg d1 + nedaplatin 40 mg d1-3. In Figure 4, we can see that DF is a second-line treatment stage, and D-line treatment is reviewed after 4 cycles. It is found that the anterior mediastinal lesion and the left supraclavicular lymph node have not changed much compared with the previous. At this time, the left supraclavicular lymph node has been less than 1.0. cm, no longer counted as target lesions, but nodules appeared in the upper lobe of the right lung, considered metastatic tumors, and started second-line treatment; E is a review after 4 cycles of second-line treatment, showing that the anterior mediastinal mass is fused to the mediastinal lymph nodes, and the boundaries are not Qing (the primary lesion was measured with the largest cross section), the metastatic lesions in the lungs slowly decreased; regular review was performed throughout the year between E and F, and the primary lesions gradually decreased.

5.1.3. Analysis of Third-line Treatment

On March 19, 2018, an outpatient CT review in our hospital showed that the anterior mediastinal cancer and right upper lobe nodules did not change much compared with the previous one, but the metastasis of inferior vena cava lymph nodes appeared, and the effect was evaluated by PD. The three-line and three-cycle gemcitabine + nedaplatin chemotherapy was performed from March 30 to May 24, 2018, as shown in Figure 5. Specific drugs and doses: gemcitabine 1.8g d1, 1.6g d8 + nedaplatin 40mg d1-3. The curative effect was evaluated as SD after 2 cycles of chemotherapy.

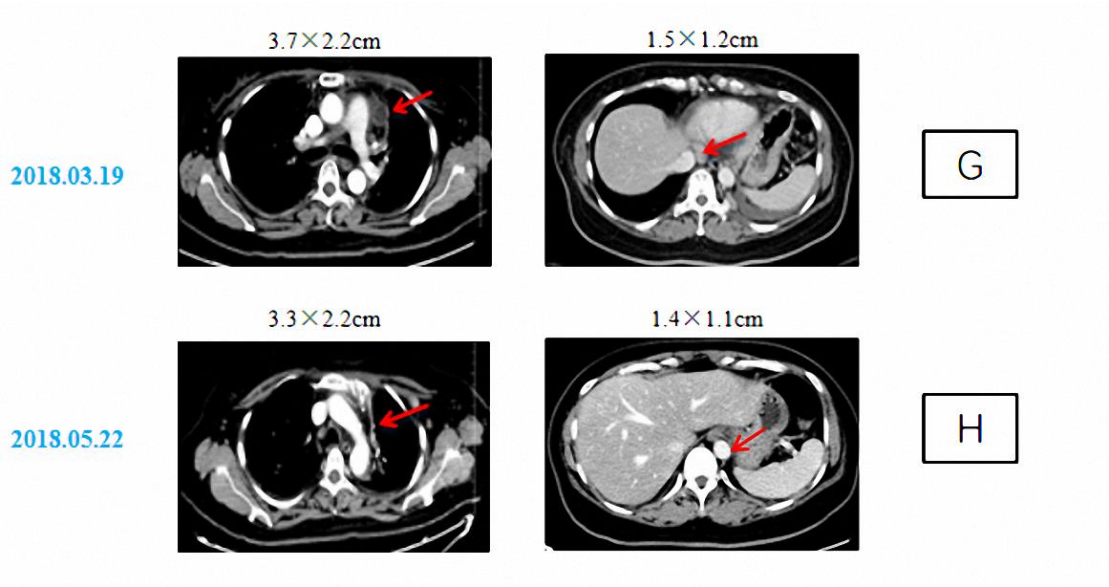

Figure 5. CT examination results of patients in the third-line treatment stage

GH is the third-line treatment stage, and the re-examination of G shows that the primary lesions and intrapulmonary metastases have not changed much from the previous, but new metastases appear in the lymph nodes next to the inferior vena cava, and the third-line treatment is started; H indicates that the second-line review is performed after 2 cycles of the third-line therapy Foci and lymph node metastases were similar.

5.1.4. Four-line Treatment Analysis

During the fourth cycle of chemotherapy on June 15, 2018, a review of blood routine showed 3 degrees of bone marrow suppression, and the patient could not tolerate the toxicity of chemotherapy and terminated chemotherapy. On October 22, 2018, a CT scan of the patient revealed left pleural effusion. At the same time, new lesions appeared in the left axillary and retroperitoneal lymph nodes. The efficacy was evaluated by PD.

At this time, the patient could not tolerate chemotherapy, and according to the relevant guidelines at the time, no fourth-line treatment plan could be used as a guide. At this time, there is no standard treatment plan for follow-up, and there is no relevant controlled study as a guide. The use of anlotinib 12mg qd on October 23, 2018 is shown in Figure 6.

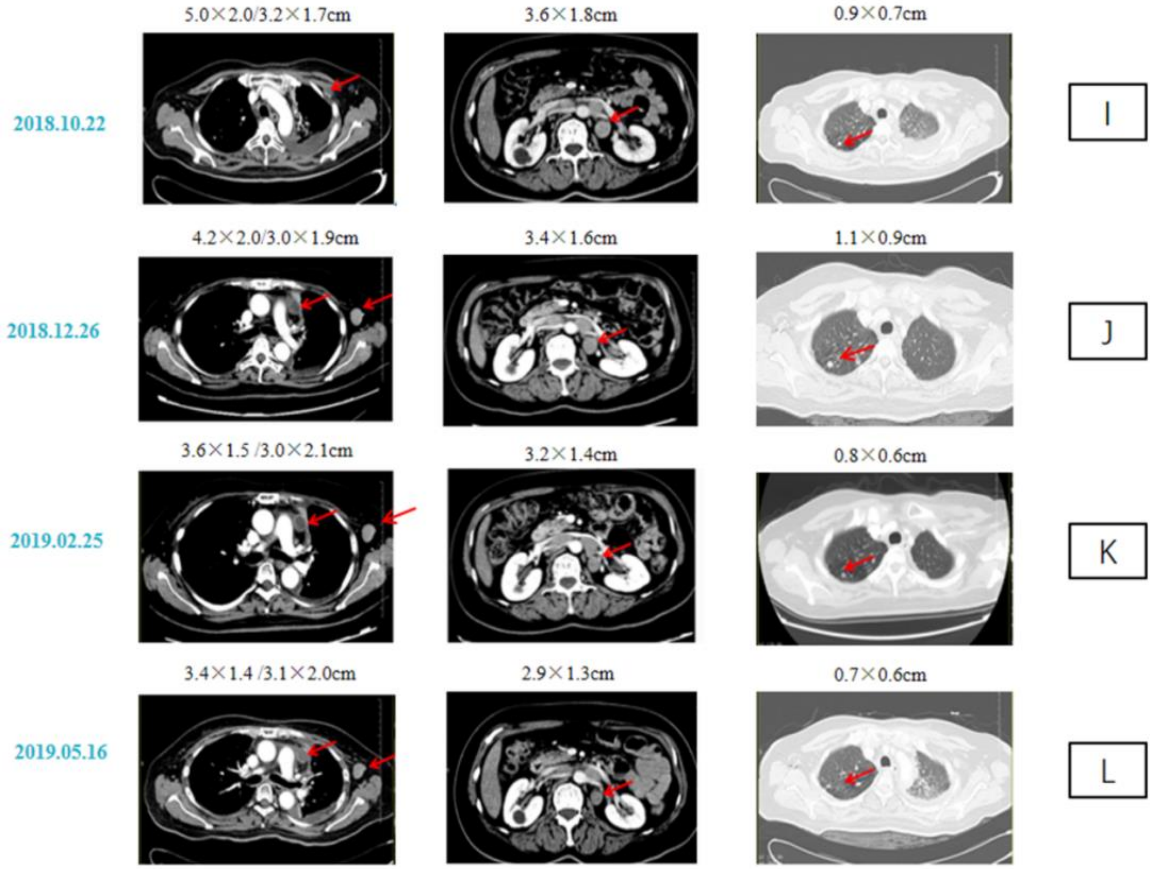

Figure 6. CT examination results of patients in the fourth-line treatment stage

IM is a fourth-line treatment stage, I is a review of the primary lesions and intra-pulmonary metastases, and the inferior vena cava lymph nodes have been less than 1.0 cm. The target lesions are no longer counted. 1. The retroperitoneal lymph nodes increased significantly. Considering metastases, four-line treatment was started. J, K, and L were reviewed at 2, 4, and 7 months after treatment. Intrapulmonary metastases slowly shrink; M shows that the axillary, retroperitoneal lymph nodes, and intrapulmonary lesions are all larger than before, pleural effusion appears on the left, and the tumor progresses again. After that, regular review was performed every 2 months, and the efficacy evaluation was SD. During the period, Grade 2 hypertension, hypertriglyceridemia (TG: 2.14mmol / L), and thyroid dysfunction (TSH: 31.35 uIU / ml) were observed.), After symptomatic treatment can return to normal as shown in Figure 7 and table 1.

Table 1. Anlotinib adverse reactions

	TSH(uIU / ml)	TG(mmol / L)
2018.11.13	5.84	0.89
2018.12.26	12.13	1.85
2019.2.25	31.35	2.14
2019.5.20	21.41	1.96
2019.6.9	4.98	0.92

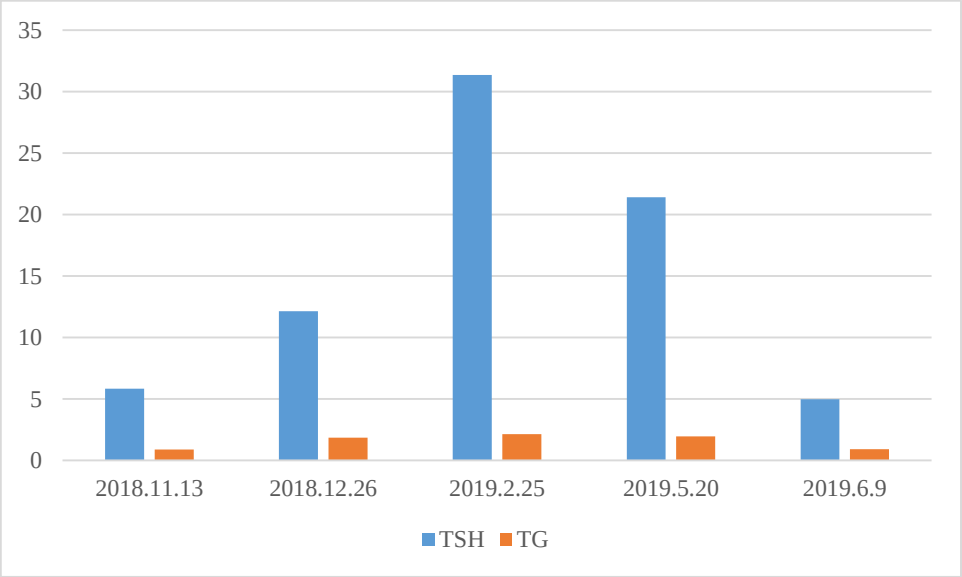

Figure 7. Anlotinib adverse reactions

The adverse reactions of anlotinib can be seen from Figure 7 .The normal value of TSH is 0.35-4.9uIU / ml, and the normal value of TG is 0.58-1.18mmol / L. As shown in Figure 7, TSH and TG began to show abnormalities after 20 days of anlotinib application, and gradually increased during the follow-up review. TG The highest: 2.14mmol / L, the highest TSH: 31.35 uIU / ml, which can gradually decrease after symptomatic treatment.

On August 25, 2019, re-examination showed progress, and the PFS of anlotinib four-line treatment reached 10 months.

5.2. Analysis of Treatment Results

Yang [7] found that among patients with stage IVb thymic cancer, only patients with lymph node metastasis have a better prognosis than patients with blood-borne metastases, and proposed that multimodal treatment (surgery and chemoradiation) may prolong survival. Subsequently, Kayata [8] and other patients also reported a case of thymic cancer with supraclavicular lymph node metastasis. Simultaneous chemoradiotherapy was performed to reduce the tumor burden and surgical resection was performed. Finally, the patient benefited from relapse-free survival for 30 months. However, in this case, the patient had multiple lymph node metastases, such as the axilla and retroperitoneum, and had no indication for surgical resection.

Immunohistochemical studies have shown that programmed death ligand 1 (PD-L1) is positive in 70% of thymic cancers [9], suggesting that anti-pd-1 antibodies may be effective, a study of nivolumab in advanced thymic cancer [10], although 15 patients did not find any responders in the first stage (response rate 0%), the DCR was 73% (11/15), and the stable condition lasted for 24 weeks or more was 33% (5 / 15). The side effects can be controlled, showing that nivolumab may bring benefits, which deserves further study. In two other Phase II clinical trials [11-12] from the United States and South Korea, Pabolizumab has similar efficacy and safety in the treatment of advanced thymic cancer, showing promising survival and response rates. At the same time, adverse reactions are controllable. At present, some prospective studies (NCT03134118, NCT030765 54, NCT02364076) are ongoing, and it is expected to further understand the role of immunosuppressants in thymic cancer. It is recommended that the patient be biopsied again to determine if there is a possibility of immunotherapy. Due to the large financial burden, the patient

and his family do not agree.

Previous research has found that thymoma is associated with multiple gene loci overexpression and mutations [13], such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2, Her2), c-kit, vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor 1 receptor (IGF-1R), PDGFR, etc. In particular, the high expression of VEGF [14] and C-KIT is related to the late staging and aggressiveness of thymic cancer, and targeted drugs have entered our field of vision. It is worth noting that EFGR is mainly overexpressed in thymic cancer [15], EGFR mutations are rare, and gefitinib or erlotinib is not effective in targeted therapy [16]; IGF-IR mutations in thymic cancer very common (approximately 86%) [17], but the targeted drug did not show complete or partial remission, only 42% maintained stable disease [18]; c-KIT gene was highly expressed in 46% of thymic cancer tissues [19-20]. However, it remains controversial whether patients benefit from imatinib treatment [21-22]. Multi-targeted tyrosine drugs such as sunitinib [23] and sorafenib [24] have achieved satisfactory results in small sample reports.

Anlotinib is a small molecule tyrosine kinase inhibitor independently developed in China, which can simultaneously inhibit VEGFR, PDGFR, FGFR, c-Kit genes and other targets, and has dual effects of anti-angiogenesis and tumor growth. Tenib and sorafenib are more active [25], and they have achieved good results in non-small cell lung cancer [26], thyroid cancer [27-29], acinar soft tissue sarcoma included in the CSCO Lung Cancer Guidelines. After obtaining the full knowledge of patients and their families, anlotinib hydrochloride was started on October 23, 2018, and the same dose and cycle were selected for the treatment of lung cancer. The tumor progressed after the third-line treatment, and the fourth-line treatment was treated with anlotinib and produced a good response [30-31]. Although the efficacy was evaluated as SD, 10-month progression-free survival was achieved. This is similar to the report of anlotinib in advanced lung cancer. Although it did not shrink the tumor significantly in a short period of time, it mainly suppressed the growth and metastasis of the tumor by inhibiting the recruitment of new blood vessels, which kept the tumor in a stable state for a long time. The main adverse reactions of the patient during the use of anlotinib were hypertension, hypertriglyceridemia, and thyroid dysfunction, all of which were below grade 2, tolerable without severe toxicity.

6. Conclusion

Cancer has always been a problem in the world, and thymic cancer is a common cancer in tumors. Precision medicine is a hot spot in cancer treatment, and multi-target drug research is an important direction. Clinical studies suggest that anlotinib has a good response and tolerance to a variety of solid tumors by targeting the anti-tumor effects of VEGFR2 / 3, PDGFRβ, FGFR1, c-Kit and other sites, and can significantly prolong patients survival period, improving its quality of life, is a low-toxic anti-tumor drug with promising prospects. This article reports on the study of anlotinib in the treatment of advanced thymic cancer.

Anlotinib is a new type of tyrosine kinase inhibitor independently developed in China, which can effectively inhibit vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) Multiple targets, such as stem cell factor receptor (c-Kit), have dual effects of anti-angiogenesis and tumor growth inhibition.

Anlotinib has good clinical efficacy in tumors such as advanced lung cancer, soft tissue sarcoma, medullary thyroid carcinoma, and renal cell carcinoma. This article reports the case of using anlotinib for advanced treatment of thymic cancer. Significant shrinkage within the tumor, but the tumor status has been in a long-term stable state, confirming that anlotinib is a reasonable choice. To our knowledge, this is the first report of anlotinib in the treatment of advanced thymic cancer,

and further preclinical and clinical studies are needed to verify its effectiveness and safety. At the same time, this also provides a reference value for the study of anlotinib in the treatment of thymic cancer.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

References

[1] Fu H, Gu Z, Fang W, et al. Long-Term Survival After Surgical Treatment of Thymic Carcinoma: A Retrospective Analysis from the Chinese Alliance for Research of Thymoma Database. Annals of surgical oncology, 2016, 23(2):619-625. https://doi.org/10.1245/s10434-015-4825-4

[2] Nobuyasu Kurihara, Hajime Saito, Hiroshi Nanjo. Thymic carcinoma with myasthenia gravis: Two case reports. International Journal of Surgery Case Reports, 2016, 27(C):110-112. https://doi.org/10.1016/j.ijscr.2016.08.010

[3] R.-Q. Wang, Y.-H. Zhang. Advances in clinical research of antitumor targeting drug anlotinib. Chinese Journal of New Drugs, 2018, 27(23):2770-2774.

[4] Yen-Han Tseng, Yi-Hsuan Lin, Yen-Chiang Tseng. Adjuvant Therapy for Thymic Carcinoma – A Decade of Experience in a Taiwan National Teaching Hospital. Plos One, 2016, 11(1):e0146609. https://doi.org/10.1371/journal.pone.0146609

[5] Ko R, Shukuya T, Okuma Y, et al. Prognostic Factors and Efficacy of First-Line Chemotherapy in Patients with Advanced Thymic Carcinoma: A Retrospective Analysis of 286 Patients from NEJ023 Study. Oncologist,2018,23(10):1210-1217. https://doi.org/10.1634/theoncologist.2017-0586

[6] Hirai F, Yamanaka T, Taguchi K, et al. A multicenter phase II study of carboplatin and paclitaxel for advanced thymic carcinoma: WJOG4207L. Ann Oncol,2015,26(2):363-368. https://doi.org/10.1093/annonc/mdu541

[7] Yang Y, Fan X W, Wang H B, et al. Stage IVb thymic carcinoma: patients with lymph node metastases have better prognoses than those with hematogenous metastases. BMC Cancer,2017,17(1):217. https://doi.org/10.1186/s12885-017-3228-2

[8] Kayata H, Isaka M, Ohde Y, et al. Complete Resection of Masaoka Stage IVb Thymic Carcinoma After Chemoradiotherapy. Ann Thorac Surg,2017,103(1):e5-e7. https://doi.org/10.1016/j.athoracsur.2016.05.048

[9] Katsuya Y, Fujita Y, Horinouchi H, et al. Immunohistochemical status of PD-L1 in thymoma and thymic carcinoma. Lung Cancer,2015,88(2):154-159. https://doi.org/10.1016/j.lungcan.2015.03.003

[10] Marx A, Chan J K, Coindre J M, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. J Thorac Oncol,2015,10(10):1383-1395. https://doi.org/10.1097/JTO.0000000000000654

[11] Giaccone G, Kim C, Thompson J, et al. Pembrolizumab in patients with thymic carcinoma: a single-arm, single-centre, phase 2 study. Lancet Oncol,2018,19(3):347-355. https://doi.org/10.1016/S1470-2045(18)30062-7

[12] Cho J, Kim H S, Ku B M, et al. Pembrolizumab for Patients With Refractory or Relapsed Thymic Epithelial Tumor: An Open-Label Phase II Trial. J Clin Oncol,2019,37(24):2162-2170. https://doi.org/10.1200/JCO.2017.77.3184

[13] Enkner F, Pichlhofer B, Zaharie A T, et al. Molecular Profiling of Thymoma and Thymic Carcinoma: Genetic Differences and Potential Novel Therapeutic Targets. Pathol Oncol Res,2017,23(3):551-564. https://doi.org/10.1007/s12253-016-0144-8

[14] Karube Y, Kobayashi S, Maeda S, et al. Tumor-related gene expression levels in thymic carcinoma and Type B3 thymoma. J Cardiothorac Surg,2016,11(1):85. https://doi.org/10.1186/s13019-016-0468-1

[15] Ming Zhou, Xiaoyuan Chen, Hong Zhang. China National Medical Products Administration approval summary: anlotinib for the treatment of advanced non-small cell lung cancer after two lines of chemotherapy. Cancer Communications, 2019, 39(1):36. https://doi.org/10.1186/s40880-019-0383-7

[16] Taurin S, Yang C H, Reyes M, et al. Abstract 3244: Treatment of endometrial cancer cells with a new small tyrosine kinase inhibitor targeting mutated fibroblast growth factor receptor-2. 2017, 77(13 Supplement):3244-3244. https://doi.org/10.1158/1538-7445.AM2017-3244

[17] Yang C H, Gaffney D K, Werner T L, et al. Abstract 1756: Genomic reclassification of endometrial carcinoma predicts drug response and facilitates refinement of current management based on PDX-guided efficacy outcomes. 2017, 77(13 Supplement):1756-1756. https://doi.org/10.1158/1538-7445.AM2017-1756

[18] Yajuan Lv, Jiandong Zhang, Fengjun Liu. Targeted therapy with anlotinib for patient with recurrent glioblastoma: A case report and literature review. Medicine, 2019, 98(22):e15749. https://doi.org/10.1097/MD.0000000000015749

[19] Teresa Bellissimo, Emanuele Russo, Federica Ganci. Circulating miR-21-5p and miR-148a-3p as emerging non-invasive biomarkers in thymic epithelial tumors. Cancer Biology & Therapy, 2015, 17(1):79-82. https://doi.org/10.1080/15384047.2015.1108493

[20] Brett W Carter, Marcelo F Benveniste, Rachna Madan. IASLC/ITMIG staging system and lymph node map for thymic epithelial neoplasms. Radiographics A Review Publication of the Radiological Society of North America Inc, 2017, 37(3):758-776. https://doi.org/10.1148/rg.2017160096

[21] Gokce Simsek, Istemihan Akin, Cem Saka. Thymoma with an incidental benign laryngeal mass mimicking laryngeal carcinoma: Case report. Ear Nose & Throat Journal, 2016, 95(2):68-80.

[22] Li Li, Yeye Chen, Shanqing Li. [Primary Neuroendocrine Carcinoma of Thymus Caused Cushing Syndrome: Surgical Treatment and Prognosis Analysis]. Zhongguo fei ai za zhi = Chinese journal of lung cancer, 2015, 18(3):451-456.

[23] Thomas A, Rajan A, Berman A, et al. Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial. Lancet Oncol,2015,16(2):177-186. https://doi.org/10.1016/S1470-2045(14)71181-7

[24] Bolzacchini E, Chini C, Pinotti G. Response of Malignant Thymoma to Sorafenib. J Thorac Oncol,2016,11(10):e125-e126. https://doi.org/10.1016/j.jtho.2016.07.011

[25] Lin B, Song X, Yang D, et al. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRbeta and FGFR1. Gene,2018,654:77-86. https://doi.org/10.1016/j.gene.2018.02.026

[26] Han B, Li K, Wang Q, et al. Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients With Advanced Non-Small Cell Lung Cancer: The ALTER 0303

Phase 3 Randomized Clinical Trial. JAMA Oncol,2018,4(11):1569-1575. https://doi.org/10.1001/jamaoncol.2018.3039

[27] Sun Y, Du F, Gao M, et al. Anlotinib for the Treatment of Patients with Locally Advanced or Metastatic Medullary Thyroid Cancer. Thyroid,2018,28(11):1455-1461. https://doi.org/10.1089/thy.2018.0022

[28] Mohammed I. Alghamdi, Neutrosophic set with Adaptive Neuro-Fuzzy Inference System for Liver Tumor Segmentation and Classification Model, International Journal of Neutrosophic Science, 2022, Vol. 18, No. 2, pp: 174-185 .https://doi.org/10.54216/IJNS.180202

[29] P. Kavitha , R. Subha Shini , R. Priya, An Implementation Of Statistical Feature Algorithms For The Detection Of Brain Tumor, Journal of Cognitive Human-Computer Interaction, 2021, Vol. 1, No. 2, pp: 57 - 62 .https://doi.org/10.54216/JCHCI.010202

[30] Ahmed N. Al Masri , Hamam Mokayed, An Efficient Machine Learning based Cervical Cancer Detection and Classification, Journal of Cybersecurity and Information Management, 2020, Vol. 2, No. 2, pp: 58-67 .https://doi.org/10.54216/JCIM.020203

[31] Cao, J., van Veen, E. M., Peek, N., Renehan, A. G., & Ananiadou, S. (2021, June). EPICURE: Ensemble Pretrained Models for Extracting Cancer Mutations from Literature. In 2021 IEEE 34th International Symposium on Computer-Based Medical Systems (CBMS) (pp. 461-467). IEEE. https://doi.org/10.1109/CBMS52027.2021.00054