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EDITORIAL

Anaplastic thyroid carcinoma: A comprehensive review of current and future therapeutic options

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Abstract

Anaplastic thyroid carcinoma (ATC) is the rarest, but deadliest histologic type among thyroid malignancies, with a dismal median survival of 3-9 mo. Even though ATC accounts for less than 2% of all thyroid tumors, it is responsible for 14%-39% of thyroid carcinoma-related deaths. ATC clinically presents as a rapidly growing mass in the neck, associated with dyspnoea, dysphagia and vocal cord paralysis. It is usually locally advanced and often metastatic at initial presentation. For operable diseases, the combination of radical surgery with adjuvant radiotherapy or chemotherapy, using agents such as doxorubicin and cisplatin, is the best treatment strategy. Cytotoxic drugs for advanced/metastatic ATC are poorly effective. On the other hand, targeted agents might represent a viable therapeutic option. Axitinib, combretastatin A4, sorafenib and imatinib have been tested in small clinical trials of ATC, with a promising disease control rate ranging from 33% to 75%. Other clinical trials of targeted therapy for thyroid carcinoma are currently ongoing. Biological agents that are under investigation include pazopanib, gefitinib and everolimus. With the very limited therapeutic armamentarium available at the present time, targeted therapy constitutes an exciting new horizon for ATC. In future, biological agents will probably represent the standard of care for this aggressive malignancy, in the same fashion as it has recently occurred for other chemo-refractory tumors, such as kidney and hepatic cancer.

Key words: Anaplastic thyroid cancer; Targeted agents

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INTRODUCTION

Although anaplastic thyroid carcinoma (ATC) accounts for less than 2% of all thyroid malignancies, it is responsible for 14%-39% of deaths related to malignant thyroid tumors[1]. The female/male ratio is 5 to 1 and the peak of incidence is in the sixth and seventh decades of life[2]. In sharp contrast to the behaviour of well differentiated thyroid carcinomas, a diagnosis of ATC is almost inevitably fatal within 3-9 mo of diagnosis, with only 10%-15% of patients alive at two years[3]. The three different morphologic patterns identifiable at histologic analysis (*squamoid*, *spindle cell* and *giant cell)* present similar biological and clinical features[4,5]. The coexistence of both well differentiated and anaplastic thyroid carcinoma has also been reported, with the prognosis being determined by the ATC compo-

nent[6]. Clinically, ATC manifests itself with a rapidly enlarging anterior neck mass, with accompanying dyspnoea, dysphagia and vocal cord paralysis. Death is often caused by tracheal and oesophageal invasion and obstruction, as well as by consequences of metastatic disease. ATC is usually advanced at diagnosis and frequently surgically unresectable[2,4]. Around 20%-50% of patients present with distant metastases, most often pulmonary[7], and another 25% develop new metastasis during the rapid course of the disease. Because of its aggressive nature, ATC is classified as stage Ⅳ according to the American Joint Committee on Cancer, regardless of the tumor size or the presence of lymph node or distant metastasis[8].

The most important prognostic factors are age, gender, presence of distant metastasis and local extent. Younger female patients (< 65 years old), with a small (less than 5 cm or intra-thyroidal) ATC and no distant metastasis at diagnosis, have a better prognosis[2,9].

Treatment of patients diagnosed with ATC is not standardized and the feasible options include surgery, radiotherapy and chemotherapy. These treatment modalities must be combined in order to maximize the clinical outcome, in terms of both local and systemic disease control[10].

TREATMENT MODALITIES

Surgery

The aim of surgery is to obtain a complete macroscopic resection, with microscopically clear resection margins. Achieving a radical resection has been shown to confer a substantial benefit[11-13]. Complete resection has been identified as a prognostic factor in several clinical trials[14-17]. In a retrospective analysis conducted in 33 patients with ATC treated with several types of surgery (either with a radical or palliative intent), Haigh *et al*[13] observed a huge increase in overall survival (OS) in patients who received potentially curative resection followed by adjuvant radiotherapy, compared with those treated with palliative resection followed by radiotherapy (OS: 43 mo *vs* 3 mo, P = 0.002). In a retrospective study of 67 patients, Pierie *et al*[7] reported a 92% 1 year OS in patients who received radical surgery plus adjuvant radiotherapy compared with 35% in those who received debulking surgery and radiotherapy (P = 0.0001). Similar results were obtained in a retrospective analysis of 50 patients by Yau *et al*[11], who demonstrated that younger patients with localized ATC benefited from an aggressive multidisciplinary approach consisting of radical surgery followed by chemoradiotherapy. When feasible, surgery must aim at a radical intent. The categories of patients that may be most suitable for this approach are young patients (< 65 years old) with small lesions (< 6 cm) and no distant metastasis. However, surgery also plays an important role for palliation. Partial resection of the tumor followed by radiotherapy and chemotherapy may delay or avoid airway obstruction, although it can improve survival only by a few months[18]. It is theoretically possible that, in selected patients, even in the setting of metastatic disease, surgery may result in an improved quality of life and prevent death from suffocation[11].

COMBINATION OF SURGERY WITH OTHER TREATMENT MODALITIES

Since surgery alone is not able to control the disease even in patients with small intra-thyroidal masses, adjuvant therapy is always required, and can be administered either with radiotherapy (RT) or chemoradiotherapy. In a retrospective study[19] conducted by Busnardo *et al*, better survival was achieved in patients with ATC undergoing a triple modality treatment (radical surgery followed by chemotherapy and RT, group 1), compared with patients who received chemotherapy alone (group 2) or RT alone (group 3). Median survival was 11 mo for group 1, 5.7 mo for group 2 and 4 mo for group 3. A French study[20] was conducted in 30 patients affected by ATC. Twenty of these patients were treated with a multimodality strategy, consisting of prior surgery followed by sequential chemo-radiation based on two cycles of three-weekly doxorubicin (60 mg/m^2) plus cisplatin (120 mg/m^2) before RT and four cycles of the same schedule after RT. RT consisted of two daily fractions of 1.25 Gy, 5 d a week for a total dose of 40 Gy (a hyperfractionated accelerated regimen). Overall survival rate at 3 years was 27% and median survival was 10 mo. Similar results were observed in a Japanese study[14] enrolling 37 patients with ATC without distant metastasis. Patients underwent surgery followed by RT. Those who had complete resection and RT survived significantly longer than other patients (median overall survival 8.1 mo *vs* 2 mo, P = 0.001).

Whether surgery should be given up-front or after neoadjuvant treatment is a matter of debate. In fact, primary chemotherapy might make inoperable lesions operable, with the additional potential advantage of preventing distant metastasis. Encouraging results in this setting were reported by Tennvall *et al*[21] who analyzed the outcome of 55 patients with ATC treated with three similar protocols of neoadjuvant chemo-radiotherapy between 1984 and 1999. RT was given according to a hyperfractionated schedule and chemotherapy consisted of weekly doxorubicin. The response to primary treatment was 72% and surgery was performed in 40 patients. No patient failed to complete the protocol due to toxicity. In only 13 cases (24%), death was attributed to local failure. Five patients (9%) had a survival exceeding 2 years. No signs of local recurrence were reported in 33 patients (60%). In a recent phase Ⅱ study[22], weekly neoadjuvant paclitaxel was employed in patients with non-metastatic disease. Patients who responded partially (23%) or totally (7%) to induction chemotherapy were subsequently treated with surgery followed by RT or exclusively RT, with an acceptable survival rate. Weekly induction paclitaxel may be considered a promising therapeutic strategy for this category of patients. Hyperfractionated RT seems to be more effective for local control than conventional treatment[23,24] and

doses above 45-50 Gy should be administered in order to achieve a radical intent[7]. RT combined with chemotherapy is more effective than RT alone[23].

SYSTEMIC TREATMENT

Cytotoxic agents

ATC cannot be regarded as a very chemo-sensitive tumor. Doxorubicin is not able to achieve more than a 20% response rate[25]. In a randomized study of the Eastern Cooperative Oncology Group, Shimaoka *et al*[26] observed that combination chemotherapy based on doxorubicin (60 mg/m^2) and cisplatin (40 mg/m^2) was more effective than doxorubicin alone and provided a higher complete response rate. In patients with thyroid carcinomas with varying histologies, De Besi *et al*[27] reported the encouraging activity of a regimen containing doxorubicin (60 mg/m^2), cisplatin (60 mg/m^2) and bleomycin (30 mg/d for three days). More recently, single drug docetaxel was tested as first-line chemotherapy in patients with advanced ATC. Out of seven patients, one obtained a complete response which lasted about 6 mo and two patients obtained stable disease[28]. In a prospective phase Ⅱ clinical trial of paclitaxel, twenty patients with metastatic ATC were enrolled and nineteen were evaluable for response. A remarkable response rate of 53% was obtained[29]. In a preclinical experiment, Voigt *et al*[29] tested the activity of topotecan, oxaliplatin, vinorelbine, gemcitabine and paclitaxel alone or in combination in ATC cell lines, but only paclitaxel, gemcitabine and vinorelbine appeared to be active in ATC[30] and the combinations of vinorelbine/gemcitabine and paclitaxel/gemcitabine seemed to act synergistically. These results should receive confirmation in clinical trials.

Biological agents

Anti-angiogenetic agents: A common feature of thyroid cancers is their markedly increased vascularisation, with an elevated expression of the vascular endothelial growth factor (VEGF) by immunohistochemistry, compared with normal thyroid tissue[31,32]. VEGF levels are correlated with stage, tumor size, nodal involvement, extra-thyroidal invasion and distant metastases[33]. On the basis of these findings, several drugs targeting angiogenesis have been evaluated against ATC.

Combretastatin A4 phosphate (CA4P) is a tubulin-binding vascular disrupting agent that inhibits tumor blood flow. In contrast to other anti-angiogenetic drugs that block the formation of new vessels in tumors, vascular disrupting agents (such as CA4P) stop blood flow through already existing vessels, with the result of depriving tumor cells of oxygen and nutrients[34,35]. CA4P has activity against ATC cell lines and xenograft[36]. In a phase I trial[37], one patient with ATC showed a progression-free survival of 30 mo, however, the drug was found to be associated with significant cardiovascular side effects at the escalating doses employed. In a phase Ⅱ trial by Cooney *et al*[38], CA4P alone was tested in 18 patients with metastatic ATC who had progressed with other standard therapies. Therapy was well tolerated at the dose selected, with no clinically meaningful myelosuppression or cardiac toxicity. No objective responses were reported. Six patients had stable disease and 25% of patients survived longer than 3 mo. On the basis of a possible synergism between CA4P and cytotoxic drugs, Yeung *et al*[39] tested the combination of CA4P with carboplatin-paclitaxel against ATC in a nude mouse xenograft model. This triple-drug combination showed remarkable activity, paving the way for the clinical evaluation of CA4P-paclitaxel-carboplatin. A phase Ⅱ study assessing the safety and activity of this triple combination therapy was carried out in 26 patients with advanced ATC. There were no objective responses and a median survival of 4.7 mo was observed. Interestingly, more than a third of patients experienced a survival longer than 6 mo. Therapy was well tolerated, with only 4% of patients experiencing any kind of G4 toxicity[40].

Axitinib (AG-013736) is an oral, potent and selective inhibitor of VEGFRs 1, 2 and 3. Preclinical studies demonstrated that axitinib rapidly and selectively inhibits VEGF-dependent fenestrations and VEGFR-2 and 3 expression in endothelial cells, with the result of blocking angiogenesis and tumor blood flow[41-44]. The principal mechanism of action of axitinib is inhibition of VEGF signalling[40]. A phase I trial[45] of 36 patients with advanced solid tumors identified axitinib 5 mg twice daily as the recommended dose for further clinical testing. A phase Ⅱ clinical trial was conducted in various types of thyroid cancers. An objective response was reported in 30% of patients, and 38% of patients had stable disease[46]. The drug showed activity in all histologic subtypes and the main side effect, hypertension, was easily managed.

Other anti-angiogenetic compounds have been evaluated in the preclinical setting. In particular, bevacizumab (a monoclonal antibody anti VEGF) was tested alone and in combination with cetuximab in an *in vivo* model compared with doxorubicin. This study demonstrated that both drugs, either alone or in combination, inhibited tumor growth and angiogenesis better than doxorubicin[47,48]. AZD2171, a tyrosine-kinase inhibitor of the VEGFR-1 and VEGFR-2, blocked tumor growth and prolonged survival of ATC-bearing mice[49].

Histone deacetylase inhibitors

Histone deacetylase inhibitors are a promising class of antineoplastic agents that are able to induce cell differentiation, cell-cycle arrest and apoptosis through hyperacetylation of histones, with the potential to enhance the cytotoxicity of drugs such as doxorubicin. Preclinical studies have shown that valproic acid, a potent anti-convulsant agent, is able to enhance the activity of doxorubicin in cell lines derived from ATC alone or in combination with other drugs[50,51].

Noguchi *et al*[52] reported on a patient with a diagnosis of non-metastatic ATC treated with a combination of neoadjuvant chemoradiation plus valproic acid (VA) followed by debulking surgery. The patient received 1200 mg

of oral VA daily, the upper therapeutic dose for epilepsy, concomitant with 100 mg/m^2 of cisplatin and 50 mg/m^2 of doxorubicin, with both drugs given at three-four week intervals with the concomitant administration of a total radiation dose of 40 Gy. The patient achieved a partial response and was then treated with surgery, achieving a disease-free-survival of more than 6 mo[52].

Tyrosine kinase inhibitors

Imatinib (STI571) is an oral inhibitor of the ABL kinase (the product of the fusion of Bcr and Abl gene). In addition, it can specifically inhibit c-Kit and PDGF receptors, which are hyper-functioning in some malignancies. On the basis of the assumption that ATC which overexpresses PDGFR and/or Abl might respond to imatinib, Ha *et al*[53] treated 11 patients with recurrent and pre-treated ATC with single agent imatinib. Of the 8 assessable patients, 2 obtained a partial response and 4 stable disease (disease control rate of 6/8), with a 6-mo progression-free survival rate of 27% and a 6-mo overall survival rate of 46%. Further clinical trials are warranted.

Sorafenib (Bay43-9006, Nexavar) is an oral, small tyrosine kinase inhibitor of the raf.1 protein kinase receptor, VEGFR2 and PDGF-β and displays strong anti-angiogenetic activity. In a phase Ⅱ study, Nagaiah *et al*[54] assessed the safety and activity of sorafenib in 16 pre-treated patients with advanced ATC. The drug was given orally at doses of 400 mg *bid* until disease progression. Disease control rate was 40% and toxicity was manageable. Lymphopenia and cutaneous rash were the main side effects reported. Sorafenib demonstrates an acceptable response rate in pre-treated ATC patients and further clinical studies are warranted.

Anti-EGFR agents

The epidermal growth factor receptor (EGFR) has been implicated in the pathogenesis of several types of cancer. There is supporting evidence that EGFR is expressed at high levels in ATC and papillary thyroid cancers[55,56]. In an *in vitro* study by Bergström *et al*[57], EGFR was expressed in all of the ATC cell lines examined and non-ligand dependent phosphorylation of EGFR was identified in half of the cell lines. High expression of EGFR appears to be a negative prognostic factor in many types of tumors, but few studies have examined its prognostic role in thyroid cancers[58]. Strong EGFR staining in papillary thyroid cancer was associated with poor prognosis[59]. These findings suggest that inhibition of EGFR may have anti-cancer efficacy in ATC.

Gefitinib (ZD1839) is an orally active EGFR inhibitor that blocks EGFR-mediated downstream signal transduction. No clinical trials have been performed to determine the effectiveness of gefitinib in ATC, however, preclinical trials have tested the activity of this drug against *in vitro* or *in vivo* models of ATC. Schiff *et al*[60] were the first to report the *in vivo* effects of EGFR inhibition on ATC xenograft in nude mice. In this study, the administration of gefitinib resulted in significant inhibition of tumor growth.

Cetuximab (C225) is a human-murine chimeric monoclonal antibody against EGFR. It has been approved by the Food and Drug Administration (FDA) for use in metastatic colorectal cancer and head and neck squamous cell carcinoma either metastatic or unresectable. There are no studies in the literature that have examined the effects of cetuximab in ATC. In preclinical trials, Kim *et al*[61] observed that combination therapy with cetuximab/irinotecan inhibits the growth and progression of orthotopic ATC xenografts in nude mice. Clinical trials are warranted to define the impact of EGFR inhibitors on ATC.

Agents targeting the NF-κB pathway

The *26s proteasome* is a large ATP-dependent multimeric complex that degrades intracellular proteins that have been marked for proteolysis by the process of ubiquitination[62]. The ubiquitin-proteasome pathway plays a significant role in neoplastic growth and metastatic spread. The proteasome is also required for activating nuclear factor κB (NF-κB) by degradation of its inhibitory protein factor κB inhibitor (I-κB). NF-κB is a transcription factor that upregulates a number of proteins involved in cancer progression including several anti-angiogenetic and anti-apoptotic factors[63].

Bortezomib (PS-341) is a proteasome inhibitor that has been approved by the FDA for the treatment of multiple myeloma and its mechanisms of action include the inhibition of I-κB, which leads to inactivation of the transcriptional factor NF-κB[64,65]. NF-κB is often constitutively activated in medullary thyroid carcinoma and ATC, and is therefore implicated in their pathophysiology[66]. A preclinical study showed that ATC cell lines are sensitive to bortezomib, alone or in combination with doxorubicin[67]. Bortezomib has also been shown to increase the expression of TRAIL (TNF-related-apoptosis-induced-ligand) receptors (TRAIL-R1 and 2) and to sensitize tumors to TRAIL-mediated killing[68]. The high cytotoxic activity and good *in vivo* tolerability of bortezomib holds promise for its future use in the treatment of ATC patients.

Agents targeting farnesyl-transferase

A new group of therapeutic agents called farnesyl-transferase inhibitors (FTIs) has been used in the treatment of solid tumors. Activating *ras* mutations are common in thyroid cancers[69]. Ras, the protein product of the *ras* proto-oncogene, requires post-translational modification by conjugation of a farnesyl moiety to its C-terminal amino acid. After farnesylation, Ras is localized to the inner surface of the cell membrane and is able to transduce the mitogenic signals mediated by tyrosine kinase receptors. Farnesylation-blocking agents therefore operate by inhibiting Ras activity.

Manumycin A is a natural product of Streptomyces parvulus that inhibits farnesyl transferase and has antitumor activity against a variety of cancers *in vitro* and in xenograft models[70,71]. In a preclinical study, Xu *et al*[72] observed good antitumor activity with the combination of manumycin A and paclitaxel against nude mice bear-

Table 1 Selected clinical trials on targeted agents for advanced/metastatic thyroid carcinomas

Trial	Phase	Setting	Patients	Targeted agent	DCR
Cooney *et al*[38]	II	Advanced pretreated disease	18 with ATC	CA4P alone	33%
Cohen *et al*[46]	II	Advanced pretreated disease	60 (2 with ATC)	Axitinib alone	71%
Ha *et al*[53]	II	Advanced pretreated disease	11 with ATC	Imatinib alone	75%
Nagaiah *et al*[54]	II	Advanced pretreated disease	16 with ATC	Sorafenib alone	40%

ATC: Anaplastic thyroid carcinoma; CA4P: Combretastatin A4; DCR: Disease control rate (complete responses + partial responses + stable disease).

ing ATC xenografts. Concordant results were obtained by Yeung *et al* in a similar study[73]. Apart from inhibition of angiogenesis, manumycin A causes apoptosis by inducing the pro-apoptotic protein Bax[74]. No clinical trials have been performed to determine the activity and/or efficacy of manumycin A against ATC.

Agents targeting matrix metalloproteinases

Matrix metalloproteinases (MMPs) are an important group of enzymes mediating the endothelial cell invasion and migration required for the formation of new capillaries, a crucial step in the angiogenesis process.

Minocycline is a semi-synthetic analogue of tetracycline active against *MMPs* through chelation of the zinc ion at the active site of the enzyme. In a preclinical study, She *et al*[75] investigated the effect of adding minocycline to manumycin A and paclitaxel against human ATC cells xenografted in nude mice, and demonstrated that the triple-drug combination resulted in the lowest average tumor growth rate, yielding significantly better survival than manumycin A alone, paclitaxel alone, or manumycin A plus paclitaxel. This novel combination deserves further investigation for the treatment of ATC.

Agents targeting PPARγ

Peroxisome proliferator-activated receptor gamma (PPARγ) agonists have demonstrated antitumor activity against a variety of human cancers in pre-clinical models and clinical trials[76]. The mechanism of action of the different classes of these compounds, which comprise non-steroidal anti-inflammatory drugs, amino-acid derivatives, polyunsaturated fatty acids, eicosanoids and thiazolidinediones, is attributed to the capacity of binding and activating PPARγ. PPARγ acts as a tumor suppressor gene, upregulating important enzymes which control the cell cycle[77].

Thiazolidonediones represent the most widely investigated pharmaceutical class among PPARγ agonists[78]. In a preclinical study, two agents belonging to this class, ciglitazone and rosiglitazone, showed promising biological effects in ATC cells, such as an increased rate of apoptosis and inhibition of anchorage-dependent and-independent growth and migration. Furthermore, rosiglitazone increased the expression of thyroid-specific differentiation markers, thus inducing a partial reversion of the epithelial-mesenchymal transition in ATC cells, which correlates with ATC growth and dissemination[79].

RS5444 is another thiazolidinedione agent and a PPARγ agonist. RS5444 demonstrated antitumor activity in preclinical studies, with a mechanism which includes the transactivation of genes regulating cell proliferation, apoptosis, and differentiation. In particular, PPARγ activation is able to upregulate p21 protein, which is known to complex and inhibit an eterodimeric complex called *cyclin dependent kinase 2* (CDK2)-cyclin E/A, responsible for cell cycle progression. Cells expressing nuclear *p21* are subsequently arrested in the G0-G1 phase of the cell cycle[80]. Copland *et al* published the first preclinical experience with *RS5444* against ATC. In this study, RS5444 alone did not induce cellular apoptosis, but when added to paclitaxel it managed to double the apoptotic index, in comparison to that of paclitaxel alone. The efficacy of RS5444 is closely linked to the proper functioning of PPARγ[81].

Selected clinical trials carried out on targeted agents are reported in Table 1.

CONCLUSION

On the basis of the data presented in this review article, it appears clear that at the present time, current therapeutic options for ATC are unsatisfactory. Surgery followed by chemoradiotherapy can significantly prolong the survival of patients carrying small, intra-thyroidal tumors, but this kind of presentation is very unusual for this cancer. ATC is often advanced and metastatic at diagnosis. For these patients, the prognosis is very poor, with an overall survival of about 3-6 mo. Patients with localized disease not amenable to surgical resection can be treated with neoadjuvant chemo-radiotherapy, but the role of this treatment modality is still debated.

There are few active compounds against ATC; the combination of doxorubicin and cisplatin has been the standard for many years. At the present time, paclitaxel plus a platinum compound (often carboplatin) also appears to have efficacy. With regard to biological drugs, axitinib, combretastatin A4, sorafenib and imatinib have been tested in clinical trials, with encouraging activity. The results from several ongoing clinical trials on ATC (Table 2), will hopefully expand the limited therapeutic armamentarium for this deadly disease.

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Table 2 Ongoing clinical trials of targeted therapies for thyroid cancer

Clinicaltrials.gov identifier	Investigational drug	Phase study	Eligible population	Planned enrolment	Primary end point	Status
NCT00389441	Axitinib	Phase Ⅱ, single arm	Radioiodine-refractory thyroid cancer, regardless of histology	52	Overall response rate	Active, not recruiting
NCT00510640	Sunitinib	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	66	Overall response rate	Recruiting
NCT00095836	Gefitinib	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	38	Overall response rate	Active, not recruiting
NCT01164176	Everolimus	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	32	Overall response rate	Recruiting
NCT01118065	Everolimus	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	42	Overall response rate	Recruiting
NCT00654238	Sorafenib	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	55	Overall response rate	Recruiting
NCT00625846	Pazopanib	Phase Ⅱ, single arm	Thyroid cancer, regardless of histology	188	Overall response rate	Recruiting
NCT01236547	Pazopanib	Phase Ⅱ, two arms Paclitaxel neoadjuvant, concomitant and adjuvant to radiotherapy with or without pazopanib	Anaplastic thyroid cancer	99	Overall response rate	Recruiting
NCT00126568	Sorafenib		Anaplastic thyroid cancer	36	Overall response rate	Recruiting
NCT00603941	CS7017	Phase Ⅰ/Ⅱ	Anaplastic thyroid cancer	54	Maximum tolerated dose/Overall response rate	Active, not recruiting
NCT00115739	Imatinib	Phase Ⅱ	Anaplastic thyroid cancer	29	Overall response rate	Active, not recruiting

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