Chemotherapy for Anaplastic Thyroid Cancer

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Introduction

Anaplastic thyroid cancers (ATC) account for roughly 2.2 % of all thyroid cancers in the USA [1] and are believed to arise from differentiated thyroid cancers (DTC) via the accumulation of genetic abnormalities that result in dedifferentiation and an aggressive phenotype [2]. Unfortunately, ATC is usually advanced at the time of diagnosis, with approximately 76–79 % of all patients having disease extending beyond the thyroid/neck at the time of presentation [1, 3]. In the vast majority of patients, surgery alone has been associated with poor outcomes, leading to investigation into additional therapeutic options.

Cytotoxic Chemotherapy

Early chemotherapy regimens were not associated with improvements in patient survival [4], though there were occasional reports of clinical complete responses and prolonged remission [5]. Selected chemotherapy regimens are summarized in Table 99.1. Gottlieb and Hill [6] reported on their initial experience in 1974 with the anthracycline antibiotic, doxorubicin, in thyroid cancer, noting that two of nine patients with ATC had a greater than 50 % decrease in the size of metastatic lesions following treatment. Several subsequent studies attempted to improve on this result.

Shimaoka and colleagues [7] reported the results of a large randomized study conducted by the Eastern Cooperative Oncology Group (ECOG) of doxorubicin alone versus doxorubicin plus cisplatin administered every 3 weeks in patients with advanced thyroid cancer. Among 39 patients with ATC enrolled in the study, there was a single partial response among the 21 patients treated with doxorubicin alone, compared to 6 responses, including 3 complete responses, among 18 patients treated with the combination chemotherapy (5 % versus 33 %, $p=0.03$). Among all patients treated in the study, response to therapy was associated with improved overall survival, but the difference in overall survival was not statistically significant between the two groups. Toxicities, specifically nausea and hematologic toxicity, were greater in the combination arm. De Besi and colleagues [8] investigated the addition of bleomycin to doxorubicin and cisplatin in a small study of 22 patients with advanced thyroid cancer of all histologies. Two of five patients with ATC had complete responses.

The Japanese Society of Thyroid Surgery [9] completed a prospective study in ATC using an intensified regimen consisting of doxorubicin, cisplatin, etoposide, and peplomycin administered every 3 weeks. Granulocyte colony-stimulating factors were given in an attempt to mitigate chemotherapy-induced neutropenia. Patients were allowed to receive local radiation therapy if it was deemed to be indicated. Responses were limited, with only two of ten patients with measurable disease having partial responses and these lasting on average 2–3 months. Despite growth factor support, all patients experienced major neutropenia.

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Table 99.1 Selected studies of chemotherapy and targeted agents in anaplastic thyroid cancer

Chemotherapy	Ref.	Treatment plan	N	Responses
Doxorubicin-based regimens				
Doxorubicin	[6]	Doxorubicin: 45–75 mg/m^2 q 3 weeks	9	2
	[7]	Doxorubicin: 60 mg/m^2 q 3 weeks	21	1
Doxorubicin, cisplatin	[7]	Doxorubicin: 60 mg/m^2; cisplatin: 40 mg/m^2 q 3 weeks	18	6
Bleomycin, doxorubicin, cisplatin	[8]	Bleomycin: 30 mg/day day 1–3; doxorubicin: 60 mg/m^2 day 5; cisplatin: 60 mg/m^2 day 5	5	2 CR
Doxorubicin, cisplatin, etoposide, peplomycin	[9]	Doxorubicin: 60 mg/m^2 day 1; cisplatin: 40 mg/m^2 day 1; etoposide: 100 mg/m^2/day day 1–5; peplomycin: 5 mg/day day 1–5 q 3 weeks	10[a]	2
Other cytotoxic chemotherapy regimens				
Paclitaxel	[11]	Paclitaxel: 120–140 mg/m^2 as a 96-h infusion weekly	20	10
	[12]	Paclitaxel: 80 mg/m^2 day 1, 8, 15 q 3–4 weeks	13	4
Docetaxel	[13]	Doxorubicin: 60 mg/m^2 q 3 weeks	7	1
Carboplatin, paclitaxel	[16]	Carboplatin: AUC 6 d1; paclitaxel: 200 mg/m^2 day 1	NR[b]	NR[c]
Vasculature-targeting agents				
Fosbretabulin	[15]	Fosbretabulin: 45 mg/m^2 IV, day 1, 8, 15 q 4 weeks	26	0[d]
Fosbretabulin, carboplatin, paclitaxel	[16]	Fosbretabulin: 60 mg/m^2 day 1, 8, 15; carboplatin: AUC 6 day 1; paclitaxel: 200 mg/m^2 day 1	NR[b]	NR[c]
Receptor kinase inhibitors				
Axitinib	[24]	Axitinib: 5 mg bid	2	1
Sorafenib	[22]	Sorafenib: 400 mg bid	2	0
	[23]	Sorafenib: 400 mg bid	4	0
Gefitinib	[21]	Gefitinib: 250 mg daily	5	0
Imatinib	[18]	Imatinib: 400 mg bid	11	2[e]
mTOR inhibitors				
Everolimus	[24]	Everolimus: 10 mg daily	5	1

[a]An additional six patients were treated adjuvantly, with 3 pts NED (3–11 months)
[b]75 patients received treatment and were randomized 2:1 to fosbretabulin combination arm versus carboplatin, paclitaxel alone
[c]Median OS 5.2 months in fosbretabulin combination arm versus 4.0 months in carboplatin, paclitaxel only arm ($p=0.065$)
[d]Median OS, 4.7 months; 6-month OS, 34 %; 12-month OS, 23 %
[e]All tumors overexpressed PDGFR by immunohistochemistry. 6-month PFS (27 %), OS (46 %)

Several alternative, non-anthracycline regimens have also been explored [10]. In 2000, the Collaborative Anaplastic Thyroid Cancer Health Intervention Trials Group reported the results of a phase 2 study of paclitaxel, administered as a 96-h continuous intravenous infusion to 20 patients with ATC [11]. Doses of paclitaxel were increased from 120 mg/m^2/week (7 patients) to 140 mg/m^2/week (13 patients). The authors used a modified WHO classification system to describe responses to therapy, requiring that optimal responses last for at least 2 weeks instead of the typical 4 weeks in an attempt to account for rapid tumor doubling time. Ten responses were reported, with one complete response and nine partial responses. At the time of progression, nine of these patients were treated off protocol with a 1-h weekly infusion of high-dose paclitaxel 225 mg/m^2. Among seven patients who had had a prior response to the 96-h infusion, there were two partial responses; among the two patients who had not responded to the 96-h infusion, there was one partial response. The 96-h continuous intravenous infusion was well tolerated, with no toxicities greater than grade 2. Five of nine patients given the 1-h weekly infusion of paclitaxel developed grade 2–3 neuropathy.

Higashiyama and colleagues [12] evaluated paclitaxel as induction therapy prior to surgery in 13 patients with stage IVB or IVC ATC between 2005 and 2008. Patients were treated with weekly paclitaxel 80 mg/m^2 as a 1-h infusion given on days 1, 8, and 15 every 3–4 weeks. Four patients had a response to chemotherapy (one complete response, three partial responses) with an additional four patients having stable disease at 8 weeks after initiating therapy. Therapy was generally well tolerated with only one patient having a grade 3 drug-related adverse event (reversible pulmonary toxicity). Retrospective comparison of outcomes with ATC patients who had not received paclitaxel induction suggested a possible benefit in patients with stage IVB, but not stage IVC disease.

A recent publication from Kawada and associates [13] investigated the second-generation taxane, docetaxel, in ATC. Seven chemotherapy-naive patients with good performance status and measurable disease were treated with docetaxel 60 mg/m^2 as a 1-h infusion every 3 weeks. One patient had a complete response, and two patients had stable disease. The median time to progression was 6 weeks. The authors recommended further investigation into docetaxel in ATC.

Targeted Therapy

As more is known about the molecular underpinnings of this disease, there has been increased interest in developing targeted therapies for ATC (see Table 99.1).

Antiangiogenic approaches have been conceptually appealing, given the highly vascular nature of ATC. Fosbretabulin (combretastatin A4 phosphate) is a novel chemotherapeutic agent which disrupts endothelial cell function leading to occlusion of vessels. Tumor microvasculature is more sensitive to the effects of fosbretabulin than normal vessels, and blood flow reduction in the phase 1 study was noted to be the greatest in highly vascular tumors, such as thyroid cancer [14]. Twenty-six patients with advanced ATC who had failed multimodality therapy were enrolled on a phase 2 trial of fosbretabulin administered at a dose of 45 mg/m^2 weekly for 3 weeks every 28 days [15]. Treatment was well tolerated. No objective responses were noted, and stable disease was seen in 27 % of patients. Median survival was 4.7 months, with a 1-year survival of 23 %. The results of a phase 2/3 randomized comparison of fosbretabulin plus paclitaxel and carboplatin versus paclitaxel and carboplatin alone have been reported [16]. Only 80 out of the intended 180 patients were enrolled to the trial due to slow accrual. Median survival in the combination arm was 5.2 months compared to 4 months in the control arm (HR 0.65 [0.38–1.1]). One-year survival was improved in the combination arm though it did not reach statistical significance (27 % versus 9 %, p=0.065). Treatment was generally well tolerated, with hypertension and neutropenia more common in patients receiving fosbretabulin. This agent has been moved into a phase 3 trial which is in development. Crolibulin, a microtubule-destabilizing agent which disrupts vascular endothelial cells and, in turn, blood flow to the tumor was combined with cisplatin in a phase 1 trial. Eight patients with ATC were treated at dose level 3, and one had a complete response and remained on study with single-agent crolibulin. One additional patient had stable disease [17].

Given that ATC cell lines and tissues have been reported to overexpress PDGFR, Ha and colleagues [18] investigated the use of imatinib (Glivec, Gleevec), a tyrosine-kinase inhibitor with activity against several targets including Bcr-Abl, PDGFR-α/β, c-KIT, and RET, in patients with ATC. Eleven patients were enrolled, all of whom had immunohistochemical evidence of PDGFR overexpression. Two patients had a partial response, with an additional four patients demonstrating stable disease at 2 months. At 6 months, overall survival was estimated at 46 %, with 27 % of patients free of progression. Further investigation is of interest, particularly in patients with evidence of overexpression of PDGFR.

EGFR has also been a target of interest in ATC. Evidence of EGFR overexpression has been documented in ATC cell lines and selected cases of ATC [19], and case reports have suggested occasional clinical response to EGFR inhibitors [20]. Response, however, may be limited in an unselected population. Of five patients with ATC enrolled in a phase 2 study of the EGFR inhibitor gefitinib, no patient had an objective response [21]. However, one patient did demonstrate stable disease of at least 12 months.

Two studies investigating the multikinase inhibitor sorafenib in advanced thyroid cancer have included patients with ATC [22, 23]. Sorafenib is approved for treatment of metastatic differentiated thyroid cancer, advanced hepatocellular carcinoma, and renal carcinoma and has activity against VEGFR, PDGFR, FLT3, KIT, Raf-1, BRAF, and RET kinases. Much of its activity is believed to be mediated via the antiangiogenic effect of VEGFR blockade, though additional signaling pathways are likely important as well. A total of six patients were enrolled on the two studies: no patient had a response to therapy, though one patient did have stable disease lasting at least 6 months. Axitinib is a second small-molecule tyrosine-kinase inhibitor with activity against VEGFR, PDGFR, and KIT. Two patients with ATC were enrolled on a phase 2 study investigating the activity of axitinib in advanced thyroid cancer: one patient had a partial response to therapy [24].

A phase 2 trial with the mTOR inhibitor everolimus included five patients with ATC and results were presented in 2013 [25]. One complete response was seen in a patient with ATC and was sustained for 18 months. Whole-exome sequencing of the tumor revealed a somatic loss of function mutation affecting the tuberous sclerosis 2 (TSC2) protein, a negative regulator of mTOR activity.

Multimodality Therapy

Unfortunately, as outlined above, overall response rates to cytotoxic chemotherapy alone are poor, and there have been no studies that have been able to demonstrate a survival benefit in patients treated with chemotherapy alone. Retrospective studies have suggested the importance of a multimodality approach in the treatment of ATC, and patients who receive all three modalities, including surgery, radiation therapy, and chemotherapy, have improved outcomes [26]. Selection of patients who will benefit most from multimodality therapy has been an area of active research [27]. Selected reports of multimodality approaches are summarized in Table 99.2.

The Swedish experience at Lund University and Karolinska University Hospital has provided important insights into the benefits and limitations of chemoradiation with or without surgery in patients with advanced ATC [28–36]. From 1971 to 1973, patients at these institutes were treated with methotrexate 5 mg daily plus external beam radiation therapy daily for 3–4 weeks to a cumulative dose of 30–40 Gy [29]. Of the initial eight patients, responses were seen in seven patients, but the majority of patients subsequently progressed locally (six of eight patients). Though median survival was 9 months, toxicity was felt to be considerable (severe mucositis, gastrointestinal bleeding, hepatotoxicity), and given the palliative aim of the therapy, the protocol was subsequently amended.

Table 99.2 Selected studies of multimodality therapy in anaplastic thyroid cancer

Treatment	Ref.	Treatment plan	N	Local control	Median survival	Comments
Doxorubicin-based regimens						
Doxorubicin + radiation + surgery[a]	[37]	Doxorubicin: 10 mg/m^2 weekly; HART: 57.6 Gy	9	13	NR	
		Above plus surgery	10			
	[31]	Doxorubicin: 20 mg weekly; HART (30 Gy pre-op, 16 Gy post-op, 1 Gyx2/day)	7	0	3.5 months	Treatment period 1984–1988
		Above plus surgery	9	5		
		Doxorubicin: 20 mg weekly + HART (30 Gy pre-op, 16 Gy post-op, 1.3 Gyx2/day)	3	0	4.5 months	Treatment period 1989–1992
		Above plus surgery	14	11		
	[33]	Doxorubicin: 20 mg weekly + HART (46 Gy pre-op, 1.6 Gyx2/day)	5	0	2 months	Treatment period 1993–1999
		Above plus surgery	17	17		
Doxorubicin, cisplatin + radiation + surgery[a]	[38]	Doxorubicin: 60 mg/m^2; cisplatin: 90 mg/m^2 q 4 weeks × 4 cycles; RT (70 Gy)	3	1	NR	Patients <65 years
		Above plus surgery	9	7		
Doxorubicin, docetaxel + radiation + surgery[a]	[40]	Doxorubicin: 60 mg/m^2; docetaxel 60 mg/m^2 × 4 cycles‡; IMRT (57.6–70 Gy)	1	7	36 months	All patients had stage IVA or IVB disease
		Above plus surgery	9			
Other regimens						
Methotrexate + radiation	[29]	MTX: 5 mg/day; RT (30–40 Gy)	8	2	9 months	Severe toxicity noted in all patients
Bleomycin, cyclophosphamide, 5-FU + radiation + surgery[a]	[35]	Bleomycin: 5 mg/day; cyclophosphamide: 200 mg/day; 5-FU 500 mg q od × 10 day; RT (30–40 Gy)	8	NR	3 months	Patient treated with surgery alive and disease-free 12+ years
		Above plus surgery	1	1		
	[28]	Bleomycin: (none); cyclophosphamide: 200 mg/day; 5-FU 500 mg q od × 10 day; RT (48 Gy)	8	1	3 months	1 long-term CR 59+ months
		Above plus surgery	5	3	5 months	
Mitoxantrone + radiation	[38]	Mitoxantrone: 14 mg/m^2 q 4 weeks × 4 cycles; RT (70 Gy)	5	2	NR	Patients >65 years
		Above plus surgery	3	3		

[a]If feasible

Between 1973 and 1979, 22 patients were recruited to a study of 5-fluorouracil (5-FU) and cyclophosphamide administered concurrently with daily radiation therapy (48 Gy over 4 weeks) [28, 29, 32]. One patient treated with chemoradiation alone had a complete response and was disease-free after 59 months, but all other patients treated with chemoradiation alone (seven of eight patients) died of progressive local disease. Local control rates were improved in patients treated with surgery in addition to chemoradiation, with only two of five patients experiencing local failure; two of these patients died of metastatic disease, and one patient was a long-term survivor. Addition of bleomycin to the above regimen (BCF) was evaluated in nine patients during the same period [35]. Objective responses were seen in seven of nine patients. Surgery was performed on a single patient at the peak of remission; this patient was the only long-term survivor (12+ years).

Subsequent protocols were amended to include surgery whenever possible, and radiation therapy was modified to include hyperfractionated regimens. From 1975 to 1980, 19 patients were treated with BCF plus ≤30 Gy neoadjuvant hyperfractionated radiation therapy, followed by surgery and followed by postoperative concurrent chemoradiation (15 Gy) [36]. Patients could then receive additional 5-FU and cyclophosphamide every other month for an additional five cycles. Median survival in patients with more advanced disease was 7 months, and there were no long-term survivors; median survival in ten patients with less advanced

disease was 12 months, and three patients were deemed long-term survivors with no evidence of disease at 31+, 61+, and 80+ months. Local failure rates were not reported, but no patients required tracheostomy.

Between 1984 and 1992, 33 consecutive patients with cytologically verified ATC were treated with a regimen of doxorubicin 20 mg weekly given concurrently with 30 Gy preoperative and 16 Gy postoperative hyperfractionated radiation therapy [31]. Radiation was given as 1 Gy twice daily prior to 1988 and 1.3 Gy twice daily after 1988, but the total dose of radiation did not differ between cohorts. The majority of patients were able to proceed to surgery. Local recurrences occurred in 17 patients (52 %) and 8 patients (24 %) died of local disease. Four patients were considered long-term disease-free survivors. All radiation was subsequently given in a neoadjuvant fashion from 1993 to 1999 as 1.6 Gy twice daily to a cumulative dose of 46 Gy [33]. All 17 patients who are able to proceed to surgery had local control, though the majority subsequently died of metastatic disease (15 of 17). Median survival remained suboptimal at 3 months. Similar results have been reported in other studies [37–39].

More recently, Foote and colleagues [40] summarized their experience at the Mayo Clinic between 2003 and 2007 with aggressive, multimodal therapy in a subset of patients with regionally advanced ATC (stages IVA and IVB). Planned therapy included surgery when feasible, four cycles of docetaxel and doxorubicin with growth factor support, and intensity-modulated radiation therapy (IMRT) initiated with the first cycle of chemotherapy. Actual chemotherapy regimens were modified based on underlying patient comorbidities, and total radiation doses ranged from 57.6 to 70 Gy. Results were encouraging, with 1-year overall survival of 70 % and five of ten patients disease-free at 32+, 40+, 44+, 52+, and 89+ months. These compared favorably to historical experience with stage IVA and IVB disease. The authors noted that the advent of IMRT, the addition of taxane therapy to anthracycline-based regimens, and the administration of adjuvant chemotherapy in addition to radiosensitizing doses of chemotherapy may have contributed to the improved outcomes. Further validation was recommended.

Summary

ATC is an aggressive, relatively chemoresistant subtype of thyroid cancer, with limited response to conventional treatment regimens. Mechanisms of chemoresistance remain poorly understood but may include overexpression of the multidrug resistance-associated protein (MRP) and mutations in p53 and other cell-cycle regulatory proteins [41, 42]. Aggressive, multimodality therapy currently provides the best opportunity for clinical response and can provide a small subset of patients with long-term disease-free survival. Additionally, even in patients with distant metastases, local control with combined treatment may prevent distressing upper airway obstruction and improve quality of life. There remains a great need for improvement in current treatment regimens, and targeted therapies have the potential to revolutionize the treatment of this disease in the future. Clinical trials open to patients with ATC are summarized in Table 99.3. Additional novel approaches to therapy are discussed in Chap. 98.

Table 99.3 Ongoing clinical trials open to patients with anaplastic thyroid cancer

Investigational therapy	Selected mechanisms	Title	Phase	Lead institution
Clinical trials with a focus on anaplastic thyroid cancer				
EPC2407 (crolibulin) ± cisplatin	Microtubule inhibitor, DNA cross-linking	A phase 1/2 trial of crolibulin (EPC2407) plus cisplatin in adults with solid tumors with a focus on anaplastic thyroid cancer (ATC)	Phase 1/2	NCI (USA)
Bevacizumab + doxorubicin	VEGF inhibitor, topoisomerase II inhibitor	Avastin and doxorubicin postoperatively for patients with anaplastic thyroid cancer	Phase 2	Lund University Hospital (Sweden)
Other clinical trials open to patients with anaplastic thyroid cancer				
Pemetrexed + paclitaxel	Antifolate, microtubule inhibitor	Pemetrexed + paclitaxel in patients with recurrent/advanced thyroid cancer	Phase 2	University of Kiel (Germany)
Pazopanib	VEGFR1–3, PDGFR, KIT inhibitor	Pazopanib in treating patients with advanced thyroid cancer	Phase 2	Mayo Clinic (USA)
PLX108-01 (PLX3397)	FMS, KIT, FLT3 inhibitor	Safety study of PLX108-01 in patients with solid tumors	Phase 1	Plexxikon (USA)
Everolimus	mTOR inhibitor	Everolimus in treating patients with progressive or recurrent, unresectable, or metastatic thyroid cancer	Phase 2	Leiden University Medical Center (Netherlands)
		Everolimus in treating patients with locally advanced or metastatic thyroid cancer	Phase 2	Yonsei University (Korea)
Dabrafenib and trametinib	BRAF inhibitor and MEK inhibitor	Efficacy and safety of the combination therapy of dabrafenib and trametinib in subjects with BRAF V600E-mutated rare cancers	Phase 2	GSK (USA)

References

1. Hossain A, et al. Epidemiology, treatment outcome, and survival of anaplastic thyroid cancer (ATC) in the United States: a period prevalence SEER database study 1973–2006. J Clin Oncol. 2010; 28(15s):abstr 5588.
2. Wiseman S, et al. Derangement of p53 and MDM2 is involved in transformation of differentiated into anaplastic thyroid cancer. J Clin Oncol. 2006;24(18s):abstr 5556.
3. Chen J, et al. Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: analysis of the surveillance, epidemiology, and end results 1983–2002. Am J Clin Oncol. 2008; 31(5):460–4.
4. Schoumacher P, et al. Anaplastic carcinoma of the thyroid gland. Eur J Cancer. 1977;13(4–5):381–3.
5. Simpson WJ. Anaplastic thyroid carcinoma: a new approach. Can J Surg. 1980;23(1):25–7.
6. Gottlieb JA, Hill Jr CS. Chemotherapy of thyroid cancer with adriamycin. Experience with 30 patients. N Engl J Med. 1974;290(4):193–7.
7. Shimaoka K, et al. A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer. 1985;56(9):2155–60.
8. De Besi P, et al. Combined chemotherapy with bleomycin, adriamycin, and platinum in advanced thyroid cancer. J Endocrinol Invest. 1991;14(6):475–80.
9. Tamura K, et al. Intensive chemotherapy for anaplastic thyroid carcinoma: combination of cisplatin, doxorubicin, etoposide and peplomycin with granulocyte granulocyte colony-stimulating factor support. Chemotherapy Committee, The Japanese Society of Thyroid Surgery. Jpn J Clin Oncol. 1995;25(5):203–7.
10. Gottlieb JA, et al. Chemotherapy of thyroid cancer. An evaluation of experience with 37 patients. Cancer. 1972;30(3):848–53.
11. Ain KB, Egorin MJ, DeSimone PA. Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group. Thyroid. 2000;10(7):587–94.
12. Higashiyama T, et al. Induction chemotherapy with weekly paclitaxel administration for anaplastic thyroid carcinoma. Thyroid. 2010;20(1):7–14.
13. Kawada K, et al. The feasibility study of docetaxel in patients with anaplastic thyroid cancer. Jpn J Clin Oncol. 2010;40(6):596–9.
14. Stevenson JP, et al. Phase I trial of the antivascular agent combretastatin A4 phosphate on a 5-day schedule to patients with cancer: magnetic resonance imaging evidence for altered tumor blood flow. J Clin Oncol. 2003;21(23):4428–38.
15. Mooney CJ, et al. A phase II trial of fosbretabulin in advanced anaplastic thyroid carcinoma and correlation of baseline serum-soluble intracellular adhesion molecule-1 with outcome. Thyroid. 2009; 19(3):233–40.
16. Sosa JA, et al. A randomized phase II/III trial of a tumor vascular disrupting agent fosbretabulin tromethamine (CA4P) with carboplatin (C) and paclitaxel (P) in anaplastic thyroid cancer (ATC): final survival analysis for the FACT trial. J Clin Oncol. 2011;29(15s):abstr 5502.
17. Gramza A, et al. Phase I/II trial of crolibulin and cisplatin in solid tumors with a focus on anaplastic thyroid cancer: phase I results. J Clin Oncol. 2013;31(suppl):abstr 6074.
18. Ha HT, et al. A phase II study of imatinib in patients with advanced anaplastic thyroid cancer. Thyroid. 2010;20(9):975–80.
19. Schiff BA, et al. Epidermal growth factor receptor (EGFR) is overexpressed in anaplastic thyroid cancer, and the EGFR inhibitor gefitinib inhibits the growth of anaplastic thyroid cancer. Clin Cancer Res. 2004;10(24):8594–602.
20. Hogan T, et al. Oncocytic, focally anaplastic, thyroid cancer responding to erlotinib. J Oncol Pharm Pract. 2009;15(2): 111–7.
21. Pennell NA, et al. A phase II study of gefitinib in patients with advanced thyroid cancer. Thyroid. 2008;18(3):317–23.
22. Gupta-Abramson V, et al. Phase II trial of sorafenib in advanced thyroid cancer. J Clin Oncol. 2008;26(29):4714–9.
23. Kloos RT, et al. Phase II trial of sorafenib in metastatic thyroid cancer. J Clin Oncol. 2009;27(10):1675–84.
24. Cohen EE, et al. Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study. J Clin Oncol. 2008;26(29):4708–13.
25. Lorch J, et al. A phase II study of everolimus in patients with aggressive RAI refractory (RAIR) thyroid cancer (TC). J Clin Oncol. 2013;31(suppl):abstr 6023.
26. Lee Y, et al. Multimodal therapeutic approach in anaplastic thyroid cancer. J Clin Oncol. 2006;24(18s):abstr 15533.
27. Orita Y, et al. Prospective application of our novel prognostic index in the treatment of anaplastic thyroid carcinoma. Surgery. 2011; 150(6):1212–9.
28. Tennvall J, et al. Undifferentiated giant and spindle cell carcinoma of the thyroid. Report on two combined treatment modalities. Acta Radiol Oncol Radiat Phys Biol. 1979;18(5):408–16.
29. Tallroth E, et al. Multimodality treatment in anaplastic giant cell thyroid carcinoma. Cancer. 1987;60(7):1428–31.
30. Tennvall J, et al. Anaplastic thyroid carcinoma. Doxorubicin, hyperfractionated radiotherapy and surgery. Acta Oncol. 1990; 29(8):1025–8.
31. Tennvall J, et al. Combined doxorubicin, hyperfractionated radiotherapy, and surgery in anaplastic thyroid carcinoma. Report on two protocols. The Swedish Anaplastic Thyroid Cancer Group. Cancer. 1994;74(4):1348–54.
32. Nilsson O, et al. Anaplastic giant cell carcinoma of the thyroid gland: treatment and survival over a 25-year period. World J Surg. 1998;22(7):725–30.
33. Tennvall J, et al. Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. Br J Cancer. 2002;86(12):1848–53.
34. Wallin G, Lundell G, Tennvall J. Anaplastic giant cell thyroid carcinoma. Scand J Surg. 2004;93(4):272–7.
35. Andersson T, et al. Combined therapy for undifferentiated giant and spindle cell carcinoma of the thyroid. Acta Otolaryngol. 1977; 83(3–4):372–7.
36. Werner B, et al. Multimodal therapy in anaplastic giant cell thyroid carcinoma. World J Surg. 1984;8(1):64–70.
37. Kim JH, Leeper RD. Treatment of locally advanced thyroid carcinoma with combination doxorubicin and radiation therapy. Cancer. 1987;60(10):2372–5.
38. Schlumberger M, et al. Combination therapy for anaplastic giant cell thyroid carcinoma. Cancer. 1991;67(3):564–6.
39. Tanaka K, Sugitani I, Fujimoto Y. A novel chemo-radiotherapy with low-dose daily cisplatin, 5-fluorouracil and doxorubicin for anaplastic thyroid carcinoma: a preliminary report. Jpn J Clin Oncol. 2011;41(9):1074–8.
40. Foote RL, et al. Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy. Thyroid. 2011;21(1):25–30.
41. Sugawara I, et al. Expression of multidrug resistance-associated protein (MRP) in anaplastic carcinoma of the thyroid. Cancer Lett. 1994;82(2):185–8.
42. Lavra L, et al. Gal-3 is stimulated by gain-of-function p53 mutations and modulates chemoresistance in anaplastic thyroid carcinomas. J Pathol. 2009;218(1):66–75.