



RESEARCH ARTICLE

ROLE OF TYROSINE KINASE INHIBITOR THERAPY IN ANAPLASTIC THYROID CANCER

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ABSTRACT

Background: Anaplastic thyroid cancer (ATC) is an orphan disease with an extremely poor prognosis. Radical surgery is possible only for stage IVA anaplastic thyroid cancer, and no effective treatments are available for stage IVB or IVC anaplastic thyroid cancer. The response rate of the disease to cytotoxic chemotherapy has been previously reported as unsatisfactory.

Objective: In 2015, lenvatinib was approved and reimbursed for anaplastic thyroid cancer in Japan, including radioactive iodine-refractory differentiated thyroid cancer. Because of its rarity, only a few reports exist regarding the collective treatment outcomes of lenvatinib for anaplastic thyroid cancer.

Methods: A comprehensive literature review was finalized in September 2018. PubMed® was used for research. Electronic search results were supplemented via hand searching of selected papers, expert consensus meeting notes, and reference lists from selected articles.

Results: We reviewed the progress of the chemotherapy for ATC before the tyrosin kinase inhibitor (TKI) treatment and collected the reports regarding the treatment outcomes of lenvatinib for ATC.

Conclusions: In this study, we reviewed the outcomes of chemotherapy for anaplastic thyroid cancer and assessed the role of tyrosine kinase inhibitor therapy in future treatment.

INTRODUCTION

Anaplastic thyroid cancer (ATC) is a rare but deadly form of thyroid cancer. Although it accounts for only 1%–2% of all thyroid cancer cases each year, the relative 5-year survival of patients diagnosed with this cancer is 7%. ATC is more common in the elderly, and it almost always arises after preexisting well-differentiated thyroid cancer (Kebebew, 2005 and Venkatesh, 1990). Because ATC is rare, there are extremely few studies involving sufficient numbers of patients to adequately assess treatment outcomes (Machens, 2001 and Haigh, 2001). In prior research, survival was improved in a subset of patients with primary pT4 ATC with negative lymph nodes who underwent macroscopic tumor resection. The survival rate of patients with ATC has not changed over the past 20 years. Clinical trials, both randomized and non-randomized, have included a total of 205 patients. Unfortunately, considerable improvement in understanding the pathogenesis and genetics of ATC has not resulted in improved outcomes (Bisof, 2015). Multimodality management of ATC provides a marginal treatment benefit (Haymart, 2012).

Radical surgery alone did not significantly increase survival duration compared to less radical surgery (Venkatesh, 1990). Similarly, chemotherapy did not improve long-term survival (Xia, 2018). Conversely, some reports indicated that the addition of chemotherapy to institutional protocols led to improved survival, but prognosis remains extremely poor (Kebebew, 2005 and Lowe, 2014). In 2015, lenvatinib was approved for treating ATC in Japan. The present review evaluated previous reports of chemotherapy for ATC and assessed the potential contribution of TKIs to improving the treatment of ATC.

MATERIALS AND METHODS

A comprehensive literature review was finalized in September 2018. PubMed® was used for research. Electronic search results were supplemented via hand searching of selected papers, expert consensus meeting notes, and reference lists from selected articles. The literature search was limited to English-language articles involving human subjects. The following medical subject heading terms were used in the search: undifferentiated (anaplastic) thyroid cancer (carcinoma), emerging therapies, chemotherapy, lenvatinib, and TKI. Conference proceedings and scientific meeting abstracts were excluded.

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RESULTS

Progress of the chemotherapy for ATC before the TKI treatment

Paclitaxel: Induction chemotherapy with weekly paclitaxel is a promising therapeutic strategy for patients with stage IVB ATC. Responders can be expected to achieve long-term survival. We did not observe a significant difference of overall survival (OS) for patients with stage IVC according to the receipt of weekly induction paclitaxel. Additionally, induction chemotherapy did not improve OS in patients with stage IVC ($p = 0.2002$), (Higashiyama, 2010). Nineteen evaluable patients exhibited a total response rate of 53% (95% confidence interval [CI] = 29%–76%), including one complete response and nine partial responses (including one off-protocol response) (Ain, 2000). The median OS time was 6.7 months (95% CI = 4.4–9.0). The 6-month OS was 54%. Among the 42 patients with an evaluable lesion, none demonstrated complete remission, 9 (21%) displayed partial remission, 22 (52%) achieved stable disease, and 8 (19%) exhibited progressive disease; meanwhile, three patients did not complete the initial treatment course. The objective response rate was 21%, and the clinical benefit rate was 73% (Onoda, 2016).

Doxorubicin: There were no signs of local recurrence in 16 patients (48%). Death was attributed to local failure in eight patients (24%). In four patients, survival with no evidence of disease exceeded 2 years (Tennvall, 1994).

Docetaxel: The response rate for docetaxel was 14% (Kawada, 2010), and the disease control rate was 43%. In addition, high efficacy was observed for concomitant treatment with radiation and docetaxel in patients with ATC (Troch, 2010).

Fosbretabulin: The median survival was 4.7 months, whereas the 6- and 12-month survival rates were 34% and 23%, respectively. Median duration of stable disease in seven patients was 12.3 months (range, 4.4–37.9 months) (Mooney, 2009).

Multimodality treatment: The median OS was 5.2 months (95% CI = 3.1–9.0) in the Carboplatin (CP)/fosbretabulin arm ($n = 55$; hazard ratio [HR] = 0.73 (95% CI = 0.44–1.21), versus 4.0 months (95% CI = 2.8–6.2) for the CP arm ($n = 25$; $p = 0.22$ [log rank test]). The 1-year survival for CP/fosbretabulin was 26%, versus 9% for CP. There was no significant difference in progression-free survival (PFS) between the two arms (Sosa, 2014). In a randomized study of Eastern Cooperative Oncology Group (ECOG), the combination of cisplatin and doxorubicin (Shimaoka, 1985) was more effective than doxorubicin alone, including a higher complete response rate (Denaro, 2013). Partial responses and stable disease were observed in three patients each. After excluding two patients receiving the treatment as adjuvant therapy, the response rate was 50% (Seto, 2015). Multimodality treatment significantly improves local control and appeared to provide long-term survival in some patients (Derbel, 2011). These results are summarized in Table 1. There are some interesting case reports and experimental results for chemotherapy for ATC. A complete response was achieved after induction chemotherapy (weekly carboplatin and docetaxel) in a patient who underwent subsequent radiotherapy (Koussis, 2015). In a mouse model, one combination regimen consisted of Combretastatin A4 phosphate (CA4P), paclitaxel, and manumycin A (a farnesyltransferase inhibitor), and a

second combination included, CA4P, paclitaxel, and carboplatin (Yeung, 2007). Carfilzomib treatment significantly increased survival in mice with established, widely metastatic disease without significant toxicity (Mehta, 2015).

The start of TKI treatment for ATC: In 2014, the Decision trial [24] reported that median PFS was significantly longer in the sorafenib group (10.8 months) than in the placebo group (5.8 months; HR = 0.59, 95% CI = 0.45–0.76; $p < 0.0001$). As reported in 2015, the median PFS in the Select trial (Schlumberger, 2015), was 18.3 months in the lenvatinib group, compared to 3.6 months in the placebo group (HR for progression or death = 0.21; 99% CI = 0.14–0.31; $p < 0.001$). Then, we started to use clinically these TKIs for radioactive iodine-refractory DTC. Regarding TKI treatment for ATC, sorafenib was reported in 2013 (Savvides, 2013), and lenvatinib was reported in 2016 (Schlumberger, 2016). Although efficacy was not a primary objective, this was the first report of an efficacy outcome for patients with ATC.

Treatment outcome of lenvatinib for ATC: In 2016, preliminary results were reported for a phase 2 study examining the safety and efficacy of lenvatinib in advanced thyroid cancer, including ATC (Schlumberger, 2018). The median PFS was 7.4 months (95% CI = 1.7–12.9), the median OS was 10.6 months (95% CI = 3.8–19.8), and the objective response rate was 24% (Tahara, 2017). Three patients experienced a partial response, and one patient exhibited stable disease. The median PFS was 4.1 months (range, 1.1–12.2) (Yamazaki, 2017). Small studies involving three (Iniguez-Ariza, 2017) and five cases (Koyama, 2018) have also been reported. Our results involving 23 patients with ATC have also been published (Iwasaki, 2018). These results are summarized in Table 2. Additionally, although some case reports have described the strong efficacy of molecular-targeted therapy, its negative side must be addressed (Ohkubo, 2018). In related articles, rare adverse events were reported, including thyroid dysfunction (Koyama, 2018), pneumothorax (Iwasaki, 2018). Additionally, one patient died from rupture of the common carotid artery 30 days after the initiation of lenvatinib therapy (Ohkubo, 2018). In experimental studies, lenvatinib provided antitumor activity mainly via angiogenesis inhibition, but the drug also inhibited FGFR and RET signaling in preclinical human thyroid cancer models (Tohyama, 2014).

Treatment that can be expected in the future

In recent years, several studies of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors have been reported, including studies of BRAF inhibition in ATC with activating BRAF mutations (Rosove, 2013) and a phase II open-label trial assessing the efficacy and safety of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) combination therapy in BRAF V600E-mutated ATC (Subbiah, 2018). In a case report, a dramatic response to vemurafenib was noted in a 51-year-old man with BRAF-mutated ATC (Rosove, 2013). The BRAF inhibitor PLX4720 induced striking tumor regression and a reversal of cachexia in a mouse model of ATC harboring the BRAFV600E mutation (Nehs, 2012). Additionally, the combination of PLX4720 and dasatinib induced apoptosis, increased immune cell infiltration, and reduced tumor volume in a preclinical model of ATC (Vanden Borre, 2014). Programmed death-1 (PD-1) checkpoint blockers may have therapeutic efficacy in patients with aggressive forms of thyroid cancer (Bastman, 2016).

Table 1. Chart review of chemotherapy for ATC

Chemotherapy	Series	Year	N	Therapies	Previous therapy		Staging			Outcomes	
					RT	S	IVA	IVB	IVC	OS	CR/PR/SD/PD
Paclitaxel	Higashiyama et al[9]	2010	13	weekly PTX 80mg/m ²	4	7	0	9	4		1/3/4/5
	Ain et al[10]	2000	19	every 3 weeks 120mg/m ²	5	11	3		16	6.3	1/9/1/8
	Onoda et al[11]	2016	56	weekly PTX 80mg/m ²	ND	25	11	19	22	6.7	ND
Doxorubicin	Tennvall et al[12]	1994	33	RT+weekly doxorubicin 20mg	33	24	22		11	4.0	ND
Docetaxel	Kawada et al[13]	2010	7	every 3 weeks 60mg/m ²	1	3	1			3.3	1/0/2/4
	Troch et al[14]	2010	6	every 3 weeks 100mg	6	3	4		2		5/1/0/0
Fosbretablin Combination	Mooney et al[15]	2009	26	45mg/m ² on days 1,8,15,28 2cycle	16	12	7		19	4.7	ND
	Sosa et al[16]	2010	80	55 PTX/CBP/FB 25 PTX/CBP	32	44	2	6	72	5.1	ND

Abbreviations: RT, radiation therapy; S, surgery; OS, overall survival; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; PTX, paclitaxel; CPB, carboplatin; FB, fosbretabulin; ND, not described

Table 2. Studies of lenvatinib efficacy for ATC

Series	year	N	Previous therapy			Staging			Response		Note	
			CT	RT	S	IVA	IVB	IVC	X	OS		PR/SD/PD/NE
Tahara et al[28]	2017	17	7	9	14	4	5	6	2	10.6	4/12/1/0	best response
Yamazaki et al[29]	2017	7	0	0	2	0	2	5	0	4.1*	3/1/0/3	best response
Iniguez-Ariza et al[30]	2017	3	3	3	2	0	1	2	0	5.0	0/3/0/0	best response
Koyama et al[31]	2018	5	1	1	1	0	1	4	0	5.3	3/2/0/0	best response
Iwasaki et al[32]	2018	23	0	1	9	0	0	23	0	5.3	4/6/7/6	final assessment

Abbreviations: CT, chemotherapy; RT, radiation therapy; S, surgery; OS, overall survival; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; * PFS, progression free survival

PD-1/PD-L1 pathway proteins are highly expressed in ATC tumor samples, and they appear to represent predictive markers of PFS and OS in patients with multimodality-treated ATC (Chintakuntlawar, 2017). The generalized dependence of ATC cells on glucose catabolism makes them susceptible to the sensitizing effects of 2-DG for radiation therapy and chemotherapy (Espinal-Enriquez, 2015). The combination of quinacrine and sorafenib targets emerging molecular hallmarks of ATC and exhibits promising efficacy in clinically relevant models of the disease (Abdulghani, 2016). In a mouse model, combined anti PD-L1 treatment potentiates the effect of BRAF inhibitors on tumor regression and intensifies antitumor immune response in an immunocompetent model of ATC (Brauner, 2016).

DISCUSSION

Diagnosis for ATC: A significant percentage of our patients (35%) had areas of well-differentiated thyroid carcinoma in other locations, supporting the hypothesis that ATC arises from preexisting well-differentiated thyroid carcinoma (Venkatesh, 1990).When ATC is recognized from recurrent lesions during postoperative follow-up for DTC, re-staging is performed for ATC, but in this case, there is no choice but to diagnose the disease as stage IVB or stage IVC irrespective of the presence of distant metastasis (Perrier, 2018). In some cases, tissue can be resected and diagnosed pathologically as ATC, and ATC has been suspected by only cytological analysis in some cases. Alternatively, there were some cases in which ATC was clinically diagnosed after acute disease progression without pathological confirmation. In patients with good prognoses, the diagnosis for ATC may be suspicious, and in some studies, the subject case was not necessarily completely confirmed histologically.

Evaluation of efficacy for ATC with rapid progression: As a method of evaluating antitumor activity, some studies assessed efficacy according to the RECIST criteria (Eisenhauer, 2009), whereas others examined significant differences in OS.

Because of the short prognosis and aggressive illness, some studies reporting effectiveness according to the best response, and some studies limited the treatment period (Kasman, 2016 and Mani, 2016). Treatment methods have also varied, and it is difficult to identify the most effective treatment for ATC among surgery, irradiation, and a combination of multiple modalities in single-arm studies (Lowe, 2014). At present, we are interested in chemotherapy and TKIs, and treatments that can be expected in the future were discussed separately. Only some adjuvant chemotherapies followed by complete resection were reported good results in stage IVA and IVB ATC. Nevertheless, the problems of chemotherapy for ATC are that CR was not recognized in the treatment for residual disease or metastatic lesions, and that OS extension was not proved yet. Lenvatinib clearly has anti-tumor efficacy compared with conventional chemotherapy. However, there are still improvements for AE managements, and from the limits of single arm study, we should consider the combination therapy in the future.

Conclusions

Because ATC management is extremely challenging, researchers have examined emerging targeted therapies with great interest. However, although TKIs have exhibited promising efficacy in clinical trials, only a few studies have been reported. Clearly, improved understanding of the use of TKIs and management of adverse events is required to identify new therapeutic strategies for ATC. This knowledge might provide strategies for using TKIs both alone and in combination with conventional methods.

Conflict of interest statement: Hiroyuki Iwasaki and other co-authors have no conflict of interest.

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