

REVIEW

Anaplastic thyroid carcinoma: review of treatment protocols

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Abstract

Anaplastic thyroid carcinoma (ATC) is an orphan disease and in most patients fatal. So far no established treatment is available that prolongs survival. Several large retrospective studies have identified negative prognostic markers, analyzed efficacy of multimodal approaches such as radiotherapy with and without concurrent chemotherapy and chemotherapy protocols. Recently, single case reports have suggested some effectiveness of newer therapies targeting single somatic alterations in ATC. Overall, the conclusions that can be drawn from published retrospective studies and the scarce prospective approaches is that new treatment protocols should be developed including surgery, radiotherapy, chemotherapy and targeted therapy approaches and combinational therapy with immunotherapies. These protocols then need to be evaluated prospectively to improve ATC patients' outcome in routine care.

Key Words

- ▶ anaplastic thyroid carcinoma
- ▶ treatment protocol
- ▶ radiotherapy
- ▶ targeted therapy

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Introduction

Anaplastic thyroid carcinoma (ATC) is an orphan disease responsible for most thyroid carcinoma-associated deaths. Incidence is estimated to be 1–2 per million per year (Smallridge *et al.* 2012).

The histological diagnosis of ATC is challenging. In immunohistochemistry, ATC is characterized by negative staining for typical thyroid markers e.g. thyroglobulin (Molinaro *et al.* 2017). ATC is *per se* classified as stage IV disease by the American Joint Committee on Cancer (AJCC) and is further divided in stage IVA (T4a: intrathyroidal ATC and M0); stage IVB (T4b: extrathyroidal ATC and M0) and stage IVC disease (any T and M1) (Smallridge *et al.* 2012). Initial stage IVC disease is found in 20–40% of all ATC (Sugitani *et al.* 2012, Sun *et al.* 2013, Zivaljevic *et al.* 2014).

Recent high-throughput sequencing investigations have further elucidated the genetic signature of ATC (Kunstman *et al.* 2015, Landa *et al.* 2016, Latteyer *et al.* 2016a, Tiedje *et al.* 2017). One important characteristic is a high mutational burden due to the accumulation of different somatic mutations (Landa *et al.* 2016). Besides *TP53* mutations, considered as a genetic hallmark of ATC, several other genetic alterations have been identified to date in ATC e.g. *BRAF* and *RAS* mutations that also occur in differentiated thyroid carcinoma (DTC) (Tiedje *et al.* 2017). Therefore, it is possible that a subset of ATC arises from DTC. Moreover, histology shows that DTC co-exists in around 30–50% of ATC (Sugitani *et al.* 2012, Zivaljevic *et al.* 2014, Tiedje *et al.* 2017).

So far, no unified ATC treatment improving overall survival (OS) is established. Several guidelines e.g. from the American Thyroid Association (Smallridge *et al.* 2012) and the British Thyroid Association (BTA) (Perros *et al.* 2014) as well as the National Comprehensive Cancer Network and Practical Guidelines for ATC (Haddad *et al.* 2015) discuss treatment options, including surgery, radio- and/or chemotherapy. Recently, in case reports, efficacy of targeted therapy approaches has been reported. Moreover, checkpoint inhibitors might represent new treatment options (Brauner *et al.* 2016, Latteyer *et al.* 2016b).

This review will summarize current knowledge on prognostic factors and treatment options for ATC patients.

Prognostic factors and risk stratification

In multiple retrospective studies analyzing disease course and aiming to identify prognostic factors for ATC, reported OS was highly variable ranging from few weeks to several years (Sugitani *et al.* 2012, Sun *et al.* 2013, Zivaljevic *et al.* 2014). This implies that although ATC is fatal in most cases, risk stratification might be helpful. This would allow the distinction of patients in whom best supportive care should be administered from patients who may be considered for more aggressive treatment, ideally as part of a clinical trial.

Retrospective multicenter studies have shown that ATC survival is stage dependent (Haymart *et al.* 2013, Wendler *et al.* 2016). In a study including 699 ATC patients diagnosed between 2003 and 2008, survival, regardless of treatment approach, was 9 months in patients with stage IVA disease, 4.8 months in stage IVB disease and 3 months in stage IVC disease (Haymart *et al.* 2013).

Negative prognostic markers such as older age, initial distant metastatic disease, large primary tumor diameter (>5 cm) and elevated white blood count (WBC) have been described in several retrospective studies (Orita *et al.* 2011, Sugitani *et al.* 2012, Zivaljevic *et al.* 2014).

In a recent retrospective Germany multicenter study including 100 ATC patients, pre-therapeutic prognostic factors for longer survival were age <70 years, absence of distant metastases and complete local resection (Wendler *et al.* 2016).

A Japanese group has prospectively evaluated 74 ATC patients using a prognostic index (PI) for treatment stratification. Four characteristics were included in the PI: acute symptoms, tumor size >5 cm, distant metastasis and WBC > 10.000/mm³ (max. 4 points). ATC patients with low PI (≤ 1) were treated more aggressively with multimodal treatment (surgery, radiotherapy and chemotherapy)

compared to subjects with higher PI. Mean survival of ATC patients with $PI \leq 1$ was significantly longer (442 days) compared to patients with $PI \geq 3$ (113 days) (Orita *et al.* 2011).

In a single-center Chinese study a prognostic score, which comprised age (<55 years: score 0, ≥ 55 years: score 1), blood platelet count (<300 $\times 10^9/L$: score 0, $\geq 300 \times 10^9/L$: score 1), WBC (<10 $\times 10^9/L$: score 0, $\geq 10 \times 10^9/L$: score 2) and stage (IVA: score 0, IVB: score 1, IVC: Score 2), was evaluated in a cohort of 42 patients. In multivariate analysis, risk group and therapeutic regimen were independent prognostic factors (Sun *et al.* 2015).

It is discussed whether patients with preceding benign thyroid disease in terms of goiter or differentiated thyroid carcinoma (DTC) that develop ATC may have better prognosis. In a retrospective study analyzing data of ATCs diagnosed in 17 Dutch hospitals from 1989 to 2009, 29 of 94 patients had preexisting goiter ($n=21$) or DTC ($n=8$). However, OS was similar in patients with preexistent goiter or DTC (55 days) compared to patients without known previous thyroid disease (56 days) (Steggink *et al.* 2015).

Surgery

Due to the nature of the disease in clinical practice, indication for surgery is often highly individualized especially since in many patients ATC is diagnosed after surgery. For instance, data from the American National Cancer Database (NCDB) show that in up to 40% of patients, the diagnosis was not made prior to surgery (Goffredo *et al.* 2015). Furthermore, available studies on the role of surgery in the setting of ATC are predominantly of retrospective nature and suffer a selection bias as the multimodal therapy is rather heterogeneous.

One must conclude that available studies are not designed to conclusively proof when and to what extent surgery is warranted in ATC and which patient will truly benefit. However, in general, it is accepted that patients with intrathyroidal and extrathyroidal ATC without invasion of the aerodigestive tract should be discussed for surgery, whereas extrathyroidal ATC with invasion of the aerodigestive tract should not primarily be considered for surgery (Dralle *et al.* 2013). Similarly, according to the 2012 American Thyroid Association guidelines, surgery in ATC patients is recommended in stage IVA and IVB disease and when gross tumor resection (at least R1) can be achieved (Smallridge *et al.* 2012).

However, data extraction and analysis from the NCDB show that this recommendation does not reflect the

clinical reality. Goffredo and coworkers identified a cohort of 680 patients treated between 2003 and 2006. 335 of 680 patients underwent surgery, and stage IVC disease was reported in 25 of these patients (Goffredo *et al.* 2015). Despite the fact that preoperative resectability must have been assumed, gross tumor resection (i.e. at least R1) was achieved in over 70% of stage IVB and stage IVC. In contrast, tumor-free resection margins were achieved in almost 60% in stage IVA disease, while this number drops by half in stage IVB and IVC disease (i.e. 30% and 36%, respectively) (Goffredo *et al.* 2015).

Retrospective studies are prone for selection bias. Based on the NCBDB study, when compared to the cohort of patients who did not undergo surgery, any kind of surgery was significantly associated with longer OS in stage IVA (9.7 vs 3.0 months without surgery) and stage IVC patients (3.4 months with vs 1.7 months without surgery) and trend toward significance in stage IVB patients (4.2 with vs 3.4 months without surgery) (Goffredo *et al.* 2015). The confounding effect might become apparent when we note that in this study, the extent of surgery (i.e. R0 vs R1 vs R2) did not affect the overall survival thus contradicting the general positive effect of surgery (Goffredo *et al.* 2015).

To this regard, Brignardello and coworkers took a unique approach as they evaluated the role of surgery in advanced ATC (i.e. stage IVB and stage IVC) (Brignardello *et al.* 2014). This group retrospectively analyzed a cohort of 55 stage IVB and stage IVC patients, treated between 1999 and 2012. Overall, 17 of 24 stage IVB and 24 of 31 stage IVC patients have been found eligible for surgery. In contrast to other studies, the extent of surgery was reported and in addition to thyroidectomy and therapeutic central and lateral neck dissection frequently resection of soft tissue, nerve structures and vascular resection was performed.

Despite their surgical expertise, in 12 of 41 patients (29%), only 'partial debulking' with gross macroscopic tumor residuum was achieved. Complete tumor resection (R0) was achieved only in 4 patients and microscopic tumor residuum (R1) was reported for 5 patients. Thus, the ATA guidelines were fulfilled only in 9 of 41

patients (21%). Predominantly, the authors report a 'maximal debulking' ($n=20$) with minimal macroscopic tumor at vital structure (i.e. aerodigestive tract, carotid artery). The retrospective data analysis suggested that maximal debulking is associated with longer OS (6.5 vs 1.5 months) independent of disease stage. As the post-surgical treatment was very heterogeneous comprising radiotherapy and in some cases chemotherapy and OS analysis was not adjusted for the adjuvant treatment, a confounder cannot be ruled out (Brignardello *et al.* 2014).

As a consequence of the rarity of this disease, reflected in the existence of multiple retrospective rather than prospective studies and the heterogeneous multimodal management, it is impossible to prove which surgical approach is most beneficial for which patient. Overall, the available literature shows that surgery is clearly warranted in stage IVA disease and when gross tumor resection can be achieved, as overall survival will significantly increase (Goffredo *et al.* 2015). This recommendation is clearly supported by the only prospective study published so far. De Crevoisier and coworkers report that in a multivariate analysis, gross tumor resection (i.e. R0 or R1) is associated with longer survival (De Crevoisier *et al.* 2004).

Similar data can be extracted from the Korean nationwide retrospective study in which 329 ATC patients diagnosed between 2000 and 2012 were analyzed. In this study, surgery with curative intent – therefore excluding debulking procedures – was associated with better survival in stage IVA and IVB but not in IVC patients (Baek *et al.* 2016). Another recent study from Korea shows surgical intervention for selected patients might indeed result in a prolonged survival benefit. Lee and coworkers reported an initial remission rate of 60.5% and a cure rate of 42% of patients after initial R0/R1 resection (Lee *et al.* 2016).

Extent and thus morbidity of surgery must be balanced to the potential benefit. Details on post-surgical morbidity is scarce but was reported by Brignardello and coworkers. This group report recurrent laryngeal nerve injury in 2 of 55 patients (3.6%) and hypoparathyroidism in 11 of 55 patients (20%). Two of 55 patients required a

Table 1 Targeted therapy in ATC patients.

Targeted molecular alteration	Drug	Response	Reference
<i>BRAFV600E</i>	Dabrafenib + Trametinib	ORR 69%	Subbiah <i>et al.</i> (2017)
	Dabrafenib + Trametinib	PFS 9 months	Agarwal <i>et al.</i> (2016)
	Vemurafenib	PFS 2 months	Marten <i>et al.</i> (2015)
	Vemurafenib	CR 38 days	Rosove <i>et al.</i> (2013)
<i>ALK</i> translocation	Crizotinib	90% tumor reduction, PFS >6 months	Godbert <i>et al.</i> (2015)
<i>TSC2</i> truncating mutation (Q1178)	Everolimus	PFS 18 months	Wagle <i>et al.</i> (2014)

ORR, overall response rate; PFS, progression-free survival.

Table 2 Currently recruiting clinical trials for ATC patients.

Study title and recruiting countries	Drug	Primary endpoint
Atezolizumab Combinations with Chemotherapy for Anaplastic and Poorly Differentiated Thyroid Carcinomas, University of Texas MD Anderson Cancer Center, Texas, USA NCT03181100	Induction: Paclitaxel Cohort 1: Vemurafenib, Cobimetinib + Atezolizumab Cohort 2: Cobimetinib + Atezolizumab Cohort 3: Bevacizumab + Atezolizumab Cohort 4: Paclitaxel + Atezolizumab	Overall survival
A Phase II Study of MLN0128 in Metastatic Anaplastic Thyroid Cancer, Dana Farber Cancer Institute, Boston, Massachusetts, USA NCT02244463	MLN0128 (mTor inhibitor)	Progression-free survival
Phase II Study Assessing the Efficacy and Safety of Lenvatinib for Anaplastic Thyroid Cancer, (HOPE), Multiple Centers Japan NCT02726503	Lenvatinib	Overall survival
Phase II Trial of Pembrolizumab in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer, UT Southwestern Medical Center, Dallas, Texas, USA NCT02688608	Pembrolizumab	Response rate
Trametinib in Combination With Paclitaxel in the Treatment of Anaplastic Thyroid Cancer, Memorial Sloan Kettering Cancer Center, New York, USA NCT03085056	Trametinib and paclitaxel	Progression-free survival
Phase II Trial of Pembrolizumab in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer, UT Southwestern Medical Center, Dallas, Texas, USA NCT02688608	Pembrolizumab	Response rate
An Open-Label, Single-Arm, Multicenter, Phase 2 Trial of Lenvatinib for the Treatment of Anaplastic Thyroid Cancer, Multiple Centers in USA NCT02657369	Lenvatinib	Objective response rate
A Pilot Study of Durvalumab (MEDI4736) with Tremelimumab in Combination With Image Guided Stereotactic Body Radiotherapy (SBRT) in the Treatment of Metastatic Anaplastic Thyroid Cancer, Memorial Sloan Kettering Cancer Center, New York, USA NCT03122496	Durvalumab and tremelimumab	Overall survival
Ceritinib in Mutation and Oncogene Directed Therapy in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer, UT Southwestern Medical Center, Texas, USA NCT02289144	Ceritinib	Progression
A Phase I, Open-label, Multicenter Dose Escalation Study of FAZ053 as Single Agent and in Combination With PDR001 in Adult Patients With Advanced Malignancies, Texas, United States; Ontario, Canada; Tel Aviv, Israel; Koto and Tokyo, Japan; Singapore, Singapore; Barcelona, Spain NCT02936102	FAZ053 (Anti-PD-L1 Antibody) and PDR001 (Anti-PD-1 Antibody)	Number of participants with Adverse Events (AEs) as a measure of safety and tolerability
A Phase II Trial of CUDC-907 in Patients With Metastatic and Locally Advanced Thyroid Cancer, National Institutes of Health Clinical Center, Bethesda, Maryland, USA NCT03002623	CUDC-907 (dual inhibitor of HDAC and PI3K signaling)	Changes in tumor size and metastases
Open-Label Multicenter Phase I/II Study of the Safety and Efficacy of PDR001 Administered to Patients With Advanced Malignancies, United States, Canada, France, Spain, Germany, Hungary, Italy, Lebanon, Netherlands, Poland, Norway, Thailand, Turkey NCT02404441	PDR001 (PD-1 inhibitor)	The exposure (AUC (0–336 h)) after first dose of treatment Incidence of dose limiting toxicities Overall response rate
A Phase II, Open-label, Study in Subjects With BRAF V600E-Mutated Rare Cancers With Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib, United States, Austria, Belgium, Denmark, Canada, France, Germany, Italy, Korea, Netherlands, Norway and Spain NCT02034110	Dabrafenib and trametinib	Overall response rate

(Continued)

Table 2 Continued.

Study title and recruiting countries	Drug	Primary endpoint
Phase II Study for the Evaluation of Efficacy of Pembrolizumab (MK-3475) in Patients With Rare Tumors, University of Texas MD Anderson Cancer Center, Texas, USA NCT02721732	Pembrolizumab	Non-progression rate
An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements, United States, Australia, Belgium, France, Germany, Hong Kong, Italy, Japan, Korea, Netherlands, Poland, Singapore, Spain, Taiwan and United Kingdom NCT02568267	Entrectinib	Objective response rate
DART: Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors, National Cancer Institute, USA NCT02834013	Ipilimumab and nivolumab	Objective response rate

tracheostoma (3.6%), and hemorrhage was found in one of 55 patients (1.8%) (Brignardello *et al.* 2014). Thus, in the hands of a trained surgeon, the type and rate of surgical complications appear not to be increased compared to the morbidity observed for other thyroid cancer surgeries.

Open questions remain to be solved, such as the timing of surgical and multimodal intervention. Only condensation of these patients in few centers and prospective clinical trials will allow generating the data mandatory. To this end, a recent study by Lai and coworkers from the MD Anderson Cancer center is notable. The group reports of a newly implemented project that allowed to reduce the time between referral to first disposition from 8.7 days to 0.5 days. If this will help to improve overall survival is questionable. However, referral rate has increased and more importantly the rate for enrollment in treatment trials was 34% which is 10 times higher than the national average for all cancers (Cabanillas *et al.* 2017).

Radiotherapy

In a meta-analysis of 17 retrospective studies including 1147 patients it was shown, that radiotherapy improves survival in ATC patients (Kwon *et al.* 2016). However, it is not certain, as to which cumulative doses and whether radiotherapy vs combined radiochemotherapy before or after surgery is beneficial. A recent large analysis of 1288 patients from the NCDB including patients with

non-resected ATC survival was significantly better in patients with radiotherapy with a cumulative dose of >45 Gy compared to no radiotherapy or less than 45 Gy (Pezzi *et al.* 2017).

A German single-center study analyzed data of 40 ATC patients treated with surgery, radiotherapy and in some cases chemotherapy between 1989 and 2008. Cumulative doses of 50 Gy or more were associated with better median survival (10.5 months vs 3 months). However, technical approaches varied, e.g. opposing field technique and 3D-conformal technique (Dumke *et al.* 2014). In another single-center study from China including 60 ATC patients, radiation with cumulative doses of 40 Gy and higher were also associated with significant better survival (Sun *et al.* 2015).

In a historic British cohort, data of 20 ATC patients treated between 2004 and 2011 were analyzed. Patients receiving radiotherapy and chemotherapy had significant longer OS ($n=3$, median 220 days) compared to patients with surgery and radiotherapy ($n=4$, median OS 176 days) and patients receiving only radiotherapy ($n=6$, median OS 58.5 days). However, no multivariate analysis is provided and the study suffers from its limited number of patients (Lowe *et al.* 2014).

Chemotherapy

Clinical studies comparing different chemotherapy regimens in ATC patients are scarce. In a recent German

Table 3 Phase II and III studies of ATC patients.

Study type	Drug	N	Therapy response	Survival	Reference
Phase II/III	C4P 60 mg/m ² +/- carboplatin AUC6+ paclitaxel 200 mg/m ²	80		1-year survival 33.3% vs 7.7%	Sosa <i>et al.</i> (2012)
Phase II	Sorafenib	20	$N=2$ PR and $n=5$ SD	Median survival 1.9 months	Savvides <i>et al.</i> (2013)
Phase II	Pazopanib	35	$N=5$ PR	OS 19.9 months	Bible <i>et al.</i> (2012)
Phase II	Lenvatinib	17	PFS 7.4 months	OS 10.6 months	Tahara <i>et al.</i> (2017)

multicenter experience including 100 ATC patients treated between 2000 and 2015, 56 patients received any chemotherapy and had significantly better OS compared to those without chemotherapy (Wendler *et al.* 2016).

Higashiyama and coworkers reported outcome in 13 ATC patients treated with weekly paclitaxel before and after surgery followed by radiotherapy. The response rate was 33% with one patient achieving complete response, two patients showing partial response and four patients showing stable disease (Higashiyama *et al.* 2010).

In a case series, 8 ATC patients with stage IVB ($n=4$) and stage IVC ($n=4$) disease were treated by surgery and radiotherapy followed by chemotherapy with docetaxel 75 mg/m² and cisplatin 75 mg/m² every 4 weeks for 6 courses. The pre-chemotherapy setting differed: two patients had adjuvant chemotherapy with an OS of 3 years and 5.3 years respectively, one patient received induction chemotherapy (OS 3 months) and 5 patients had chemotherapy for distant metastatic disease with an OS of 9 months, 1.7, 4.3, 1 and 3.3 years respectively (Seto *et al.* 2015).

So far, in the largest placebo-controlled prospective chemotherapy trial for ATC, 80 patients were enrolled. The efficacy of the addition of vascular disruptive agent fosbretabulin (Combretastatin A-4 phosphate) 60 mg/m² to carboplatin AUC6 and paclitaxel 200 mg/m² every 3 weeks for 6 cycles was investigated. Patients undergoing surgery ($n=44$) benefited most from additional fosbretabulin treatment ($n=30$) with OS of 8.2 months compared to 4.0 months in the control group ($n=14$). The effect was enhanced by younger age: Patients younger than 60 years who received surgical treatment ($n=23$) had significantly prolonged OS (10.9 months) when treated additionally with fosbretabulin ($n=17$) compared to patients only treated with carboplatin and paclitaxel ($n=6$; 6.8 months). In patients who did not undergo surgery OS was similar in both treatment groups (4.0 and 4.6 months) (Sosa *et al.* 2012). These data suggest that a subgroup of ATC patients may benefit from additional fosbretabulin therapy after surgery. In fact, 1-year survival was longer in patients treated with the combination of carboplatin, paclitaxel and fosbretabulin compared to chemotherapy only (26% vs 9%), however, without reaching statistical significance (Sosa *et al.* 2014).

Multimodal therapy

Several retrospective studies have demonstrated significant survival benefit for ATC patients treated with a multimodal approach (Haymart *et al.* 2013, Mohebat

et al. 2014, Wendler *et al.* 2016). In an analysis of the Memorial Sloan Kettering Cancer Center, New York, 95 ATC patients treated between 1985 and 2010 were included. Patients who had surgery, radiotherapy and/or chemotherapy had 42% 1-year disease-specific survival (DSS) compared to patients without surgery or surgery alone, showing only 6% 1-year DSS (Mohebat *et al.* 2014). In contrast, an analysis of 2742 ATC patients diagnosed between 1998 and 2008 (US National Cancer Database) showed only marginal treatment benefit: median survival rates in patients receiving multimodal treatment ranged between 11.2 months in stage IVA patients, 9.9 months in stage IVB patients and 4.9 months in stage IVC patients (Haymart *et al.* 2013).

Targeted therapy

The growing knowledge of ATC tumor biology has led to the exploration of targeted therapy approaches. In single case reports, impressive response to BRAF inhibitors vemurafenib (Rosove *et al.* 2013, Marten & Gudena 2015, Prager *et al.* 2016), dabrafenib combined with MEK-Inhibitor trametinib (Agarwal *et al.* 2016), ALK-inhibitor crizotinib (Godbert *et al.* 2015) and the mTOR-Inhibitor everolimus (Wagle *et al.* 2014) were reported. Very recently, a phase II trial including 16 BRAFV600E-positive ATC patients reported an overall response rate of 69% when patients were treated with the dabrafenib in combination with trametinib (Subbiah *et al.* 2017). An overview is given in Table 1. These encouraging results suggest that sequencing to detect potential targets may be a reasonable approach and in addition to ongoing trials (Table 2), subsequent multibasket studies should be initiated.

Apart from these single cases, treatment with multiple tyrosine kinase inhibitors has been explored in ATC patients in several phase II studies with small patient cohorts. In 15 ATC patients treated with pazopanib (800 mg/day), the median time to progression was 62 days (Bible *et al.* 2012). In 20 ATC patients treated with sorafenib, 2 patients achieved partial response (PR) and 5 stable disease (SD). The median progression-free survival (PFS) was only 1.9 months (Savvides *et al.* 2013).

In DTC and PDTC, lenvatinib treatment showed impressive response with even a complete remission (CR) in 4 patients in the SELECT trial (Schlumberger *et al.* 2015). Recently, a phase II study including 17 ATC patients has shown acceptable treatment response. The OS was 10.6 months and the objective response rate 24% (Tahara *et al.* 2017). A more detailed overview is given in Table 3.

However, since ATCs are characterized by a high mutational burden, the question whether one driver mutation is responsible for disease progression remains open (Landa *et al.* 2016). Moreover, the field of immuno-oncology has emerged in the past years and an interaction between somatic mutations and the tumor microenvironment has impressively been shown in several human malignancies (Danilova *et al.* 2016). Whether combining targeted therapies and immune therapy in ATC patients as suggested for other advanced human malignancies and by *in vivo* data from preclinical thyroid cancer animal models is an effective approach which needs to be further elucidated (Brauner *et al.* 2016).

Future perspectives and conclusion

The treatment of ATC patients is very challenging. ATC is an orphan disease and very aggressive with fatal outcome so far. In addition, in routine care, ATC awareness is lacking. Moreover, no treatment protocols for which improved patient outcome has been demonstrated, are available. Studies evaluating treatment protocols are mostly retrospective, and the investigated populations are very heterogeneous. However, from available data, it may be possible that younger patients with stage IVA and B disease benefit most from aggressive multimodal treatment.

Often ATC is diagnosed intraoperatively and no precedent scans and endoscopic procedures have been performed to precisely determine local tumor situation. Having a better comprehension would help to decide whether to perform surgery or not and which surgical approach should be chosen. It is still debatable whether patients benefit from debulking operations, due to the high rate of complications. On the other hand, single cases have shown that OS can be improved if aggressive surgery is performed. Prospective studies are needed to clarify the benefit of surgery.

In small cohorts, addition of chemotherapy to radiotherapy has led to an improvement of OS. Moreover, data have shown that at least 40 Gy should be administered to achieve local tumor control.

Whether chemotherapy or radiochemotherapy improves patient outcome is still unclear. Moreover, whether it should be performed only in stage IVC patients or also in stage IVA and IVB patients remains open. Thus, most reports are retrospective and only very few are prospective in nature. However, since around 80% patients develop metastatic disease, which often ends fatally, chemotherapy should be administered if possible.

Treatment with new agents targeting driver mutations in ATC has shown effectiveness in single case reports. However, this implies that screening for somatic alterations is done. This is far from being established in routine care.

To improve ATC patient treatment in Germany, a therapy protocol was developed that allows standardized therapy with acceptable toxicity including surgery in selected cases, followed by combined radiochemotherapy and mutational screening of known oncogenes with subsequent targeted therapies (Tiedje *et al.* 2015).

In conclusion, prospective treatment protocol evaluations are needed and further ATC patients need to be included in multibasket studies including testing for combination of targeted and immune therapies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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