Combination of Lenvatinib and Pembrolizumab Is an Effective Treatment Option for Anaplastic and Poorly Differentiated Thyroid Carcinoma

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Background: Anaplastic thyroid carcinoma (ATC) and metastatic poorly differentiated thyroid carcinomas (PDTCs) are rare aggressive malignancies with poor overall survival (OS) despite extensive multimodal therapy. These tumors are highly proliferative, with frequently increased tumor mutational burden (TMB) compared with differentiated thyroid carcinomas, and elevated programmed death ligand 1 (PD-L1) levels. These tumor properties implicate responsiveness to antiangiogenic and antiproliferative multikinase inhibitors such as lenvatinib, and immune checkpoint inhibitors such as pembrolizumab.

Patients and Methods: In a retrospective study, we analyzed six patients with metastatic ATC and two patients with PDTC, who received a combination therapy of lenvatinib and pembrolizumab. Lenvatinib was started at 14–24 mg daily and combined with pembrolizumab at a fixed dose of 200 mg every three weeks. Maximum treatment duration with this combination was 40 months, and 3 of 6 ATC patients are still on therapy. Patient tumors were characterized by whole-exome sequencing and PD-L1 expression levels (tumor proportion score [TPS] 1–90%).

Results: Best overall response (BOR) within ATCs was 66% complete remissions (4/6 CR), 16% stable disease (1/6 SD), and 16% progressive disease (1/6 PD). BOR within PDTCs was partial remission (PR 2/2). The median progression-free survival was 17.75 months for all patients, and 16.5 months for ATCs, with treatment durations ranging from 1 to 40 months (1, 4, 11, 15, 19, 25, 27, and 40 months). Grade III/IV toxicities developed in 4 of 8 patients, requiring dose reduction/discontinuation of lenvatinib. The median OS was 18.5 months, with three ATC patients being still alive without relapse (40, 27, and 19 months) despite metastatic disease at the time of treatment initiation (UICC and stage IV). All patients with long-term (>2 years) or complete responses (CRs) had either increased TMB or a PD-L1 TPS >50%.

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Conclusions: Our results implicate that the combination of lenvatinib and pembrolizumab might be safe and effective in patients with ATC/PDTC and can result in complete and long-term remissions. The combination treatment is now being systematically examined in a phase II clinical trial (Anaplastic Thyroid Carcinoma Lenvatinib Pembrolizumab [ATLEP]) in ATC/PDTC patients.

Keywords: anaplastic thyroid cancer, ATC, lenvatinib, PDTC, pembrolizumab, poorly differentiated thyroid cancer

Introduction

Anaplastic thyroid carcinoma (ATC) is a rare disease with an extremely high mortality rate and a 10-year survival below 5% (1). ATCs grow very fast, infiltrate into cervical structures, such as the esophagus, trachea, or blood vessels, and metastasize to the lung, brain, and bone. Even with extensive multimodal therapy (surgery, external beam radiotherapy, and chemotherapy), the median overall survival (OS) is only 3–5 months (1–3). ATC frequently arises with extensive multimodal therapy (surgery, external beam radiotherapy, and chemotherapy), the median overall survival (OS) is only 3–5 months (1–3). ATC, the PFS is even shorter (5.6–7.4 months) with variable failure in eight patients with metastatic ATC (n=6) or PDTC (n=2) and examined treatment outcome and biomarkers for this approach.

Materials and Methods

Study population and patient characteristics

This is a retrospective, single-center (University Medical Center Freiburg) cohort study of eight patients with metastatic ATC (n=6) or PDTC (n=2) treated with a combination of the multikinase inhibitor lenvatinib and the immune checkpoint inhibitor pembrolizumab (L/P). Patient data were collected from March 2016 to December 2019 (Table 1). ATC/PDTC diagnosis was histopathologically confirmed by the Institute for Pathology, Freiburg, in all patients. Patients had no BRAFV600E mutation, but numerous other mutations were present (Supplementary Table S1). All patients were pretreated with irradiation, chemotherapy, or RIT (Table 1 and Supplementary Table S2). Adverse events (AEs) were reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 5)–GBG (Table 2). The retrospective study was approved by the Institutional Review Board (IRB) of the University Freiburg.

Treatment strategy

Patients started with lenvatinib 24 mg oral daily if the body weight (BW) was more than 80 kg, or 20 mg for BW less than 80 kg. Pembrolizumab infusions were started in between 1 and 4 weeks after initiation of lenvatinib at a fixed dose of 200 mg total every 3 weeks. Dose for lenvatinib was stepwise reduced
Cervical relapse, Location of metastases, Pathological diagnosis, Sex, Median age at treatment start (range), years 63.5 (49–88)

Cervical bleeding 1/8 (13) Abdominal pain 1/8 (13) Proteinuria 1/8 (13) Diarrhea 1/8 (13) Hand–foot syndrome 1/8 (13) Joint/muscle pain 1/8 (13) Oral mucositis 2/8 (25) Anorexia 2/8 (25) Oral mucositis 2/8 (25) Radiation ± chemosensitizing 7 (87.5) Chemotherapy 6 (75) RIT 2 (25) Location of metastases, n (%) Lung 8 (100) Bone 2 (25) Kidney 1 (12.5) Brain 1 (12.5) Liver 1 (12.5) Skin 1 (12.5) Cervical relapse, n (%) 6 (75)

Previous therapy, n (%) Surgery 8 (100) Radiation ± chemosensitizing 7 (87.5) Chemotherapy 6 (75) RIT 2 (25)

Table 1. Baseline Characteristics

ATC, anaplastic thyroid carcinoma; ECOG, Eastern Cooperative Oncology Group; PDTC, poorly differentiated thyroid carcinoma; RIT, radioiodine therapy.

upon occurrence of side effects according to clinical judgment. Lenvatinib was given at least for 1 year and was then stopped in patients with confirmed complete response (CR). Pembrolizumab was given for up to 40 months. It will be continued in all patients reaching a CR for two more years.

Response assessment
Radiology assessment including cervical, chest, and abdominal computed tomography (CT) scans was performed before treatment and then every 3–4 months. Response to therapy was determined centrally using the RECIST 1.1 criteria (Fig. 1A and Supplementary Table S3). Positron emission tomography (PET)–CT using \([^{18}\text{F}]\) fluorodeoxyglucose (FDG) (PET/CT) was performed before treatment, and after 12–16 months of treatment to confirm CRs (the European Organisation for Research and Treatment of Cancer [EORTC] response criteria for PET). In case of persistent lesions without tracer uptake on PET/CT (PR according to the RECIST 1.1 [CT scan], but CR according to the EORTC criteria for PET), lesions were surgically removed (1/8) to confirm the absence of viable tumor tissue (pathological CR criteria, Supplementary Table S4).

The efficacy of the combination treatment was assessed by ORR 3–4 months after starting treatment, best overall response (BOR) (Fig. 1B), PFS, and OS. PFS was defined as the time elapsed between starting treatment and progression or death, whichever occurred first. OS was defined as the time between starting treatment and death.

Molecular testing and immunohistochemistry

Molecular testing by whole-exome sequencing (WES) was performed from formalin-fixed and paraffin-embedded tissue specimens at the Deutsches Krebsforschungszentrum Heidelberg (DKFZ) as described previously (44,45). PD-L1 status was determined by immunohistochemistry (antibody clone SP263; Ventana) in tumor tissue specimens obtained at initial diagnosis before treatment. The tumor proportion score (TPS) was determined as proportion of PD-L1-positive tumor cells of 100 tumor cells. The combined proportion score (CPS), as amount of PD-L1-positive tumor and immune cells within 100 tumor cells, was also determined centrally at the Department of Pathology of the University Medical Center Freiburg.

Statistical analysis
Kaplan–Meier curves were used for OS and PFS. Descriptive statistics were used to summarize patients’ characteristics and AEs. Statistical analysis was performed using IBM SPSS Statistics version 25.

Results
Eight patients with metastatic ATC (n = 6) or PDTC (n = 2) were treated with a combination of lenvatinib and pembrolizumab after failing chemotherapy, irradiation, or RIT (Table 1 and Supplementary Table S2). All the 8 patients had been extensively pretreated with surgery (8/8), local cervical external beam radiation therapy (6/8), RIT (2/2), local cerebral irradiation therapy (1/8), or systemic chemotherapy alone (6/8) (carboplatin/paclitaxel [4/8], cisplatin/paclitaxel [1/8], cisplatin/doxorubicin [1/8], and paclitaxel only [1/8]) (Table 1 and Supplementary Table S2). The median patient age was 66.4 years. At the beginning of treatment with lenvatinib/pembrolizumab, all patients had stage IVC. All patients had lung metastasis (8/8), and 2 of 8 skeletal metastasis, 1 of 8 liver metastasis, 1 of 8 kidney metastasis, 1 of 8 skin metastasis, and 1 of 8 brain metastasis. Six of eight patients also had progression of their local tumor. Eastern Cooperative Oncology Group (ECOG) performance status ranged from 0 to 2, with 3 ECOG 0 (38%), 3 ECOG 1 (38%), and 2 ECOG 2 (25%). Molecular diagnostics showed that none of the patients had a BRAFV600E mutation, but numerous other mutations typical for ATC/PDTC were detected and are listed in Supplementary Table S1.

Table 2. Adverse Events According to the Common Terminology Criteria for Adverse Events Version 5.0

| Event                  | Grade I/II (%) | Grade III/IV (%) |
|------------------------|----------------|------------------|
| Total                  | 8/8 (100)      | 3/8 (36)         |
| Hypertension           | 5/8 (63)       |                  |
| Fatigue                | 2/8 (25)       | 1/8 (13)         |
| Anorexia               | 2/8 (25)       | 2/8 (25)         |
| Oral mucositis         | 2/8 (25)       |                  |
| Joint/muscle pain      | 1/8 (13)       |                  |
| Hand–foot syndrome     | 1/8 (13)       |                  |
| Diarrhea               | 1/8 (13)       |                  |
| Proteinuria            | 1/8 (13)       |                  |
| Abdominal pain         | 1/8 (13)       |                  |
| Cervical bleeding      | 1/8 (13)       |                  |

Data are given as totals and %. Events reported are listed in descending frequency of columns for grade I/II and grade III/IV. A patient with multiple adverse events is counted only once with the highest grade. A patient with multiple adverse events is counted only once in the total row.
Lenvatinib was started at a daily dose of 24 mg in 5 of 8 patients (BW more than 80 kg) and 20 mg in 2 patients with bodyweight less than 80 kg. An 88-year-old woman started on 14 mg/day (Fig. 1C and Table 3). Pembrolizumab treatment was initiated after a median of 2.7 weeks (ranging from 1 to 4 weeks after starting lenvatinib) and was given i.v. at a fixed dose of 200 mg every 3 weeks. In general, the therapy was well tolerated with the predominant grade II to IV AEs (AEs according to the CTCAE) being hypertension (5/8), fatigue (4/8), weight loss/anorexia (3/8), oral mucositis (2/8), diarrhea (2/8), joint/muscle pain (1/8), and hand–foot syndrome (1/8) (Table 2). The lenvatinib dose was reduced stepwise upon occurrence of intolerable side effects from 24 to 20, 14, 12, and 10 mg/day (Fig. 1C). Most side effects resolved after reducing the dose of lenvatinib, but in two patients, lenvatinib-induced AEs required treatment discontinuation (patients 3 and 6, Table 3). One grade IV serious adverse event (SAE) with a lethal cervical bleeding occurred after removal of the tracheostomy in patient 5 despite being in complete remission (Tables 2 and 3).

After four months of treatment, lenvatinib/pembrolizumab was discontinued due to severe weight loss/anorexia (grade III) in the 88-year-old patient (patient 6), and she died due to disease progression three months later. One patient was intolerant to lenvatinib treatment due to grade III abdominal pain and weight loss/anorexia (patient 3). Lenvatinib was reduced from 24 to 20 to 14 and 12 mg/day in a stepwise manner, and after 14 months, lenvatinib/pembrolizumab treatment was discontinued. Two patients received the full dose of lenvatinib 24 mg for 24 months (Fig. 1C). Pembrolizumab was given for up to 40 months and will be continued in all patients reaching a CR for two more years (Fig. 1D).

Treatment regimen and AEs

Treatment response was first assessed 3–4 months after lenvatinib/pembrolizumab treatment. Six of eight patients had a PR according to the RECIST v1.1 criteria (Fig. 1A). ORR for ATCs was 66% (4/6 PR). The 88-year-old patient (ATC) at 14 mg lenvatinib had SD (patient 3). Lenvatinib/pembrolizumab treatment combination and died within the first month of treatment due to cervical tumor progression (1/8 progressive disease) (Fig. 1A and Supplementary Data).
BOR changed in four ATC patients from PR to CR within 16 months of treatment (total CR rate 50%, CR rate for ATC 66%) (Fig. 1B). Individual patient history is summarized in the Supplementary Data. ATC patient 2 had a confirmed CR for all target- and nontarget lesions 16 months after lenvatinib/pembrolizumab treatment, and stopped taking lenvatinib after 2 years (24 mg daily for 24 months), but continued pembrolizumab for 16 more months (40 months total). He stopped treatment for 6 months and is still in CR. ATC patient 4 with lung and brain metastases had a PR 12 months after starting treatment, but all lesions in the lung were without FDG uptake (CR according to the EORTC criteria for PET). All lung lesions were surgically removed and showed a pathological CR (no viable tumor cells). Therefore, the patient was judged as having a CR and has stopped lenvatinib after 1 year of treatment, and continues with pembrolizumab only (26 months total). Patient 7 with a massive neck tumor and lung metastasis had a PET/CT confirmed CR 12 months after starting treatment. He stopped lenvatinib after 15 months and now continues with pembrolizumab only (19 months total). ATC patient 5 had confirmed CR 10 months after treatment start, but unfortunately

| Patient | Entity | Age, years | Prior treatment | ORR in 3/4 months | BOR CT+PET | PFS, months | OS, months | Adverse events (CTCAE in grade °) | Median dose lenvatinib, mg/day | Current therapy/outcome |
|---------|--------|------------|----------------|-------------------|------------|-------------|------------|-------------------------------|-----------------------------|----------------------|
| 1       | PDTC   | 63         | S Rx C/T       | PR                | PR         | 25          | 27         | Hypertension °II Fatigue °II Anorexia °I Oral mucositis °I | 24                          | PD/death after stopping lenvatinib due to a knee surgery |
| 2       | ATC    | 76         | S Rx C/T       | PR                | CR         | 40          | 40         | Hypertension °II Anorexia °II | 24                          | Alive, CR after 12 months lenvatinib/pembrolizumab, now without treatment |
| 3       | PDTC   | 49         | S RIT C/T      | PR                | PR         | 15          | 23         | Anorexia °III Abdominal pain °III | 14                          | PD/death, lenvatinib on/off due to weight loss/abdominal pain |
| 4       | ATC    | 68         | S Rx C/T       | PR                | CR         | 26          | 26         | Anorexia °I Loss of appetite °II Proteinuria °I Hypertension °II | 20                          | Alive, CR after 10 months of treatment, now pembrolizumab mono |
| 5       | ATC    | 63         | S Rx C/T       | PR                | CR         | 11          | 11         | Diarrhea °II Hypertension °II Cervical bleeding °IV | 20                          | CR after 7 months of treatment. Death due to cervical bleeding |
| 6       | ATC    | 88         | S Rx C/T       | SD                | SD         | 4           | 7          | Diarrhea °II Anorexia °III Proteinuria °II Fatigue °III Oral mucositis °II | 14                          | PD/death after stopping medication due to side effects |
| 7       | ATC    | 64         | S RIT Rx       | PR                | CR         | 19          | 19         | Hypertension °II Fatigue °II Joint pain °II Hand–foot syndrome °I | 24                          | Alive, CR, lenvatinib/pembrolizumab for 12 months, now pembrolizumab mono |
| 8       | ATC    | 60         | S R C/T        | PD                | PD         | 1           | 1          | Hypertension °II | 24                          | PD/death due to cervical tumor progression |

BOR, best overall response; C/T, chemotherapy; CT, computed tomography; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; FDG, [18F] fluorodeoxyglucose; ORR, overall response rate; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PFS, progression free survival; PR, partial response; Rx, radiation therapy; S, surgery; SD, stable disease.

**Table 3. Patient History**

Patient characteristics including diagnosis, previous therapy (S, RIT, Rx, C/T), patient age, PFS, ORR, BOR, OS, response after 3 months, maximum response, main side effects, median dose lenvatinib in mg/day, dose pembrolizumab, current treatment/outcome. CTCAE grades in roman numbers. Responses were assessed via the RECIST v1.1 radiology assessment and FDG uptake according to the EORTC criteria for PET.
died due to bleeding complications after removal of the tracheostomy tube (Table 3 and Supplementary Table S2).

Treatment durations ranged from 1 to 40 months (ATC: 40, 26, 19, 18, 4, and 1 month; PDTC: 25 and 15 months, respectively), with three patients being treated for more than 2 years (Fig. 1D). At the time of data cutoff, 3 of 8 patients (patients 2, 4, and 7, all ATCs) were still alive and on therapy (40, 26, and 19 months). We stopped the treatment of patient 2 after 40 months of treatment, and he is now regularly monitored by CT scans every 3 months. The other patients died due to disease progression (2/6 ATC, 2/2 PDTC) or hemorrhage (grade IV SAE, patient 5, Table 3). ATC patient 8 was resistant to the treatment. ATC patients 1 and 6 died shortly after discontinuation of the lenvatinib treatment caused by lenvatinib intolerance in patient 6 (grade III anorexia), and because lenvatinib had to be discontinued due to an infectious complication after a knee surgery in patient 1 (Table 3). The median PFS for the total cohort was 17.6 months, and the median OS was 19 months (Fig. 2). Data analysis for ATC only showed a median PFS of 16.8 months and a median OS of 17.3 months (Fig. 2).

**Biomarkers**

To assess potential predictors of treatment response, we investigated the PD-L1 expression of the tumor cells and macrophages/immune cells. Furthermore, WES was performed in 7 of 8 patients, and sequences were compared to germ line sequences to assess somatic mutations and the TMB. In 1 patient (1/8), targeted sequencing for 11 frequently mutated genes (Supplementary Table S1) was performed due to low material. All tumors were positive for PD-L1 expression with a TPS ranging from 1% to 90%, and 5 of 8 patients with TPS >50% (Table 4). The CPS ranged from 5 to 100 (Table 4). Interestingly, the ATC patient with the lowest TPS (1%) and CPS 5 did not respond to the treatment (patient 8). In contrast, the patients with responses lasting more than two years and those achieving a CR all had PD-L1 TPS >50% (5/8), a CPS

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**Table 4. Biomarker Analysis**

| Patient | ORR after 3/4 months (RECIST 1.1) | BOR (CT/MRI/PET-CT) | Response according to PET-CT | TPS, % | CPS | Somatic mutations | TMB (mutations/Mb) |
|---------|---------------------------------|---------------------|------------------------------|--------|-----|-------------------|-------------------|
| 1       | PR                              | PR                  | PR                           | 50     | 40  | 106               | 13.79             |
| 2       | PR                              | CR                  | CR                           | 60     | 75  | 1447              | 81.87             |
| 3       | PR                              | PR                  | PR                           | 10     | 10  | 79                | 4.08              |
| 4       | PR                              | CR                  | CR                           | 90     | 100 | 19                | 3                 |
| 5       | PR                              | CR                  | n.a.                         | 80     | 100 | 29                | 3.3               |
| 6       | SD                              | SD                  | n.a.                         | 60     | 65  | 24                | 3.58              |
| 7       | PR                              | CR                  | CR                           | 5      | 7   | 138               | 5.59              |
| 8       | PD                              | PD                  | n.a.                         | 1      | 5   | n.a.              | n.a.              |

CPS, combined proportion score; MRI, magnet resonance tomography; n.a., not applicable; TMB, tumor mutation burden; TPS, tumor proportion score.
Discussion

Current treatment options for ATC are limited, and response rates are low and short-lived, with marginal to absent CR (13,14). Only the small proportion of \( B_{RAF}^{V600E}\)-mutated ATC (about 20%) can be effectively treated with a BRAF/MEK inhibitor combination of dabrafenib and trametinib (10,11), but for the other 70–80% of ATCs, no treatment options are approved after chemotherapy failure in most countries.

ATC and PDTC are characterized by a very high proliferation rate and tumor invasiveness, driven by concurrent mutations in several pro-proliferative pathways (RAS, WNT, loss of TP53), and strongly activated VEGF/FGF signaling. PD-L1 and TMB are upregulated, but the response to single immune checkpoint inhibition often comes too late and is overrun by the aggressiveness of the disease (36).

In contrast to single-agent therapy, the combination of lenvatinib and pembrolizumab was highly effective in our treatment cohort. Eight ATC/PDTC patients who had previously been treated with several lines of therapy including chemotherapy, chemoirradiation, and even single immune checkpoint inhibition (>18) received a combination of lenvatinib and pembrolizumab for a maximum of 40 months. The combination treatment was well tolerated and could be sustained over one year in half of the patients, and even over two years in 37% (3/8) of the patients. Half of the ATC patients (3/6) were still on therapy at data cutoff with no sustained grade III/IV toxicities despite having initially metastatic disease; three patients had confirmed CR by PET/CT and/or histopathologic examination of former metastatic sites. Seventy-five percent of all patients and 66% of the ATC/PDTC patients (ATLEP trial, Anaplastic Thyroid Carcinoma Lenvatinib Pembrolizumab, EudraCT No. 2017-004570-34).

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