Individualized multimodal treatment strategy for anaplastic thyroid carcinoma—Case report of long-term remission and review of literature

S. Eckhardt a, *, S. Hoffmann a, A.I. Damanakis a, P. Di Fazio a, A. Pfestroff b, M. Luster b, A. Wunderlich a, D.K. Bartsch a

a Department of Visceral, Thoracic and Vascular Surgery, Philipps University Marburg, Baldingerstrasse, D-35043 Marburg, Germany
b Department of Nuclear Medicine, Philipps-University, Baldingerstraße, 35043 Marburg, Germany

Article history:
Received 25 March 2016
Accepted 7 June 2016
Available online 16 June 2016

Keywords:
Anaplastic thyroid carcinoma
Case report
Individualized therapy
Tyrosine kinase inhibitors
Multimodal treatment strategy

ABSTRACT

INTRODUCTION: The prognosis of anaplastic thyroid cancer (ATC) is poor with a mean survival time of six months following diagnosis. Despite various attempts to modify common treatment modalities including surgery, external beam radiation and chemotherapy, an effective treatment is not available yet. We report here, a patient who achieved long-term survival based on multimodal treatment, including in vitro evaluation of drug response of his tumor cells.

PRESENTATION OF CASE: A 42 years old male patient underwent total thyroidectomy with central and lateral neck dissection for ATC (pT4b, pN0 (0/36), L0, V0, Pn1, R0 cMO – UICC-Stage: IV b). From the tumor tissue a primary cell culture was established. While the patient received a combined radio-chemotherapy cell viability assays were performed using Sorafenib, Vandetanib and MLN8054 (Aurora kinase inhibitor) as inhibitors. Cell viability was determined by MTT-assay after 72 and 144 h of treatment.

DISCUSSION: All the three compounds affected cell viability in a time- and dose dependent manner. These effects were most pronounced by Sorafenib. Based on in vitro findings, the patient was treated daily with 400 mg Sorafenib for 75 days. 43 months after initial diagnosis, the patient had no evidence of disease as shown by MRI, CT and FDG-PET-CT imaging.

CONCLUSION: In the setting of multimodal treatment, in vitro drug evaluation of individual tumor cells of patients might be a promising tool to ameliorate the fatal prognosis of selected ATC patients.

© 2016 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Although anaplastic thyroid carcinoma (ATC) accounts only for 2% of thyroid carcinomas, it is one of the most aggressive diseases with a median survival time of 6 months after the diagnosis and a mortality rate higher than 90% [1]. Effective treatment strategies to overcome this fatal prognosis are still lacking. Multimodality treatment consisting of surgical resection, if possible, in combination with radio- and/or chemotherapy is generally recommended [2]. Nevertheless new therapeutic strategies are urgently required to overcome the poor prognosis of ATC [3].

New insights into the biological behavior, the genetic and molecular pathogenesis of ATC might offer the possibility of novel targeted therapies [4].

But as more new systemic agents become available, it is important to get information on the drug response of different compounds on individual ATC tumor cells.

Based on the current literature and on the results of our own investigations, three compounds (Aurora kinase inhibitor MLN8054, multikinase inhibitors Vandetanib and Sorafenib) were selected to be evaluated in this setting.

The BRAF- and multikinase inhibitor Sorafenib (Nexavar®, BAY49-3006) has proven to inhibit multiple intracellular signaling pathways leading to cell cycle arrest and initiation of apoptosis in thyroid carcinoma cell lines regardless of their tumor subtype origin or the BRAF-status [5]. Several studies evaluated the effect of Sorafenib in thyroid cancer and reported positive effects [6,7]. Based on these results, Sorafenib got granted marketing authorization since 2014 for the treatment of patients with progressive, locally advanced or metastatic, differentiated thyroid carcinoma in Europe.

Vandetanib (AstraZeneca, Macclesfield, UK) is an oral multikinase inhibitor that selectively targets RET, VEGFR and EGFR tyrosine kinases [8,9]. Its efficacy was determined in a phase II-trial enrolling...
patients with poorly differentiated thyroid carcinoma (PDTC). It was shown that patients receiving Vandetanib had longer progression-free survival (PFS 11 months) compared to the placebo group (5 months) [10].

Aurora kinases (A–C) are serine/threonine kinases that play a crucial role in cell division. They are overexpressed in many human tumors including ATC, where they account for aberrant cell proliferation. MLN8054 has shown profound antitumor activity in ATC cells in vitro and in vivo [11,12].

Here we report a patient suffering from ATC, who was free of disease 43 months after multimodal treatment with surgery, radiochemotherapy and individualized targeted therapy with Sorafenib based on in vitro testing of drug efficacy in his tumor cells. This approach might represent an effective strategy for an optimized, tailored treatment of ATC.

2. Presentation of case

A 42-year-old man was referred to our institution in September 2012, two weeks after he underwent a subtotal thyroidectomy in an external hospital for a rapidly growing scintigraphically cold nodule in the right thyroid lobe. Histopathological examination stated an ATC in the right lobe showing a negative staining for thyroid transcription factor 1 (TTF-1) and thyroglobulin (Tg). Postoperative laryngoscopy demonstrated paresis of the laryngeal nerve on the right side.

At this time, CT scan of the thorax, MRI scan of the neck, thyroid scintigraphy and ultrasonography demonstrated a persisting lesion of 21 × 18 mm on the right side of the neck without evidence of distant metastatic disease, but with some enlarged suspicious lymph nodes (max. 26 × 20 mm). Fine needle aspiration biopsy confirmed remnants of an ATC. Bronchoscopy and gastroscopy showed no evidence of infiltration of the esophagus or the trachea.

After multidisciplinary tumor board decision, the patient underwent a multimodal therapeutic strategy, including an individualized targeted therapy.

The patient first underwent completion thyroidectomy with a bilateral cervicocentral and cervicoventral lymphadenectomy in September 2012. The tumor was classified as ATC pT4b, pN0 (0/36), L0, V0, Pn1, R0 cM0 – IUCC-Stage: IV b. A second expert confirmed the diagnosis of an ATC, immunonegative for TTF1 and Tg and without a BRAFV600E mutation. Ki-67 index was 60–70%. Four weeks after surgical resection, a combined radio-chemotherapy was started for four weeks with four cycles of Cisplatin 25 mg/m² and Docetaxel 20 mg/m² combined with an external radiation beam therapy for a total dose of 64.8 Gy. A MRI-scan, performed after receiving the combined therapy, was negative for metastases or tumor recurrence.

From fresh tumor tissue a primary cell culture was established and in vitro analysis of three different drugs demonstrated Sorafenib as the most effective one (Fig. 1A–C). Thus, Sorafenib was administered as an individual treatment strategy in off-label use to the patient, with 400 mg twice a day starting in January 2013. Because of adverse events (polyneuropathy, pain in muscles and bones) the initial dose was reduced to 400 mg once a day. Sorafenib was given in three cycles over a period of 75 days.

After completion of multimodal treatment, the patient staging, evaluated by CT scan of the thorax and MRI scan of the neck, showed neither recurrent disease nor metastases.

In June 2013, a complete re-staging, including MRI of the neck, CT of the thorax and FDG–PET–CT, was performed. Imaging detected a new solitary lesion of 10 × 7 mm size in the right upper lobe of the lung that was suspicious for a metastasis (Fig. 2). According to the recommendation of our tumor board, based on the absence of additional lesions, the patient underwent a video-assisted thora
coscopic wedge resection of this lesion. Histopathology of the collected fresh tissue confirmed the metastatic lesion originated from the primary ATC. Collected tissue was once again transferred to the laboratory and established as a primary cell culture. The case was discussed again in our interdisciplinary tumor board, where an additional adjuvant therapy with taxans and platin was considered, but the patient refused this therapy and preferred to undergo close surveillance with CT imaging of the thorax and MRI of the neck in 6 months intervals. At the last staging, in January 2016, 43 months after his initial operation, the patient was without evidence of recurrent or metastatic disease.

2.1. Methods and experiments for individualized in-vitro testing of drug efficacy

2.1.1. Preparation of patient-derived human tumor tissue

Tumor cells were attained by mechanical dissociation of tumor tissue, obtained from the completion thyroidectomy and the pulmonary lesion and successfully established as primary cell culture.

2.1.2. Compounds

Sorafenib, Vandetanib and MLN8054 were used as inhibitors. Stock solutions (10 mM each) were prepared in dimethylsulfoxid (DMSO) and stored at −20 °C.
2.2. In vitro experiments

Primary cell culture was maintained by propagating the cells in DMEM-h21/Ham's F12 1:1 (v/v) supplemented with 10% FCS and 10U/ml penicillin and 100 μg/ml streptomycin (all: Biocrom, Berlin, Germany) under standard conditions (37°C, 5% CO2). Before use in experiments, cell viability was assessed by Trypan blue exclusion.

To test the sensitivity of the tumor cells towards the various inhibitors, cells were seeded in 96 well plates (1 x 10^4 cells/well) and treated with increasing concentrations (0.1–10 μM) of Sorafenib, Vandetanib and MLN8054 for up to 144 h. Cell viability was determined by MTT-assay and dose-response curves were created.

2.2. Results

Effects on cell viability of the individual tumor cells caused by treatment with Sorafenib, Vandetanib and MLN8054

2.2.1. Cells established from the primary tumor

Cell viability of the individual tumor cells was considerably affected by all the three compounds. As documented here for Sorafenib, each compound induced a dose- and time-dependent decrease in cell viability (Fig. 1B and C). This effect was most pronounced by Sorafenib (Fig. 1B and C). Here cytoviability was reduced to about 50% at a drug concentration about 2 μM after 72 h, whereas for Vandetanib and MLN8054 IC50 values were calculated as ≈7 μM and ≈5 μM (Fig. 1B and C).

Prolonged treatment with 5 μM Sorafenib and Vandetanib resulted in 100% reduction of cell viability, MLN8054 showed a lower effect, here cell viability was decreased only to about 30% at 10 μM (Data not shown). Further, the effect of combined therapy with Sorafenib and Vandetanib was evaluated in vitro. In comparison with the single treatment, no synergistic effect or increase of efficacy could be measured (Data not shown).

2.2.2. Cells established from the pulmonary metastasis

Tumor cells originated from the pulmonary metastasis where established as primary culture as well and treated with Sorafenib and Vandetanib similarly. As assessed by MTT-assay, comparable results were revealed. Once again after 72 h about 50% of the cells were killed at concentrations about 3 μM (Sorafenib) and 7 μM (Vandetanib), documenting a similar behaviour of the cells from the primary tumor and the metastasis (Fig. 3A and B).

Fig. 2. FDG-PET-CT screen of a pulmonary metastasis of ATC nine months after diagnosis.
Our patient first received a combined radio-chemotherapy. Meanwhile a primary cell culture was established and the effects of two multi-kinase inhibitors (Sorafenib, Vandetanib) and of one aurora kinase inhibitor (MLN8054) were evaluated in vitro. From these the mostly effective one was Sorafenib. Further, similar effects were shown for cells of the primary tumor and the metastasis. These results point out the feasibility of preclinical in vitro evaluation, especially, since it is well known, that the biological behavior of ATC – like other tumors – is inconsistent. Therefore a successful therapy may be more common, if the patient receives – corresponding to the individual evaluated ATC – the most effective treatment.

As younger age is associated with improved survival in patients affected by ATC [15], it must be pointed out that the positive clinical course in the presented case might have been also promoted by the limited disease at the time of diagnosis and the young age of the patient.

4. Conclusion

Our case report demonstrates – to our best knowledge – for the first time that pre-therapeutic in vitro investigation of novel drugs could succeed for a personalized antitumor therapy in a patient affected by ATC. By availability of vital tumor cells, this approach might offer the possibility for reflection of the individual tumor cell characteristics and optimize therapeutic options for patients suffering from ATC.

Conflict of interest

None.

Funding

None.

Ethical approval

This is not a research study.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors’ contributions

S. Eckhardt: analysis and interpretation of data, acquisition of data, drafting the article.

S. Hoffmann: conception and design of the study, acquisition of data.

A.I. Damanakis: final approval of the version to be submitted.

P. Di Fazio: revising the article for important intellectual content.

A. Pfestroff: analysis and interpretation of data.

M. Luster: conception and design of the study.

A. Wunderlich: analysis and interpretation of data, acquisition of data.

D.K. Bartsch: conception and design of the study, revising the article for important intellectual content.
Guarantor

This is not a research study. All authors read and approved the final manuscript. Therefore, all authors are responsible for this report.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijscr.2016.06.013.

References

[1] E. Kebebew, F.S. Greenspan, D.H. Clark, K.A. Woebner, A. McMillan, Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors, Cancer 103 (2005) 1330–1335.
[2] G. Nagahah, A. Hossain, C.J. Mooney, J. Parmentier, S.C. Remick, Anaplastic thyroid cancer: a review of epidemiology, pathogenesis, and treatment, J. Oncol. 2011 (2011) 542358.
[3] D.S. Dean, H. Chari, Epidemiology of thyroid nodules, Best Pract. Res. Clin. Endocrinol. Metab. 22 (2008) 901–911.
[4] R.C. Smallridge, K.B. Ain, S.L. Asa, K.C. Bible, J.D. Brierley, et al., American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 22 (2012) 1104–1139.
[5] M. Broecker-Preus, S. Müller, M. Britten, K. Worm, S. Kurt Werner, et al., Sorafenib inhibits intracellular signaling pathways and induces cell cycle arrest and cell death in thyroid carcinoma cells irrespective of histological origin or BRAF mutational status, BMC Cancer 15 (2015) 184.
[6] L. Thomas, S.Y. Lai, W. Dong, L. Feng, R. Dadu, et al., Sorafenib in metastatic thyroid cancer: a systematic review, Oncologist 19 (2014) 251–258.
[7] P. Savvides, G. Nagahah, P. Lavertu, P. Fu, J.J. Wright, et al., Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid, Thyroid 23 (2013) 600–604.
[8] F. Carluomagni, D. Vitaglione, T. Guida, F. Ciardiello, G. Tortora, et al., ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic RET kinases, Cancer Res. 62 (2002) 7284–7290.
[9] S. Hoffmann, G. Gläser, A. Wunderlich, S. Linglebach, C. Dietrich, et al., Targeting the EGF/VEGF-R system by tyrosine-kinase inhibitors—a novel antiproliferative/antangiogenic strategy in thyroid cancer, Langenbecks Arch. Surg. 391 (2006) 589–596.
[10] S. Leboulleux, L. Bastholt, T. Krause, C. de la Fouchardiere, J. Tennvall, et al., Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial, Lancet Oncol. 13 (2012) 897–905.
[11] A. Wunderlich, M. Fischer, T. Schlosshauer, A. Ramaswamy, B.H. Greene, et al., Evaluation of Aurora kinase inhibition as a new therapeutic strategy in anaplastic and poorly differentiated follicular thyroid cancer, Cancer Sci. 102 (2011) 762–768.
[12] M.G. Manfredi, J.A. Ecsedy, K.A. Meetze, S.K. Balani, D. Buremova, et al., Antitumor activity of MLN8054, an orally active small-molecule inhibitor of Aurora A kinase, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 4106–4111.
[13] R.C. Smallridge, J.A. Copland, Anaplastic thyroid carcinoma: pathogenesis and emerging therapies, Clin. Oncol. (R. Coll. Radiol.) 22 (2010) 486–497.
[14] R. Granata, L. Locati, L. Licitra, Therapeutic strategies in the management of patients with metastatic anaplastic thyroid cancer: review of the current literature, Curr. Opin. Oncol. 25 (2013) 224–228.
[15] M.R. Haymart, M. Banerjee, H. Yin, F. Worden, J.J. Griggs, Marginal treatment benefit in anaplastic thyroid cancer, Cancer 119 (2013) 3133–3139.
[16] M. Schlumberger, C. Parmentier, M.J. Delisle, J.E. Couette, J.P. Droz, et al., Combination therapy for anaplastic giant cell thyroid carcinoma, Cancer 67 (1991) 564–566.
[17] P.E. Voutilainen, M. Multanen, R.K. Haapiainen, A.K. Leppäniemi, A.H. Sivula, Anaplastic thyroid carcinoma survival, World J. Surg. 23 (1999) 975–978, discussion 978–979.
[18] J. Tennvall, E. Talloth, A. el Hassian, G. Lundell, M. Akerman, et al., Anaplastic thyroid carcinoma. Doxorubicin, hyperfractionated radiotherapy and surgery, Acta Oncol. 29 (1990) 1025–1028.
[19] P.C. Levendag, P.M. De Porre, W.L. van Putten, Anaplastic carcinoma of the thyroid gland treated by radiation therapy, Int. J. Radiat. Oncol. Biol. Phys. 26 (1993) 125–128.
[20] A. Seto, I. Sugitani, K. Toda, K. Kawabata, S. Takahashi, et al., Chemotherapy for anaplastic thyroid cancer using docetaxel and cisplatin: report of eight cases, Surg. Today 45 (2015) 221–226.