VIA MEDICA

CASE REPORT

Anita Gorzelak, Ewa Wachuła, Agnieszka Boratyn-Nowicka

Department of Oncology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice

The use of everolimus in a patient with metastatic atypical bronchial carcinoid undergoing haemodialysis: a single--centre experience with one case

Address for correspondence:
Lek. Ewa Wachuła
Department of Oncology, School of Medicine with the Division of Dentistry in Zabrze, Medical University of Silesia, Katowice
ul. Ceglana 35, 40–527 Katowice
e-mail: e.wachula@wp.pl

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ABSTRACT

Background. The treatment of lung neuroendocrine tumours is still a challenge due to their rare occurrence and the lack of prospective randomised studies. We present the case of patient with metastatic atypical lung carcinoid treated with everolimus undergoing haemodialysis due to end-stage renal failure as a result of renal cirrhosis.

Methods. A 68-year-old man was followed up in our hospital for an atypical lung carcinoid diagnosed in 2006. The patient initially underwent left upper lobectomy for a well-differentiated tumour — atypical carcinoid. Pathology stage was pT3N0M0PL0 (Ki67 3%). Nine years later, the evaluation revealed a progressive disease (metastases in the liver, bones, and spleen). Hepatic metastasectomy was performed and progression of carcinoid (Ki67 1%) was confirmed. In the same year end-stage renal failure as a result of renal cirrhosis was diagnosed and the patient required dialysis three times a week. The patient was qualified to start the treatment with somatostatin analogues by multidisciplinary team. In February 2017, new liver metastases occurred. Due to clinical symptoms (flush, diarrhoea) associated with hormonal activity (serotonin, chromogranin A), the decision to use molecular-targeted therapy with everolimus was made. In February 2017, everolimus therapy at the full dose of 10 mg daily was initiated.

Results. The evaluation of treatment effects after 12 weeks of everolimus administration revealed the decrease of chromogranin A and serotonin levels with stabilisation of the hepatic metastases on computed tomography scans — stable disease according to RECIST criteria was found. At the time of publication, the patient was receiving everolimus, somatostatin analogues, and dialysis therapy.

Conclusions. Targeted therapy with everolimus seems to be very promising for patients with lung carcinoid and renal failure, but further trials need to be conducted.

Key words: bronchial carcinoid, everolimus, renal failure, haemodialysis

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Introduction

Bronchial carcinoids account for a small proportion of all resected pulmonary tumours — there are only 2% of resected lung masses confirmed as a: typical carcinoid (TC) and 0.2% as an atypical carcinoid (AC) [1, 2]. Neuroendocrine tumours include a heterogeneous group of neoplasms; they are classified into four histological variants: TC clinically defined as low-grade malignant tumours, atypical carcinoids (AC) as the intermediate-grade malignant tumours, large-cell neuroendocrine carcinoma (LCNEC), and small-cell lung carcinoma (SCLC), both of the latter defined as high-grade carcinomas [3]. The choice of therapy depends on histological characteristics [2]. Surgical removal is the treatment of choice in patients with limited TC and AC; furthermore, metastasectomy should be considered whenever possible, with the aim to achieve prognosis improvement. Several therapeutic options are available for front-line treatment of advanced/metastatic

carcinoids; chemotherapy and radiotherapy are linked with extremely limited efficacy, while somatostatin analogues and peptide receptor radionuclide treatment produce promising results [2]. Somatostatin analogues are used as the first-line systematic treatment of neuroendocrine tumours due to their antiproliferative characteristics [4].

Case report

A 68-year-old man, a never-smoker, with non-insulin-dependent diabetes mellitus (NIDDM), hypertension, postoperative hypothyroidism after thyroidectomy during thyroid hormone replacement therapy, and with end-stage renal failure during haemodialysis was followed up in our hospital for lung carcinoid. Carcinoid was diagnosed in 2006. The patient initially underwent left upper lobectomy due to well-differentiated tumour — AC (pT3N0M0PL0, Ki-67 3%). Nine years later, end-stage renal failure as a result of renal cirrhosis was diagnosed and the patient required dialysis three times a week. During the first year of haemodialysis, due to bloody dialysate and peritonitis, imaging examinations were performed; abdominal computed tomography (CT) showed multiple polycyclic focal liver lesions and a single focal splenic lesion. The thoracic CT did not reveal progression of the disease. In January 2015, the patient underwent exploratory laparotomy; the caecal mass was removed (pathology examination revealed sessile serrated adenoma) as well as the hepatic tumour (metastatic neuroendocrine tumor NET G1 Ki-67 1%). In March 2015, the patient was admitted to the Division of Endocrinology and Neuroendocrine Cancers, Silesian Medical University in Katowice. The results of laboratory tests indicated elevated concentration of chromogranin, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA) in 24-hour urine sampling. The abdominal CT scan scheduled in March 2015 revealed numerous metastatic liver lesions replacing 40% of liver volume and a single metastatic splenic lesion. The decision was taken to start somatostatin analogue therapy (Sandostatin LAR 30). A positron emission tomography (PET) scan using gallium-68-labelled somatostatin analogues (^{68}Ga-PET/CT) revealed heterogenous somatostatin receptor expression in focal hepatic lesions, which may indicate the differentiation of neoplasm cells into a more aggressive phenotype. On ^{68}Ga-PET/CT new lesions in the left pubic bone were found and somatostatin receptor expression was confirmed. The focal splenic lesion did not show any uptake. In December 2015, PET scan with fluorine-labelled glucose analogue (^{18}FDG-PET/CT) was performed and revealed increased glucose metabolism within the liver, spleen, and pubic bone lesions. Further results indicated elevated concentration of chromogranin, serotonin, and 5-HIAA in 24-hour urine sampling. Due to stage of the disease, heterogenous receptor expression, and numerous lesions with no receptor expression, the patient was disqualified for peptide receptor radionuclide therapy (PRRT). The decision to continue the only somatostatin analogue therapy was made. Eight months later, ^{68}GaDOTA-TATE scan and ^{18}FDG PET scan were performed, revealing new liver metastases and the disease progression was detected. Due to clinical symptoms (flush, diarrhoea) associated with hormonal activity (serotonin, chromogranin A), the decision to use molecular-targeted therapy with everolimus was made. In February 2017, everolimus therapy at the full dose of 10 mg per day was initiated. Patient's ECOG performance status was good (ECOG 1). During the third week of treatment, the patient started to experience dyspnoea, non-productive cough, and fever. Non-infectious pneumonia was diagnosed (Grade 2 CTCAE). Steroid therapy was required. Consequently, the treatment with everolimus was interrupted for one week, and after symptom relief the treatment at the same dose was continued. Nine weeks later, the patient experienced symptomatic anaemia (Grade 2 CTCAE) requiring red blood cell transfusion. Other side effects include nausea in first CTCAE, lower extremity oedema in first CTCAE, and dry skin in first CTCAE. At the time of publication, the patient is continuing treatment with everolimus, somatostatin analogues, and dialysis. The patient's condition currently is described as good (PS-1). The ongoing treatment is well tolerated, and drug dose adjustments have not been needed so far. The concentrations of neuroendocrine tumour markers decreased in comparison with previous test results, and stabilisation of the hepatic metastases on CT scans (stable disease [SD] according to RECIST criteria) was achieved. In the ^{18}FDG-PET/CT (Dec 2017) assessment, a partial metabolic response was obtained in the liver, spleen, and bones.

Discussion

There are several well-known therapeutic options available for treatment of metastatic lung AC, whereas evidence on the value of these methods for patients with coexisting end-stage renal insufficiency is limited. There are still no established guidelines for the administration of chemotherapy or targeted therapy in patients who undergo haemodialysis.

In patients with progressive lung neuroendocrine tumours treatment with everolimus (mammalian target of rapamycin inhibitor — m-TOR inhibitor) may be considered (Fig. 1). This type of management significantly prolongs progression-free survival [5]. However, the

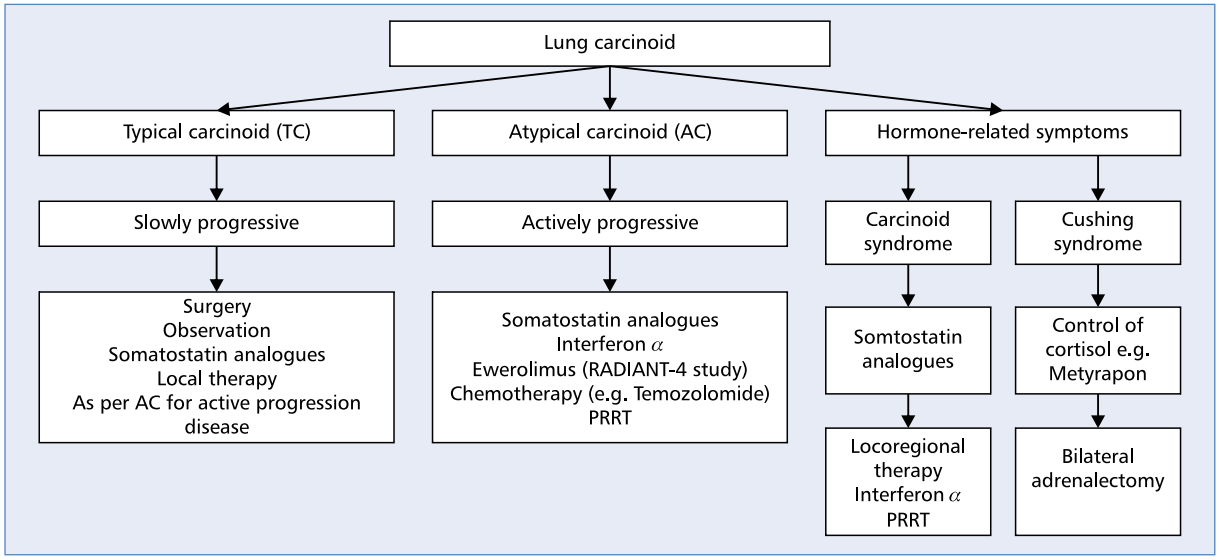

Figure 1. European Neuroendocrine Tumor Society (ENETS) recommendations for the control of carcinoid hormone-related symptoms and tumor growth — algorithm according Caplin et al. [2], modified by authors this publication. PRRT — peptide receptor radionuclide therapy

efficacy of everolimus monotherapy and combination therapy still need to be confirmed in clinical studies in patients suffering from advanced carcinoid and end stage renal insufficiency.

Everolimus is predominantly metabolised by the liver and excreted in the bile. Dose adjustment is not needed for renal insufficiency because only 5% of the drug is eliminated in the urine [6, 7]. It is suggested that haemodialysis does not influence everolimus blood concentrations [8, 9]. Taking into consideration its elimination profile, the patient was qualified to treatment with everolimus.

On the basis of the experience of our department and case reports described so far, the conclusion was reached that everolimus can be safely used in patients with end-stage renal disease requiring haemodialysis in the treatment for solid tumours and make it possible to achieve the stabilisation of the disease [10–12].

Tolerability of everolimus is usually acceptable. In the presented case, non-infectious pneumonitis (grade 2 CTCAE) was the most serious side effect of therapy manifested by the patient. Clinical assessment and imaging tests during the third week of treatment resulted in treatment withdrawal. Seven days later symptom relief was noted and the treatment at the same dose was reinstituted. Non-infectious pneumonitis is a class effect of rapamycin analogues such as everolimus [13].

Furthermore, it should be emphasised that the other side effects manifested by the patient were not connected with the necessity for discontinuation of everolimus administration. Given the literature review, the significantly higher incidence of side effects in patients undergoing haemodialysis and treated with everolimus has not been documented, except adverse effects associated with antiangiogenic activity (especially bleeding, which may occur with higher frequency and more severely in this setting) [12].

Conclusions

This report describes a case of a 12-year course of the disease, including administration of everolimus over 15 months. To the best of our knowledge, this is the second report of a haemodialysis patient with metastatic lung AC treated with everolimus [10]. Summing up, the application of everolimus in full dose and somatostatin analogues in patients with generalised carcinoid with end-stage renal failure and low proliferative potential offers patients the chance to prolong their survival and maintain a good quality of life.

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