VIA MEDICA

CASE REPORT

Adam Fałkowski[1], Aleksandra Żołnierek[2], Jakub Żołnierek[1]

[1]LUX MED Onkologia, Warsaw, Poland
[2]Faculty of Medicine, Medical University of Warsaw, Poland

Spectacular clinical benefit achieved by multidisciplinary management of a kidney cancer patient

Address for correspondence:
Jakub Żołnierek, MD, PhD
LUX MED Onkologia
ul. Szamocka 6, 01–748 Warsaw, Poland
e-mail: qbazolnier@wp.pl

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ABSTRACT

The present study is a case report of a patient with a diagnosis of renal cell carcinoma with poor prospects, in whom long-term tumor control at the level of deep cytoreduction was achieved through aggressive multidisciplinary management using surgery, stereotactic radiotherapy, and sequential systemic therapy with immunotherapy based on a checkpoint inhibitor with anti-PDL1 activity combined with anti-angiogenic treatment, and by a non-selective tyrosine kinase inhibitor.

Keywords: renal cell carcinoma, multidisciplinary treatment, molecularly targeted drugs, immune checkpoint inhibitors

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Introduction

According to the Polish National Cancer Registry's report, 2727 men and 1755 women developed kidney cancer in 2020. The disease caused the deaths of 1434 men and 946 women. Among solid tumors, kidney cancer is the seventh (for men) and ninth (for women) most commonly diagnosed histological type of cancer in Poland [1].

Case report

In August 2012, a right kidney tumor was diagnosed in, at that time, a 52-year-old active and fit man. The lesion was initially visualized by abdominal ultrasonography (USG), which was performed in the course of the diagnosis of recurrent and worsening right lumbar pain observed for several preceding weeks and followed by an episode of macroscopic hematuria. The location of the pole-positioned tumor and dimensions of 67 × 66 × 76 millimeters were confirmed by a computed tomography (CT) scan while ruling out the presence of other lesions.

The patient had type 2 diabetes mellitus (which was well controlled with insulin use from 2001) and persistent hypothyroidism (which was secondary to a thyroidectomy performed in November 2012 due to cystic goiter, compensated with levothyroxine supplementation).

The patient received a radical right-sided nephrectomy (on 17 September 2012). On pathomorphological examination, we diagnosed a clear-cell renal cell carcinoma with a rhabdoid component (ccRCC) with a high Furhman grade (G4) at the pT1bNx stage. In the post-surgery period, the patient remained under clinical observation and received periodical radiological check-ups.

After approximately two years, that is, in November 2014, a follow-up CT scan showed a recurrence of the cancer in the form of dissemination to the liver (Fig. 1). In addition to the largest lesion of 45 mm in diameter, which had been observed earlier and recognized as

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a hemangioma, three further metastatic tumors of up to 15 mm in diameter appeared in the organ. Furthermore, a dynamic growth of a mediastinal lymph node located paratracheally with ambiguous dimensions of 13 × 18 mm was observed during CT. No abnormalities were visualized in the post-nephrectomy bed.

An exploratory laparoscopy procedure was performed with conversion to laparotomy, and two sections of metastatic tumor were taken. Clear cell cancer type in the tissue specimen was confirmed.

Due to the spread of the neoplastic process with the metastatic location described above, a decision was made to qualify the patient for systemic treatment. Given the availability of an experimental treatment using next-generation immunotherapy and anti-angiogenic treatment in February 2015, the patient was enrolled in the phase II clinical trial NCT01984242 (after obtaining his informed consent). In this study, causative treatment included atezolizumab (ATEZO), an immune checkpoint inhibitor with anti-PD-L1 activity, and bevacizumab (BEV), a monoclonal antibody with anti-angiogenic activity.

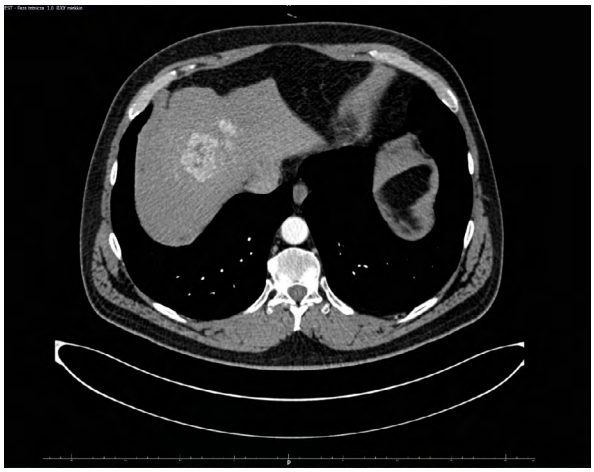

Figure 1. Recurrence in the form of dissemination to the liver (2014)

The patient received and tolerated this treatment, apart from moderate secondary hypertension, which was well controlled with a beta-blocker. Clinically significant adverse effects were virtually non-existent.

The systemic treatment went smoothly, but a follow-up CT scan (performed in August 2015) showed a new hypervascular lesion with metastatic morphology and a dimension of 19 × 13 millimeters, in the choroid plexus of the left lateral ventricle of the brain (Fig. 2).

This was observed in addition to stabilization of the measurable liver lesions. Tumor progression with a new lesion was confirmed by magnetic resonance imaging (MRI) of the central nervous system with the use of a contrast agent.

The patient did not consent to the proposed neurosurgical treatment involving removing the lesion in his brain, but he decided to try radiosurgery, and only if radiosurgery was confirmed as unsuccessful, he agreed to consider surgical treatment. In September 2015, the patient underwent stereotactic radiosurgery (SRS), with the use of a Gamma Knife. Radiation was applied at a dose of 18 Gy in one fraction to a target of 5.8 cm^3.

Given his good tolerance of the local treatment, the absence of general or focal neurological deficits or clinical and radiographic features of tumor progression in the central nervous system, at withdrawal of anti-edematous treatment with corticosteroids, the patient was put back to immunotherapy with the approval of the trial sponsor. At the same time, the decision was made to withhold anti-angiogenic treatment due to safety concerns.

Subsequent imaging assessments using CT imaging revealed complete remission (CR) of the metastatic liver lesions — scarred hypodense areas remained at the site of the hypervascular foci, which did not undergo contrast

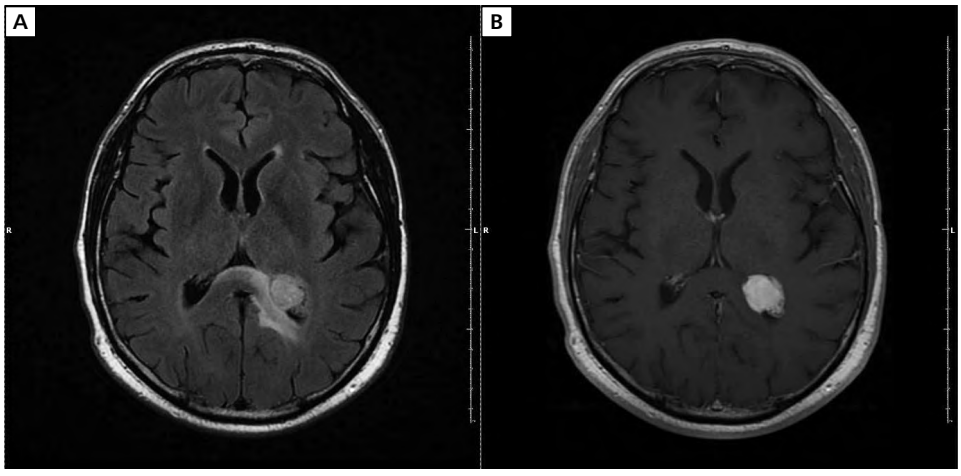

Figure 2A–B. New metastatic lesion in the choroid plexus of the left lateral ventricle (2015)

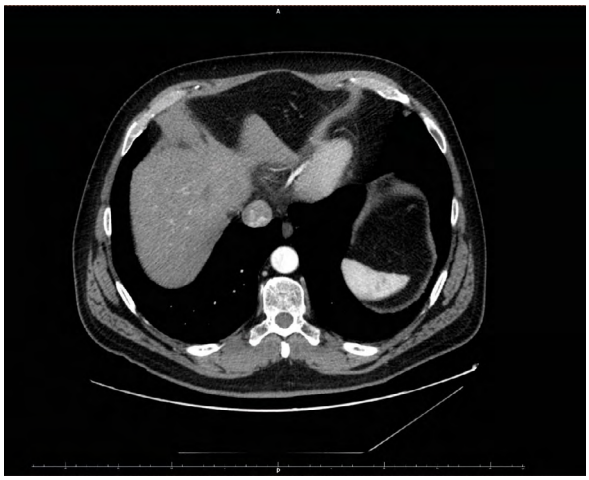

Figure 3. Complete remission of metastatic lesions in the liver (2017)

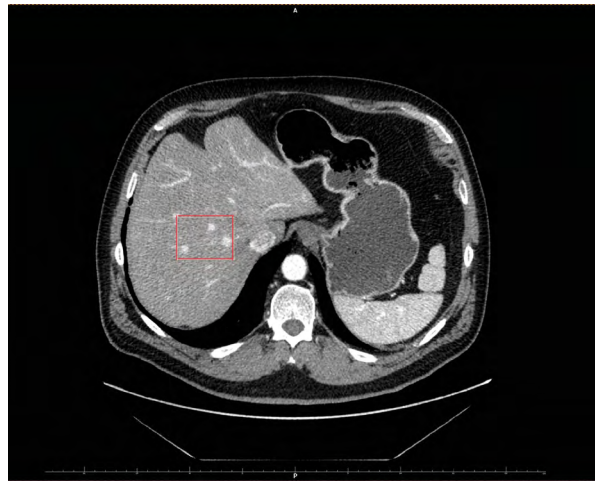

Figure 4. Progression of the disease in the liver, with the metastatic lesions highlighted in the frame (2019)

enhancement (Fig. 3). Regular MR imaging confirmed radiation necrosis of the metastasis after SRS use.

In August 2017, the treatment with atezolizumab was discontinued, due to another tumor progression in the form of a solitary metastatic lesion enlargement to a size of 15 × 20 mm in a lymph node located in the aortopulmonary window. For this reason, the patient was again qualified for SRS at a dose of 30 Gy administered in three fractions.

In the course of regular follow-up examinations after this treatment phase, including positron emission tomography (PET), no features of malignancy were found. In particular, MRI of the brain described further regression of the hypervascular lesion in the vicinity of the left lateral ventricular triangle.

During this period, the patient remained under observation. He felt well. He did not display any symptoms suggestive of cancer recurrence.

However, in January 2019, a routine follow-up CT scan of the patient, who still had no symptoms, revealed progression with the appearance of focal lesions in both lungs (dimensions up to 10 mm), nodal lesions in the mediastinum and lung hilum (up to 20 mm in the short dimension), and in the pancreas (up to a maximum diameter of 22 × 17 mm). The recurrence of the renal cell carcinoma was dynamic, as a follow-up CT performed a few weeks later showed the appearance of approximately ten hypervascular focal lesions up to 14 mm in size in the liver (Fig. 4).

A decision was made to use cabozantinib, an oral multikinase inhibitor with anti-angiogenic activity, exerted through inhibitory effects on vascular endothelial growth factor receptor (VEGFR)-related kinases. The drug also stimulates antiproliferative activity, through inhibition of MET and AXL kinases. Treatment with a tyrosine-kinase inhibitor (TKI), which had become available only a few months earlier, began in April 2019, under the accelerated access program. The drug was administered at a typical daily dose of 60 mg once per day.

As several adverse effects were associated with the treatment, a change to the cabozantinib dosing regimen was required.

After a transient and clinically insignificant increase in hepatic transaminase activity, which normalized after the temporary introduction of hepatoprotective drugs (e.g. ornithine aspartate), diarrhea became the main problem. An adverse event of grade 2 intensity according to the CTCAE (Common Terminology Criteria for Adverse Events) occurred despite the patient's adherence to the recommended dietary restrictions and was alleviated to grade 1 intensity after interventional use of loperamide in several daily doses and its prophylactic use (1–2 tablets before the first meal each day). The patient reported gastrointestinal disorders, which were present already before treatment under the extended access program for cabozantinib, and a family history in this respect, which warranted further diagnosis by performing a colonoscopy. During the procedure, no significant abnormalities were found apart from a small 3-mm polypus, which was removed and verified microscopically as a hyperplastic lesion. Chronic loosening of stools with exacerbations to diarrhea of G1 severity, secondary to dietary errors, resulted in annoying irritation of the anal area, with a sensation of severe burning aggravated after defecation accompanied by periodic itching. Damage to the mucosa and skin around the anus required topical treatment with hydrocortisone ointment.

During the course of TKI treatment, hand-foot skin reaction (HFSR) lesions of grade 3 and a papulopustular rash of grade 1 according to CTCAE also occurred. The skin lesions required two-week discontinuation of the drug and, together with adverse events described above, eventually a reduction of the daily

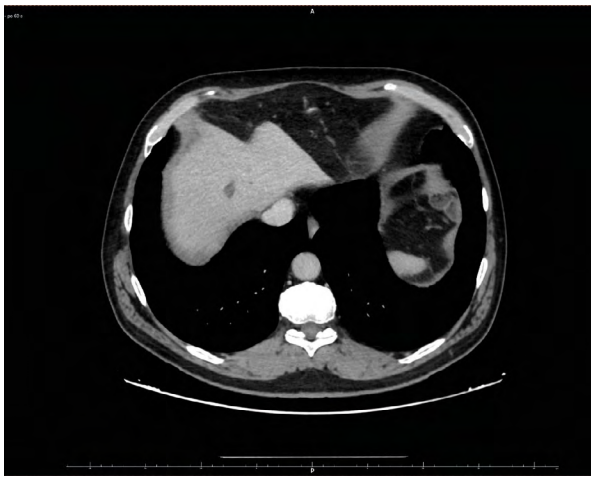

Figure 5. Cicatricial hypodense liver lesions (2023)

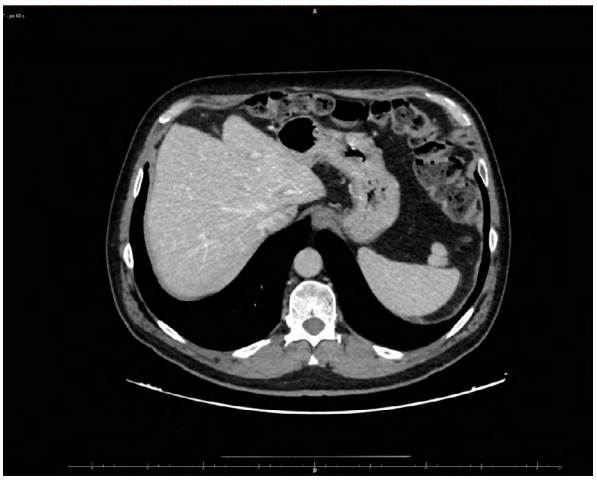

Figure 6. Regression of metastases in the liver (2023)

dose to 40 mg in August 2019, significantly improving treatment tolerability.

Blood pressure was well controlled. However, systolic hypertension persisted in the afternoon, which was the reason for introduction of amlodipine. Given the incomplete response, the patient was referred to cardiology counseling after a Holter examination, and it was decided to use a preparation containing perindopril and amlodipine, which was successful.

In laboratory tests, apart from hyperglycemia and the aforementioned elevation of aminotransferases, no clinically significant abnormalities were observed. Improvement in glycemia occurred after diabetology consultation, correction of insulin doses, and changes in dietary habits.

To date, (June 2023) that is, for a period of four years after the start of cabozantinib treatment, the disease remains under TKI control. In the last imaging assessment performed in March and April 2023, signs of regression of the metastatic tumor in the brain structures (MRI of the brain), and the absence of pathological contrast enhancement within this lesion was confirmed. At the same time, a profound response (very good partial remission, VGPR) of peripheral metastatic lesions (CT) was found (Fig. 5, 6) — we found a complete regression of secondary lesions from the lung parenchyma, scarred hypodense liver lesions, and calcified involutional foci in the pancreatic parenchyma resembling post-inflammatory lesions of 1–2 mm in size (Fig. 7).

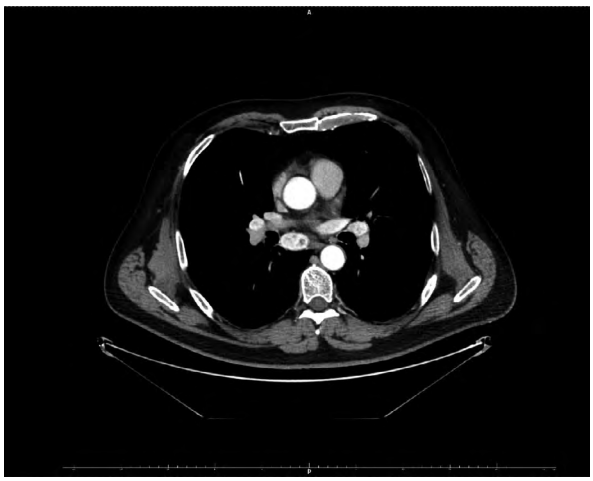

Figure 7. Nodal recurrence in the mediastinum (2019)

Discussion

The course of treatment of renal cell carcinoma in this patient demonstrates the clinical benefits that can be achieved by taking an aggressive approach using all available management modalities, from localized progression to recurrence with dissemination. Nowadays, the standard for planning treatment strategies is to use available methods when patients' general condition and the other analyzed variables allow the use of treatment. A decade ago, experience with multidisciplinary treatment was starting to build. At that time, the role of surgical treatment — typically limited to nephrectomy and palliative orthopedic or neurosurgical procedures — was being discussed. The role of radiotherapy, used mainly as a palliative treatment for metastatic foci in the bones or as whole-brain irradiation for central nervous system metastases, was considered. The effectiveness was evaluated, and the optimal use of systemic treatments with anti-angiogenic drugs was sought. After using TKIs, the objective response rate (ORR) was expected to be achieved in about 30% of patients (usually — partial responses, rarely — complete

responses), and median progression-free survival (PFS) reached about 11 months and median overall survival (OS) about two years. The above parameter values for evaluating the efficacy of TKIs are derived from registration and comparative studies of sunitinib and pazopanib, most commonly used in the first-line systemic treatment of patients with generalized clear cell renal cell carcinoma [2–5]. The typical, at that time, a clinical situation when a significantly locally advanced renal tumor is diagnosed only after onset of alarming symptoms with hematuria is now seen much less frequently. Nowadays, most of the primary lesions in the kidney are found incidentally at an early stage of development, which makes it possible to eliminate the risk of dissemination worsening the prognosis. The procedure performed in patients diagnosed with significantly locally advanced renal cell carcinoma used to involve complete removal of the kidney. Currently, when the location of the tumor within the kidney allows, a sparing procedure is preferred.

Nowadays, when the presentation of local or loco-regional stage and/or higher histological/nuclear grade of the primary tumor is observed with high risk of tumor recurrence (30–50%), adjuvant treatment is considered.

Anti-angiogenic TKIs, despite attempts to use them in this indication, have failed [6–12]. They did not provide a benefit in terms of prolonging disease-free survival (DFS) or significantly improving OS. Sunitinib was one exception. The benefit of adjuvant treatment with sunitinib, compared to observation, was clinically debatable when the risk of TKIs generating side effects and the cost of treatment are taken into account. The weakness of TKIs in adjuvant treatment is probably due to the mechanism of anti-tumor action itself. Neo-angiogenesis begins to play an important role in promoting the growth of tumor lesions only after tumor micro-focuses have reached a critical tumor mass. Antiangiogenic treatment has no effect on small lesions, which are secondarily responsible for recurrence. The effect of preventing recurrence persists for the duration of active TKI use and disappears after treatment is discontinued.

The publication of the results of the KEYNOTE-564 trial, in which pembrolizumab was used as an adjuvant treatment, was a breakthrough in adjuvant treatment [13]. Compared to placebo, adjuvant immunotherapy for patients with tumors at high risk of recurrence/spread [pT2 G4 or pT3 — irrespective of G trait, and/or N(+) — irrespective of T and G trait, or NED (no evidence of disease) tumors after oligo resection] statistically and clinically significantly increased DFS. The benefit was greater in cases of more advanced resected tumors and/or tumors characterized by greater histologic malignancy. The KEYNOTE-564 data on evaluating the impact of the intervention on OS are still immature. Interestingly, analogous trials of adjuvant use of atezolizumab or ipilimumab with nivolumab have failed [14, 15].

In the case we described, the neoplasm was relatively small, but the complex histologic composition with a rhabdoid component determined the rather rapid recurrence of the neoplasm in the form of dissemination.

After the diagnosis of tumor recurrence, data confirming the relatively low activity of available TKIs against tumors with histology other than clear cell (in particular, lesions with either a sarcomatoid or rhabdoid component) were taken into account. Faced with the possibility of an experimental systemic treatment, intensifying classical anti-angiogenic therapy with a drug from the next-generation immunotherapy group, the patient agreed to participate in a clinical trial.

At present, the choice of treatment with an immune checkpoint inhibitor in combination with antiangiogenic treatment seems natural, but that method of disease management is not reimbursed in Poland. However, according to international recommendations [16–18] — it is the treatment of choice, which should be considered first. The treatment regimen used in the patient, combining atezolizumab and bevacizumab, ultimately failed to gain registration — in a conducted clinical trial, there was no advantage over sunitinib. Nevertheless, several other prospective phase III clinical trials demonstrated that treatment with immunotherapy together with TKIs is effective and safe [19–22].

The benefits of two-drug regimens are achieved by taking advantage of the completely different mechanisms of action of their components. The tyrosine kinase inhibitor exerts an almost immediate inhibitory effect on tumor growth. It allows for overcoming the weakness of immunotherapy, which consists in the slow and staggered generation of a clonal immune response directed against tumor cells. This phenomenon is the cause of early progression, which can occur within the first three to six months of immunotherapy in about half of patients. In addition, TKI induces necrosis within tumor lesions and leads to the release or exposure of further tumor antigens (neoantigens), which increases immunogenicity. In contrast, immunotherapy included in two-drug regimens is responsible for generating long-lasting therapeutic responses, which translate into prolonged OS. Following a two-drug regimen, we expect an ORR rate of 50–60% (including about 10% complete remission of lesions), median PFS of 18 months and median OS exceeding 40 months. This spectacular effect is particularly evident in patient populations with unfavorable or very unfavorable prognosis on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) scale and in tumors of complex histology with the presence of a sarcoma component.

The case presented here concerns a patient classified as having a favorable prognosis on the IMDC scale. However, it is obvious that the parameters considered in determining the prognostic category in this scale, do not exhaust all the clinical conditions that have a potential impact on the survival time of patients.

The administered treatment was well tolerated. Experience gained over several years of intensive use of PD-1/PD-L1 inhibitor-based immunotherapy in various cancer diagnoses indicates that it is a safe treatment provided that complications are recognized promptly and appropriate management is followed. Most side effects associated with immunotherapy are moderate in severity and can be easily managed with supportive treatment or deferral of immunotherapy infusion [19–24]. Allergic reactions are rare. Nevertheless, it should be remembered that some patients develop reactions that are severe and life-threatening. Those reactions are mainly induced by an autoimmune mechanism with involvement of the gastrointestinal tract, liver, lungs, or, less frequently, the heart, central or peripheral nervous system structures, and kidneys. Therefore, education of patients and caregivers about early signs of potential toxicity with new-generation immunotherapy is crucial for safe provision of causal treatment. The goal of that education is to sensitize patients to the need to react quickly and contact the medical center when symptoms that may suggest treatment toxicity arise. The identification of specific side effects allows for early differential diagnosis and appropriate symptomatic or causal treatment with glucocorticosteroids or, in extreme cases, immunosuppression.

In our patient, the metastatic lesion in the central nervous system was exposed and grew. At the same time, good control of "peripheral" metastatic lesions was confirmed. The mentioned situation of so-called oligoprogression (increase in the isolated number of metastatic lesions) was due to weaker biological effects induced by immunotherapy. Cells of the immune system (including helper and cytotoxic lymphocytes) penetrate the brain structures to a lesser extent, which allows the growth of metastatic lesions. The fact that a metastatic lesion in the brain is revealed within the first six months after the start of causal systemic treatment suggests its formation even before the initiation of therapy. It was decided to implement local treatment, and the patient made his choice by undergoing stereotactic radiotherapy. The issue of systemic treatment was discussed extensively in correspondence with the sponsor of the clinical trial, with the final decision to continue it. The decision, as further observation of the disease course confirmed, turned out to be the right one.

Eventually, however, after further two years, it became necessary to terminate immunotherapy. The reason was another cancer progression, in the form of an isolated enlargement to 15 × 20 mm of a metastatic altered lymph node in the aortopulmonary window, which was an indication for a repeat local treatment. However, for formal reasons dictated by the provisions of the clinical trial protocol, after the second episode of tumor progression was detected, treatment with atezolizumab was stopped. The tumor progression escaping treatment was irradiated. Since radiographically documented remission of the remaining tumor lesions was achieved, the patient was referred for active observation, which allowed him to function normally for another 18 months. Nevertheless, in January 2019, another recurrence occurred with tumor dissemination appearing as multiple metastatic lesions in both lungs, mediastinal lymph nodes, pancreas, and liver.

In daily clinical practice, oncologists use the imperfect Response Evaluation Criteria in Solid Tumors (RECIST) classification system for causal treatment, which was developed mainly to monitor effects of chemotherapy and is not optimal for evaluating response to treatment with molecularly targeted drugs or immunotherapy. The use of RECIST in cases of slow growth of pre-existing tumor foci may suggest observation of the patient as the best course of action. In the case described here, with dynamic growth of existing lesions and new metastatic foci, there was no doubt about the necessity for prompt initiation of next-line systemic treatment. The decision was fairly obvious, but the choice of second-line therapy was a subject of discussion. At that time, there was no data to make an informed choice of treatment after the failure of previously administered immunotherapy.

The efficacy of sunitinib or pazopanib after failure of antiangiogenic treatment (in our case — bevacizumab) was poorly documented. Both drugs are listed as highly effective when used as first-line systemic therapy. Tivozanib was unavailable, and everolimus — an inhibitor of the mammalian target of rapamycin (mTOR) complex — with a 2% objective response rate and median PFS of four to five months was a purely palliative option. Moreover, due to its toxicity profile, everolimus was not a valuable option for a patient with diabetes as a comorbidity. Axitinib, which is a selective VEGF receptor inhibitor with almost exclusively anti-angiogenic activity, had registration [25]. However, the efficacy of axitinib was documented mainly for the sequential use after treatment with sunitinib (cases of axitinib use after bevacizumab accounted for about 10% of the population evaluated in the registration trial and was not high). The objective response rate in the AXIS trial was estimated at 20%, and median PFS at five months. In addition, later analyses [26] indicated that axitinib should be used in patients with small tumor masses, as significant process progression and localization of metastases in the liver significantly limits the activity of this TKI.

Cabozantinib, a recently registered non-selective new-generation TKI with high antineoplastic and antiproliferative activity due to inhibition of AXL and MET kinases, seemed to be the optimal choice. Both of these proteins have a significant impact on the biology of renal cell carcinomas [27, 28]. Constitutively stimulated, they are responsible for aggressive tumor growth, invasion, and metastasis formation early in the process. Thus, the use of a drug that inhibits AXL and MET function may be decisive in overcoming secondary resistance and offer a chance for clinical benefit. In the METEOR registration study, cabozantinib, compared to everolimus after the failure of prior TKI-based treatment, showed a statistically and clinically significant advantage with regard to the ORR, median PFS, and median OS. The rates were 21% *versus* 5% and 7.4 months *versus* 3.8 months, for the ORR and PFS, respectively. A 33% reduction in the relative risk of death was also demonstrated ($p = 0.005$). In addition, cabozantinib was shown to be highly effective for metastases localized in the bone and liver, as well as when tumor progression was significantly advanced. The above circumstances justified the use of cabozantinib in a patient who was relatively young and in good general performance status with dynamically growing cancer with a starting point in the kidney. Cabozantinib was used as part of the extended access programme. The course of treatment has been described above. Apart from the long-lasting and profound TKI response achieved, attention should be paid to treatment tolerability. Typically for a non-selective tyrosine kinase inhibitor, significant toxicities are observed. The described management with the introduction of lifestyle and nutrition modifications, appropriate symptomatic and supportive treatment, modification of cabozantinib dosing regimen preceded by differential diagnosis, indicates the important role of the above-mentioned management methods with the participation of experts from other specialities. The measures taken have translated into success, which, without a doubt, is the patient's survival of more than seven years, counted from the start of treatment of the disseminated renal cell carcinoma.

As mentioned in the introduction of the paper, the presented case report — although describing an increasingly common scenario of multidisciplinary treatment today — is interesting from the perspective of a clinician in Poland. After the introduction of new generation immunotherapy into reimbursement and wider possibilities of sequential treatment within the B.10. drug programme [29]. In the authors' opinion, it may facilitate therapeutic decision-making and support the building of their own experience in the use of molecularly targeted drugs and immune checkpoint inhibitors in patients with generalised renal cell carcinoma.

Article Information and Declarations

Ethics statement

Prepared with patient consent to use anonymised medical data.

Author contributions

A.F., J.Ż.: medical care, collection and analysis of clinical data, preparation of the manuscript.
A.Ż.: clinical data analysis, preparation of the manuscript and translation of the study into English.

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Conflict of interest

A.F.: professional fees for conducting clinical trials from the following companies: Janssen, BMS, MSD, Merck, Pfizer, Ipsen, Roche — with no influence on the design of the study or the content contained therein.
J.Ż.: professional fees for lectures and participation in advisory committees from the following companies: Janssen, MSD, Astra Zeneca, Pfizer. Professional fees for conducting clinical trials from the following companies: Janssen, BMS, MSD, Merck, Pfizer, Ipsen, Roche — no influence on the design of the study or the content contained therein.
A.Ż.: declare no conflict of interest.

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