Review

The first line therapy for intermediate/ high risk patients with advanced renal cell carcinoma according to therapeutic program B.10

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ABSTRACT

The purpose of this article is to discuss the use of therapeutic options for the first-line systemic treatment of patients with advanced renal cell carcinoma under the B.10 drug program effective in Poland as of May 2022 – with a focus on intermediate and high-risk patient populations according to the IMDC. The specific situation created by reimbursement conditions with the exclusion of regimens combined with a tyrosine kinase inhibitor and immune checkpoint inhibitors along with the marginalisation of the use of an mTOR inhibitor necessitates a choice between two-drug immunotherapy or an antiangiogenic drug in monotherapy. In this context, choosing the right treatment in the context of specific clinical situations is a challenge.

Key words: renal cell carcinoma, intermediate risk group, unfavourable risk group, tyrosine kinases inhibitor, immune check-point inhibitor

INTRODUCTION

Kidney cancer, despite its many diverse histological types [1], is a relatively rare diagnosis among solid tumours [2]. Due to the specific biology of this tumour, almost every case (with just a few exceptions) requires specific approach to systemic treatment of patients with disseminated malignant process. These approaches include molecularly targeted drugs from the group of tyrosine kinase inhibitors (TKIs) with antiangiogenic and/or antiproliferative activity, and immunotherapy using checkpoint inhibitors (CPIs), specifically PD1/PD-L1 (programmed death receptor-1/programmed death ligand-1) or CTLA4 (cytotoxic T-cell antigen-4). They are used as monotherapies or in therapeutic regimens combining drugs with different mechanisms of action. Numerous prospective randomized phase III clinical trials with (except for [3]) an active comparator design [4–11] confirmed the high effectiveness and acceptable toxicity profile of the above mentioned therapies.

However, the choice of a treatment method depends on many factors. First of all, we resort to systemic treatment after excluding the possibility of local treatment [12], which mainly involves the resection of the primary tumour, although metastasectomy is being increasingly attempted in patients diagnosed with oligometastatic cancer. In the case of a single tumour or a few clustered metastatic lesions, their resection seems to improve the patient's prognosis [12, 13]. Nowadays, it opens up the possibility of applying modern adjuvant therapy with the use of immunotherapy.

Radiotherapy is being increasingly used as a local treatment in everyday clinical practice. Thanks to technological progress in planning and carrying out radiation therapy, it has long gone beyond the largely palliative radiotherapy of bone metastases or secondary lesions in the central nervous system.

One of the important factors (though not the only one) taken into account when choosing pharmacotherapy is the prognostic category determined by the IMDC (International Metastatic Kidney Cancer Data Base Consortium) class (tab. 1).

In the group of patients with favourable prognosis, sunitinib, pazopanib and tivozanib remain valuable systemic treatment options [12]. Complex regimens, which include immunomodulatory drugs, are characterized with high activity and a high rate of objective response rate (ORR), as well as long-term response with the possibility of inducing complete remission, long progression-free survival (PFS) of up to 18 months, and median overall survival (OS) ranging from 36 to 40 months. However, their significant advantage over sunitinib applies mainly to patients with moderate or unfavourable prognosis. In turn, the phase II

Table 1. Prognostic factors and the IMDC prognostic score (International Metastatic Kidney Cancer Data Base Consortium).

Karnofsky Performance Status Scale < 80%
Time from primary diagnosis to initiation of molecularly targeted treatment < 1 year
Hemoglobin concentration in peripheral blood lower than the lower limit of normal (LLN)
Calcium concentration in peripheral blood serum higher than the upper limit of normal (ULN)
The number of neutrophils in peripheral blood greater than the upper limit of normal (ULN)
Platelet count in peripheral blood greater than the upper limit of normal (ULN)
Risk categorization
Prognosis favorable: none of the above factors present
Intermediate prognosis: presence of 1 or 2 of the above factors
Unfavorable prognosis: presence of ≥ 3 of the above factors

CABOSUN study [6], conducted only in a group of patients with moderate or unfavourable prognosis, demonstrated a significant advantage of cabozantinib monotherapy over sunitinib in terms of such measures of efficacy as PFS and ORR. The low activity of temsirolimus, which is not balanced, due to relatively high rate of adverse effects, makes both combined regimens containing immunocompetent drugs and cabozantinib monotherapy the only reasonable alternatives in this indication.

THERAPEUTIC OPTIONS AVAILABLE IN POLAND

Molecularly targeted therapy and next generation of cancer immunotherapy are financed as part of the drug program procedure – separately contracted. The exception are drugs moved to the chemotherapy catalogue upon patent expiration.

The current drug program provides financing for first-line treatment of metastatic kidney cancer using monotherapy with tyrosine kinase inhibitors, two-drug immunotherapy using ipilimumab (IPI) and nivolumab (NIVO), and mTOR (mammalian target of rapamycin) complex inhibitor – temsirolimus.

In general terms, the reimbursement applies to three lines of systemic therapy conducted in a sequential strategy (Announcement of the Minister of Health of February 20, 2023 on the list of medicines, foodstuffs for particular nutritional uses and medical devices as of March 1, 2023).

According to the recommendations [12–15] developed by experts from the Polish Society of Clinical Oncology and the Polish Society of Urology, the selection of first-line treatment should be made with regard to the prognostic group according to IMDC.

Sunitinib or pazopanib should be used in patients with a favourable prognosis. This results from the data obtained in the above mentioned phase III clinical trials comparing combination therapies, IPI + NIVO or TKI + CPI with sunitinib [7–11]. Although these studies achieved their endpoints, the advantages over TKIs concerned PFS, OS and ORR in the moderate and unfavourable prognosis group. At the same time, the superiority of TKI used as a comparator in these studies over combination regimens was demonstrated in the group of patients with a favourable prognosis. The data regarding sunitinib contained in the recommendations also refer to pazopanib, taking into account the results of previously conducted phase III clinical trials (PISCES and COMPARTZ) directly comparing both drugs – they confirmed, with some reservations, their equivalence.

MODERATE PROGNOSIS GROUP

In the groups of patients with moderate or unfavourable prognosis, the options are varied.

According to the approved indication [3, 4], the use of sunitinib or pazopanib may be considered in patients with moderate prognosis. However, taking into account the results of registration studies of two-drug regimens and cabozantinib monotherapy, it should be emphasized that older generation TKIs are significantly inferior to them in terms of achievable ORR, PFS and OS. Therefore, they constitute an alternative solution to the above-mentioned options, which, however, should be used only in rare situations where there is no access to any form of modern treatment or there are documented absolute contraindications to their administration.

International recommendations [12–15] indicate combined TKI and CPI regimens as the treatment of choice in patients with moderate prognosis according to the IMDC classification. The concurrent use of such combinations as axitinib with pembrolizumab (AXI with PEMBRO), cabozantinib with nivolumab (CABO with NIVO), axitinib with avelumab (AXI with AVE) or lenvatinib with pembrolizumab (LENVA with PEMBRO) [7–11] have revolutionized the systemic treatment of metastatic renal cell carcinoma with clear cell histology and tumours with a clear cell component. Previously unencountered objective response rate exceeding 50% (71% for the LENVA with PEMBRO combination) with a nearly 10% complete remission rate, one-and-a-half-year (2-year for the LENVA with PEMBRO combination) PFS and OS ranging from 40 to 48 months constituted a breakthrough in this area (tab. 2). Adverse effects observed during combination therapy include known toxicities typical of TKIs (with induced hypertension, thyroid hormonal dysfunction, skin eruptions, diarrhoea and dyspepsia) and previously unknown adverse effects resulting from the immunomodulatory effect of CPI. The latter, although partially similar (e.g. diarrhoea, skin rash, dysthyroidism, increased liver transaminase activity) in clinical presentation, result from a different mechanisms of action of the two classes of drugs. Adverse effects related to immunotherapy have different dynamics and constitute a clinical challenge, as described below.

Unfortunately, none of the combination therapies discussed above are reimbursed in Poland. This is a significant problem from a clinical perspective, preventing the use of pharmacotherapy perceived as the treatment of choice.

An attractive form of modern treatment with the use of immunotherapy, being reimbursed in our country, is the combination regimen of ipilimumab with nivolumab (IPI with NIVO). The CheckMate 214 registration study [7] was one of the first prospective phase III trials to confirm the value of this therapeutic strategy, emphasizing the high rate of objective response with the possibility of achieving complete remission of metastatic lesions and sustained response, with median remission length counted in tens of months. Paradoxically, the advantage over sunitinib increases with the number of unfavourable prognostic factors contributing to the IMDC classification. In population with favourable prognosis, the hazard ratio (HR) for cancer progression or death was 1.84 (95% confidence interval [CI]: 1.29–2.62), and for the population with moderate or unfavourable prognosis – 0.74 (95% CI: 0.62–0.88) [7]. Similarly, the hazard ratio values for death after a median follow-up of 4 years were 0.93 (0.62–1.40) and 0.65 (0.54–0.78), respectively [16]. Interestingly, the OS curves already intersected with the ones for the population with favourable prognosis, which indicates long-term advantage of combination treatment with IPI and NIVO also in this group of patients.

The latest published data for the intent-to-treat (ITT) population after a median follow-up of 67.7 months confirm the advantage of combination immunotherapy over TKIs in terms of median OS (respectively: 55.7 months vs. 38.4 months, HR 0.72) and ORR (39.3% vs. 32.4%), at the same time indicating no differences in terms of median PFS (respectively: 12.3 months vs. 12.3 months, HR 0.86) [17].

The second modern therapy among those reimbursed under the B.10 drug program is cabozantinib. For several years, the drug has been approved for use in patients with metastatic kidney cancer after failure of previous treatment with one or two lines of older generation TKIs. In this indication, it has become, alongside

Table 2. Summary of data on the design and results of clinical trials using modern immunotherapy in the first line of systemic treatment of kidney cancer patients.

Trial	CheckMate 214		JAVELIN Renal 101		KEYNOTE-426		CheckMate 9ER		CLEAR		
Combined regimen	CPI + CPI		CPI + TKI		CPI + TKI		CPI +TKI		CPI + TKI		
FDA registration date	04.2018		05.2019		04.2019		01.2021		08.2021		
Indication											
	IR/PR		FR/IR/PR		FR/IR/PR		FR/IR/PR		FR/IR/PR		
Primary endpoint											
	ORR. OS. PFS		OS. PFS		OS. PFS		PFS		PFS		
FU median (months)	67.7		19.3		42.8		32.9		26.6		
Drugs	IPI + NIVO→NIVO	SUN	AVE + AXI	SUN	PEMBO + AXI	SUN	NIVO + CABO	SUN	PEMBRO + LENVA	EVE + LENVA	SUN
Patients number	550	546	442	444	432	429	323	328	355	357	357
Prognostic group IMDC (%)											
FR	23	23	21.3	21.6	31.9	30.5	22.9	22	31	31.9	34.7
IR	61	61	61.3	62.2	55.1	57.3	58.2	57.3	59.2	54.6	53.8
PR	17	16	16.3	16	13.0	12.1	18.9	20.7	9.3	11.8	10.4
Previous nephrectomy (%)											
	82	80	79.6	80	82.6	83.4	68.7	71	73.8	72.8	77
Results											
mOS	55.7	38.4	NR	NR	45.7	40.1	37.7	34.3	NR	NR	NR
OS HR (HR; 95% CI)	0.72 (0.62–0.85); $p < 0.0001$		0.8 (0.616–1.027); $p = 0.039$		0.73 (0.60–0.88); $p < 0.001$		0.70 (0.55–0.90)		0.66 (0.49–0.88); $p = 0.005$	1.15 (0.88–1.5); $p = 0.30$	
mPFS	12.3	12.3	13.3	8	15.7	11.1	16.6	8.3	23.9	14.7	9.2
PFS HR (95% CI)	0.86 (0.73–1.01); $p = 0.063$		0.69 (0.57–0.83); $p < 0.0001$		0.68 (0.58–0.80); $p < 0.0001$		0.56 (0.46–0.68); $p < 0.0001$		0.39 (0.32–0.49); $p < 0.001$	0.65 (0.53–0.80); $p < 0.001$	
ORR (%)	39.3	32.4	52.5	27.3	60.4	39.6	56	28	71	53.5	36.1
CR (%)	11.6	3.1	3.8	2.0	10	3.5	12.0	5	16.1	9.8	4.2
PR (%)	27.6	29.3	48.6	25.2	50.5	36.1	43	23	54.9	43.7	31.9
PD (%)	17.6	14.1	12.4	19.4	NA	NA	6%	14%	5.4	7.3	14.0
mDOR (months)	NR	24.8	18.5	NE	23.6	15.3	23.1	15.1	25.8	16.6	14.6
Dose reduction (%)	NA	NA	42.2	42.6	NA	NA	61	54	68.8	73.2	50.3
TRAE, n (%)	515 (94)	522 (98)	414 (95.4)	423 (96.4)	413 (96.3)	415 (97.6)	311 (97)	298 (93)	341 (96.9)	347 (97.7)	313 (92.1)
G ≥ 3 AEs, n (%)	263 (48)	344 (64)	246 (56.7)	243 (55.4)	270 (62.9)	247 (58.1)	208 (65)	172 (54)	252 (71.6)	259 (73.0)	200 (58.8)
AEs leading to treatment discontinuation, n (%)	127 (23)	70 (13)	33 (7.6)	59 (13.4)	111 (25.9)	43 (10.1)	87 (27)	33 (10)	NR (37.2	NA (27.0)	NA (14.4)
AE leading to death, n (%)	8 (1.5)	5 (1)	3 (0.7)	1(0.2)	4 (0.9)	7 (1.6)	1 (0.3)	2(0.6)	4 (1.1)	3 (0.8)	1(0.3)

FR – *IMDC favourable risk group*; IR/PR – *IMDC intermediate/poor risk group*; IMDC – *International Metastatic Kidney Cancer Data Base Consortium*; CPI – *check–point inhibitors*; TKI – *tyrosine kinases inhibitor*; FU – *follow–up*; IPI – ipilimumab; NIVO – nivolumab; SUN – sunitinib; AVE – avelumab; AXI – axitinib; PMBRO – pembrolizumab; CABO – cabozantinib; LENVA – lenvatinib; EVE – everolimus; OS – *overall survival*; mOS – *median OS*; HR – *hazard ratio*; CI – *confidence interval*; PFS – *progression-free survival*; mPFS – *median PFS*; DOR – *duration of response*; mDOR – *median DOR*; ORR – *objective response rate*; CR – *complete response*; PR – *partial response*; SD – *stable disease*; PD – *progessive disease*; NR – *not reached*; NA – *not available*; NE – *not estimable*; AE – *adverse event*; TRAE – *treatment–related adverse event*; G – *grade*.

nivolumab, the pharmacotherapy of choice based on the results of the METEOR study [18], in which, compared to everolimus, it demonstrated significantly higher efficacy (measured by ORR, and significantly prolonged PFS and OS). The results obtained in the METEOR study stem from the drug's mechanism of action. In addition to its strong angiogenesis-inhibiting effect, cabozantinib also exerts an inhibitory effect on cMET (c-mesenchymal-epithelial transition factor; a tyrosine kinase constituting a receptor for hepatocyte growth factor) and AXL (Greek: *anexelekto*, uncontrolled; a protein with tyrosine kinase activity). The molecular signal transduction pathways controlled by these two proteins have a significant impact on the biology of kidney tumours. In a situ-

ation of constitutive stimulation, tumours with hyperactivity of one of the pathways are characterized by aggressive biology and dynamic growth, infiltration of surrounding tissues and a high tendency to form distant metastases. The above-mentioned hyperactivity may also be secondary, induced by exposure to older generation tyrosine kinase inhibitors – sunitinib, sorafenib or pazopanib. In this situation, the activity of AXL and/or cMET kinases constitutes the mechanism of secondary resistance to these drugs. Due to its molecular mechanism of action, cabozantinib is a drug that overcomes this induced resistance.

The recommendation regarding the use of cabozantinib in the first-line pharmacotherapy of metastatic renal cancer is based on the results of the prospective phase II clinical trial CABOSUN [6]. This study was conducted on 157 patients diagnosed with clear cell carcinoma (or with clear cell component). Only patients with moderate risk (81%) and unfavourable risk (19%) were included in the study, and sunitinib was used as an active comparator. The subjects were randomly divided in a 1:1 ratio in a fully unblinded manner. Three quarters of patients had previously undergone nephrectomy with primary tumour removal. In approximately 40% of people in both study groups, MET protein expression was confirmed in cancer cells. Bone metastases were found in a similar percentage of patients, and liver metastases were detected in 19% and 26% of patients in the cabozantinib and sunitinib groups, respectively. The primary endpoint was cancer progression-free survival. The secondary endpoints were: ORR, PFS and the assessment of the administered drug safety profile.

The study demonstrated a significant superiority of cabozantinib in terms of PFS (HR 0.48; 95% CI: 0.31–0.74; p = 0.0008). The median PFS was 8.6 months and 5.3 months, respectively. The ORR in the group receiving cabozantinib was twice as high as in the control group treated with sunitinib (20% vs. 9%). At the same time, there was no statistically significant advantage of cabozantinib treatment in terms of median OS. The adverse event profile was consistent with previously published data. There were no new, clinically significant signals regarding the safety of treatment with this drug.

UNFAVOURABLE PROGNOSIS GROUP

Therapeutic options for this prognostic category of patients with renal cell carcinoma – both recommended and reimbursed in Poland under the B.10 drug program – are consistent with the recommendations and financing for the patients with moderate prognosis. The only difference is the possibility of using temsirolimus (TEM), an mTOR complex inhibitor, in this prognostic group. In the past, this drug was important due to the lack of a formal requirement for prior removal of the primary tumour and the possibility of its administration to patients diagnosed with tumours of non-clear cell histology, which was supported by the registration study inclusion criteria [19]. Nowadays, due to its toxicity barely balanced by moderate anticancer activity and the availability of much more effective and safe therapeutic alternatives, TEM has lost its importance and has become marginalized. The drug is used only when there are absolute contraindications to the use of modern therapeutic options or lack of access to them.

RENAL CANCERS WITH NON-CLEAR CELL HISTOLOGY

Until recently, the B.10 drug program only allowed to finance the systemic treatment of clear cell carcinomas, and the only option of pharmacotherapy in patients diagnosed with other histological subtypes was temsirolimus. The changes introduced in the new version of the drug program entitled "Treatment of patients with kidney cancer" have expanded the treatment options for less common types of this cancer by introducing modern therapeutic options.

As already mentioned, in patients with moderate and unfavourable prognosis, these options include two-drug immunotherapy using CTLA4 and PD1 immune checkpoint inhibitors – ipilimumab and nivolumab, and a non-selective tyrosine kinase inhibitor – cabozantinib.

The reimbursed treatment using a combination immunotherapy regimen is possible in the case of the diagnosis of tumours with mixed histology – more precisely, tumours with a clear cell or sarcomatous component. This is dictated by the inclusion criteria of the CheckMate 214 registration study and the data obtained in this study documenting the efficacy of the regimen against these tumours. Particularly noteworthy is the high efficacy of IPI and NIVO combination in patients with sarcomatous tumours. This is a subpopulation with a particularly unfavourable prognosis, for which there were no effective treatments until recently. The two-drug IPI immunotherapy regimen with NIVO changed this situation dramatically. Thanks to its application, it is possible to obtain a high percentage of objective response and significantly extend PFS and OS. After a median follow-up of 42 months, 48% of patients had no cancer progression and 50% were still alive [20].

In turn, cabozantinib, thanks to the provisions included in the section on treatment eligibility criteria for "renal cell carcinoma", is reimbursed in the case of all histological subtypes of metastatic renal cell carcinoma, except for collecting duct carcinoma (de-

tails below). Such broad scope of indications are justified by the mechanism of action of cabozantinib as a non-selective inhibitor of tyrosine kinases with not only antiangiogenic but also antiproliferative activity, as discussed above.

From a practical point of view, this makes it possible to treat a relatively large group of patients diagnosed with papillary renal cell carcinoma. It accounts for approximately 10% of renal cell carcinoma cases and is the most common histological form among non-clear cell tumours. Considering the fact that the pathogenesis of type 1 papillary tumours is associated with MET gene mutations, and the mechanism of action of cabozantinib includes inhibition of the activity of the kinase encoded by it, the drug seems to be a natural therapeutic choice for people with this diagnosis.

For substantive reasons, due to the biology of cancers originating from the epithelial cells of the collecting ducts, which makes them similar to urothelial cancers, cabozantinib should not be used in such cases.

THERAPEUTIC CHOICES

Progress in the field of molecular biology is undeniable. And it is accelerating. So far, it has enabled more accurate characterization of the tumours being diagnosed. Slowly but systematically, it leads to a transition from morphological classification (cytoplasmic, tissue architecture, etc.) to a system that takes into account the molecular pathomechanism of individual histological types of kidney tumours. This enabled the identification of specific subtypes among the previously defined types of cancer and the emergence of entirely new diagnoses. This process has been reflected in the changes implemented in the WHO classification in 2016 and 2022 [1]. New publications herald subsequent changes that may further complicate this classification in the near future, although the authors' intention is to provide a simple, indexed presentation of the genomic intricacies underlying the neoplastic process.

Although progress in the molecular characterization of kidney tumours has been spectacular, so far it has unfortunately only led to the development of the histological classification system. Some of the achievements could be perceived as successful identification of attractive molecular targets, but attempts to clinically verify these discoveries yielded negative results. In short, progress has not resulted in the identification of effective molecular predictors of response to currently available therapeutic options.

Therefore, the choice of appropriate systemic therapy for metastatic renal cancer is not simple and must be based on available clinical data. Making the right decision regarding treatment may be most problematic in patients with moderate prognosis according to the IMDC classification. And it is the largest subpopulation with this diagnosis.

Ipilimumab with nivolumab or cabozantinib?

Under the B.10 drug program currently in force in Poland, it actually comes down to making a decision about the use of two-drug combination immunotherapy with ipilimumab and nivolumab or the use of a non-selective tyrosine kinase inhibitor – cabozantinib.

IMDC prognosis group

Since the considerations were limited to patients with moderate or unfavourable prognosis according to the IMDC classification, and both treatments (combination immunotherapy with IPI and NIVO, and cabozantinib) are highly effective, this factor does not enable the determination of the population that may benefit from either therapeutic option.

According to the recommendations, the use of immunotherapy should be considered first – provided that the decision concerns a patient diagnosed with clear cell carcinoma or a carcinoma with a clear cell or sarcomatous component. Where there are contraindications to its use or we are dealing with tumours of different histology, an alternative solution should be considered – only carbozantinib in the Polish health care system. A contraindication to the implementation of immunotherapy is hypersensitivity to drugs included in the considered therapeutic regimen. Additional factors limiting its use may include autoimmune diseases requiring immunosuppressive treatment (e.g., glucocorticosteroids at a daily dose equivalent to 10 mg of prednisone or higher) and chronic viral infections. Relative contraindications, such as concomitant diseases that pose an additional risk to the safe use of immunotherapy (gastrointestinal diseases with diarrhoea, cardiovascular or pulmonary diseases with symptoms of insufficiency, or renal failure), are consistent with relative contraindications to the use of TKIs. Therefore, they do not constitute a factor differentiating between patient populations being qualified for these two different therapeutic strategies. This is also the case with the age of the patient. Subgroup analysis in the CheckMate 214 study indicated lower activity of immunotherapy in patients over 75 years of age. Due to the nature of the data, their interpretation should be approached with caution. Similarly, cabozantinib should be used with caution in elderly patients.

Molecular markers

The above mentioned lack of molecular predictors of response to available forms of treatment does not help.

In the frequently cited CheckMate 214 study, there was no statistically significant advantage of immunotherapy over sunitinib in terms of PFS in the population of patients included in the study. However, statistical significance was found in patients whose PD-L1 expression was equal to 1% or higher (HR 0.46 vs. HR 1.00 in the group with PD-L1 expression < 1%). At the same time, it was found that kidney tumours in patients with favourable IMDC prognosis, in whom sunitinib maintained its superiority over IPI and NIVO combination, were characterized by low PD-L1 expression on tumour cells [21].

Nevertheless, it is generally accepted that the level of PD-L1 expression on renal cancer cells has a negative prognostic significance, but it should not be taken into account when selecting systemic treatment due to the questionable predictive value of this biomarker. The current attempts to apply molecular diagnostics focus on searching for gene expression profiles (GEP) that could have predictive significance and support therapeutic decision-making. It was found that there might be a correlation between the efficacy of combination immunotherapy with IPI and NIVO and the expression of a panel of genes responsible for controlling the inflammatory processes accompanying the development of a malignant tumour, or, more precisely, the processes taking place in its microenvironment. Similar attempts were made in the course of the ongoing clinical trials, IMmotion150 and JAVELIN Renal 101, by identifying the angiogenetic expression profile (so-called angio profile), which is a positive predictor of response to sunitinib, and the so-called immunogenic profile, positively correlated with higher activity of immunotherapy, which is typical for dedifferentiated or sarcomatous tumours [9, 22].

In the previously mentioned CABOSUN study [6], it was possible to assess the level of MET expression and its impact on the efficacy of cabozantinib in 80% of the included patients It was demonstrated that a higher level of kinase expression seemed to correlate with higher drug efficacy in terms of PFS. However, due to small study groups and the descriptive nature of the analysis, these data should be treated with caution. The level of MET expression is not used in clinical practice for predictive purposes.

Tumour mass and growth dynamics

The strengths of the IPI and NIVO combination regimen are discussed above. The ability to induce long-term objective responses, even after the necessary interventional termination of treatment due to intolerable toxicities, the possibility of achieving complete remission and a significant impact on overall survival undoubtedly constitute the advantages of immunotherapy. Considering the long follow-up period, the available data on the IPI and NIVO combination regimen is regarded to be safe and well tolerated – especially after the induction phase of treatment, in which four doses of ipilimumab are administered [23]. However, it is emphasized that the incidence of long-term remissions is relatively low and limited to patients who achieved complete or very good partial responses to cancer treatment occurring shortly after the introduction of immunotherapy. Here, the IPI and NIVO combination regimen seems to be inferior to other combination therapies (TKI and CPI) or, more broadly, treatment with the use of TKI [24].

Another challenge is the relatively high percentage of primary resistance of the tumour to immunotherapy, reaching 20% for the IPI and NIVO combination regimen. This, once again, makes it a suboptimal treatment, inferior to TKI-based regimens (combination or monotherapy) in patients with a dynamically progressing neoplastic process. This is particularly important in the case of people with full-blown clinical progression of metastatic renal cancer observed in the period preceding the commencement of the scheduled systemic treatment.

Risk categorization according to the IMDC prognostic classification is not sufficient. It does not exhaust the list of unfavourable prognostic factors, which include the tumour growth dynamics, tumour mass (measured, for example, by the number of organs affected by metastases) and specific locations of metastatic lesions. As mentioned earlier, rapidly growing tumours that increase in volume and the number of symptomatic metastatic foci increasing from one CT scan to another constitute an indication for TKI therapy. Due to the lack of reimbursement for regimens combining molecularly targeted drugs and immunotherapy in Poland, the use of cabozantinib should be seriously considered in this situation. This drug is also worth attention in case of metastases to the bones or liver. The fact that the ligand for cMET kinase, which remains in the spectrum of the kinome inhibited by cabozantinib, is a hepatocyte growth factor (HGF), physiologically deposited in bone tissue and released with the intensification of bone tissue remodelling, may explain high efficacy of this drug in patients with secondary renal cancer lesions in these locations.

Adverse effects

At this point, it is worth going back to the issue of the adverse effect profile that was observed during the CheckMate 214 study.

The adverse effects were reported by the vast majority of patients included in the registration study (93% in the IPI and NIVO combination regimen group and 97% in patients treated with sunitinib), and the clinically significant ones (intensity grades 3 and 4 according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0) were recorded in 46% and 63% patients, respectively.

However, it is not the incidence of events, which would indicate a more favourable toxicity profile of the IPI and NIVO combination regimen compared to TKIs, that is the most important. It is their nature. It is not about their quite typical clinical picture either. In the experimental treatment group within the CheckMate 214 study, the dominant symptoms were general fatigue, skin rash and itching, diarrhoea, decreased appetite, nausea and/or vomiting, increased activity of serum liver transaminases and thyroid hormone imbalance. It is rather about the mechanism of their development based on the immunomodulatory activity of the drugs used in study. It conditioned the dynamics of their occurrence and development as well as specific inertia, forcing a specific control regime, and finally the use of immunosuppressive treatment, usually based on glucocorticosteroids, optimally without unnecessary delay, immediately after identifying the indications, i.e. often from ≥ 2/3 degree of the adverse affect intensity. At the same time, it should be emphasized that, in patients who had to use glucocorticosteroids to suppress the adverse effects resulting from the overactivity of the immune system, paradoxically, higher rates of overall survival were observed after 18, 30 and 42 months of follow-up compared to patients who had not encountered such problems. The rates amounted to: 83% vs. 77%, 70% vs. 64% and 66% vs. 56%, respectively [25].

All this makes immunotherapy, with its element of unpredictability in terms of induced adverse effects, a much more demanding treatment compared to TKI. It is absolutely necessary to thoroughly educate the patient and his or her relatives about the symptoms accompanying the development of complications that threaten the patient's safety and how to react in the event of their occurrence.

Organizational aspects, coordination

Immunotherapy requires a well-organized facility that the patient is be able to contact easily and reach quickly if necessary. Due to the intravenous route of administration, it is also a treatment that absorbs the attention and time of much more personnel, which in turn requires more efficient work organization in the facility and generates much higher indirect costs compared to cabozantinib therapy. It is therefore a treatment appropriate for a patient who is able to understand the specific risks, act proactively – usually with the support of family – and lives close to the treatment facility. In turn, the centre requires a professional, well-prepared team in terms of expertise and organization, who are also provided with the support from physicians of other specialties if necessary.

Costs

The final issue that needs to be addressed is the cost directly related to the use of medications. It is not only the obvious price difference between a single-drug oral treatment provided on an outpatient basis and two-drug immunotherapy requiring intravenous administration as part of day care treatment. It is also a problem of dispensing ipilimumab used in the systemic therapy of metastatic renal cancer at a dose of 1 mg/kg body weight. The drug is supplied in 50-milligram vials. Due to the current provisions, according to which the National Health Fund reimburses only the costs of the appropriately calculated dose of the drug actually administered to the patient, only patients with a body weight of 50 kg and the multiplications of this value will not generate financial losses for the facility. In this situation, a solution may be to aggregate patients who are to receive immunotherapy with IPI and NIVO on specific days of the week to optimize the use of ipilimumab and minimize losses. However, in the case of small facilities, this solution is difficult to implement because, for organization reasons, not every patient can wait for the right moment to start treatment. Moreover, a carefully prepared schedule may quickly turn out to be an illusion due to the possibility of adverse effects occurring in one of the treated patients, which would be an indication to postpone the infusion. At the induction stage involving the use of 4 doses of ipilimumab combined with nivolumab, such situations are not uncommon. And it is not always possible to substitute one patient with another to ensure the financial security of the facility. For this reason, in small facilities, the personnel are often instructed to refer people for whom two-drug immunotherapy is the treatment of choice to large reference centres. This consequently delays the initiation of causal treatment.

CONCLUSION

The progress in the systemic treatment of patients with kidney cancer is spectacular, and numerous indicated therapeutic options now make it possible to personalize the causal treatment and make a choice based on a number of clinical factors that should be taken into account. However, the reimbursement system in Poland specified in the provisions of the B.10 drug program significantly limits these opportunities, making the

available choices suboptimal. A major omission from the drug program are regimens combining molecularly targeted treatment (TKI) with next generation immunotherapy, which is indicated in international recommendations as the treatment of choice in the first line of systemic therapy. This is important because the choice of first-line treatment – in terms of strategy and drug composition – determines the entire context of sequential therapy. On the one hand, in the event of failure of the initial use of two highly efficient drugs significantly complicates the selection of a reasonable rescue therapy. The results of the CONTACT-03 trial presented at this year's ASCO conference indicate no benefit from the use of a combo regimen consisting of atezolizumab and cabozantinib compared to cabozantinib monotherapy. The publication of the results of the ongoing phase III TiNivo 2 trial verifying the effectiveness of immunotherapy using nivolumab (in combination with tivozanib), which is perceived as more efficient, is expected within a dozen or so months. On the other hand, the published data indicate that only 50–60% patients can receive second-line treatment in the event of failure of previously administered treatment, and another 20–30% qualify for third-line pharmacotherapy. From this perspective and in view of the low percentage of primary resistance and high chances of achieving long-term clinical control of cancer, regimens consisting of TKIs and CPIs seem to be a very attractive option. The situation would be simpler if biomarkers with predictive significance are identified, but currently we still cannot count on such support and therapeutic choices are based solely on clinical data.

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