Everolimus in every day practice of metastatic renal cell carcinoma therapy – one center experience

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ABSTRACT

Introduction: Everolimus is a selective mTOR inhibitor which received approval for treatment of advanced renal cell carcinoma (mRCC) after progression on or after treatment with VEGF-targeted therapy. The aim of this study was to evaluate the efficiency and toxicity profile of everolimus in second line therapy of mRCC. The authors also assessed the impact of clinicopathological factors on the effectiveness of everolimus.

Methods: The retrospective analysis was conducted on the medical records of 33 mRCC patients who were treated with everolimus in second line therapy after progression on interferon or tyrosine kinase inhibitors (sunitinib or pazopanib) during the years 2010–2016.

Results: Median time of treatment with everolimus was 4 months (range from 1 to 58 months). Median progression free survival was 4 months and overall survival (OS) was 11 months. The best response (PR + CR + SD) was reported in 57% of patients. Toxicity in grade 3–4 was reported in 9 (27%) of patients. Clinicopathological factors associated with progression during everolimus therapy were: smoking and alcohol abuse ($p = 0.029$), higher Furman grade ($p = 0.166$), tumor necrosis ($p = 0.383$), fat tissue infiltration ($p = 0.040$), lymph node ($p = 0.193$) and adrenal metastases ($p = 0.067$). Factors which increase the risk of everolimus toxicity were worse performance status ($p = 0.333$) and more advanced disease at the beginning (lymph nodes metastases, $p = 0.05$) and higher Furman grade ($p = 0.04$).

Conclusions: Cigarettes use and/or alcohol abuse, adrenal metastases, fat tissue had significantly negative influence on survival. Grade 3–4 toxicity were reported more frequently in patients with worse performance status and more advanced disease at the time of diagnosis.

KEY WORDS: mRCC, mTOR inhibitors, toxicity, clinicopathological factors

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INTRODUCTION

Renal cell cancer (RCC) represents 3% of cancers of adults. In Silesian region mRCC morbidity was observed in 3.8% of population during the years 2011–2013: 11,2% of men and 5,6% of women, respectively. Deaths from kidney cancer have been reported in 2.9% of patients (men and women together).

Molecular targeted therapy cause the extension of progression free survival (PFS) in metastatic renal cell carcinoma (mRCC) patients. One of them are mTOR inhibitors used in second line therapy in mRCC patients. mTOR signaling pathway plays a key role in many cellular processes such as: control of the cell cycle and cell proliferation [1–3]. mTOR regulates protein synthesis of cyclin D1**,** which controls progression through the G1/S checkpoint. They also prevent angiogenesis by two mechanisms: decreasing synthesis and release of angiogenic growth factors (esp. VEGF and PDGF) from the cancer cells and blocking growth and proliferation of vascular cells. mTOR increased cytotoxicity of drugs that damage DNA regulates transcription of p21 mTOR inhibition prevents p21-mediated cell cycle arrest [4]. The mammalian target of rapamycin (mTOR) is a downstream effector of the PI3-K/Akt/mTOR pathway. mTOR consists of two complexes with distinct inputs and downstream effects: mTORC1 and mTORC2 [5]. mTORC1 regulates cell growth by promoting translation, ribosome biogenesis and autophagy [6]. mTORC2 responds primarily to growth factors, promoting cell-cycle entry, cell survival, actin cytoskeleton polarization, and anabolic output [7].

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. It reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel -associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours *in vitro* and *in vivo* [8].

In March 2009, everolimus received approval by Food and Drug Administration (FDA), for treatment of advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy. The other therapeutic indications are hormone receptor-positive, HER2/neu negative advanced breast cancer, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor and unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease [8, 9].

The aim of this study was to evaluate the efficiency and toxicity profile of everolimus in second line therapy of mRCC. The authors also assessed the impact of clinicopathological factors on the effectiveness of everolimus.

MATERIAL AND METHODS

The retrospective analysis was conducted on the medical records of 33 metastatic renal cell carcinoma (mRCC) patients who were treated with everolimus in second line therapy after progression on interferon or TKI (sunitinib or pazopanib) during the years 2010–2016 at Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch in Poland. All patient met inclusion criteria for everolimus therapy set by Polish Ministry of Health.

The median age of patients was 63.5 years (range from 42 to 82). 11 (34%) of patients were women and 22 (66%) were men. All of them were in good performance status (Zubrod 0–1). The complete characteristics of patients with regard to demographic and clinicopathological features are presented in table 1 and table 2. Patients were qualified for the second line treatment with an mTOR inhibitor (everolimus) after progression on tyrosine kinase inhibitors such as sunitynib (73%) and pazopanib (21%). 6% of patients was treated by interferon before second line treatment. All patients have received everolimus at dose of 10 mg per day. Therapy was continued to disease progression (PD) or unacceptable toxicity. The dose may have been delayed or reduced to 5 mg daily in case of clinically significant adverse events.

TABLE 1.
Baseline characteristics according to prior therapies.

Characteristics	Sunitynib (n = 24)	Pazopanib (n = 7)	Interferon (n = 2)
Gender			
Women	8 (24%)	2 (6%)	1 (3%)
Men	16 (49%)	5 (15%)	1 (3%)
Age median (range)	63 years (43–82 years)	65 years (42–78 years)	49 years (48–50 years)
< 65	14 (58%)	3 (%)	2 (100%)
> 65	10 (42%)	4 (57%)	0
Performance status			
ZUBROD 0–1	24 (100%)	7 (100%)	2 (100%)
ZUBROD > 2	0	0	0
Overweight			
Yes	15 (63%)	4 (57%)	1 (50%)
No	9 (38%)	3 (43%)	1 (50%)
Obesity			
Yes	8 (33%)	1 (14%)	0
No	16 (67%)	6 (86%)	2 (100%)

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First symptoms			
• weight loss	6 (25%)	3 (43%)	1 (50%)
• bleeding	4 (17%)	1 (14%)	0
Comorbidities			
• hypertension	12 (50%)	4 (57%)	0
• diabetes	5 (21%)	1 (14%)	0
• cardiovascular disease	2 (8%)	1 (14%)	0
Cancer in the family			
• Yes	13 (54%)	4 (57%)	0
• No	11 (46%)	3 (43%)	2 (100%)
Smoking cigarettes			
• Yes	8 (33%)	3 (43%)	0
• No	16 (67%)	4 (57%)	2 (100%)

TABLE 2.
Histopathological factors according to prior therapies.

Characteristics	Sunitynib (n = 24)	Pazopanib (n = 7)	Interferon (n = 2)
Fuhrman grade			
1–2	12 (50%)	4 (57%)	1 (50%)
> 2	12 (50%)	3 (43%)	1 (50%)
Tumor size			
< 10 cm	16 (67%)	5 (71%)	0
> 10 cm	8 (33%)	2 (29%)	2 (100%)
Necrosis			
Yes	1 (4%)	2 (29%)	0
No	23 (96%)	5 (71%)	2 (100%)
Infiltration of adipose tissue			
Yes	9 (38%)	4 (57%)	1 (50%)
No	15 (63%)	3 (43%)	1 (50%)
Lymph nodes metastases			
Yes	3 (13%)	0	1 (50%)
No	21 (88%)	7 (100%)	1 (50%)
Infiltration of blood vessels			
Yes	7 (29%)	4 (57%)	1 (50%)
No	17 (71%)	3 (43%)	1 (50%)
Metastases in the adrenal glands			
Yes	1 (4%)	2 (29%)	0
No	23 (96%)	5 (71%)	2 (100%)

The tumor response was evaluated due to RECIST 1.0. scale. Anatomical, histological characteristics and clinical data were gathered from hospital records and pathology reports according to national regulations. Qualification for the study included: histologically confirmed diagnosis of clear cell renal cell carcinoma, prior nephrectomy (radical or saving), advanced tumor stage (primary dissemination or inoperable relapse after primary surgery), documented organ metastases, metastases possible for objective evaluation in computed tomography (CT) or magnetic resonance (MR), absence of metastases in the central nervous system and favorable or intermediate prognosis according to MSKCC scale.

Statistical analysis was carried out using STATISTICA 7 software. The frequency of side effects appearance was counted. The qualitative features were presented as the percentage of their occurrence and evaluated with Fisher test and Chi-squared test with Yates correction. The Mann-Whitney test was used to compare the time of therapy in both groups. Survival curves were obtained by Kaplan-Meyer method. Differences were considered as significant if the p value was ≤ 0.05.

RESULTS

During the observation period 16 (48%) of patients died. Three (9%) patients still receive everolimus. 27 patients (82%) ended therapy due to disease progression and only 9 patients (27%) stopped therapy due to unacceptable toxicity related to mTOR inhibitor. Median time of treatment with everolimus was 4 months (range from 1 to 58 months). Median of progression free survival was 4 months and overall survival was 11 months. In 9 patients (27%) dose reduction (5 mg every day) was necessary due to treatment side effects (grade 3). At the beginning of the treatment all patients were in good performance status (Zubrod 0–1). Performance status got worse during everolimus therapy in 11 (33%) of patients. In 4 of patients (12%) treatment was ended due to worsening of performance status.

Toxicity of all grades (grade 1–4) were observed in 23 patients (70%). Most of them were side effects in grade 2 (30%), including: rash (9%), mucositis (9%), infection (3%), gastrointestinal toxicity (3%) and renal dysfunction (6%). Hematological toxicity (anaemia or neutropenia) were additionally observed in 24% of patients. Adverse events in grade 3–4 was reported in 9 (27%) of patients. Grade 4 toxicity was detected in 3 (9%) of patients including: hematological side effects (3%), renal dysfunction (3%) and mucositis (3%). Infection was reported in 15% of patients: 12% in grade 1 and 3% in grade 2. Mucositis was observed in all grades: 1 (3%), grade 2 (9%), grade 3 (3%) and grade 4 (3%). Local treatment allowed the relief of symptoms or reduce the degree of toxicity. Noninfectious pneumonitis was no detected (table 3). Grade 3–4 toxicity were reported more frequently in patients with lymph nodes metastases (p = 0.05) and higher Furman grade (p = 0.04) (more advanced disease at the beginning). Additionally, adverse side effects (grade 3–4) were insignificantly more often detected in patients with worse performance status (p = 0.333).

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TABLE 3.
Adverse events of everolimus.

Characteristics	Grade 0–1	Grade 2–4	Discontinuation of treatment
Hematologic side effects	23 (70%)	10 (30%)	3
Renal dysfunction	29 (88%)	4 (12%)	2
Gastrointestinal side effects	32 (97%)	1 (3%)	0
Inflammation of the oral mucosa	28 (85%)	5 (15%)	1
Rash	30 (91%)	3 (9%)	0
Deterioration of performance status	27 (82%)	6 (18%)	4

The best response (PR + CR + SD) was reported in 57% of patients who received everolimus. In 45% of patients disease stagnation (SD) as best response was observed. Partial regression (PR) was detected in 9%. 3% of patients have achieved complete remission (CR). There was observed tendency to disease progression in patients with cardiovascular disease (67% vs. 40%, p = 0.561). In our analysis PD was significantly more frequently reported in patients using cigarettes and alcohol (69% vs. 25%, p = 0.029). The other factors predisposing to disease progression were higher Furman grade (56% vs. 29%, p = 0.166), tumor necrosis (67% vs. 40%, p = 0.383), adrenal metastases (100% vs. 37%, p = 0.067), fat tissue infiltration (64% vs. 26%, p = 0.040) and lymph node metastases (75% vs. 38%, p = 0.193).

Everolimus was used in second line therapy after progression on first line treatment with sunitynib or pazopanib in 73 of patients and 21, respectively. The median duration of first line therapy was 8.26 months (all together for sunitinib and pazopanib). Radiotherapy was applied to 48% of patients as palliative third line therapy. In patients with higher Furnann grade duration of first line therapy last shorter than in patients with lower Furmann grade tumors (6.8 vs. 10.3 months, p = 0.094). Similarly, the time of first line therapy was shorter in case of tumors with a larger area of necrosis (4.5 vs. 9.1 months, p = 0.064). There was observed also tendency to shortening the duration of treatment in patients with weight loss as the first symptom of disease in comparison to normal weight patients (6.3 vs. 9.2 months, p = 0.193). Leukocytosis (5.2 vs. 9.4 months, p = 0.025) and higher calcium level (6.4 vs. 10.2 months, p = 0.056) in blood tests were also associated with shorter time of therapy. There was no relationship between treatment side effects and duration of first line therapy (40% vs. 33%, p = 1). Only severe side effects (grade 3–4) correlated with shorter time of first line therapy (42% vs. 25%, p = 0.431).

Higher Furmann grade (2.7 vs. 4.8 months, p = 0.117), adrenal metastases (1,6 vs. 4.5 months, p = 0.103), fat tissue infiltration (2.6 vs. 5.0 months, p = 0.030) and a larger area of necrosis (1.6 vs. 4.5, months p = 0.125) were also associated with shorter time of second line therapy with everolimus. In analyzed group, patients smoking cigarettes or using alcohol had shorter time of everolimus therapy than other patients (2.3 vs. 4.9, months p = 0.008). Neutropenia (all grades) was related to longer duration of second line therapy in comparison to normal leukocyte level (10.6 vs. 3.7, months p = 0.116). There was also tendency to longer therapy with everolimus in women in comparison to men (5.9 vs. 4.1 months, p = 0.233).

DISCUSSION

The efficacy and safety of everolimus were evaluated in an international phase III, multicenter, randomized, double-blind trial RECORD-1 in which everolimus 10 mg/day was compared to placebo. Progression-free survival, assessed using RECIST (Response Evaluation Criteria in Solid Tumours) and evaluated by a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumour response rate, overall survival, disease-related symptoms, and quality of life. Everolimus was superior to placebo for the primary endpoint of progression-free survival (4,90 vs 1,87 months, p < 0.001), with a statistically significant 67% reduction in the risk of progression or death [10]. Progression free survival was also evaluated in phase II RECORD-4 trial, which assessed everolimus in patients with mRCC who progressed after 1 prior anti-VEGF or cytokine. Median overall PFS was 7.8 (5.7–11) months, 5.7 (3.7–11.3) – months with prior sunitinib therapy and 7.8 (5.7–11.0) – months with prior other anti-VEGFs therapy. These results confirm the PFS benefit of second-line everolimus after first-line sunitinib or other anti-VEGF therapies [11]. The effectiveness and tolerability of everolimus following the first VEGF-targeted therapy in routine clinical practice was also assessed in prospective, non interventional CHANGE study in Germany. Median PFS was 7.0 (5.4–8.8) months for group with sunitynib as first line therapy and 6.9 (5.4–8.6) months for group with VEGF targeted therapy as only prior systemic treatment [12]. In retrospective analysis – US Chart Review median PFS was 10.1 months and median overall survival was 19 months for everolimus group [13]. In study conducted by Albiquest et al. median progression-free survival

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was 5.5 months (95% CI, 5.0–6.1) for the overall population and 5.8 months (95% CI = 5.0–6.4) for second-line everolimus population [14]. In our analysis median of progression free survival was 4 months and overall survival 11 months, respectively. Median time of treatment with everolimus was 4 months (range from 1 to 58 months).

Overall disease control was reported in 81% of patients who received everolimus in second line therapy of metastatic renal cell carcinoma in RECORD-1 trial. Partial response (PR) and disease stagnation were described in 19% and 62% of patients, respectively. Disease progression occurred in 19% of patients. This study found a strong correlation between the clinical response on first line therapy and the activity of everolimus ($p < 0.001$) [15]. In study conducted by Albiquest et al. best tumour response was complete or partial remission in 12% of patients and stable disease in 59% of patients [14]. In our analysis, the best response (PR + CR + SD) was reported in 57% of patients who received everolimus. In 45% of patients disease stagnation as best response was observed. Partial regression was detected in 9%. 3% of patients have achieved complete remission. These results are consistent with literature data. Clinicopathological factors for outcome in mRCC patients treated with everolimus still are sought. Conteduca et al. suggest that SCTE (stomatitis-cutaneous toxicity event) may be a predictive marker of favorable outcome in mRCC patients treated with everolimus. In their study partial response or stable disease was achieved in 15 (79%) of patients with SCTE and in 28 (48%) with no SCTE ($P = 0.03$). The presence of SCTE correlated with longer PFS (7.8 months) and OS (30.6 months) versus PFS (4.3 months) and OS (13.5 months) in non-SCTE patients ($p = 0.0029$; $P = 0.0007$) [16]. In other studies Karnofsky performance score < 80%, duration of mRCC < 1 year, progression on first-line TKI, liver metastasis and clear cell histology were significant prognostic factors for shorter survival [17]. Another described prognostic factor was (mTOR) inhibitor-associated non-infectious pneumonitis (NIP). Atkinson et al. reported that patients with NIP had a significantly longer duration of treatment (median 4.1 vs 2 months) and overall survival (median 15.4 vs 7.4 months) [18]. In our study, clinicopathological factors which influenced disease progression and shorter duration of treatment were: cardiovascular disease ($p = 0.383$), cigarettes and alcohol abuse ($p = 0.029$), higher Furman grade ($p = 0.166$), tumor necrosis ($p = 0.383$), adrenal metastases ($p = 0.193$), fat tissue infiltration ($p = 0.040$) and lymph node metastases ($p = 0.193$). No one of patients in our group suffered from SCTE.

In RECORD-1 trial, the most common adverse reactions (incidence ≥ 30%) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥ 3 %) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine (incidence ≥ 50%). The most common grade 3/4 laboratory abnormalities (incidence ≥ 3%) were neutropenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7%), infection (0.7%) and acute renal failure (0.4%) occurred on the everolimus arm but not on the placebo arm. Side effects in all grades together was reported in 75% of patients [10]. In the RECORD-4 trial toxicity profile was similar [11]. In CHANGE study the most common adverse events (any grade) were dyspnea (17%), anemia (14%), and fatigue (12%) [13]. In study conducted by Albiquest et al. commonly reported adverse events (AEs) (any grade) were stomatitis (25%), anaemia (15%) and asthenia (11%) [14]. Similar results were reported by the Korean Cancer Study Group GU 14-08. The most common non-hematologic and grade 3/4 adverse events included stomatitis, fatigue, flu-like symptoms, and anorexia as well as elevated creatinine level [19]. In our *study* toxicity in all grades (grade 1–4) together was observed in 23 (70%) of patients. Most of them were: rash (9%), mucositis (9%), infection (3%), gastrointestinal toxicity (3%) and renal dysfunction (6%). Adverse events in grade 3–4 was reported in 9 (27%) of patients. The commonest severe toxicity were: hematological side effects (3%), renal dysfunction (3%) and mucositis (3%). We have distinguished factors associated with toxicity of everolimus such as: worse performance status and more advanced disease at the beginning (lymph nodes metastases, $p = 0.05$) and higher Furman grade ($p = 0.04$).

In study of Rizzo et al. response to previous treatment with VEGER TKI was one independent factor influencing effectiveness for everolimus therapy [15]. Similarly, Park et al. identified the better response at first-line VEGFR-TKI (PR vs. non-PR, $p = 0.003$), and TTR (≤ 12 months vs. between 12 and 24 months vs. > 24 months, $p = 0.026$) as prognostic factors for longer OS [20]. In our study there was not observed association between response to first line therapy and best response to everolimus. Patients who achieved response during everolimus therapy received from 3 to 10 cycles of previous regiment.

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CONCLUSION

Toxicity profile and efficacy of everolimus in our group of patients were consistent with the results of clinical trials and multicenter experience. Cigarettes use and/or alcohol abuse, adrenal metastases, fat tissue had significantly negative influence on survival. Grade 3–4 toxicity were reported more frequently in patients with worse performance status and more advanced disease at the time of diagnosis.

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Authors' contributions:
Joanna Huszno: 70%
Elżbieta Nowara: 30%.

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