JBUON 2016; 21(6): 1442-1448
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

# Safety profile of temsirolimus in patients with metastatic renal cell carcinoma

Ivan Levakov[1,2], Sasa Vojinov[1,2], Goran Marusic[1,2], Milan Popov[1], Olivera Levakov[3], Mladen Popov[1], Dimitrije Jeremic[1,2]

[1]Urology Clinic, Clinical Center of Vojvodina, Novi Sad; [2]Medical Faculty in Novi Sad, University of Novi Sad, Novi Sad; [3]Dermatology Clinic, Clinical Center of Vojvodina, Novi Sad, Serbia

## Summary

***Purpose:*** *Various targeted disease-specific therapeutics are currently approved, demonstrating a survival benefit over therapy with interferon-alpha (IFN-a) in patients with metastatic renal cell carcinoma (mRCC). Temsirolimus, a highly specific inhibitor of the mammalian target of rapamycin (mTOR), improves the overall and progression-free survival of high-risk patients with mRCC. The purpose of this study was to estimate the effects of temsirolimus on several laboratory parameters and to report the potential adverse events (AEs) in patients with mRCC.*

***Methods:*** *This research was a controlled, open, prospective and partly retrospective randomized study that included 60 patients up to 65 years of age, divided into the experimental and control group, each containing 30 patients. Patients in the experimental group were treated with temsirolimus. The control group comprised patients in the same stage of disease, treated with IFN-a. The effect of therapy in both groups was monitored during the first year of administration.*

***Results:*** *The overall incidence of AEs was 40% in both groups. Sixteen laboratory parameters were analyzed and the total number of deviations from the reference range was 263 in the experimental group and 229 in the control group. The total number of AEs regarding patient general clinical condition in the experimental group was 193 (asthenia 53.3%, urinary infection 43.3% and pyrexia 40%) and 175 in the control group (pyrexia 76.7%, asthenia 50% and tremor 50%).*

***Conclusion:*** *Monitoring the renal function parameters during the temsirolimus administration has proved that the therapy had no significant influence on the remaining kidney function. By evaluating the AEs we concluded that there was no significant difference in the number of AEs of all grades between the groups, while the laboratory parameters and physical status deterioration differed qualitatively.*

***Key words:*** *adverse events, interferon-alpha, renal cell carcinoma, temsirolimus*

## Introduction

The 5-year survival rate in patients with mRCC is approximately 9.9% [1]. It is estimated that 20-40% of patients with RCC develop metastases following surgery. The treatment of metastatic disease includes local interventions, such as metastasectomy or radiotherapy, however the benefits of local treatments for metastases from RCC are controversial [2]. Metastasectomy may provide a possible survival benefit for a selected group of patients with lung metastases only, a long disease-free interval and a response to immunotherapy/targeted therapy before resection [3]. ESMO Clinical Practice Guidelines recommend as the first line of systemic therapy for

*Correspondence to:* Ivan Levakov, MD, PhD. Medical Faculty in Novi Sad, University of Novi Sad, Novi Sad, Hajduk Veljkova 3, 21000 Novi Sad, Serbia. Tel: +381 21 487 2205, Fax: +381 21 487 2204, E-mail: ivan.levakov@mf.uns.ac.rs
Received: 03/02/2016; Accepted: 18/02/2016

patients with good or intermediate risk treatment with sunitinib (cytokines, including high dose IL2 as option) or bevacizumab + IFN-α (sorafenib as option) or pazopanib, whereas for patients with poor prognosis the recommended therapy is temsirolimus (sunitinib or sorafenib as options) [3]. Vascular endothelial growth factor (VEGF) inhibitors and mTOR inhibitors represent two major classes of targeted therapies, which elicit significant improvements in mRCC patients survival, by inhibiting angiogenesis and growth factor pathways critical to progression of mRCC [4,5]. mTOR is an intracellular protein kinase affecting cellular proliferation, cell growth and its survival, which makes it a convenient target in the antitumor therapy [6,7]. Two commercially available mTOR inhibitors are approved for therapy of RCC. Temsirolimus is approved for use in treatment-naive mRCC patients based on level 1 evidence that it increases overall survival in poor-risk disease [4,8].

Both mTOR-inhibitor therapies are reasonably well tolerated and have similar AEs [9]. These include stomatitis, cutaneous AEs, wound-healing complications (eg, lymphocele, incisional hernia), diabetes/hyperglycemia, dyslipidemia, proteinuria, nephrotoxicity, delayed graft function, pneumonitis, anemia, hypertension, gonadal dysfunction, and ovarian toxicity [10]. For the cytokine therapy of RCC, the two immune modulators recommended are IFN-α and interleukin-2 (IL-2). IFN-α was more widely used in RCC therapy prior to the approval of the VEGF- and mTOR-directed therapies, due to its considerable side-effects profile (fever, malaise, depression) [9].

The main goal of this study was to evaluate the incidence of AEs associated with temsirolimus and to compare them with the AEs observed in IFN-α-treated patients. Based on the results of this study, the future strategies to effectively manage AEs may be selected in order to minimize the risks of AEs, along with best practices for identifying and managing AEs of both mTOR inhibitors and cytokine IFN-α therapy.

## Methods

This research was conducted as a controlled, open, prospective, partly retrospective and randomized study at the Urology Clinic of the Oncology Institute in Sremska Kamenica. In total, 60 patients were included, diagnosed with T3 RCC, who developed lung metastases in the first two years following radical nephrectomy at the Urology Clinic of the Clinical Center of Vojvodina. The control group comprised patients in the same stage of disease treated with immunotherapy, i.e. IFN-α at the Oncology Institute in Sremska Kamenica. The patient inclusion criteria were: age range from 18 to 65, T3 stage of RCC, prior radical nephrectomy, lung metastases, and patient signed consent after being informed about the aim of this research. The exclusion criteria were: patients older than 65, metastases in other organs and patients with inoperable RCC.

All procedures performed in this study were in accordance with the ethical standards of the Institutional Ethical Committee. Informed consent was obtained from all individual participants included in the study.

The treatment protocol of temsirolimus was a once-weekly dose of 25 mg intravenously over 30 min. Half an hour before administration the patients were administered the antihistaminic synopen (20mg/2ml intravenously) in order to prevent any allergic reaction. The control group was composed of patients who had undergone radical nephrectomy due to RCC, and after developing lung metastases the protocol of immunotherapy at the Oncology Institute in Sremska Kamenica was administered. The immunotherapy protocol consisted of IFN-α-2a, administered 3 times a week, in doses of 6 million s.c. up to a total dose of 180 million. Following a 4 to 6 week break, the protocol was repeated, as long as there was a positive response to therapy. Each patient with confirmed lung mRCC had his anamnesis taken and was clinically examined. Before administration of therapy the patients were subjected to chest X-ray and heart scan, ultrasound of upper abdomen and kidney, and the following laboratory analyses: erythrocyte sedimentation rate, complete blood count, glucose blood level, urinalysis, urea, creatinine, uric acid, and electrolytes. The diagnostic protocol involved a weekly check of laboratory parameters on the third day after therapy, monthly abdomen and kidney ultrasound (CT if needed), heart and chest x-ray scan (chest CT if there was a significant change in the results) every three months, as well as monitoring of all AEs events and changes in the general health of the patient.

### *Statistics*

The data gathered during the research entered into a custom designed database and were analyzed by methods of descriptive and inferential statistics. For all numerical values, the arithmetic mean, standard deviation, variation coefficient and value range (minimum and maximum value) were calculated. Descriptive parameters were presented in frequency tables. Comparison of mean values of features between the two groups was carried out by the Student's t-test. Z-test was used for comparison of the proportions. For analysis of feature interdependence the independence test was used. Statistical analysis was carried out by the *Statgraphics Centurion* software package. Probability value less than 0.05 was considered as statistically significant.

## Results

The total number of AEs represented the total incidence of AEs, including the deterioration of laboratory values and general disorders in both groups and per patient. The main indicators of the features represented by the number of disorders per patient were as follows: In the experimental group, each patient had 15.2 AEs on average, while in the control group the number of disorders was lower, i.e. 13.47. Student's t-test showed no statistically significant difference in the number of disorders per patient between the two groups. In the experimental group there was a higher standard deviation in the number of disorders (6.23), compared to 4.29 in the control group. The lowest number of disorders recorded in both groups was the same in both groups (4). The highest number of AEs was 33, registered in a patient in the experimental group, while in the control group the maximum number of AEs developed by a patient was 24 (Table 1).

In both groups there was an equal number of disorders per patient (t-value=1.2547; p value=0.2146).

The total disorders recorded in more than 40% of the patients in the control group were pyrexia, decreased Fe serum values, hyperglycemia, elevated fibrinogen values, elevated creatinine level, uremia, increased ALT value, elevated tryglycerides levels, asthenia, tremor, leucopenia, elevated AST level, lymphopenia, and hypercholesterolemia. The disorders that were more frequent in the experimental than in the control group are listed in Table 2.

Sixteen laboratory parameters for the period of one year of research were analysed (Table 3). Deviation of laboratory parameters was recorded in patients of both groups. The total number of deviations compared to the reference laboratory range in the experimental group was 263, while in the control group it was 229. The minimum number of laboratory parameters per patient was 3 in both groups, while the maximum number was 15 in the experimental group and 12 in the control group. The mean number of deviations from the reference laboratory parameters range was 8.77 in the experimental group and 7.63 in the control group. Grade 3 and 4 laboratory disorders were recorded in two patients, one in each group, involving the decrease of serum Fe.

In both groups there was an equal number

**Table 1.** Total incidence of adverse events in the experimental and control groups (t value=1.2547; p value=0.2146)

| *Adverse events* | *Experimental group Total number of AEs* | *Control group Total number of AEs* |
|---|---|---|
| Number of patients | 30 | 30 |
| Number of AEs per patient (mean±SD) | 15.2±6.2 | 13.47±4.29 |
| Minimal number of AEs per patient | 4 | 4 |
| Maximal number of AEs per patient | 33 | 24 |
| Total number of all AEs | 456 | 404 |

AE: adverse events, SD: standard deviation.

**Table 2.** Adverse events that were more frequent in the experimental than in the control group

| *Adverse events* | *Experimental group (%)* | *Control group (%)* |
|---|---|---|
| Rash | 33.3 | 6.67 |
| Hypercholesterolemia | 63.3 | 43.44 |
| Stomatitis | 30 | 0 |
| Pharyngitis | 13.33 | 3.33 |
| Pruritus | 33.33 | 6.67 |
| Taste disorder | 20 | 6.67 |
| Elevated fibrinogen levels | 76.67 | 56.67 |
| Uremia | 73.33 | 56.67 |
| Peripheral edema | 16.67 | 6.67 |

**Table 3.** Total incidence of adverse events in laboratory parameters in the experimental and control groups (t value=1.45987; p value=0.149722)

| *Adverse events* | *Experimental group Total number of AEs* | *Control group Total number of AEs* |
|---|---|---|
| Number of patients | 30 | 30 |
| Number of AEs in laboratory parameters per patient | 8.77 | 7.63 |
| Minimal number of AEs per patient | 3 | 3 |
| Maximal number of AEs per patient | 15 | 12 |
| Total number of all AEs | 263 | 229 |

AEs: adverse events

**Table 4.** Comparative list of adverse events of laboratory parameters in the experimental and the control groups

| *Laboratory parameters* | *Experimental group (%)* | *Control group (%)* |
|---|---|---|
| Se | 100 | 86.7 |
| Fibrinogen | 76.7 | 58 |
| Fe | 70 | 63 |
| Lymphocytes | 43.3 | 43.3 |
| Neutrophils | 20 | 28 |
| Platelets | 40 | 33 |
| WBC | 40 | 46 |
| Glycemia | 66.7 | 60 |
| ALT | 66.7 | 53.3 |
| AST | 40 | 46.7 |
| Creatinine | 60 | 56.7 |
| Urea | 73 | 66.7 |
| Uric acid | 30 | 20 |
| Total cholesterol | 63.3 | 43.3 |
| Triglycerides | 66.7 | 53 |

**Table 5.** Adverse events in general condition in the experimental and control groups (t value: 0.650777; p value=0.517761)

| *Adverse events* | *Experimental group Total number of AEs* | *Control group Total number of AEs* |
|---|---|---|
| Number of patients | 30 | 30 |
| Number of AEs in general state per patient | 6.43 | 5.83 |
| Minimal number of AEs per patient | 1 | 0 |
| Maximal number of AEs per patient | 18 | 12 |
| Total number of all AEs | 193 | 175 |

AE: adverse events

of total laboratory disorders per patient (t-value=1.45987; p value=0.149722).

The most common laboratory disorder of all grades in the experimental group was the elevated level of fibrinogen in 70% of the patients, while in the control group it was the decreased level of serum Fe in 63.33% of the patients. The most common general disorder of all grades in the experimental group was urinary infection, which occurred in 43.33% of the patients, while in the control group it was pyrexia, recorded in 76.67% of the patients.

Complete list of laboratory parameters in the experimental and control groups are listed in Table 4.

The total number of general disorders was 193 in the experimental and 175 in the control group. The minimum number of general disorders was 0 in the experimental group, and 1 in the control group, while the maximum number of general disorders per patient was 18 in the experimental, and 12 in the control group. The mean number of general disorders was 6.43 in the experimental group, and 5.83 in the control group during the first year of therapy (p>0.05) (Table 5).

In both groups there was an equal number of general condition disorders (t-value=0.650777; p=0.517761). A comparative list of general condition disorders in the experimental and control group is displayed in Table 6.

In the experimental group the disorders were the cause for discontinuation of therapy in 2 patients, one of whom developed asthenia, and the other one dyspnea. In the control group the disorders were also the reason for discontinuation of therapy in 2 patients (pyrexia in one and asthenia in the other). Therapy discontinuation was due to AEs in 8% of patients in the experimental group and 8.7% in the control group.

## Discussion

During the research, various AEs and hypersensitivity reactions were recorded in both groups of patients while on treatment for a period of one year. All patients treated with temsirolimus and most patients treated with IFN-α (>75%) experienced at least one AE of any grade. For any grade, pyrexia, asthenia and urinary infection were the most common AEs associated with both temsirolimus and IFN-α treatment.

In the study of Hudes et al., AEs were the reason of therapy discontinuation in 7% of the patients on temsirolimus and in 14% of patients on IFN-α [11]. Although in our study there were no deaths that could be ascribed to the AEs, Bellmunt et al. states - in relation to Hudes et al. study - that AEs were the cause of fatal outcome in two patients on temsirolimus [12]. In their study, for one patient the cause of death was fatal arrhythmia caused by electrolytic imbalance, while for the other one the reported cause of death was acute renal failure. Among the patients on interferon therapy, an AE was the cause of death in one pa-

**Table 6.** Comparative list of adverse events of general condition in experimental and in a control group (t value:0.650777; p-value=0.517761).

| *Adverse events* | *Experimental group (%)* | *Control group (%)* |
|---|---|---|
| Asthenia | 53.3 | 50 |
| Urinary infection | 43.3 | 40 |
| Pyrexia | 30 | 76.7 |
| Pain | 36.7 | 33.3 |
| Rash | 33.33 | 6.67 |
| Nausea | 33.3 | 33.3 |
| Stomatitis | 30 | 0 |
| Infection | 33.3 | 16.7 |
| Dyspnea | 23.3 | 23.3 |
| Vomiting | 23.3 | 30 |
| Pruritus | 23.3 | 10 |
| Weight loss | 20 | 30 |
| Tremor | 20 | 50 |
| Cough | 20 | 10 |
| Taste disorder | 20 | 6.7 |
| Insomnia | 20 | 20 |
| Edema | 16.7 | 6.7 |
| Anorexia | 16.7 | 20 |
| Abdominal pain | 13.3 | 10 |
| Constipation | 13.3 | 13.3 |
| Pharyngitis | 13.3 | 3.3 |
| Headache | 10 | 10 |
| Chest pain | 10 | 3.3 |
| Rhinitis | 10 | 0 |
| Back pain | 10 | 6.7 |
| Arthralgia | 10 | 6.7 |
| Myalgia | 10 | 20 |
| Epistaxis | 10 | 3.3 |
| Arrhythmia | 6.7 | 6.7 |
| Depression | 6.7 | 26.7 |

tient, who died due to cerebrovascular accident caused by grade 3 anemia [12].

In all patients of both groups, a number of AEs of varying grades were recorded without significant difference in the mean number of total disorders between the groups. The most common laboratory disorder of all grades in the experimental group was an elevated level of fibrinogen in 70% of the patients, while in the control group it was the decreased level of serum Fe in 63.33% of the patients. The most common general disorder of all grades in the experimental group was urinary infection, which occurred in 43.33% of the patients, while in the control group it was pyrexia, recorded in 76.67% of the patients.

Compared with the study of Hudes et al. [11], we have observed similar results. Hudes et al. reported that the AEs being frequent in the temsirolimus group compared to the interferon group were: rash (47 vs 6%), hyperlipidemia (27 vs 14%), peripheral edema (27 vs 8%), hyperglycemia (26 vs 11%), hypercholesterolemia (24 vs 4%) and stomatitis (20 vs 4%), whereas in our cohort rash was present in 33.3 vs 6.67%, peripheral edema in 16.67 vs 6.67%, hyperglycemia in 66.67 vs 60%, hypercholesterolemia in 63.3 vs 43.33%, and stomatitis in 30% in the experimental vs 0% in the control group.

In the study of Gerullis et al. [13] with reference to Hudes et al.'s study, the toxicity of temsirolimus was evaluated in all subjects [11,13]. During therapy, AEs were recorded in 29 patients (91%). The incidence of 71 AEs was recorded, and all of them were grade 1 or 2. The most common disorder was asthenia (43.8%), elevated creatinine level (40.6%), mucositis (31.3%), decreased level of Mg/phosphates (31.3%), diabetes (28.1%), rash (12.5%), hypothyroidism (12.5%), hyperlipidemia (9.4%), dyspnea (6.3%) and nausea (6.3%). AEs that jeopardized the quality of life of the patients and therefore called for prompt action were: diabetes, impaired kidney function and rash. In this study, no case of pneumonitis was recorded, while the most common AE related to the respiratory function was dyspnea.

Based on the data stated in *Wyeth Pharmaceuticals* from 2008, laboratory disorders of all grades in patients with mRCC were: anemia (94%), hypercholesterolemia (87%), hyperglycemia (89%), hypertriglyceridemia (83%), hypophosphatemia (49%), elevated creatinine level (57%), neutropenia (19%), and thrombocytopenia (40%). According to the study by Creel, general disorders of all grades in patients with mRCC were: anorexia (32%), dyspnea (28%), mucositis (41%), nausea (37%), pneumonitis (8%), rash (47%) and stomatitis (41%), reported in higher incidence compared to our patients, both in the experimental and control group [14]. One of the interesting differences between the experimental and control group in our patients was the absence of stomatitis in the IFN-α-treated group, since grade≥3 stomatitis was present as a painful and dose-limiting AE in the study of Hidalgo et al. [15].

According to data obtained in a phase III study [16], safety monitoring of temsirolimus included clinical and laboratory parameter assessments and electrocardiograms. Toxicities were graded using the National Cancer Institute Com-

mon Toxicity Criteria, version 3.0. Single-agent temsirolimus was associated with a lower overall incidence of grade 3 and 4 adverse reactions and serious adverse events than IFN-α or the combination of IFN-a and temsirolimus.The incidence of adverse reactions leading to treatment discontinuation and dose reduction were also lower in the temsirolimus monotherapy arm, although this arm had a higher incidence of adverse reactions resulting in dose delays [16].

Grade 3 and 4 of general condition disorders were 6 in the experimental and 7 in the control group ($p>0.05$). Grade 3 and 4 general condition disorders in the experimental group were–asthenia, infection and dyspnea, while in the control group were asthenia and pyrexia.

Comparing previous studies on AEs of temsirolimus and interferon with ours, a high percentage of them can be noticed [11,16]. This is indicated by the fact that almost all patients experienced at least one of the noted disorders of laboratory parameters and general condition. In comparison to our study, Hudes et al. [11] recorded a significantly higher percentage of patients with grade 3 and 4 disorders in both groups, as well as in the interferon group compared to the temsirolimus, which was not the case in our study.

Although no case of pneumonitis was recorded in our study, patients on temsirolimus therapy should be carefully monitored because of potential occurrence of pulmonary toxicity, which involves regular radiologic monitoring. The interrelation of temsirolimus and pulmonary toxicity was first described in patients with kidney transplantation [17], and since then, 41 new cases have been described in the literature. In a phase 2 study by Atkins et al. [18], 6 out of 111 patients on temsirolimus had potential nonspecific pneumonitis and in a phase 3 study, 4 patients had pneumonitis of all grades, with one fatal outcome [12].

Hypersensitivity reactions were sporadic and occurred on the day of therapy administration in the form of transient dyspnea, chest pain and pruritus. Bellmunt et al. [12] in reference to Hudes et al. study [11], stated that hypersensitivity reactions occurred in 10 out of 208 (5%) patients on temsirolimus despite antihistamine premedication. Four patients had two or more allergic reactions on the day of treatment administration and two patients were reported with edema, vasodilatation, vertigo, and dyspnea. In addition, anaphylaxis, chest pain and pruritus were recorded.

## Conclusions

The results of the present study may be regarded as an important observational data source, not previously available in Serbia. The importance of this study may be emphasized by the fact that the susceptibility to develop AEs might be related to individual differences in drug-metabolizing-enzyme gene variability. Both everolimus and temsirolimus are primarily metabolized by CYP3A, a highly polymorphic enzyme, which raises the possibility of differences in metabolism, potentially contributing to variable outcomes and AEs. Substantial interindividual variability existed in the expression of CYP3A, and in particular, racial differences in the CYP3A4/3A5 ratio as well as in specific CYP genotypes [19,20].

The number of side effects, as well as the percentage of patients in whom they were recorded, was not lower in the temsirolimus group compared with the control group on IFN-α therapy, although the AEs, including laboratory and general condition disorders, differed qualitatively.

Owing to the limited number of patients, the results of this study suggest the need for additional investigation and should be interpreted with caution to enable complex analyses and consistent conclusions. The analysis reported in this article is an initial attempt to evaluate the complications of therapy with temsirolimus, being the only drug for the treatment of mRCC with a proven overall survival benefit over IFN-α in high-risk patients.

## Conflict of interests

The authors declare no confict of interests.

## References

1. Heng DY, Signorovitch J, Swallow E et al. Comparative Effectiveness of Second-Line Targeted Therapies for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-Analysis of Real-World Observational Studies. PLoS One 2014 10;9:e114264.
2. Dabestani S, Marconi L, Hofmann F et al. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol 2014;15:e549-e561.
3. Escudier B, Porta C, Schmidinger M et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25:iii49-56.

4. Harshman LC, Kroeger N, Rha SY et al. First-Line Mammalian Target of Rapamycin Inhibition in Metastatic Renal Cell Carcinoma: An Analysis of Practice Patterns From the International Metastatic Renal Cell Carcinoma Database Consortium. Clin Genitourin Cancer 2014;12:335-340.
5. Dimova I, Popivanov G, Djonov V. Angiogenesis in cancer - general pathways and their therapeutic implications. J BUON 2014;19:15-21.
6. Chiarini F, Evangelisti C, McCubrey JA, Martelli AM. Current treatment strategies for inhibiting mTOR in cancer. Trends Pharmacol Sci 2015;36:124-135.
7. Vitale MG, Cartenì G. Clinical management of metastatic kidney cancer: the role of new molecular drugs. Future Oncol 2016;12:83-93.
8. Esbah O, Demirci U, Helvaci K et al. Sequential therapy and prognostic factors in metastatic renal cell carcinoma: single centre experience. JBUON 2014;19:1062-1069.
9. Randall JM, Millard F, Kurzrock R. Molecular aberrations, targeted therapy, and renal cell carcinoma: current state-of-the-art. Cancer Metastasis Rev 2014;33:1109-1124.
10. Kaplan B, Qazi Y, Wellen JR. Strategies for the management of adverse events associated with mTOR inhibitors. Transplant Rev 2014;28:126-133.
11. Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
12. Bellmunt J, Szczylik C, Feingold J, Strahs A, Berkenblit A. Temsirolimus safety profile and management of toxic effects in patients with advanced renal cell carcinoma and poor prognostic features. Ann Oncol 2008;19:1387-1392.
13. Gerrulis H, Bergmann L, Maute L, Eimer C, Otto T. Experiences and practical conclusions concerning temsirolimus use and adverse event management in advanced renal cell carcinoma within a compassionate use program in Germany. Cancer Chemother Pharmacol 2009;63:1097-1102.
14. Creel PA. Management of mTOR Inhibitor Side Effects. Clin J Oncol Nurs 2009;13:19-23.
15. Hidalgo M, Buckner JC, Erlichman C et al. A phase I and pharmacokinetic study of temsirolimus (CCI-779) administered intravenously daily for 5 days every 2 weeks to patients with advanced cancer. Clin Cancer Res 2006;12:5755-5763.
16. Kwitkowski VE, Prowell TM, Ibrahim A et al. FDA approval summary: temsirolimus as treatment for advanced renal cell carcinoma. Oncologist 2010;15:428-435.
17. Hadoux J, Vignot S, De La Motte Rouge T. Renal Cell Carcinoma: Focus on Safety and Efficacy of Temsirolimus. Clin Med Insights Oncol 2010;4:143-154.
18. Atkins MB, Hidalgo M, Stadler WM et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. J Clin Oncol 2004;22:909-918.
19. Dees EC, Carey LA. Improving endocrine therapy for breast cancer: it's not that simple. J Clin Oncol 2013;31:171-173.
20. Anglicheau D, Legendre C, Beaune P, Thervet E. Cytochrome P450 3A polymorphisms and immunosuppressive drugs: an update. Pharmacogenomics 2007;8:835-849.