HEPATOTOXICITY OF TEMSIROLIMUS AND INTERFERON ALPHA IN PATIENTS WITH METASTASISED RENAL CANCER: A CASE STUDY

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HEPATOKSIČNOST TEMSIROLIMUSA I INTERFERONA ALFA KOD PACIJENATA SA METASTATSKIM KARCINOMOM BUBREGA: SERIJA SLUČAJEVA

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ABSTRACT

Temsirolimus is a drug used for the treatment of renal cell carcinoma. The target of action of temsirolimus is mTOR (mammalian target of rapamycin) kinase, a cellular protein that regulates the growth of tumour cells and blood vessels. The aim of the present study was to determine whether temsirolimus has greater hepatotoxic potential than standard therapies for renal cancer, including interferon alpha and vinblastine.

The current study was conducted on patients treated at the Institute for Radiology and Oncology of Serbia, Belgrade for metastasised renal cell carcinoma. In total, nine patients were administered 25 mg of temsirolimus per week for four weeks. Another fourteen patients were treated with standard therapy, including interferon alpha (6 MJ, three times a week) and vinblastine. Biochemical parameters of liver function (aspartate amino-transferase, alanine amino-transferase, alkaline phosphatase, lactate dehydrogenase, γ glutamine trans-peptidase, bilirubine [direct and total] and serum proteins) were analysed prior to administration and four weeks after treatment.

In total, six patients developed hepatotoxicity, which was defined as a 3-fold increase in aspartate amino-transferase and alanine amino-transferase levels after the administration of therapy. Three patients showing signs of hepatotoxicity received temsirolimus, and three were treated with interferon alpha and vinblastine. Except for the level of aspartate amino-transferase, the studied factors including age, sex, drug, diabetes, heart failure, hypertension, nephrectomy, stage of cancer and serum urea and creatinine levels were not associated with hepatotoxicity. Namely, in patients who experienced hepatotoxicity, the aspartate amino-transferase content was significantly lower prior to the administration of drugs (13.3±6.1 vs. 20.1±7.4; T = -2.400, df = 12, p = 0.033).

The results of the present case study suggest that temsirolimus is not more hepatotoxic in patients with metastasised renal cancer than standard therapies such as interferon alpha and vinblastine.

Key words. Temsirolimus; liver; toxicity; metastasised renal cancer.

SAŽETAK


Studija je sprovedena kod pacijenata sa metastatskim karcinomom bubrega lečenih na Institutu za onkologiju i radiologiju Srbije u Beogradu. Bilo je 9 pacijenata koji su uznimali temsirolimus 25 mg nedeljno, tokom 4 nedelje. Drugih 14 pacijenata je bilo na standardnoj terapiji (interferon alfa 6 M, tri puta nedeljno) i vinblastin 10 mg dva dana u ciklusu, tokom 4 ciklusa. Kod pacijenata su analizirani biohemijjski parametri funkcije jetre na dolasku i četiri nedelje nakon uvodenja terapije; transaminaze (aspartat aminotransferaza i alanin aminotransferaza), alkalina fosfataza, laktat dehydrogenaza, gamma glutamin transpeptidaza, bilirubin (direktni i ukupni), i proteini u serumu. Bilo je šest pacijenata kod kojih je došlo do oštećenja jetre, definisanog kao najmanje trostruk prostrasti serumskog nivoa aspartat aminotransferaza i alanin aminotransferaza posle primene terapije; troje od njih je primilo temsirolimus, a troje interferon alfa i vinblastin. Nijedan od ispitivanih faktora (starost, pol, lek, dijabetes, nefrektomija, stadium carcinoma, nivo uree i kreatinina u serumu) nije bio udružen da hepatotoksičnosti, izuzev nivoa aspartat aminotransferaze, koji je pre primene lekova bio značajno niži kod pacijenata koji su razvili oštećenje jetre (13.3±6.1 vs. 20.1±7.4; T = -2.400, df = 12, p = 0.033).

Rezultati naše serije slučajeva sugerišu da temsirolimus nije više hepatotoksičan kod pacijenata sa metastatskim karcinomom bubrega od standardne terapije kombinacijom interferona alfa i vinblastina.

Ključne reči. Temsirolimus; jetra; toksičnost; metastatski karcinom bubrega.
INTRODUCTION

Temsirolimus binds mTOR (mammalian target of rapamycin) kinase, a cellular protein that regulates the growth of tumour cells and blood vessels. An intravenous preparation of temsirolimus was developed by Wyeth and received marketing authorisation from the Food and Drug Administration in May 2007 and from the European Medicine Agency in November 2007 for the treatment of metastasised renal cell cancer (RCC)1,5

Kinase mTOR (mammalian target of rapamycin) is a component of intracellular signalling pathways involved in the growth and division of cells and in the cellular response to hypoxia. Temsirolimus binds FKBP-12, an intracellular protein, forming a complex that inhibits signals initiated by mTOR. The blockage of mTOR signals prevents the production of proteins that regulate cell cycle progression and angiogenesis3,4,5,6

In general, temsirolimus is efficacious in patients with metastasised renal cell cancer, and it causes adverse effects of moderate severity. The most frequent side effects of temsirolimus include rash, nausea, weakness, inflammation of mucous membranes, anorexia and anaemia.7,8,9

The aim of the present study was to determine whether temsirolimus is more hepatotoxic than standard therapies for metastasised renal cancer, including interferon alpha and vinblastine.

MATERIALS AND METHODS

The patients

The present observational study was conducted on patients treated at the Institute for Oncology and Radiology of Serbia, Belgrade for metastasised renal cell cancer from January 1st, 2000 to April 1st, 2007. In total, 23 patients were included in the study. Nine patients (average age 59.2 ± 7.2 years) received 25 mg of temsirolimus per week (for four weeks) and 14 patients (average age 54.6 ± 9.8 years) were treated with interferon alpha (6 MI, three times a week) and vinblastine (10 mg, two days per cycle, for four cycles). The study was approved by the research committee of the Institute for Oncology and Radiology of Serbia.

The variables

Biochemical parameters of liver function (aspartate amino-transferase, alanine amino-transferase, alkaline phosphatase, lactate dehydrogenase, γ glutamime trans-peptidase, bilirubine [direct and total] and serum proteins) and the concentration of serum urea, creatinine, sodium, potassium and calcium were analysed prior to drug administration and four weeks after treatment. The patient’s age, sex, chronic diseases, therapy and stage of cancer were obtained from their files.

Statistics

The prevalence of each risk factor was determined for patients with liver injury (cases) and patients with normal serum levels of liver enzymes (controls). Differences between patients with liver injury and those in the control group were assessed with a Student T-test for continuous variables and with a Fisher’s exact test for frequencies. Differences were considered significant when the probability of the null hypothesis was less than 0.05. To estimate the association between potential risk factors and hepatotoxicity, crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using logistic regression10,11.

RESULTS

The study population included 23 patients with metastasised renal cell cancer. The characteristics of patients with and without liver injury are shown in Table 1. Significant differences in the age, sex, nephrectomy, hypertension, chronic heart failure, diabetes, drugs, grade of tumour, skin rash, serum urea level and creatinine and alanine amino-transferase levels content of patients were not observed among groups. However, prior to treatment, significant differences in the serum level of aspartate amino-transferase were detected (see Table 1).

The results of logistic regression analysis (Cox & Snell R² = 0.486, Nagelkerke R² = 0.713, Hosmer and Lemeshow Chi² = 3.187, df = 8, p = 0.922) with adjustments for potential confounders are shown in Table 2. As shown in the table, significant associations between liver injury and the studied factors were not observed. Although the adjusted odds ratio for drugs and tumour grade were 16.64 and 4.88, respectively, the confidence limit included the value of one, indicating that the association was not significant.

DISCUSSION

In several phase II and III clinical trials on temsirolimus, the following adverse effects were observed: skin rash (47%), weakness (51%), inflammation of mucous membranes (41%), nausea (37%), edema (35%) and loss of appetite (32%).12,13

Serious adverse reactions to temsirolimus have been reported, including hypersensitivity reactions (skin redness, chest pain and/or breathing difficulties), extreme hyperglycaemia, interstitial lung disease, intestinal perforation and acute renal insufficiency. The most frequent laboratory abnormalities in patients receiving temsirolimus were anaemia (94%), hyperglycaemia (89%), hyperlipidaemia (87%), hypertriglyceridemia (83%), increased serum levels of alkaline phosphatase (68%), aspartate amino-transferase (38%) and creatinine (57%), lymphopenia (53%), hypophosphatemia (49%), decreased platelet count (40%), and leukopenia (32%).14,15,16

In the present study, surrogate markers for liver injury (a 3-fold increase in the serum level of aspartate aminotransferase and alanine amino-transferase compared to
Patients with elevated serum levels of liver enzymes (3-fold higher than the baseline (n=6)) | Patients without elevated serum levels of liver enzymes (n=17) | Test value and significance of null hypothesis | Crude odds ratios and confidence intervals (1.96*SE)

| Variable | Sex (M/F) | Age (years, mean ± SD) | Nephrectomy (yes/no) | Diabetes mellitus (yes/no) | Hypertension (yes/no) | Tumour grade (C64/C65/C61/C67/C25) | Chronic heart failure (yes/no) | Skin rash (yes/no) | Drug (temsirolimus/interferon+vinblastine) | Serum urea content before treatment (mM/l) | Serum creatinine content before treatment (μM/l) | Serum aspartate amino-transferase content before treatment (IU/l) | Serum alanine amino-transferase content before treatment (IU/l) | χ² = 3.679, p = 0.451 | 0.97 (0.40, 2.38) |
|----------|-----------|------------------------|----------------------|---------------------------|-----------------------|-------------------------------|----------------------------------|-----------------|---------------------------------------------|-----------------------------|---------------------------------------------|----------------------------------------------|-----------------------------------------------|---------------------------------------------|
|          | 5/1 (83%/17%) | 60.1 ± 7.3            | 6/0 (100%/0%)        | 0/6 (0%/100%)             | 2/4 (34%/66%)         | 4/1/1/0/0 (66%/17%/17%/0%/0%) | 2/4 (34%/66%)                   | 3/3 (50%/50%) | 3/3 (50%/50%)                                | 6.4 ± 1.1                    | 117.5 ± 28.4                                 | 13.4 ± 6.1                                     | 15.5 ± 12.4                                | 6.7 ± 3.1                                      | -0.200, p = 0.843                           | 0.96 (0.67, 1.39) |
|          | 12/5 (71%/29%) | 54.5 ± 9.1            | 16/1 (94%/6%)        | 4/13 (24%/76%)            | 6/11 (36%/64%)        | 13/2/0/1/1 (76%/12%/0%/6%/6%) | 6/11 (36%/64%)                   | 6/11 (36%/64%) | 6/11 (36%/64%)                                | 5.9 ± 1.1                    | 120.7 ± 47.0                                 | 21.1 ± 8.4                                     | 20.1 ± 7.4                                 | 20.1 ± 7.4                                    | -1.090, p = 0.288                           | 0.94 (0.83, 1.06) |

*significant difference

Table 1. Characteristics of the Patients.

Table 2. Crude and adjusted odds ratios of the risk factors for liver injury in patients with metastasised renal cell cancer receiving temsirolimus or interferon alpha plus vinblastine.

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug (temsirolimus/interferon+vinblastine)</td>
<td>1.83 (0.28, 12.07)</td>
<td>16.64 (0.07, 4142.91)</td>
</tr>
<tr>
<td>Tumour grade</td>
<td>0.97 (0.40, 2.38)</td>
<td>4.88 (0.13, 180.87)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.92 (0.12, 6.56)</td>
<td>0.75 (0.01, 99.18)</td>
</tr>
<tr>
<td>Serum urea content before treatment</td>
<td>0.96 (0.67, 1.39)</td>
<td>0.80 (0.18, 3.45)</td>
</tr>
<tr>
<td>Serum aspartate amino-transferase content before treatment</td>
<td>0.83 (0.67, 1.01)</td>
<td>0.77 (0.58, 1.02)</td>
</tr>
</tbody>
</table>

* Adjusted for age†, sex†, nephrectomy†, hypertension, chronic heart failure†, diabetes†, drug, tumour grade, skin rash†, serum level of urea, creatinine†, aspartate amino-transferase and alanine amino-transferase†.

†Crude and adjusted odds ratios are not shown in the table for the sake of clarity.

OR = odds ratio
expected with the use of temsirolimus. To prevent severe forms of liver injury, serum levels of liver enzymes should be measured weekly during the first month of therapy and monthly thereafter.

REFERENCES