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ORIGINAL ARTICLE

Experiences and practical conclusions concerning temsirolimus use and adverse event management in advanced renal cell carcinoma within a compassionate use program in Germany

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Abstract
Purpose To detail tolerance of temsirolimus in a routine practice setting within a compassionate use program for patients with renal cell carcinoma.
Methods We treated 32 patients with advanced renal cell carcinoma with temsirolimus within the German compassionate use program on an individual patient basis free of charge according to EU guidelines at our two institutions. Twenty-five milligrams of temsirolimus was applied weekly in an inpatient clinical setting. Adverse events were classified following National Cancer Institute Common Toxicity Criteria.
Results No dose modification or therapy interruptions were necessary due to adverse events. Adverse events like asthenia/fatigue were observed in 43.8%, increased creatinine in 40.6%, mucositis in 31.3%, secondary diabetes in 28.1%, hypothyreosis in 12.5% and rash in 12.5%, hypercholesterolemia and hypertriglyceridemia in 9.3% of the patients.
Conclusion Therapy with temsirolimus in advanced renal cell carcinoma is well tolerated. In a routine practice setting it results in a predictable adverse event profile that can be managed medically.

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Keywords Adverse event management · Compassionate use program · Renal cell carcinoma · Temsirolimus

Abbreviations

TEMSR	Temsirolimus
CUP	Compassionate use program
AE	Adverse event
RCC	Renal cell carcinoma
EU	European Union
QoL	Quality of life
CTX	Chemotherapy
MSKCC	Memorial Sloan-Kettering Cancer Center
NCICTC	National Cancer Institute Common Toxicity Criteria
EMEA	European Medicines Agency
CHMP	Committee for medicinal products for human use

Introduction

The main treatment objective in the management of patients with advanced metastasised renal cell carcinoma (RCC) is to prolong survival with the minimum of toxicity and to improve symptoms. Therapy options are expanding and a number of novel 'targeted' therapies has been recently developed and investigated [1, 2]. Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR) kinase. Inhibition of angiogenesis by temsirolimus has clinical relevance because unregulated angiogenesis is significant in renal cell carcinoma [3]. As Hudes and co-workers [4] could show in a phase III clinical trial, single treatment regimen with temsirolimus improved significantly overall- and progression-free survival among patients with metastatic renal cell carcinoma and poor prognosis versus IFN-α

or IFN-α/temsirolimus combination. Temsirolimus was clearly well tolerated in previously reported studies. No deaths were directly attributable to drug toxicity among the 761 patients, reported to this day, who participated in phase I–III trials [5]. Most referred adverse events were fatigue/asthenia, dyspnoea, rash, nausea, hyperglycaemia, mucositis/stomatitis [5]. The entire information of available data regarding efficacy/safety of temsirolimus was promising and approval as well as availability of the drug were increasingly demanded ever since the data was acquirable first. Therefore, a compassionate use program (CUP) was introduced in 2006 in order to fill the resulting 'unmet medical need' prior to the official approval of temsirolimus. CUP in general facilitates the availability of promising medicinal products to patients at an early stage in the drug development process. The medicinal product is to be made available to a selected group of patients with a chronically or seriously debilitating or a life threatening disease, and who cannot be treated satisfyingly by an authorised medicinal product. This product has to be implemented into a clinical trial or authorisation process as in the present report [6]. The German compassionate use program temsirolimus was carried out from 19 December 2006 until 27 November 2007. Overall 200 patients with histologically confirmed, advanced metastatic RCC were treated. Of those 200 patients 181 were treated in hospitals and 19 treated by office based oncologists. This report summarises the findings of two main single centre experiences regarding treatment of 32 patients within the German CUP-temsirolimus. We made temsirolimus available to patients with advanced RCC and collected data related to safety of the drug.

Patients and methods

TEMSR compassionate use program

Prior to approval through EMEA/CHMP temsirolimus was available to patients with advanced renal cell carcinoma (RCC) through a compassionate use program (CUP) within Europe on an individual patient basis free of charge according to EU guidelines concerning CUP [6]. The German compassionate use program was carried out between 19 December 2006 and 27 November 2007. Two hundred patients with histologically confirmed, advanced metastatic RCC as determined by the criteria of the 2004 WHO classification of renal tumours of the adults were treated within the entire German CUP. The program was finished by the approval of temsirolimus (TORISEL®) at the time of 27 November 2007. From December 2006 to November 2007 we treated 32 patients with TEMSR at our two institutions. This cohort includes 21 men and 11 women, aged 36–81 years. The complete treatment and the corresponding data collection were carried out at the Department of Urology at Lukas Hospital in Neuss, Germany (Institution A) and the Department of Internal Medicine II, Haematology and Oncology, J. W. Goethe-University, Frankfurt am Main, Germany (Institution B).

Patients

CUP TEMSR was extensively explained to all participating patients to help them to reach a decision on their own. All patients had to sign a written informed consent including information on specific prognosis and alternative therapies in RCC. This included character of disease, general and specific prognosis, previous knowledge about the therapeutic effect of TEMSR. Furthermore, cytokines, like interferon alpha (IFN-α) and interleukin-2 (IL-2) as well as tyrosine kinase inhibitors like sunitinib and sorafenib were particularly mentioned as alternative therapeutic options. The regulatory status of the drug, information on expected side effect profile and pharmacovigilance obligations including control examinations were extensively explained before patients implementation into the program.

The cohort included patients with histologically confirmed advanced metastatic renal cell carcinoma (stage IV or recurrent disease). Additionally tumour size (primary tumour and metastases) had to be measurable under the terms of Response Evaluation Criteria in Solid Tumours [7–9]. Paraclinical setting and adequate bone marrow, renal and hepatic functions were confirmed as proposed by Hudes et al. [4].

Risk stratification following the Memorial Sloan-Kettering Cancer Center (MSKCC) model for prognostic features graduated 59.4% of the patients as high risk RCC patients whereas 40.6% of the included patients were classified as intermediate risk RCC patients (Table 1).

If technically possible patients had undergone radical nephrectomy previously. Previous systemic treatment was not mandatory in the patients′ group since temsirolimus had shown to improve overall survival among patients with metastatic renal cell carcinoma and a poor prognosis compared with interferon alpha [4].

Treatment

The treatment was conducted in an inpatient setting at every single week. After clinical examination and blood analysis application of temsirolimus was performed. Therefore, patients received 25 mg of temsirolimus in a weekly 30-min intravenous infusion. Premedication with 50 mg of intravenous dimetindenmaleat or diphenhydramine or a similar H1 blocker were given approximately 30 min prior to each weekly temsirolimus infusion as prophylaxis against allergic reactions [10].

Table 1 Patient characteristics

Characteristics (n = 32)	No.	Institution A	Institution B	Percentage/ mean
Female	11	8	3	34.4%
Male	21	13	8	65.6%
Age (years)	36–81	49–81	36–78	65.8
Previous nephrectomy	31	20	11	96.9%
Bilateral disease	1	1	0	3.1%
Previous chemotherapy	13	2	11	40.6%
Mono-Sutent®	7	–	7	21.9%
Combined Sutent®/Nexavar®	1	–	1	3.1%
Combined Sutent®/immuno-CTX	5	2	3	15.6%
Secondary surgery (resection of metastases)	6	2	4	18.8%
MSKCC risk classification				
Poor risk	19	13	6	59.4%
Intermediate risk	13	8	5	40.6%
Karnofsky performance				
<70	5	3	2	15.6%
≥70	27	18	9	84.4%

Demographic and disease-related characteristics at baseline. Institution A: Department of Urology, Lukas Hospital, Neuss, Germany. Institution B: Department of Internal Medicine, Haematology and Oncology, J. W. Goethe-University, Frankfurt am Main, Germany

Tolerability assessment

Adverse events (AE's) during temsirolimus treatment were recorded and graded according to the National Cancer Institute Common Toxicity Criteria (NCICTC) which report toxicity with details of type and grade, including all grades [11]. AE′s reported as temsirolimus-related were those considered by the attending physician to be probably or possibly related. Patients were monitored for clinical and laboratory toxicities every week during the hospital stay prior and after infusion of temsirolimus.

Results

General

Though, in comparison to ARCC, our cohort consisted of 59.4% high-risk RCC patients and 40.6% intermediate risk RCC patients following the MSKCC (ARCC: 69% high risk, 31% intermediate risk) and 96.9% of the patients had previously undergone nephrectomy in order to reduce the primary tumor (ARCC 66%) as well as 40.6% have received temsirolimus as second line treatment we observed a similar side effect profile with only grade 1–2 toxicities.

Patient characteristics

Patients' and disease characteristics at baseline are shown in Table 1. A total of 32 patients with advanced RCC were evaluable for activity and toxicity. Histopathological evaluation is summarised in Table 2. Repartition of the peripheral metastatic dissemination is pictured in Table 3.

Prior treatments

A total of 31 patients had previously undergone nephrectomy, and 1 patient presented with a RCC that was technically not resectable. Another 6 patients had undergone additional surgery such as resection of pulmonary metastases

Table 2 Histopathological results

Tumor entity (n = 32)	No.	Percentage (%)
Clear Cell Carcinoma	30	93.8
Bellini Duct Carcinoma	1	3.1
Chromophile Carcinoma	1	3.1

Table 3 Metastatic dissemination

Metastases localization	No.	Percentage (%)
Pulmonary	16	50
Mediastinal	1	3.1
Hepatic	5	15.6
Cerebral	2	6.3
Bone	12	37.5
Peritoneal	3	9.4
Peripheral lymph nodes	21	65.6
Others	6	18.8

A total of 32 patients were accessible for exact histopathological assessment. Positive peripheral lymph nodes were classified as metastatic dissemination

($n = 3$), peritoneal metastases ($n = 2$), peripheral lymph node dissection ($n = 1$). In 13 patients temsirolimus has been given as second line treatment following Sutent® therapy (single agent, $n = 7$) or combined ($n = 6$).

Treatment

Median number of temsirolimus treatment weeks completed at the time of data collection was 6.5 (1–16); 71.4% of patients completed at least 4 weeks of treatment and 47.6% finished 8 weeks. The recommended start dose of 25 mg weekly was given to 100% of the patients. No dose modification had to be performed.

Tolerability

All patients were evaluable for toxicity. During temsirolimus treatment, adverse effects were reported by 29 patients (91%). Altogether, 71 adverse events (AE) were documented. All events were grade 1 or 2. The most frequently reported AE's, are summarised in Table 4. No cases of temsirolimus-related cardiac adverse reactions were noted. In one case paravasation of temsirolimus was observed with only a mild local reaction.

Discussion

Hudes and co-workers described promising results of the Global Advanced Renal Cell Carcinoma (ARCC) phase III trial including 626 patients with advanced, poor prognosis RCC regarding safety and efficacy of single agent temsirolimus. A compassionate use program "temsirolimus" was introduced in 2006 in order to fill the 'unmet medical need' which resulted from the increasing demand of availability of temsirolimus although the drug was not officially licensed yet. We took the opportunity to participate in a 1-year compassionate use program before approval. To our knowledge this is the first report collecting and analysing clinical data of patients with advanced RCC, treated with temsirolimus in Germany, in routine oncology configurations out of a clinical trial setting. From a methodological point of view, clinical trials practically are the only means of obtaining reliable and interpretable efficacy and safety data for a medicinal product. Compassionate use cannot replace properly conducted clinical trials for investigational purposes. Temsirolimus was provided by means of CUP. This report announces early side effect experiences, additional safety data.

Table 4 Adverse events

Adverse events	Number of patients	Percentage of patients (%)
Fatigue/asthenia	14	43.8
Increased creatinine	13	40.6
Mucositis	10	31.3
Mg^{2+}/phosphate decrease	10	31.3
Diabetes	9	28.1
Rash/erythema	4	12.5
Hypothyreosis	4	12.5
Hypercholesterolemia/ hypertriglyceridemia	3	9.4
Dyspnoea	2	6.3
Nausea/vomiting	2	6.3

Documented adverse events (AE's). Adverse events (AE's) during Temsirolimus treatment were recorded and graded according to the National Cancer Institute Common Toxicity Criteria (NCICTC) which report toxicity with details of type and grade, including all grades. Only grade 1–2 toxicities were observed

Adverse events like asthenia/fatigue, mucositis, rash, secondary diabetes, depressed renal function and rash seem to be temsirolimus-related and may negatively affect QoL. Therefore, a prompt management is advised [5]. Overall, we did not remark any significant change in patients' mental and physical status apart from their response to treatment. 40.6% of our patients showed a mild impairment of renal function expressed by increased creatinine. No acute renal failure was observed, no therapy related dialysis was necessary. Although renal insufficiency was not reported as a frequent AE of temsirolimus in Phase I–III studies [5], a potentially nephrotoxic effect which is associated to reported mTOR inhibitors like sirolimus and everolimus (the use of both drugs had become widespread in the field of transplantation) should be considered. It may be related to induction of downregulation of vascular endothelial growth factor (VEGF). This is of importance especially due to the fact that most of the treated patients with RCC have a predisposition to nephrotoxicity because of the previously undergone nephrectomy [12–14]. Experiences from early sirolimus use suggest relevance for close monitoring of proteinuria and blood levels for creatinine/urea, use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in order to protect renal function [15, 16].

We did not observe any case of pneumonitis as reported by Duran and co-workers from initial Phase I-II trials. Nevertheless, we recommend a close clinical monitoring of respiratory symptoms indicative of restrictive interstitial pulmonary disease since pneumonitis seems to be the most concerning AE despite its infrequent appearance [17]. Dyspnea as the most frequent respiratory AE was reported with a significantly higher frequence in patients treated with temsirolimus compared to patients treated with sunitinib and sorafenib [5]. The fact that 6.3% of patients of our cohort complained of a new appearing mild dyspnea could be interpreted as early manifestation of first clinical

symptoms of interstitial pneumonitis [17, 18]. However, radiological evidence of interstitial pneumonitis was not demonstrated within the follow-up period. No specific treatment was given to the concerned patients. In addition, we did not observe hand–foot syndrome as a reported toxic effect of multikinase inhibitors as sunitinib and sorafenib reflecting the distinct targeted mechanisms of those pharmaceuticals in comparison to temsirolimus [5, 19, 20]. Regarding prevention and therapy of oral mucositis/stomatitis grade 2 that occurred in 10 (31.3%) patients we agree with Bhojani and colleagues who recommended a rigorous oral hygiene, use of salt and baking soda moutwash solutions and mucosal-coating agents, if necessary local anaesthetics (candy). Since no mucositis grade 3 or 4 was detectable in our group we did not see any need for dose reduction like recommended by Bhojani [5]. A newly developed diabetic metabolic situation with hyperglycemia expressed by excessive thirst, increased volume and frequency of urination or increased blood glucose levels was observed in 9 (28.1%) patients. Glucose levels were checked weekly, increased blood sugar values were treated with antidiabetic agents (metformin) or insulin. In case of constantly elevated blood sugar concentration we initiated therapy with metformin 500 mg twice daily. During the entire temsirolimus therapy this dose was maintained in the respective patients or elevated up to 1,000 mg twice daily in 3 cases in order to establish a fasting blood sugar level not higher than 6.5 mmol/l and post-prandial blood sugar level ($\geq$ 2 h after food-intake, venous blood) not higher than 11.5 mmol/l. Insulin was administered only in hyperglycemic situations $\geq$ 16 mmol/l as single shot treatment. Continuous metformin therapy was sufficient in all 9 affected patients during the program, no patient required continuous insulin application. No change in haemoglobin A1c (HbA1c) was observed in the affected group. We recommend constant measurements of fasting blood sugar and HbA1c in order to monitor the metabolic status of the patient. If further antidiabetic medication is necessary, dose reduction of temsirolimus should be reconsidered since second line antidiabetics like glyburide are inhibitors of CYP450 3A4 and could interfere with the metabolism of temsirolimus. As mTOR is involved in the insulin signalling pathway and its inhibition by temsirolimus may cause hyperglycemia [21, 22] it does not surprise that symptoms are reversible after dose reduction or definite termination of temsirolimus therapy. As cutaneous AE′s we noticed rash/erythema grade 1–2 in 12.5% of the patients. This corresponds to the analysis of Bhojani and colleagues who considered both symptoms to be the most frequent cutaneous side effects to the already separately mentioned mucositis. In case of rash local application of corticoids may be a useful treatment option. However, dermatologic survey should be available in case of exacerbation. Most frequently observed laboratory side effects with the respective consecutive clinical image were hypophosphataemia/hypomagnesaemia in 10 (31.3%) cases with consecutive fatigue/asthenia. As the above mentioned events were all grade 1/2 we did not see severe complications like haemolysis, encephalopathy or rhabdomyolysis. Secondary hypothyroidism grade 1–2 expressed in alternated levels of TSH, T3, T4 is another probable reason for the frequently observable fatigue symptoms.

Since we did not notice clinically relevant AE's grade 3–4 and the observed events were grade 1–2 and easily controlled, no dose reduction was necessary during the program. Compared to the experiences of Hudes et al. our cohort was less selective and probably more resistant to toxic effects of systemic therapy. As shown in table 1 our cohort consisted of 59.4% high risk RCC patients and 40.6% intermediate risk RCC patients following the MSKCC model for prognostic features. In comparison the respective stratification in the ARCC was 69% poor risk and 31% intermediate risk following MSKCC. In addition only 66% (139/209) of the ARCC patients had previously undergone nephrectomy whereas 96.9% (31/32) of our patients underwent radical surgery in order to reduce the primary tumor. In a routine practice setting temsirolimus therapy results in a predictable adverse event profile that can be managed medically. It is comparable to the side effect profile monitored during the previous clinical trials using this drug. Since we did only observe grade 1–2 toxicities which is different from the ARCC trial a higher ability to tolerate temsirolimus treatment seems to be imaginable in a clinical setting comparable to the one described here where main differences are a higher percentage of intermediate risk patients and a higher number of previously nephrectomised patients. Though 32 patients is a small number it is imaginable that both distinctive predictors may potentially influence tolerability as well as efficacy. However, knowledge and management of toxicity is of essential impact in this palliative setting of patients and dose reduction due to side effects which are medically manageable should be avoided whenever possible in order to maintain treatment efficacy.

Conclusions

Comparisons of not preselected cohorts from daily oncology practice (like CUP) versus those from clinical trials are difficult due to differences in patient demographics and selection, settings, as well as in study design (prospective vs. retrospective).

Since these evident discrepancies between clinical trials and daily practice exist, it is important to not only analyse the activity of an anticancer agent in clinical trials, but also

to investigate its effects in daily practice, as was done in the present project. Based on our particular experience the use of temsirolimus as first or second line treatment in daily clinical practice seems to result in a comparable and predictable adverse event profile in patients with advanced RCC as in reported studies.

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Conflict of interest statement There was no potential performance of this program.

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