EUROPEAN JOURNAL OF CANCER 48 (2012) 340–346

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

The risk of skin rash and stomatitis with the mammalian target of rapamycin inhibitor temsirolimus: A systematic review of the literature and meta-analysis

Cristina Gomez-Fernandez [a,e], *Benjamin C. Garden* [b,e], *Shenwong Wu* [c], *Darren R. Feldman* [d], *Mario E. Lacouture* [b,*]

[a] *Dermatology Department, University Hospital La Paz, Madrid, Spain*
[b] *Dermatology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*
[c] *Division of Medical Oncology, Department of Medicine, State University of New York at Stony Brook, Stony Brook, NY, USA*
[d] *Genitourinary Oncology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

ARTICLE INFO

Article history:
Available online 27 December 2011

Keywords:
Cancer
mTOR inhibitor
Renal cell carcinoma
Skin rash
Stomatitis
Temsirolimus

ABSTRACT

Objective: We conducted a systematic review of the literature and performed a meta-analysis to determine the risk of developing skin rash and stomatitis among patients receiving temsirolimus.

Methods: Databases from PubMed and Web of Science from January, 1998 until June, 2011 and abstracts presented at the American Society of Clinical Oncology annual meetings from 2004 through 2011 were searched to identify relevant studies. The incidence and relative risk (RR) of skin rash and stomatitis were calculated using random-effects or fixed-effects model depending on the heterogeneity of included studies.

Results: A total of 779 patients from 10 clinical trials were included in this analysis. The overall incidence of all-grade rash was 45.8% (95% confidence interval (CI): 35.6–56.3%), with a RR of 7.6 (95% CI: 4.4–13.3; $p < 0.001$). The overall incidence of high-grade rash was 3.3% (95% CI: 1.9–5.6%), with a RR of 13.70 (95% CI: 0.82–227.50, $p = 0.07$). The overall incidence of all-grade stomatitis was 44.3% (CI: 32.1–57.1%), with a RR of 11.10, 95% CI: 5.60–22.00; $p < 0.001$). The overall incidence of high-grade stomatitis was 3.2% (95% CI: 1.9–5.4%), with a RR of 13.2 (95% CI: 0.80–218.50, $p = 0.07$).

Conclusion: There is a significant risk of developing skin rash and stomatitis in cancer patients receiving temsirolimus. The risk is independent of underlying tumour. Adequate monitoring and early intervention are recommended to prevent debilitating toxicity and suboptimal dosing.

1. Introduction

The mammalian target of rapamycin (mTOR) signalling pathway plays a key role in the regulation of many essential aspects of cell growth, division and angiogenesis. Dysregulation of this pathway in tumour cells is strongly associated with cancer development and progression of a number of malignancies, thereby making it an important and confirmed target in the

* *Corresponding author:* Address: Memorial Sloan-Kettering Cancer Center, Rockefeller Outpatient Pavilion, Suite 228, 160 E 53rd St., New York, NY 10022 USA. Tel.: +1 212 610 0079; fax: +1 212 308 0739.
E-mail address: lacoutum@mskcc.org (M.E. Lacouture).
[e] These authors contributed equally to this manuscript.
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.11.028

treatment of cancer.[1] Temsirolimus, a small-molecule mTOR inhibitor, has been approved in 2007 by the United States Food and Drug Administration (US FDA) and the European Medicines Agency for treatment of advanced renal cell carcinoma (RCC).[2] Temsirolimus binds to an intracellular protein (FKBP-12), and the protein–drug complex binds to mTOR to inhibit its kinase activity.[3] Therapy with temsirolimus inhibits the ability of mTOR in tumour cells to phosphorylate proteins that are downstream of mTOR in the phosphatidylinositol 3′ kinase–AKT signalling pathway. mTOR inhibition reduces levels of hypoxia-inducible factor (HIF)-1 and HIF-2α and VEGF in various *in vitro* tumour models.[4] Inhibition of mTOR kinase results in cell cycle arrest, antiangiogenesis and apoptosis.[5] Antiangiogenic properties are particularly significant as unregulated angiogenesis is prominent in RCC.[4] However, this drug is associated with dermatological adverse events (AE), potentially affecting aesthetically sensitive areas in treated patients.

Commonly experienced dermatologic AE of temsirolimus include skin rash, stomatitis, acne, hair changes, pruritus, xerosis and nail changes, including paronychia.[6] Although this adverse effect profile may be primarily dermatologic, the recognition and subsequent management of skin toxicity are critical issues because severe skin toxicity leads to morbidity and compromises the efficacy of treatment due to dose reductions or even discontinuation. Skin rash and stomatitis are among the most common AE of temsirolimus.[7] However, the incidences of skin rash and stomatitis have not been systemically investigated and are currently unknown. We conducted a systematic review of the literature to identify published clinical trials of the mTOR inhibitor temsirolimus and performed a meta-analysis to determine the overall incidence and risk of developing skin rash and stomatitis.

2. Methods

2.1. Data source

An independent search of citations was conducted using the PubMed database (January 1998–June 2011) with 'temsirolimus' as a keyword. The search was limited to clinical trials. Additionally, we searched abstracts containing the term 'temsirolimus', that were presented at the American Society of Clinical Oncology (ASCO) conferences held between 2004 and 2011 to identify relevant clinical trials. The poster presentations of the abstracts were reviewed for complete AE data. An independent search using the web of Science database (a product developed by the Institute for Scientific Information, a citation database) was also conducted to ensure that no additional relevant studies have been missed. We reviewed each publication, and only the complete or most recent report of a clinical trial was included when duplicate publications of the trial were identified. When data were not clear, efforts were made to contact the investigators of the trials. We extracted details on study characteristics, treatment information, results and safety profiles from selected trials.

2.2. Study selection

Temsirolimus has been approved by the US FDA and the European Medicines Agency for use at 25 mg infused over a 30–60 min period once a week for advanced RCC.[2] To ensure practical significance, we determined the risk of skin rash and stomatitis in cancer patients receiving temsirolimus at this dose level. Thus, phase I clinical trials have been excluded from analyses due to multiple dose levels. Additionally, as chemotherapy may affect the risk of temsirolimus-associated skin rash and stomatitis, trials containing chemotherapeutic agents in combination with temsirolimus were excluded. Skin rash in the studies were defined as: 'rash', 'rash/erythema', 'rash/dermatitis', 'rash/desquamating', and 'maculopapular rash'. Stomatitis was defined as 'stomatitis' and 'mucositis'. The term stomatitis is preferred over mucositis to assist in differentiating mTOR-associated mucosal ulceration from mucositis seen in cytotoxic chemotherapy and radiotherapy.[8] The trials that met the following criteria were selected for the final analysis: (1) prospective phase II and III clinical trials and compassionate use programmes in cancer patients; (2) assignment of participants to the treatment with temsirolimus as a single agent at the approved dose; (3) data available regarding the incidence of skin rash or stomatitis.

2.3. Clinical end-points

Clinical end-points were extracted from a safety profile of each trial. The included studies reported the incidence of skin rash and stomatitis as grade 1–5 (all-grade) or grade 3 and above (high-grade). They were recorded according to versions II or III of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute. Both versions are similar regarding the grading of skin rash. The grading of skin rash is described below: grade 1, macular or papular eruption or erythema without associated symptoms; grade 2, macular or papular eruption or erythema with pruritus or other associated symptoms; localised desquamation or other lesions covering <50% of the body surface area (BSA); grade 3, severe generalised erythroderma or macular, papular or vesicular eruption; desquamation covering ⩾50% BSA; grade 4, generalised exfoliative, ulcerative, or bullous dermatitis and grade 5, death. The grading of stomatitis according to version II is described below: grade 1, painless ulcers, erythema, or mild soreness in the absence of lesions; grade 2, painful erythema, oedema, or ulcers, but can eat or swallow; grade 3, painful erythema, oedema, or ulcers requiring IV hydration; grade 4, severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation. The grading of stomatitis according to version III is described below: grade 1, erythema of the mucosa; grade 2, patchy ulcerations or pseudomembranes; grade 3, confluent ulcerations or pseudomembranes, bleeding with minor trauma, or interfering with activities of daily living (ADL); grade 4, tissue necrosis, significant spontaneous bleeding, or life-threatening consequences; grade 5, death.

2.4. Statistical analysis

All statistical analysis was performed using version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, New Jersey, United States of America (USA)). The number of patients with skin rash or stomatitis and the number of those