EUROPEAN JOURNAL OF CANCER 48 (2012) 340–346

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

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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

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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

patients receiving temsirolimus were extracted from the selected clinical trials. For each study, the proportion of patients with skin rash or stomatitis was calculated and the 95% exact confidence interval (CI) was derived. For studies with a control arm, the relative risk of skin rash or stomatitis among patients assigned to temsirolimus was also calculated and compared with those assigned to the control treatment.

For meta-analysis, both fixed-effects model (weighted with inverse variance) and random-effects model were considered. For each meta-analysis, the Cochran's Q statistic was first calculated to assess the heterogeneity among the proportions of the included trials. For *p*-value for Cochran's Q statistic of less than 0.1, the assumption of homogeneity was deemed invalid, and random-effects model was reported after exploring the causes of heterogeneity. Otherwise, both the fixed-effects model and the random-effects model results were reported. A two-tailed *p*-value of less than 0.05 was judged as statistically significant.

3. Results

3.1. Search results

Our literature search yielded a total of 126 potentially relevant studies of temsirolimus. The search of PubMed identified 43 clinical studies of which 34 were excluded after review (Fig. 1). Nine original studies, including one randomised controlled Phase III, one compassionate use programme, two randomised Phase II trials of different dose levels and five single arm Phase II trials were included in a final analysis.[9–17] Our search of ASCO abstracts yielded 83 potentially relevant studies, of which only one single arm Phase II trial met our inclusion criteria.[18] Overall, we have included 10 prospective clinical trials in our final analysis (Table 1).

3.2. Patients

A total of 779 patients who met our criteria from 10 clinical trials were available for analysis. A total of 579 patients received temsirolimus monotherapy at a dose of 25 mg. There was one randomised trial, in which we used as a control 200 patients receiving interferon alpha.[14] Skin rash or stomatitis were not listed as a preexisting condition in any of the selected trials. Underlying malignancies included RCC (three trials),[10,13,14] mantle cell lymphoma,[9] neuroendocrine carcinoma,[11] multiple myeloma,[12] soft tissue sarcoma,[15] small-cell lung cancer,[16] non-mantle cell non-Hodgkin's[17] and endometrial cancer.[18]

3.3. Incidence of all-grade rash

Data for all-grade rash were available for analysis from a total of 490 patients. The incidence of all-grade rash ranged between 12.5% and 72.2% with the highest incidence observed in a phase II trial in patients with RCC[10] and the lowest in the compassionate use trial in patients with RCC.[13] Based on data from 8 trials with a total of 490 patients, the overall incidence of all-grade rash was 45.8% (95% CI: 35.6–56.3%), according to the random-effects model (Fig. 2).

3.4. Incidence of high-grade rash

High-grade skin rash is associated with increased morbidity and can result in dose-modification or treatment interruption. The incidence of high-grade rash ranged from 0.6% to 4.4% with the highest incidence observed in a phase II trial in patients with small-cell lung cancer[16] and the lowest in a phase II trial in patients with non-mantle cell non-Hodgkin's lymphoma.[17] Based on data from seven trials with a total of 454

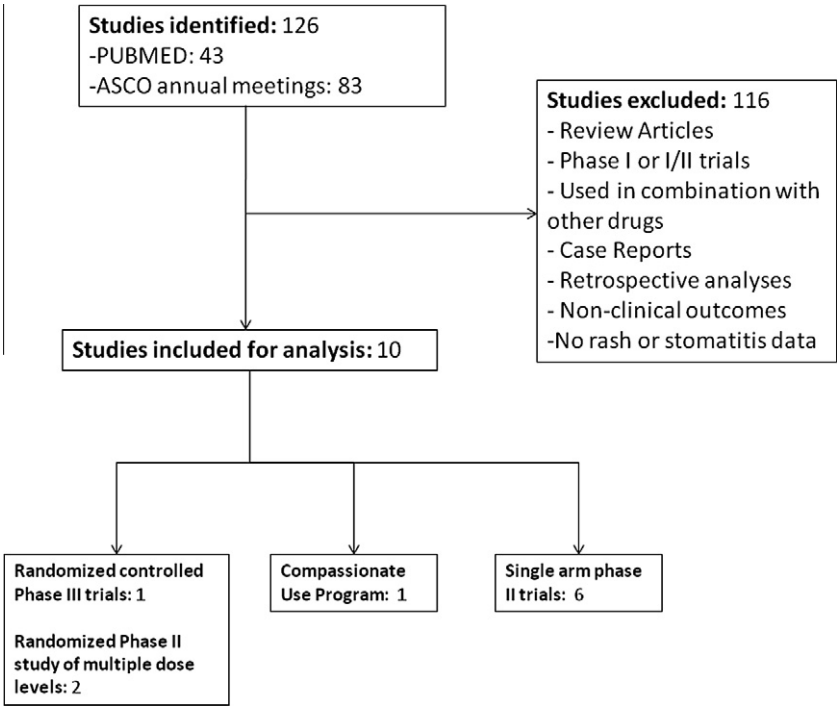

Fig. 1 – Selection process for studies included in the meta-analysis.

Table 1 – Characteristics of studies included in the meta-analysis.

Trial	Trial design	Temsirolimus arm	Control or other study arms	Sample size	Underlying cancer	CTCAE version
Ansell et al.[9]	Single arm phase II	Single agent	n/a	28	Mantle cell lymphoma	2
Atkins et al.[10]	Randomised phase II	Single agent	Temsirolimus: 75 mg; Temsirolimus: 250 mg	110	RCC	2
Duran et al.[11]	Single arm phase II	Single agent	n/a	36	Neuroendocrine carcinoma	3
Farag et al.[12]	Single arm phase II	Single agent	n/a	16	Multiple myeloma	3
Gerullis et al.[13]	Compassionate use programme	Single agent	n/a	32	RCC	3
Goodwin et al.[18]	Single arm phase II	Single agent	n/a	49	Endometrial cancer	n/a
Hudes et al.[14]	Randomised phase III	Single agent	IFN; IFN + temsirolimus	616	RCC	3
Okuno et al.[15]	Single arm phase II	Single agent	n/a	40	Soft tissue sarcoma	3
Pandya et al.[16]	Randomised phase II	Single agent	Temsirolimus 250 mg	86	Small-cell lung cancer	2
Smith et al.[17]	Single arm phase II	Single agent	n/a	89	Non–mantle cell non-Hodgkin's lymphoma	3

CTCAE = Common Terminology Criteria for Adverse Events; RCC = renal cell carcinoma; IFN = interferon.

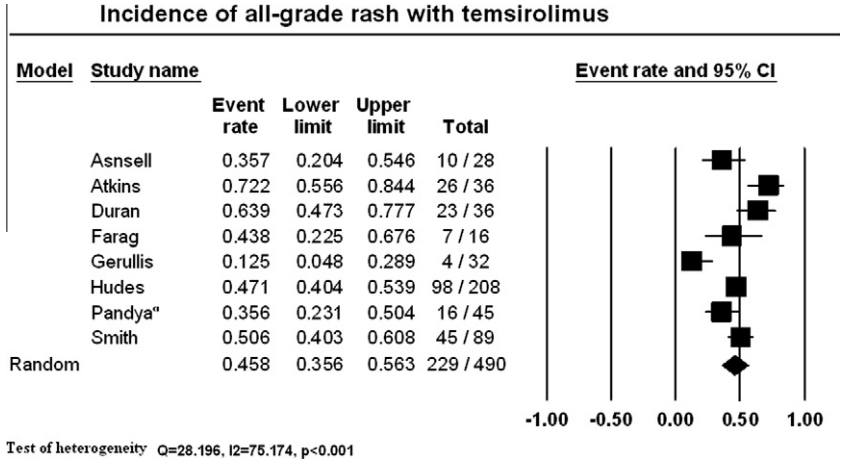

Fig. 2 – Incidence of all-grade rash to temsirolimus. The summary incidence of all-grade rash is calculated using the random-effects model. The incidence rate and 95% confidence interval (CI) for each trial and the final combined results are demonstrated numerically on the left and graphically as a forest plot on the right. For individual trials: filled-in square, incidence; lines, 95% confidence interval; diamond plot, overall results of the included trials. [a]Personal communication with author, 28th October 2010.

patients, the overall incidence of high-grade rash was 3.3% (95% CI: 1.9–5.6%), according to the fixed-effects model.

3.5. *Incidence of all-grade stomatitis*

Data for all-grade stomatitis were available for analysis from a total of 579 patients. The incidence of all-grade stomatitis ranged between 20.2% and 72.2% with the highest incidence observed in a phase II trial in patients with neuroendocrine carcinoma[11] and the lowest in a phase III trial in patients with RCC.[14] Based on data from 10 trials with a total of 579 patients the overall incidence of all-grade stomatitis was 44.3% (CI: 32.1–57.1%), according to the random-effects model (Fig. 3).

3.6. *Incidence of high-grade stomatitis*

High-grade stomatitis is associated with increased morbidity and can result in dose-modification or treatment interruption. The incidence of high-grade stomatitis ranged from 1.0% to 7.5% with the highest incidence observed in a phase II trial in patients with soft tissue sarcoma[15]; and the lowest in a phase III trial in patients with RCC.[14] Based on data from 9 trials with a total of 543 patients, the overall incidence of high-grade stomatitis was 3.2% (95% CI: 1.9–5.4%), according to the fixed-effects model.

3.7. *Incidence of all-grade rash and stomatitis in patients with RCC versus non-RCC solid tumours*

In order to explore the heterogeneity of the above studies, we have further analysed the incidence of rash and stomatitis in patients with RCC and non-RCC cancers to investigate the potential relationship between tumour type and temsirolimus-associated AE. Among 276 patients with RCC, the incidence of all-grade rash and all-grade stomatitis was 42.6% (95% CI: 18.4–70.9%) and 36.5% (95% CI: 14.9–65.4%), respectively, while

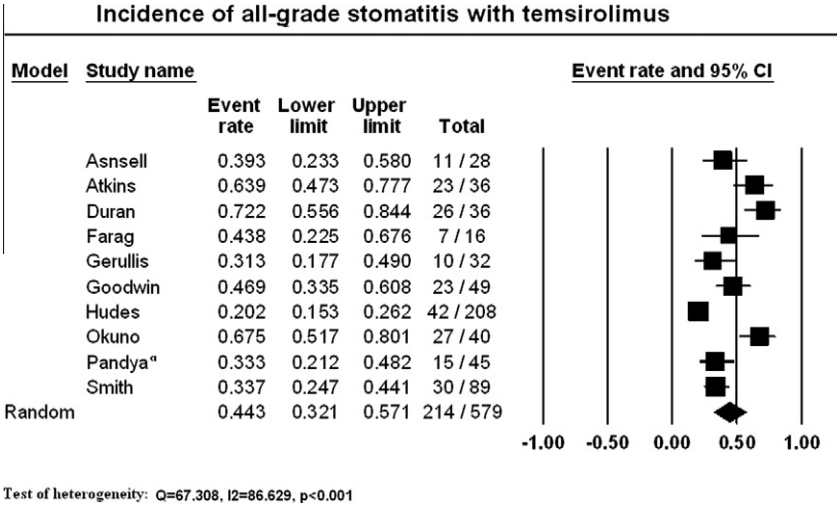

Fig. 3 – Incidence of all-grade stomatitis to temsirolimus. The summary incidence of all-grade stomatitis is calculated using the random-effects model. The incidence rate and 95% confidence interval (CI) for each trial, and the final combined results are demonstrated numerically on the left and graphically as a forest plot on the right. For individual trials: filled-in square, incidence; lines, 95% confidence interval; diamond plot, overall results of the included trials. [a]Personal communication with author, 28th October 2010.

Table 2 – Summarised incidences and relative risks of skin rash and stomatitis with temsirolimus.

Category	Incidence (95% CI)	Relative Risk (95% CI)
All-grade		
Skin rash	45.8% (35.6–56.3%)	7.6 (4.4–13.3)
Stomatitis	44.3% (32.1–57.1%)	11.1(5.6–22.0)
High-grade		
Skin rash	3.3% (1.9–5.6%)	13.70 (0.82–227.50)
Stomatitis	3.2% (1.9–5.4%)	13.21 (0.80–218.56)

CI = confidence interval.

for 303 patients with non-RCC malignancies, the incidence was 46.4% (95% CI: 36.3–56.9%) for rash and 47.8% (95% CI: 35.8–60.1%) for stomatitis. There was no significant difference detected between RCC and non-RCC in terms of the incidence of all-grade temsirolimus-associated skin rash or stomatitis ($p = 0.81$ and 0.47, respectively).

3.8. *Relative risk of skin rash and stomatitis*

To investigate the specific contribution of temsirolimus to the development of skin rash and stomatitis and exclude the influence of confounding factors such as underlying malignancy and history of other therapeutic interventions, we determined the RR of skin rash and stomatitis to temsirolimus. An analysis of RR for all-grade and high-grade skin rash and stomatitis associated with temsirolimus was performed for the RCT with a control arm, in which the incidence of rash and stomatitis was reported for 200 patients who received interferon alpha.[14] The RR for all-grade skin rash and all-grade stomatitis was 7.63 (95% CI: 4.37–13.32; $p < 0.001$) and 11.08 (95% CI: 5.58–21.97; $p < 0.001$), respectively. The risk of high-grade rash and stomatitis was increased (RR = 13.70, 95% CI: 0.82–227.50 and RR = 13.21, 95% CI: 0.80–218.56) but it did not reach statistical significance ($p = 0.07$). Thus, temsirolimus is associated with an increased risk for all-grade and with a strong trend towards increased risk for high-grade rash and stomatitis when compared with controls (Table 2).

4. Discussion

Our meta-analysis has demonstrated a high risk of all-grade skin rash and stomatitis with single-agent temsirolimus in patients with a variety of solid tumours. The overall incidence of all-grade and high-grade (grade $\geqslant 3$) skin rash was 45.8% (95% CI: 35.6–6.3%) and 3.3% (95% CI: 1.9–5.6%), respectively. The overall incidence of all-grade and high-grade stomatitis was 44.3% (CI: 32.1–57.1%) and 3.2% (95% CI: 1.9–5.4%). Temsirolimus was associated with significantly increased risk of all-grade rash and all-grade stomatitis (RR = 7.6, 95% CI: 4.4–13.3; $p < 0.001$ and RR = 11.1, 95% CI: 5.6–22.0; $p < 0.001$). The risk of high-grade rash and stomatitis was also increased (RR = 13.70, 95% CI: 0.82–227.50 and RR = 13.21, 95% CI: 0.80–218.56) without reaching statistical significance ($p = 0.07$). No significant difference in incidence of all-grade rash between RCC and non-RCC patients was noted (42.6%, 95% CI: 18.4–70.9% versus 46.4%, 95% CI: 36.3–56.9%, respectively, $p = 0.81$). Similarly, no difference in all-grade stomatitis between RCC and non-RCC patients was observed (36.5%, 95% CI: 14.9–65.4% and 47.8%, 95% CI: 35.8–60.1%, respectively, $p = 0.47$). The high incidence of skin rash and stomatitis demands appropriate assessment and management by treating physicians. As temsirolimus is being increasingly used as a single agent or in combination with other antitumour agents in the setting of routine cancer treatment and clinical trials, it is important for physicians and patients to recognise the risk of these AE associated with temsirolimus in order to monitor and treat the skin toxicity in a timely manner (Fig. 4). High-grade AE may affect activities of daily living and can result in dose reduction or even

discontinuation of therapy. In one of the reviewed studies, five patients needed to discontinue treatment due to skin rash and 16% of patients needed to reduce the dose due to stomatitis.[10] Better management of skin rash and stomatitis may help to reduce morbidity and therapy interruptions.

The temsirolimus-induced skin rash usually occurs within the first couple weeks of treatment.[7,19] Erythematous papules and pustules constitute the main primary lesion morphology. Typically affected areas include those rich in sebaceous glands, including the upper trunk and the face, with frequent involvement of extremities, neck and the scalp. Eczematous eruptions on antecubital areas have been observed as well. There is also a tendency for a rash to coalesce into plaques, particularly on upper extremities. Histological examination of papular lesions in these patients has revealed perifollicular suppurative inflammation with a non-specific accumulation of neutrophils in the dermis and epidermis.[19] Careful monitoring and quick intervention with topical moisturizers and powders may be effective for low-grade rashes. Patients should also be instructed to avoid hot water and harsh soaps that may dry the skin. Antihistamines may provide benefit for pruritic rashes. Dose interruptions may be required for severe (grade 3 or higher) rash until the rash improves.[20]

The occurrence of stomatitis to temsirolimus appears to be dose-related and occurs more frequently in earlier cycles, often within the first week.[7,21] The stomatitis that is seen in patients treated with temsirolimus appears differently than the mucositis that is seen with chemotherapy or radiation. The pseudomembrane formation that typically occurs with conventional chemotherapy is not seen with temsirolimus. Stomatitis seen with temsirolimus patients presents with discrete aphthous-like ulcerations in contrast to ulceration associated with radiotherapy and chemotherapy. Ulceration of mucosal surfaces involved includes non-keratinised oral tissues such as labial and buccal mucosa and the ventral surface of the tongue and floor of the mouth. It is rarely seen on the hard palate.[7,8] Although chemotherapy- or radiation-induced oral stomatitis often occurs simultaneous with injury to other areas of the gastrointestinal tract, temsirolimus rarely does so.[22] Management strategies for stomatitis include avoiding spicy food and harsh agents such as hydrogen peroxide.[21] Unless a fungal infection has been diagnosed, antifungal agents should also be avoided. Oral care with saline rinses, in addition to a soft toothbrush and mild toothpaste should be initiated with temsirolimus therapy. Bioadherent oral gels with topical corticosteroids (clobetasol or triamcinolone in Orabase®) applied to the lesions prior to meals may reduce discomfort during eating.[23] In addition, ice chips and keratinocyte growth factor (palifermin®) have shown some benefit in preventing stomatitis to capecitabine and prior to hematopoietic stem cell transplants, respectively.[24]

The mechanism of the skin rash and stomatitis associated with temsirolimus is unknown. However, it can be hypothesised that there is a direct inhibitory effect on signalling pathways that regulate cell growth and tissue repair.[25–27] One study showed that mouse keratinocytes that had decreased Akt/mTOR signalling activity had depressed protein translation and were smaller in size compared with normal mouse keratinocytes.[28]

The present study has several limitations. The findings described here are affected by the limitations of the individual clinical trials that are included for analysis. First, the assessment of rash and stomatitis may vary among investigators and institutions involved in these studies. However, the non-heterogeneity of included studies for high-grade AE suggests a relative consistency in detecting and reporting of skin toxicity. Second, trials in this study may have underestimated the incidence of severe skin rashes and stomatitis associated with temsirolimus because of the imperfection of the CTCAE grading criteria, which may fail to reflect the clinical situation. Third, meta-analysis is subjected to the inherent methodologic deficiencies of the included trials. Finally, the results presented here were obtained from clinical trials conducted in major centres and institutes for patients with adequate organ function and therefore may not apply to a patient population with organ dysfunction treated in the community.

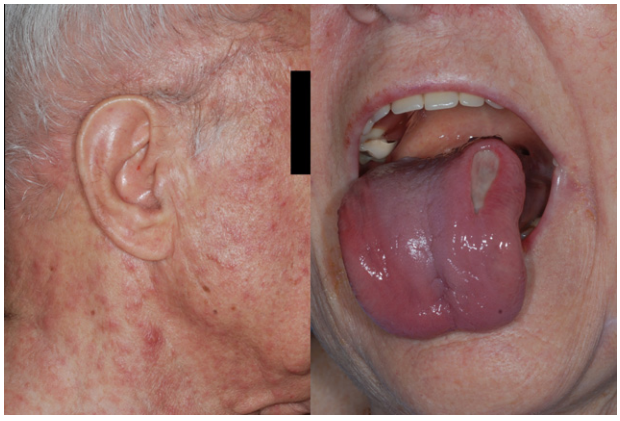

Fig. 4 – Dermatological adverse events to temsirolimus. Left panel: temsirolimus-induced erythematous maculopapular rash with scattered pustules; Right panel: temsirolimus-induced stomatitis.

5. Conclusion

Our study has demonstrated that temsirolimus is associated with a significant risk of skin rash and stomatitis in cancer patients. Early detection and effective management may reduce this risk, which may also be modified by concurrent chemotherapy. Further studies are needed to investigate risk factors and pathogenesis and to develop effective measures for the prevention and treatment of skin toxicity.

Conflict of interest statement

M.E. Lacouture and D.R. Feldman have worked as consultants for Pfizer Inc. S. Wu serves on the advisory board and as a speaker to Pfizer Inc. B.C. Garden and C. Gomez-Fernandez have no conflicts to declare.

Acknowledgement

M.E.L. is supported by a Career Development Award from the Dermatology Foundation.

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