Research Review™
SPEAKER SERIES
Management of mTOR inhibitor-associated stomatitis

Making Education Easy

Thursday 23rd June, 2016 Adelaide, Australia

This publication summarises presentations given during the Novartis symposium 'Management of mTOR inhibitor-associated stomatitis' which was held in conjunction with the 2016 Multinational Association for Supportive Care in Cancer (MASCC) / International Society of Oral Oncology (ISOO) Annual Meeting on Supportive Care in Cancer. Professor Fran Boyle, Medical Oncologist and Director of the Patricia Ritchie Centre for Cancer Care and Research at Mater Hospital in Sydney, and Professor of Medical Oncology at the University of Sydney, chaired the symposium. The four speakers, Medical Oncologist Hope Rugo (USA), Oral Oncologist Mark Chambers (USA), Clinical Pharmacist Abhimanyu Phatak (Australia) and Transitional Nurse Practitioner Jenny Gilchrist (Australia), bought a range of clinical perspectives and expertise to bear on the subject of mTOR-inhibitor-associated stomatitis.

In this review:

Abbreviations used in this review:

ER+ = hormone receptor positive;
HER2- = human epidermal growth factor receptor 2 negative;
HR = hazard ratio; **PFS** = progression-free survival;
mTOR = mammalian target of rapamycin;
VAS = visual analogue scale.

Managing mTOR inhibitor-associated stomatitis: what is the evidence?

Speaker: Professor Hope S Rugo, Medical Oncologist, University of California, San Francisco

Summary: Dr Hope Rugo became interested in the management of mTOR inhibitor toxicities after her involvement in early clinical trials of these agents, including the everolimus trial BOLERO-2. She opened her presentation by reminding the audience of the importance of the goals of treatment in patients with advanced breast cancer, which include management of symptoms, delaying time to chemotherapy, prolonging PFS and maintaining or improving quality of life. Adding targeted agents in order to reverse resistance to hormone therapy, or at least improve response and delay time to progression is clearly an important strategy she noted, and one in which huge progress has been made in the past few years.

Everolimus was the first targeted agent to be approved for use in ER+ HER2- breast cancer in combination with hormone therapy, and this was based on the data from BOLERO-2. This phase III trial randomised patients who had progressed on first line hormone therapy for metastatic ER+ breast cancer to receive exemestane and placebo or exemestane and everolimus. In the local assessment, which was the primary endpoint, median PFS more than doubled from 3.2 to 7.8 months, (HR 0.45; 95% CI 0.38, 0.54; Log Rank P < 0.0001)[1] with the addition of everolimus and this was confirmed in central assessment where PFS increased from 4.1 to 11 months, (HR 0.38; 0.31, 0.48; Log Rank P < 0.0001).[2] Considering the trial was not powered to detect differences in overall survival, it was encouraging to find that that median overall survival was 4.4 months longer with the addition of everolimus, although this difference was not statistically significant.[3] Similarly, at 39 months of median follow-up there were 5% more deaths in the placebo arm than in the everolimus arm.[3]

Stomatitis has now emerged as the most common class-related toxicity for mTOR inhibitors and can be dose-limiting or even treatment-limiting for a substantial proportion of patients. In BOLERO-2 the overall rate of stomatitis in everolimus-treated participants was 59%; with rates of 29%, 22% and 8% for grades 1, 2 and 3 stomatitis respectively.[3,4] In an analysis of the toxicities observed in BOLERO-2 and their time-courses,[4] it was observed that stomatitis had a rapid onset and the majority of cases occurred within the first two months. (Figure 1.) It was suggested that, if patients could get through those first 8 weeks, they would be more likely to stay on the drug, and be more likely to maintain their dose, and potentially, be more likely to obtain benefit.

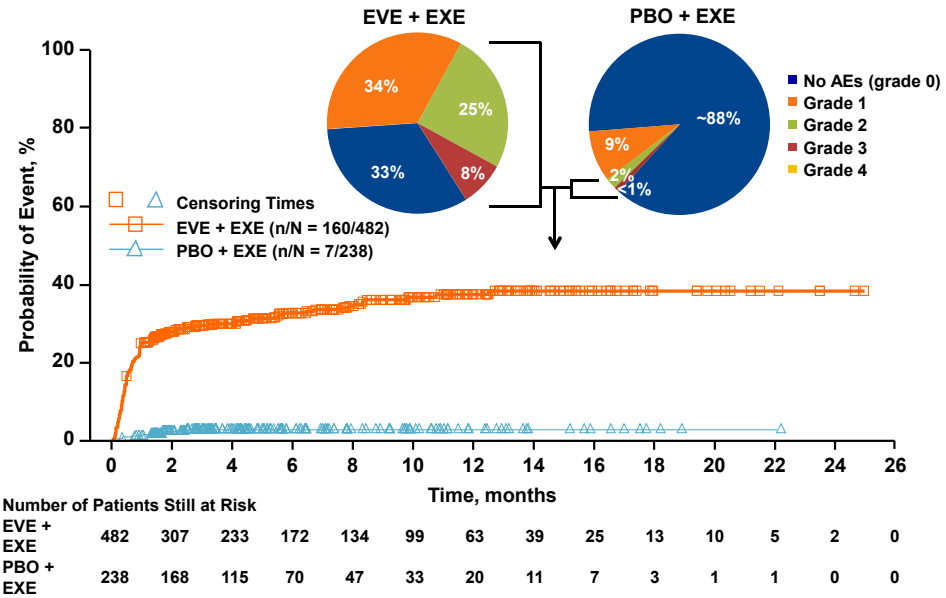

Figure 1: Rapid onset of grade ≥ 2 stomatitis in BOLERO-2. (Rugo HS et al. Ann Oncol. 2014;25(4):808-15)

A meta-analysis was conducted to investigate whether the incidence of everolimus-associated stomatitis was the same across different disease groups, and whether or not stomatitis itself was an indicator of drug exposure, i.e. did patients who got stomatitis do better? Data were included from studies of everolimus in breast cancer (BOLERO-2 and -3), renal cell carcinoma (RECORD-2), carcinoid (RADIANT-2), pancreatic neuroendocrine tumours (RADIANT-3) and tuberous sclerosis complex (EXIST-1 and -2).[5] The overall rate of stomatitis was 67% (9% grade 3-4), and was similar across the different diseases. Approximately 60% of patients experienced only one episode of stomatitis, and almost 90% of episodes occurred within the first 8 weeks of starting everolimus.

In terms of the impact of stomatitis on PFS, in both BOLERO-2 and RADIANT-3 patients who developed stomatitis within 8 weeks of starting treatment with everolimus had a longer PFS compared to patients receiving everolimus who didn't get stomatitis. This was really intriguing data because the patients who developed stomatitis would have had dose delays and treatment interruptions and yet they still did better. There was also a trend toward longer PFS in renal cell carcinoma, and similarly in BOLERO-3, the later line study that looked at everolimus added to vinorelbine

Based on this data, we thought that if we could control stomatitis in these patients then it would really improve their quality of life and also potentially their chance to benefit from this drug. We were aware that recurrent benign aphthous ulcers can be treated with a topical, steroid-containing dental paste and began using this to treat patients with stomatitis and anecdotally they seemed to do better. However, there was no clinical evidence to guide prophylactic use. The next step was the development of a compounded product that included hydrocortisone plus an antifungal medication, and with prophylactic use we stopped seeing much stomatitis. We wanted to test these results in a multicentre clinical trial, but it became evident that between-site differences in compounded formulas can be problematic and looked for alternative agents, eventually coming up with an alcohol-free dexamethasone solution used for paediatric dosing.

The SWISH (dexametha**S**one mouth**W**ash for everol**i**mus-related stomatiti**S** prevention in **H**R+ metastatic breast cancer) trial[6] aimed to evaluate the use of a steroid-based mouthwash to prevent everolimus-associated stomatitis of grade 2 or greater. In order to avoid the need for randomisation to a control group and have patients miss out on the potential benefits of the mouthwash, BOLERO-2 participants were used as a historical control cohort.

The study was a single-arm, phase II clinical trial with 23 sites in the US. Participants were post-menopausal women with a diagnosis of metastatic ER+ HER2- breast cancer for which the oncologist had prescribed everolimus (10 mg/day) and exemestane (25 mg/day). At baseline they had an oral assessment, completed a VAS oral pain score (scale 1-10) and normalcy of diet score (scale 0-100), and were instructed on routine good oral care. The objective was to look at the incidence of grade 2 or greater stomatitis at 8 weeks where 90% of first events would occur, and compare this to the BOLERO-2 historical controls. Stomatitis had to be confirmed by physical exam and at least one of the following: normalcy of diet score ≤ 50 (50 indicates soft, chewable foods can be eaten) and patient-reported VAS oral pain score of 7 on two consecutive days or 8-10 on any one day. Patients used 10 mL of alcohol-free dexamethasone (0.5 mg/mL) and were asked to swish for 2 minutes before spitting out the mouthwash, four times a day for 8 weeks. They were not permitted to eat for 1 hour after the mouthwash. Mouthwash was started on the first day of the treatment cycle (each cycle = 28 days) and was continued at physician discretion past the first two cycles where patients felt they were benefitting from it. A standard dose modification/dose interruption schedule was used for management of everolimus-related adverse events. Patients received informational material and a timer for monitoring the duration of mouthwash use.

In total 96 patients were enrolled and 86 were evaluable. Their median age was 61 years (range 34-87), 61.6% were Caucasian and 93% had an ECOG performance status of 0-1. More than 35% received everolimus in the 2nd or greater line setting (they had received aromatase inhibitors first line), 67.5% had at least 3 metastatic sites including visceral involvement of lung (51%) and liver (36%). Twenty three percent received oral antifungal prophylaxis. More than 70% remained on the mouthwash and the two treatment drugs for more than 8 weeks. The median dose intensities for everolimus and exemestane were maintained at 10 mg (range 3, 10) for everolimus and 25 mg for exemestane (range 8, 25).

The primary outcome measure, the incidence of grade 2 or greater stomatitis occurred in 2.4% of mouthwash-treated patients (n = 2) at 8 weeks vs an overall incidence of 33% in the BOLERO-2 historical cohort (P < 0.001). (Figure 2.) All grade stomatitis occurred in 21.2% (n = 18) vs 67% amongst BOLERO-2 participants. No SWISH study participants developed grade 3 stomatitis. There did not appear to be any association between use of antifungal prophylaxis and the development of stomatitis. Amongst 18 patients who developed grade 1 or 2 stomatitis, antifungal prophylaxis was used by 3. Amongst patients who used antifungals (n = 20), 7 developed stomatitis. Oral candidiasis was reported by 2 patients, both of whom were intermittently using antifungal prophylaxis due to previous fungal infections. Two patients developed grade 2 stomatitis which resolved to grade 1 or less after durations of 11 and 15 days.

Results: incidence of stomatitis

- The incidence of > grade 2 stomatits at 8 weeks was 2.4% (n=2, 95% CI 0.29-8.24, *P*<0.001)
  - > Compared with a total of 33% in BOLERO-2
- The incidence of all-grade stomatitis at 8 weeks was 21.2% (n=18, 95% CI 13.06-31.39)
  - > Compared with BOLERO-2 all-grade stomatitis of 67%

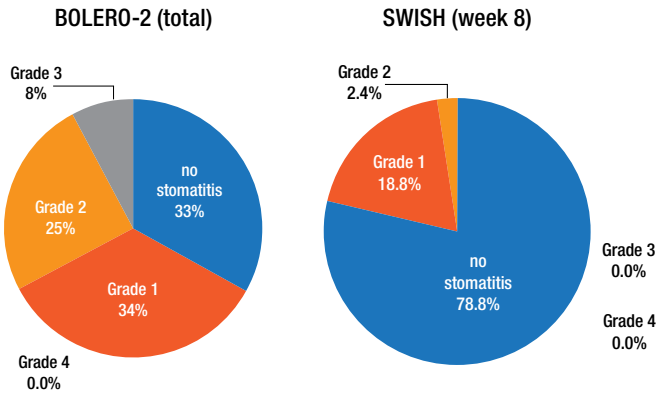

Figure 2: Incidence of stomatitis in the SWISH study vs a historical control cohort from BOLERO-2 (Rugo HS et al. J Clin Oncol. 34;2016 [suppl; abstr 525])

A pharmacokinetic evaluation was conducted in a subset of 50 patients to determine whether there was an impact of the dexamethasone mouthwash on everolimus levels. It found everolimus levels were consistent with a 10 mg daily dose (mean 13.91 ng/mL, median 11.10 ng/mL) suggesting there was no effect of the dexamethasone mouthwash.

Toxicities amongst SWISH study participants appeared to be modest and primarily related to everolimus. The number of participants who discontinued as a result of adverse events was 13% in total; 2% discontinued as a result of stomatitis. The most common adverse effects (all grades) occurring in 10% or more of participants were stomatitis (27.2%), fatigue (17.4%), hyperglycaemia (15.2%), nausea (15.2%), dyspnoea (14.1%), dysgeusia (13.0%), cough (10.9%), diarrhoea (10.9%) and headache (10.9%). Very few grade 3 toxicities were observed with hyperglycaemia being the most common (7.6%) with levels not dissimilar to those seen in BOLERO-2.

In conclusion, the SWISH trial found prophylactic use of dexamethasone mouthwash significantly minimised the incidence of all grades of stomatitis, especially those of grade 2 or greater, in post-menopausal women receiving everolimus and exemestane for the treatment of ER+ HER2- metastatic breast cancer. This treatment should now be considered as a new standard of care, not only in this patient cohort, but should also be considered for other cancer patients receiving treatment with mTOR inhibitors.

References

1. Yardley DA et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther. 2013;30(10):870-84 http://link.springer.com/article/10.1007%2Fs12325-013-0060-1
2. Baselga J et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520-9 http://www.nejm.org/doi/full/10.1056/NEJMoa1109653
3. Piccart M et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. Ann Oncol. 2014;25(12):2357-62 http://annonc.oxfordjournals.org/content/early/2014/09/17/annonc.mdu456
4. Rugo HS et al. Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. Ann Oncol. 2014;25(4):808-15 http://annonc.oxfordjournals.org/content/25/4/808.full
5. Rugo HS et al. Meta-analysis of stomatitis in clinical studies of everolimus: incidence and relationship with efficacy. Ann Oncol. 2016;27(3):519-25 http://annonc.oxfordjournals.org/content/early/2016/01/11/annonc.mdv595
6. Rugo HS et al. Prevention of everolimus/exemestane (EVE/EXE) stomatitis in postmenopausal (PM) women with hormone receptor-positive (HR+) metastatic breast cancer (MBC) using a dexamethasone-based mouthwash (MW): Results of the SWISH trial. J Clin Oncol 34, 2016 (suppl; abstr 525) http://meetinglibrary.asco.org/content/162147-176

The practicalities of treating mTOR inhibitor-associated stomatitis

Speaker: Professor Mark S Chambers, Oral Oncologist, MD Anderson Center, University of Texas

Summary: The presentation of mTOR inhibitor-associated stomatitis is quite a different clinical presentation to that seen in patients with chemotherapy-induced mucosal injury. It can be quite aphthous-like, with discreet ulcers located on non-keratinised, mobile mucosal surfaces prone to friction. They are superficial, oval ulcers, usually ≤ 1 cm in diameter, which are well demarcated, with white pseudomembranous centres and erythematous margins. (Figure 3.) Symptoms associated with stomatitis include mucosal hypersensitivity, inflammation, burning sensation, oral pain, dysgeusia and dysphagia. In comparison, the mucositis seen in patients receiving solid tumour therapy is a confluent mucosal injury. Both are painful and may be dose limiting, but the latter presentation is longer lasting and has a different time-course.

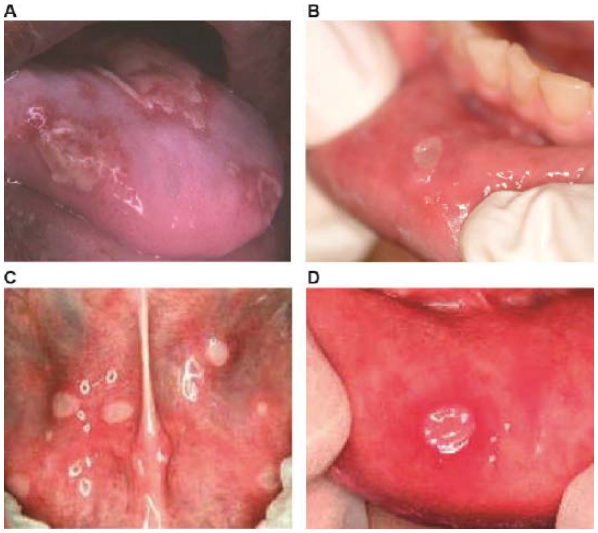

Figure 3: Types of oral mucosal injury. A. Chemotherapy-induced oral mucositis with diffuse injury. B. Aphthous-type ulcer in mTOR inhibitor-associated stomatitis. C. Herpetiform stomatitis. D. Recurrent, benign aphthous ulcers. (Peterson DE et al. Cancer Med. 2016;5(8):1897–1907)

It appears that regardless of the location of disease, including breast cancer, renal cell carcinoma, pancreatic neuroendocrine tumours and neuroendocrine tumours, mTOR inhibitor-associated stomatitis tends to occur within 8 weeks of initiating therapy and at a substantial level.[1] In BOLERO-2, the onset of mTOR inhibitor-associated stomatitis was 15 days with everolimus plus exemestane vs 24 days with placebo, the severity was typically limited to grades 1 or 2, and associated pain was related to daily activity.[2]

In practical terms, how do we go about treating stomatitis? Within our service, which is a high volume practice at MD Anderson, we will typically culture every ulcer that we see. We want to assess microbiologically if we have a superinfection or other challenge, or if we have a therapeutic toxicity. We have developed a step-wise approach to treatment for our patients who develop stomatitis. In terms of education we advise them to eliminate cigarette smoke, smokeless tobacco products, alcohol and phenol containing mouthwashes. We strongly advise our patients to alkalinise the oral cavity by using a sodium bicarbonate rinse once or twice a day after they have brushed their teeth. We usually start treatment with locally applied pharmacotherapeutics such as alcohol-free chlorohexidine and an antimicrobial toothpaste. In patients with severe discomfort (e.g. grade 2 stomatitis) we also consider topical systemic therapy, again a stepped approach with topical analgesics and topical corticosteroids, which in this patient population we have found to be quite effective. For patients on everolimus we try and avoid systemic anti-fungal therapy, consequently for most low-grade mucosal injuries and low-grade stomatitis we culture and treat as appropriate.

We also use magic mouthwash which will typically contain diphenhydramine and some form of a corticosteroid and possibly an antibiotic. I believe this to be the most practical form of therapy for mTOR inhibitor-associated stomatitis. We tend to compound it for many of our patients but we also use the commercially available dexamethasone alcohol-free mouthwash. We also use a commercial paste or a compounded paste where applicable.

All grades	Checklist
• Use magic mouthwash for stomatitis prevention • Ensure patients use mouthwashes as directed • At onset of any degree of stomatitis add chlorhexidine mouthwash (10 mL swish and spit QID) and continue magic mouthwash with hydrocortisone **Grade 1 (patient follows a normal diet)** • Rinse several times per day with a non-alcoholic mouthwash or 0.9% saline **Grade 2 (symptomatic but can follow a modified diet)** • Use topical mouth treatment analgesics (e.g. benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, phenol) ± topical corticosteroids (e.g. triamcinolone oral paste, clobetasol gel, dexamethasone solution) • Avoid agents containing alcohol, hydrogen peroxide, iodine and thyme derivatives **Grade 3 (symptomatic and unable to adequately eat or drink)** • Follow the same recommendations as Grade 2 **Grade 4 (life-threatening symptoms)** • Follow the same recommendations as Grade 2 and institute additional medical interventions as appropriate	**1. Culture……culture……culture** a. Diagnosis & sensitivity **2. Eliminate alcohol and phenol containing mouthwashes** **3. Locally applied pharmacotherapies** a. Selective decontamination b. Basic oral care c. Chlorhexidine (alcohol-free) d. Magic mouthwash **4. Topical/systemic pharmacotherapies (stepped approach)** a. Topical analgesia b. Topical corticosteroids* (risk of fungal contamination) *Avoid systemic imidazole antifungal use in conjunction with everolimus.

Figure 4: Stepped management approach for management of mTOR inhibitor-associated stomatitis. (Divers J & O'Shaughnessy J. Clin J Oncol Nurs. 2015;19(4):468-74)

Secondary outcomes from the SWISH trial, which included patient-reported outcomes, have highlighted the benefits of using a steroid-based mouthwash to prevent stomatitis.[3]

Most participants in the study did very well. Complete ECOG performance status evaluations were available for 75% of patients; 88% maintained or improved their scores between baseline and week 8. The proportion of patients with ECOG scores of 0, 1, 2 and 3 was 66.3%, 26.7%, 7.0% and 0% at baseline. When patients were rated with their worst scores occurring between baseline and week 8, the proportions at ECOG 0, 1, 2 and 3 respectively were 66.7%, 29.3%, 2.7% and 1.3%.[3]

The majority of patients had little oral pain, mean oral pain score (VAS range 0-10) was < 1 throughout. In terms of normalcy of diet scale score, the proportion of patients who had a score ≥ 90 (range 0-100) was above 90% at all timepoints. The vast majority of participants experienced little diet restriction throughout the study.[3]

Most participants (95%) were adherent to the mouthwash regimen and most used it 3-4 times a day (median 3.95, range 1.9, 4). Patients were also adherent to other aspects of their oral care routines. Over 85% reported brushing their teeth twice-daily at each study evaluation, and no patients brushed their teeth less than once-daily. Over 70% used a soft bristled toothbrush, and over 90% reported daily flossing.[3]

In conclusion, when coupled with good, daily oral care, concomitant daily use of dexamethasone mouthwash is well tolerated in this patient population and is effective in preventing mTOR inhibitor-induced stomatitis. Patients participating in the SWISH trial were adherent to the mouthwash regimen and other aspects of oral care. They experienced minimal to no oral pain, were able to eat a normal diet and maintained their performance status. The key to managing and preventing mTOR inhibitor associated-stomatitis is good patient education on recognition of the signs and symptoms of stomatitis, vigilance, maintenance of good oral hygiene and prophylactic use of corticosteroid mouthwash.

References

1. Divers J & O'Shaughnessy J. Stomatitis Associated With Use of mTOR Inhibitors: Implications for Patients With Invasive Breast Cancer. Clin J Oncol Nurs. 2015;19(4):468-74 http://tinyurl.com/zegg29w
2. Rugo HS et al. Incidence and time course of everolimus-related adverse events in postmenopausal women with hormone receptor-positive advanced breast cancer: insights from BOLERO-2. Ann Oncol. 2014;25(4):808-15 http://annonc.oxfordjournals.org/content/25/4/808.full
3. Chambers MS et al. Patient-reported outcomes in postmenopausal women with HR+ metastatic breast cancer treated with everolimus/exemestane and dexamethasone-based mouthwash: the SWISH trial. Poster presented at MASCC 2016. http://simul-europe.com/2016/mascc/posters

RESEARCH REVIEW™
The Australian Perspective — Since 2007

Steroid mouthwash for mTOR inhibitor-associated stomatitis: a pharmacist's perspective

Speaker: Abhimanyu Phatak, Clinical Pharmacist, Royal Adelaide Hospital

Summary: mTOR inhibitors currently listed in Australia are everolimus, temsirolimus and sirolimus. They are associated with a number of adverse effects which include metabolic effects, renal effects, haematological and haemodynamic effects, and hormonal issues. However the most important adverse effect tends to be stomatitis. The exact pathogenesis of mTOR inhibitor-induced stomatitis is unclear, but it is certainly clinically distinct from the mucositis associated with conventional chemotherapy. It tends to occur around 4-5 days after the start of treatment, with the peak at about 10 days. The lesions are quite painful and this can cause functional disturbance and adversely affect the patient's quality of life. Consequently early recognition and grading of stomatitis is important so that appropriate interventions can be carried out.

My first encounter with the 'magic mouthwash' was when one of the medical oncologists came to me, handed me a piece of paper and said, 'Can we make this mouthwash?' After conducting some research we discovered there were numerous potential formulas. In general they contain an anticholinergic agent, usually diphenhydramine, an anaesthetic such as viscous lignocaine, a mucosal coating agent such as an antacid or sucralfate, a corticosteroid and often antimicrobial agents. Administration is usually 10-30 mL every 4-6 hours.

We also investigated the evidence base in support of these preparations and found little scientific documentation, and a lack of data supporting the use of any one particular formulation. In one case series involving three patients a mouthwash formulation was used to treat everolimus-associated stomatitis.[1] The ulcers healed in 4-15 days of QID dosing, so quite a large quantity of mouthwash was required and this was quite an intensive therapy for the patients. An earlier Cochrane review investigated studies of agents studied for oral mucositis prophylaxis in patients receiving chemotherapies and found mouthwashes were ineffective for shortening the time to healing of oral mucositis related to chemotherapies.[2]

From a pharmacy perspective other potential concerns were that nystatin has not been shown to be effective in treating oral fungal infection associated with mucositis, and that long-term use of corticosteroids may in fact lead to candidiasis. Preparations to avoid include alcohol-based mouthwash preparations, and also the imidazole antifungal preparations unless treating a fungal infection because of their known interaction with mTOR inhibitors.

Other challenges in terms of compounding these types of mouthwashes include the availability and cost of the ingredients, particularly in the public sector, the shelf-life of the mouthwash (there are no quality control studies), formulation issues such as the need to avoid elixir as this contains alcohol, and compatibility issues between certain ingredients, for example combining lignocaine and sucralfate results in a thick gel.

There are no alcohol-free steroid mouthwashes commercially available in Australia, so currently the simplest and most economic way to make this available to patients is use tablets. Patients can be prescribed 0.5 mg dexamethasone tablets and can be instructed to crush two tablets and mix them with 10 mL of normal saline, and rinse with it four times daily. This is probably the easiest way in the Australian setting to enable patients to access a corticosteroid mouthwash while we wait for some stronger data around the compounded formula.

We also looked at other treatment options which could be utilised immediately. Non-pharmacological measures included patient education around oral hygiene, encouraging them to brush and floss regularly after each meal, alkalising the oral mucosa with baking soda rinses, making dietary changes such as avoiding spicy food and eating at moderate temperatures, and avoiding crunchy foods that could damage the oral mucosa. Good education should also ensure patients are aware of the signs and symptoms of stomatitis, and are instructed to seek advice at the first signs of oral discomfort.

There are also a number of pharmacological agents already available in Australia which are useful in managing stomatitis. These include topical analgesics such as benzydamine alcohol free mouthwash (Difflam®), lignocaine viscous gel (Xylocaine®) and high potency corticosteroid preparations e.g. triamcinolone 0.1% (Kenalog® in Orobase®). A new mucosal medication delivery system (MucoLox®) may also have potential although costs may be prohibitive. This product is a mouthwash containing a polymer which binds to the oral mucosa. The polymer can be impregnated with an active pharmaceutical ingredient in order to deliver it to the oral mucosa, and has been used to deliver oral opioids to patients with head and neck cancer who develop mucositis.

In conclusion, stomatitis can be debilitating for patients and early intervention is required. We need to standardise the ingredients in magic mouthwash in order to fully evaluate the efficacy of this product, however there are commercially available products that can be used to substitute when magic mouthwash is not readily available, and there are novel delivery systems on the horizon which may revolutionise the treatment of stomatitis.

References

1. Kalogirou EM et al. mTOR inhibitor-associated stomatitis (mIAS) in three patients with cancer treated with everolimus. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015 Jan;119(1):e13-9 http://www.oooojournal.net/article/S2212-4403(14)01247-4/abstract
2. Worthington HV et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD000978. http://tinyurl.com/h5vzboy

The management of patients with mTOR inhibitor-associated stomatitis: a nurse's perspective

Speaker: Jenny Gilchrist, Transitional Nurse Practitioner, Macquarie University Hospital

Summary: As a transitional nurse practitioner working in a private hospital in Sydney, Jenny Gilchrist manages all the breast cancer patients treated by a single oncologist. A very large part of her role involves education, and also managing oral chemotherapies and targeted therapies including everolimus. As such she is the key point of contact, not only for patients and family members, but also for clinicians such as GPs and pharmacists who may not be so familiar with these treatments.

Jenny discussed the kinds of education and advice she provides to her patients. I sit down with the patients after they've seen the oncologist and do an education session with them for half an hour to an hour. We provide them with printed material and also a side effect diary which helps patients keep track of any adverse events and I encourage them to use it. Before starting a new treatment such as everolimus we like to do a baseline CT as a reference point, and we'll also do fasting bloods at baseline. We do a follow up at 2-3 weeks which is usually when the peak of problems occur, and then we usually see them monthly and do monthly bloods. If there are blood changes we usually stop the drug, wait a week and repeat the test. We do restaging every 3 months unless clinically indicated.

We educate patients on all their treatments. In terms of everolimus I describe it as like a chemotherapy, but not a chemotherapy, and that it helps the cancer to become sensitive to endocrine therapy again. I think honesty is important and that you need to manage patient expectations around adverse effects so I tell them that there can be side effects and that they can be bad, but I also tell them that they will likely subside, which usually happens after the two month mark. I really encourage contact with my patients and good communication, I tell them I'm going to get cranky with them if they turn up to clinic and they've got a problem and I haven't heard from them! Over time I develop a rapport and so hopefully they do feel comfortable enough to call me if they do have a problem. I tell them that as soon as there's a problem we need to know about it because if we can treat it early then they're not going to be off treatment for long. People are sometimes hesitant to report problems because they don't want their treatment to be stopped.

The key to management of side effects with everolimus is early identification and intervention. I like to keep things simple and most of this is common sense. The principles of management are the same for most of the adverse effects - if in doubt interrupt the treatment until the problem resolves then restart at the same or lower dose. Approximately 60-65% of patients who take everolimus require a dose interruption or reduction, but we find problems don't tend to reoccur.

In order to manage the risk of stomatitis we educate patients on appropriate mouth care. We advise them to use sodium bicarbonate mouthwashes four times daily from the start of treatment with everolimus and to follow standard oral care advice including using a soft toothbrush, and avoiding spicy, acidic, hard or hot foods. If ulcers develop I suggest soluble pain relief e.g. paracetamol or a topical agent such as triamcinolone acetonide (Kenalog®). We also commonly suggest Difflam® mouthwash, and if needed we dose interrupt the everolimus.

Patients may also develop a rash during everolimus treatment. It tends to be a maculopapular or papulopustular rash, similar to an EGFR rash, which is red, itchy and pimply and occurs on the scalp, face, neck and trunk. We advise patients to moisturise regularly, use a fragrance-free soap or body wash and cover up in the sun. In some cases we suggest some OTC topical corticosteroids or antihistamines for the itch, and in severe cases we would usually refer to a dermatologist.

Key points

- Encourage contact and communication with patients.
- Early identification and intervention for adverse effects is key.
- Keep it simple and use common sense.

Research Review SPEAKER SERIES™
Management of mTOR inhibitor-associated stomatitis

Jenny Gilchrist

Jenny Gilchrist is a Transitional Nurse Practitioner in Breast Oncology at Macquarie University Hospital in Sydney. She has over thirteen years nursing experience in oncology and palliative care. Jenny completed a Graduate Certificate in Cancer Nursing in 2004 and is currently in the final year of a Masters of Nursing (Nurse Practitioner) at the University of Sydney. Her clinical interests include breast cancer and supportive care and she has a strong interest in clinical research, particularly that which aims to improve patient symptoms, care and quality of life.

Professor Mark S Chambers

Dr Mark Chambers is a tenured Professor and clinical investigator with a focus on developing novel therapeutic approaches to the oral sequelae of cancer therapy. Dr Chambers is Chief of the Section of Oral Oncology and Maxillofacial Prosthodontics in the Department of Head and Neck Surgery and Vice Chair of Research Compliance and Regulatory Affairs at The University of Texas MD Anderson Center. His clinical research focus is to develop strategies to reduce cancer treatment-related oral morbidity and protocols to prevent or reduce such complications.

Professor Hope S Rugo

Dr Hope Rugo is a Medical Oncologist and Haematologist specialising in breast cancer research and treatment at the University of California, San Francisco. Dr Rugo is the Director of the Breast Oncology Clinical Trials Program, and is the principal investigator of multiple clinical trials focusing on combining novel targeted therapeutics with standard treatment to improve the treatment of both early and late stage breast cancer. In addition, Dr Rugo is working on studies to evaluate cognitive function in women receiving chemotherapy for breast cancer, as well as novel ways to reduce toxicity from therapy.

Abhimanyu Phatak

Abhimanyu Phatak is a Clinical Pharmacist at the Chemotherapy Day Centre, Royal Adelaide Hospital. He has been working in Medical Oncology, Haematology and Bone Marrow Transplant for the last 7 years. Abhi completed his Masters in Clinical Pharmacy from UNISA in 2006. He worked in a regional hospital prior moving to RAH.

RESEARCH REVIEW
The Australian Perspective Since 2007

Australian Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.

Speaker Series are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au.
Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists. **Privacy Policy:** Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.
Research Review publications are intended for Australian health professionals.

