Combination therapy of metastatic hormone receptor positive HER2 negative breast cancer

Side-effect management and dose reduction of everolimus in combination therapy with exemestane

In addition to clinical experiences with combination therapies with everolimus the authors Dr. med. Ziad Atassi, Baden, Dr. med. Urs Breitenstein, Zürich, and PD Dr. Nik Hauser, Baden, treat in this article the management of combination therapy induced side effects.

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Introduction

Steroidal and non-steroidal aromatase inhibitors have long been recognised as the therapy of choice – and recommended in international guideline consensus statements – for the treatment of hormone receptor-positive and HER2-negative metastatic breast cancer (MBC) (1). In therapy of this kind, the development of drug resistance within the cancer cell has become a significant issue in preclinical and subsequent clinical research. It is suspected that a resistance mechanism develops through activation of the PI3K signalling pathway (phosphatidyl-inositol 3 kinase) in the "crosstalk" between the mTOR (mammalian Target Of Rapamycin) and the oestrogen receptor. The use of specific agents may inhibit mTOR as the central protein complex in this signal transduction pathway (2). Everolimus (EVE, Afinitor®, Novartis) is an mTOR inhibitor, which, in combination with the aromatase inhibitor exemestane (EXE), increases the response to treatment by disrupting the resistance mechanism through inhibition of the PI3K pathway and increases hormone sensitivity (3). The synergistic antitumour effects and resulting clinical benefit were demonstrated in the randomised phase 3 BOLERO II trial. Patients who were given EVE in addition to the aromatase inhibitor EXE after disease progression had been diagnosed on aromatase inhibitors alone were examined for progression-free survival. Progression was defined as a recurrence of the disease either during adjuvant hormone therapy with an aromatase inhibitor or within 12 months of completion of adjuvant therapy in the case of advanced disease. Median progression-free survival was 4-6 months longer in the EVE group than in the placebo group, which was statistically significant (4). The proportion of patients that were given EVE/placebo plus EXE directly after adjuvant therapy was approximately 20%. In this patient group, progression-free survival increased from 4.1 to 11.5 months (hazard ratio=0.39; 95% CI 0.25 - 0.62). The authors therefore infer that patients receiving EVE/EXE in early therapy lines possibly obtain higher benefit (5).

The adverse event profile of EVE in combination with EXE is similar to EVE alone. The potential side-effects of EVE include stomatitis, skin rash, hyperglycaemia, hyperlipidaemia and non infectious pneumonitis (NIP). The treatment options for the individual side effects of EVE are reviewed in detail below. The aim is to achieve greater knowledge of the side-effect profile of EVE which is markedly different from that of other therapy options to date and is important to manage for reasons of patient safety and setting the treatment duration. All following adverse event management recommendations refer to the combination of EVE + EXE.

Stomatitis

Stomatitis is typically characterised by apthae: oval, circumscribed, whitish lesions with a pseudomembrane. A distinction is made between small lesions (<1 cm) and large lesions (>1 cm) as well as between multiple herpetiform lesions. Four grades of severity are distinguished (grades I-IV) (Fig. 1).

In contrast to chemotherapy-induced mucositis, these lesions occur exclusively in the oral region and predominantly in areas of non-keratinised mucosa. The cause of stomatitis induced by mTOR inhibitor therapy is not yet completely understood. It is suspected that a T-cell-mediated inflammatory process with direct effect on the oral mucosa is involved. Incidence in the BOLERO II trial was 67%. Higher-grade stomatitis (grade III/IV) was observed in 8% of patients. About one third of sto-

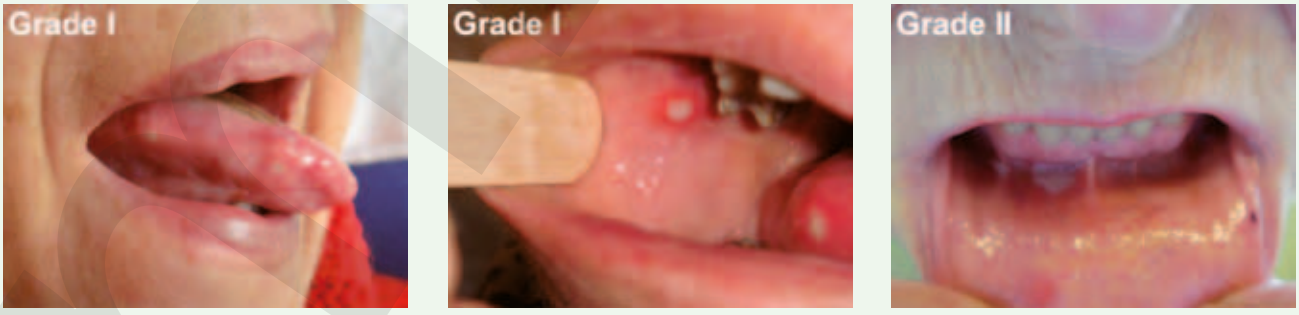

Fig. 1: Clinical manifestation of stomatitis. In optical appearance, stomatitis grade I and grade II are often hardly distinguishable from eachother. The difference is determined by the associated symptoms. Stomatitis grade II is, in contrast to grade I, associated with pain and problems with eating and drinking (images courtesy of Prof. Guy Jerusalem).

matitis cases occurred in the first 2 weeks after starting therapy (6). Recurrent stomatitis was confirmed in 37% of all women, on average 35 days after the lesions had completely subsided (4). Therapy of stomatitis should begin early to aid prevention. All patients should be warned before the start of therapy of the probability that stomatitis will occur. The baseline status should always be assessed before the start of therapy. Patients should be made aware of recommended changes to diet. Spicy, sour and overly hot food and drink, and anything high in salt should be avoided. Foods that are too solid should not be eaten as these may cause microtrauma to the mucosa or palate. Oral hygiene requires that special precautions are taken. It is important to ensure that soft toothbrushes and mild toothpaste are used. It is helpful to rinse the mouth regularly with suitable products by way of prevention. Oral care products containing alcohol, iodine or sage should be avoided. Steroid mouth rinses may have prophylactic and therapeutic benefits when used correctly (7). Table 1 shows a selection of suitable oral care products.

Regular visits to the dentist can help in the early identification of lesions that have not been noticed to date. In full denture wearers a dental opinion should be sought before starting therapy with everolimus.

Patients should be encouraged to visit a dentist as soon as possible if they have discomfort in the oral cavity. Consultation with a doctor is recommended if a patient has 3 ulcerations simultaneously that persist for more than 3 days.

Therapy for stomatitis is adapted according to severity (Fig. 2). No official therapy guidelines are available to date. It is highly probable that effective local treatment brings relief from symptoms (8). Topical analgesics for the oral region should be used from grade II stomatitis onwards (see products listed in Tab. 1). With higher grades of stomatitis, agents with systemic anti-inflammatory effects can be administered. If ulceration is associated with bacterial or viral infection and/or mycosis, use of appropriate antimicrobial or antiviral substances is recommended (see Tab. 1). It is essential to take a detailed medical history of chronic infections before the start of therapy because chronic infectious diseases can be exacerbated by mTOR therapy. A positive correlation has been demonstrated between the severity of stomatitis and the efficacy of therapy (9). This makes prophylaxis and the control of side effects all the more important. An algorithm with therapy adapted to severity and recommendations for modifications is given in the flow chart in the appendix (Fig. 2).

Tab. 1: Substances for the prophylaxis and therapy of stomatitis

Prophylaxis of stomatitis			
LOCASEPTIL NEO® Solution	10 ml	3 x/day	Apply using a cotton bud 3x/day to the oral mucosa and gums.
MAGIC MOUTHWASH® *	16/24 doses		See Fig. C
Therapy of stomatitis			
STREPSILS® Dolo Lozenges		3–6 x/day	Maximum duration of therapy: 3 days.
ULCOGANT® Suspension 0.2 g/ml	250 ml bottle	4–6 x/day	Put 5 ml suspension into ½ glass of water and rinse the oral cavity. Do not take antacids 30 min before or after taking sucralfate.
SANGEROL® (lidocaine) Mouth rinse	200 ml	Several times daily	Rinse the oropharyngeal cavity with 15 ml for 30–60 s and gargle.
Mouth and throat spray	20 ml		Apply 1–2 sprays to the inflamed areas.
Lozenges	20 lozenges		Dissolve one table in the mouth every 1–2 hours.
GELCLAIR® Vifor	180 ml bottle	3 x daily	Rinse the mouth for 1 minute undiluted or diluted (15 ml + 40 ml water) 1 hour before taking food or drink.
LOCASEPTIL NEO® Solution	10 ml	4–6 x/day	Use a cotton bud to apply to the affected place.
KENACORT A® Orabase Haftpaste 0.1%	5 g	After meals	Apply a ½ cm-length of cream directly to the lesion. Use just enough paste to cover the lesion with a thin film. Do not rub in. During application, make sure that the paste is applied directly to the desired area.
MALVEOL® Emulsion	100 ml	3 x/day	To rinse the oropharyngeal cavity, add ½ teaspoon Malveol to ½ glass lukewarm water.
MAGIC MOUTHWASH® *			See Fig. C
Local antimycotic therapy			
MULTILIND® Nystatin	24/48 ml suspension	2–3 x/day	Apply to the affected parts of the mucosa.
AMPHO MORONAL® Lozenges	100 mg	4 x/day	In addition: Diflucan single-dose 200 mg tablet as a single shot.
MAGIC MOUTHWASH® *			

* Note on Magic Mouthwash®: In the US, the product Magic Mouthwash® is from the First® product range from Cutispharm Inc.® which recommends it for the prophylaxis and treatment of stomatitis for which it is currently undergoing clinical trials (7). Various versions are available: Mouthwash BLM® and BXS® both contain the components lidocaine and diphenhydramine. Mouthwash BXS also contains nystatin. The Duke's® and Mary's® versions also contain hydrocortisone and nystatin or tetracycline in addition. The solution has to be produced from several single components and subsequently has a shelf-life of 15 days. It must be produced by a qualified specialist. It can be purchased through the international pharmacy.

Tab. 2: Moisturising creams for prophylaxis and treatment of skin rash

- EUCERIN® Dry Skin Repair Ointment 10% Urea, Beiersdorf AG, Hamburg, Germany
- EXCIPIAL® U10 Lipolotio, Spirig Pharma AG, Egerkingen, Switzerland
- LIPIKAR® Baume AP, La Roche-Posay Laboratoire Pharmaceutique, La Roche Posay, France

Non-infectious pneumonitis

Non-infectious pneumonitis (NIP) is defined as drug-induced, non-malignant pneumopathy characterised by non-inflammatory infiltrates. The symptoms consist of cough, dyspnoea and more rarely hypoxia. In rare cases, sub-febrile temperatures or fever may also occur and make differentiation from an infectious event more difficult. Isolated cases of haemoptysis or fatal outcomes have been reported (10). The cause of NIP is not completely understood. Autoimmune T-cell activation is suspected. Severity is classified in grades I-IV.

The incidence for all stages of NIP was 20% in the BOLERO II trial study arm. Higher grade (grade III) events were detected in 4% of patients. A quarter of all NIP cases occurred within 12 weeks after starting therapy. After a median 3.8 week treatment break, regression to grade I NIP was observed in 80% of patients with grade III NIP. After a median 5.4 week treatment break, complete regression of NIP was seen in 75% of patients (4). The therapy of NIP already starts at the stage of risk stratification and risk minimization. Before starting therapy with EVE, a complete medical history should be taken to exclude chronic obstructive pulmonary disease or pulmonary fibrosis. If medical history and clinical bronchopulmonary findings are normal, the treating physician may decide to perform baseline imaging and/or pulmo-

Stomatitis prevention: Educate patients to maintain good dental care and good oral hygiene including regular brushing with a soft toothbrush and mild toothpaste, flossing and frequent rinsing of the mouth with sterile water. Patients should also be strongly advised to avoid agents that contain alcohol, hydrogen peroxide, iodine, and thyme derivatives. Do not consume spicy, hot, hard or adicic foods and drinks.

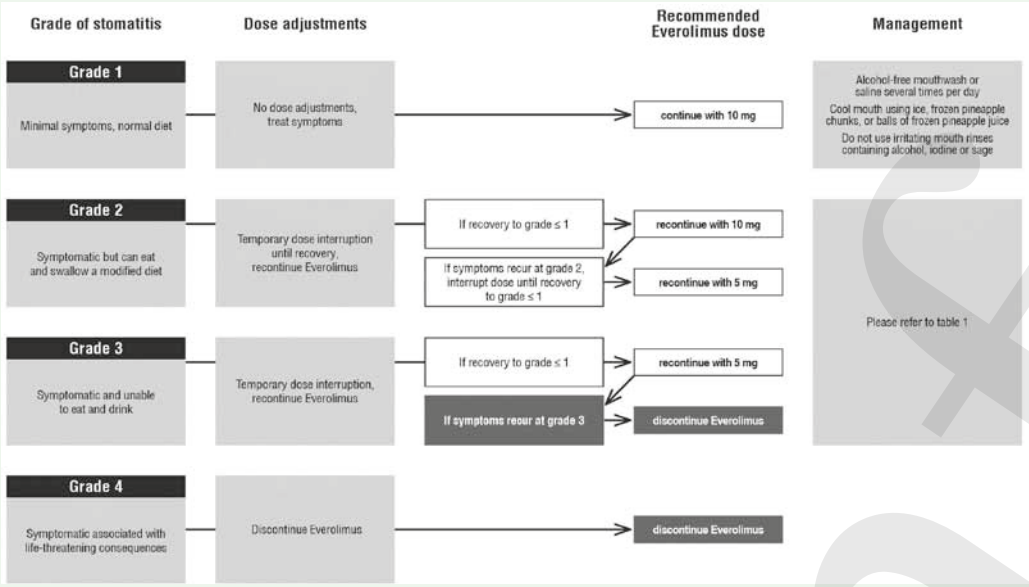

Fig. 2: Flowchart showing toxicity-adjusted management of stomatitis

* For patients with grade 2b or 3 consider re-starting Everolimus and the concomitant administration of prednisolon p.o. (≤0.5 mg/kg) may be considered. NIP prevention: Educate patients to contact their treating physician in case of any early, new or worsening respiratory symptoms. Recommendation of monitoring for patients with existing pulmonary disorders; ADL = activotoes of daily livings.

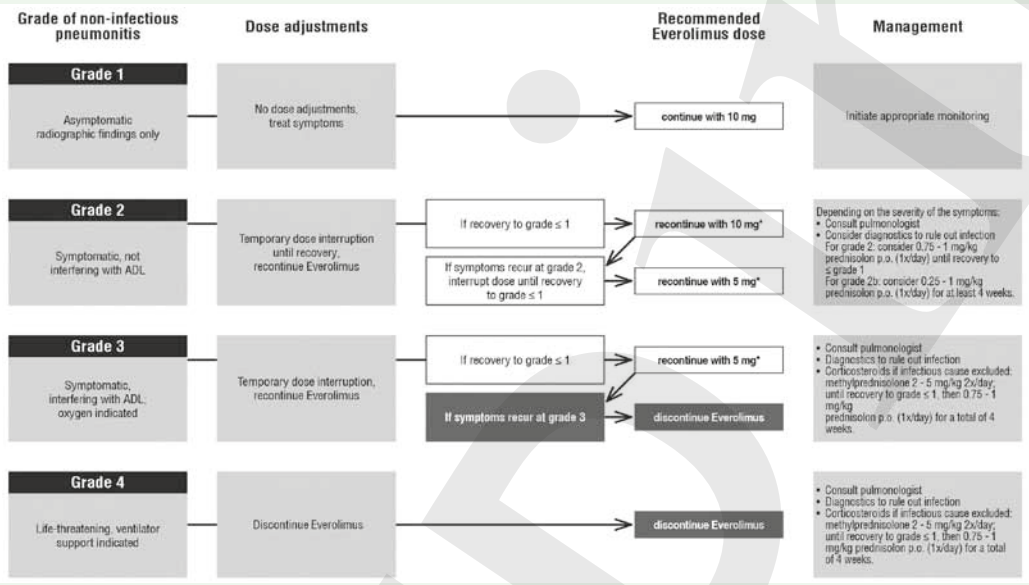

Fig. 3: Flowchart showing toxicity-adjusted management of non-infectoius pneumonitis

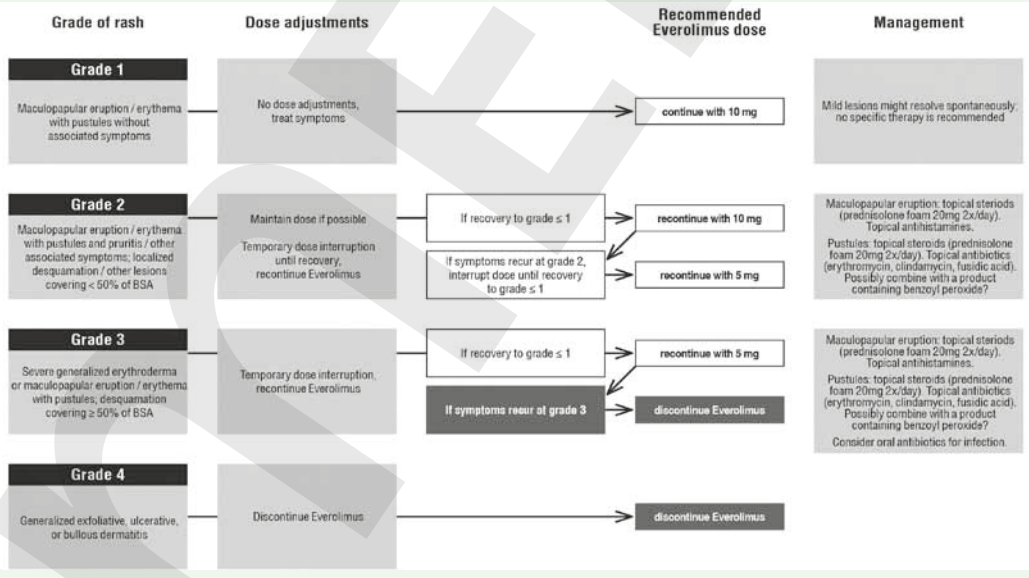

Fig. 4: Flowchart showing toxicity-adjusted management of skin rash

nary function tests. In many cases, these examinations are carried out automatically with the determination of the oncological status before starting the EVE-modulated antihormonal treatment. When dyspnoea or known pulmonary metastasis is present, CT imaging and pulmonary function diagnosis should be performed before starting therapy. The presence of pulmonary fibrosis or COPD is an absolute contraindication to EVE therapy. A risk assessment for NIP should be carried out depending on the degree of pulmonary function impairment and therapy alternatives such as metronomically dosed chemotherapy can be considered. Before starting therapy, patients should be informed about the risk of NIP and should be told to report to the treating physician immediately if they have incipient dyspnoea or a cough. Computed tomography is recommended for both initial diagnosis and diagnosis of progression, because the changes, some of which are very minor, require more sensitive and specific diagnosis (Fig. 5).

To exclude an infection as the source of the cough, bronchoscopy with bronchoalveolar lavage or biopsy should be performed (10). Depending on clinical and radiological severity, therapy management involves EVE dose reduction, a treatment interruption or treatment disruption as well as taking steroids as an option for drug treatment. The symptom management flowchart in the appendix (Fig. 3) presents an algorithm showing therapy and modification recommendations appropriate to the severity of symptoms.

Corticosteroids should be administered only after any source of infection has been excluded.

Prednisolone can be administered at 0.75-1.0 mg/kg of bodyweight. When grade III or IV NIP is present, methylprednisolone i.v. doses of 2-5 mg/kg of bodyweight twice daily should be considered over a total period of at least 5 days in the first few days after onset of NIP. Steroid therapy should be given until symptoms are alleviated (grade I) and then continued at 0.75 - 1 mg/kg/day for a

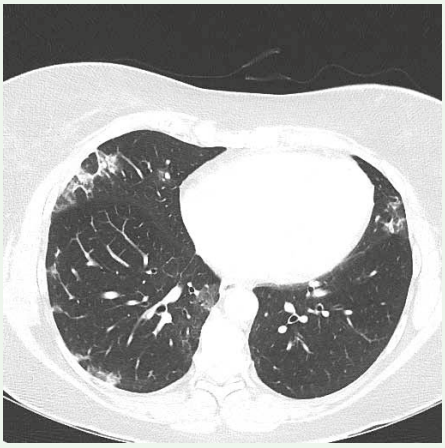

Image courtesy of Dr Eichenberger (Radiology, Basel University Hospital) and Dr Vetter (Oncology, Basel University Hospital).

Fig. 5: A 44-year-old patient with subpleural pneumonitis approximately 4 months after initiation of everolimus.

total period of 4 weeks. When EVE is reintroduced after higher grade NIP, temporary preventative steroid treatment with 0.5 mg/kg of bodyweight can be considered (11).

Skin rash

Cutaneous efflorescence which takes the form of maculopapular lesions is most frequently seen on the trunk and face during EVE therapy. In addition, increased pustular efflorescence may occur on the scalp. Aetiology is unclear in this case. It is assumed to be a delayed sensitivity reaction (12). Severity is classified in grades I–IV. Skin reactions generally occur within the first two weeks of treatment. Overall incidence in the BOLERO II trial was 39%. Higher-grade skin rashes affected only 1% of all patients (10). Patients should be informed of the risks of skin rashes and be told to consult a doctor promptly if a skin rash appears. With EVE therapy, the skin should be kept moist as a prophylactic measure. Fatty moisturising creams are suitable for this purpose (Tab. 2).

Only short lukewarm showers should be taken. Unscented soap products can lessen skin reaction. Regular use of cream products with a light-protection factor of at least 15 can also prevent skin reactions. The algorithm showing therapy adapted to severity and recommendations for modification can be seen in the flow chart in the appendix (see Fig. 4).

Metabolic side effects

Hyperglycaemia and hyperlipidaemia are known side effects caused by EVE therapy. The incidence of hyperglycaemia in the BOLERO II trial was 69%. Diabetes requiring therapy was diagnosed in 14% of patients. About half of all new hyperglycaemia cases occurred within 6 weeks of the start of therapy (10). Fasting blood glucose and lipid status should be determined before starting therapy. Patients with diabetes mellitus should have properly controlled serum glucose concentrations before therapy with EVE is started. Patients should be informed about the symptoms associated with new-onset diabetes such as polyuria and increased thirst. Serum glucose should be tested regularly after starting therapy with EVE. Therapy of recently diagnosed diabetes mellitus during on-going EVE therapy is conducted in line with the guidelines issued by the specialist societies. The incidence of hyperlipidaemia in the BOLERO II trial was 14%. Serum lipids should be tested every 6 weeks after the start of therapy. Patients should be encouraged to eat a balanced low fat diet.

Summary

Combination therapy with everolimus and exemestane significantly improved the disease-free survival of patients with metastatic hormone receptor-positive, HER2 negative breast cancer. This clinical benefit is associated with a side-effect profile which is substantially different from that of the standard treatments used to date. However, this synergistic therapeutic approach is now increasingly applied, resulting in a higher degree of experience and safety in the management of side effects. Adherence to therapy can be improved by carefully considered preliminary information, good patient management and the consequent use of prophylactic procedures, particularly in the first weeks of therapy. This results in fewer premature therapy discontinuations and improved therapeutic benefits because treatment can be administered continuously.

Recommendations at a glance:

- Consultation with a doctor on a weekly basis initially and then monthly. The interval can be increased if treatment is well tolerated.
- Chest X-ray, fasting glucose, serum lipids, liver function tests and blood count as well as clinical status of the oral mucosa form the baseline diagnosis. Consultation with a dentist before therapy for denture wearers (to determine pressure points).
- Use mouth rinses as prophylaxis. There is no reliable clinical evidence of the benefit of steroid mouth rinses.
- Start treatment with 10 mg per day. Dose reduction takes place according to the specified regimen or a general dose reduction regimen (see Fig. 2, Fig. 3 and Fig. 4).
- Patients older than 70 years: An increased therapy discontinuation rate, due to the occurrence of side effects, has been observed in this age group (13). Starting therapy with 5 mg EVE per day and then increasing the dose should be considered.
- Treatment of metabolic side effects is based on the relevant guidelines issued by the specialist societies

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IMPRESSUM

Redaktion: Dr. Heidrun Ding

Unterstützt von Novartis Pharma Schweiz SA, Rotkreuz