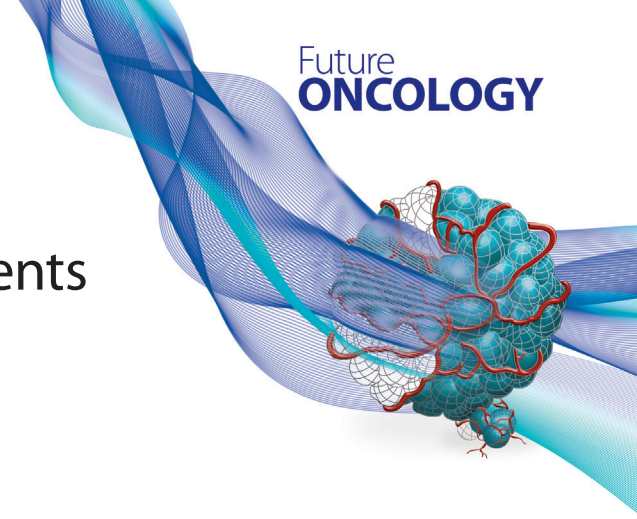
EDITORIAL



Everolimus-based therapy in patients with hormone receptor-positive, HER2$^-$ advanced breast cancer: management considerations

"The multidisciplinary management of each single breast cancer case, based on the involvement of several medical specialists dedicated to cancer treatment ... may further improve patient's compliance to the administered treatment and, therefore, the management of everolimus-based therapy in clinical practice."

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• adverse events • breast cancer • compliance • dosing • everolimus • management • multidisciplinary follow-up • toxicity

Everolimus – an inhibitor of the mTOR pathway – has an established role in the treatment of advanced renal cell cancer (RCC), neuroendocrine tumors of pancreatic origin (pNET) and renal angiomyolipoma and tuberous sclerosis complex (TSC) [1]. Moreover, everolimus, combined with the aromatase inhibitor exemestane, has been approved for the treatment of postmenopausal patients with advanced breast cancer positive for the hormone receptors (HR$^+$) and negative for the HER2$^-$ recurring or progressing after treatment with nonsteroidal aromatase inhibitors [2]. Everolimus is administered orally, at a dose of 10 mg/day continuously. At this dosage, no evidence of cumulative toxicity has been reported in clinical trials over a period of 20–52 weeks [2]. The optimal use of everolimus in breast cancer relies upon adequate management, in order to maximize treatment exposure and, therefore, optimize the clinical outcomes. However, since everolimus has only recently entered the breast cancer arena, physicians may be unfamiliar with its adverse event profile and their management. Given the low threshold for change in therapy in the breast cancer setting – which can be likely attributed to the availability of multiple treatment options – we believe that information on the correct management of everolimus-based treatment in breast cancer patients is important to improve outcomes. This editorial discusses some open issues related to the clinical management of breast cancer patients receiving everolimus.

Management of adverse events

Adverse events associated with everolimus might differ from those that oncologists endorsed to the breast cancer treatment are more familiar with. We comment on the management of some adverse events characteristic of everolimus therapy, namely stomatitis and noninfectious pneumonitis. Other specific considerations on the management of specific everolimus-associated

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adverse events and other events commonly reported with everolimus-based therapy are reported elsewhere [1,3–5]. We believe that gaining 'field-practice' experience on the management of these adverse events might lead to better prevention and treatment approaches.

• Stomatitis

Stomatitis is the most frequent event potentially associated with everolimus-based therapy, and usually occurs the first 8 weeks of treatment [4,6]. In the BOLERO-2 trial, the incidence of any-grade stomatitis was 56%, while grade ≥3 stomatitis was reported in 8% of patients [2].

Everolimus-associated stomatitis is usually located to the mucosa of the palate, gingiva, inner lips, or dorsal tongue surface. If not correctly managed, stomatitis can lead to dose reductions and/or therapy discontinuation, thus denying patients from the full benefit of everolimus therapy. Therefore, proper prevention and early management of stomatitis are of utmost importance.

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Differing from stomatitis associated with chemotherapy or radiation therapy, stomatitis associated with mTOR targeted-therapy presents an inflammatory component with lymphocyte infiltrates, which often mimics aphthous stomatitis. In addition, mTOR-targeted therapy-associated stomatitis differs from viral lesions as these latter are often located to the nonkeratinized movable oral and oropharynx mucosa. Therefore, mTOR-associated stomatitis should be managed with dedicated strategies [4].

Given the early onset and the potentially relevant clinical sequaelae, prophylactic treatment and early recognition of stomatitis is highly important. In particular, patients should be seen 10–15 days since the initiation of therapy, with the aim to early detect the occurrence of stomatitis. Preventive and management measures are based on the education of patients to oral hygiene. This should be based on regular brushing with a soft toothbrush, daily flossing, rinsing with sterile water, normal saline, or sodium bicarbonate; alcohol or peroxide-containing mouthwash should be avoided. Mild, sodium lauryl sulfate-free toothpaste is preferred, whereas the use of strong-flavored toothpastes or those containing sodium lauryl sulfate is not recommended. At the same time, acid, spicy, hot and crunchy foods may be avoided. To further reduce the risk of mucositis, any contact of everolimus with oral mucosa should be avoided [4], for example, by using cornstarch capsules to incapsulate everolimus in line with the ongoing experience of one of the authors (F Testore).

Management strategies are determined by symptom severity. Oral rinses with mouthwash solution (dexamethasone oral drops solution 2 mg/ml, lidocaine gel 2%, sucralfate oral suspension 1000 mg/5 ml, dissolved in sodium chloride 0.9%) may be helpful. Topical corticosteroids should be used as needed. Patients should be monitored for fungal or viral infections; antifungal agents should be used with caution because of their interaction with mTOR therapy.

• Noninfectious pneumonitis

Pneumonitis may occur during everolimus therapy; however, the causative mechanisms underlying the association of everolimus with this event – if any – are not known [7]. Before initiating everolimus therapy, clinicians should evaluate pulmonary history in order to identify any pre-existing condition (i.e., pulmonary fibrosis or chronic obstructive pulmonary disease) requiring pulmonary function tests.

Although some patients remain asymptomatic, the evaluation of symptoms (cough, dyspnea during exertion or at rest, occasionally pleural diffusion) is the first step for the identification of noninfectious pneumonitis in patients treated with everolimus. In these symptomatic patients, radiographic imaging by chest high resolution CT scan should be performed and, in some cases, bronchoalveolar lavage may be useful to rule out infection (microbiologic and virologic samples, alveolar cell count and alveolar lymphocytes phenotyping) and evaluate lung inflammation. Lymphocytic alveolitis without fungal or viral positivity strongly suggest a noninfectious pneumonitis associated with mTOR inhibitors [8]. Therapy with everolimus should be continued unless the symptoms become severe; in this case, corticosteroid treatment should be instituted in order to allow a fast recovery and the prosecution of everolimus therapy. Follow-up is performed by spirometry.

Everolimus dosing

Whenever possible, everolimus should be administered at full dose (10 mg/day). Dose reductions to 5 mg/day might be considered only in patients with moderate-to-severe adverse events [9].

The potential existence of an association between the occurrence of adverse events and efficacy remains an open issue. Ravaud *et al.* recently performed a meta-analysis of clinical trials aimed

at evaluating the potential relationship between everolimus exposure and the safety and efficacy of this molecule [10]. However, in this analysis no patients with breast cancer were included; therefore, these data need to be considered with caution before extending them to breast cancer patients. The meta-analysis considered patient pharmacokinetic data deriving from five Phase II or Phase III studies. Efficacy was evaluated in a total of 945 patients, and safety in 938 subjects. The analysis showed that a twofold increase in the minimum concentration of everolimus is associated with an increased likelihood of reduction of tumor size (odds ratio: 1.4), a trend to a reduced risk of progression-free survival (risk ratio [RR]: 0.9), and an increased risk of ≥grade 3 pulmonary toxicity (RR: 1.9), stomatitis (RR: 1.5), and metabolic toxicity (RR: 1.3). Overall, these data show that increased exposure to everolimus is associated with both increased efficacy and a higher rate of high-grade toxicities, thus suggesting a dose-dependent antitumor effect of everolimus.

The importance of compliance

Oral administration with everolimus is associated with enhanced patients' comfort, but also poses some challenges in terms of compliance. To our knowledge, the compliance to everolimus therapy in field-practice has never been addressed in breast cancer patients. While dedicated studies appear advocated, a German multicenter noninterventional study on 196 mRCC patients has documented high adherence (approximately 97%) to everolimus therapy [11].

Communication with patients plays a central role in improving compliance. To this respect, breast cancer patients treated with everolimus-based treatment should be considered as those undergoing chemotherapy, and should receive clear instructions on therapy, administration measures, potentially associated adverse events and their prevention/management at the institution of therapy. The management team should, if possible, remain the same over time and clinicians should meet each patient at least twice at the initiation of therapy. Patients should in particular be encouraged to promptly report any symptom experienced during therapy, in particular respiratory symptom such as persistent cough and dyspnea or the appearance of oral lesions, mouth pain and dysphagia. Moreover, early monitoring (within 2 weeks since the initiation of therapy) is recommended to assess the potential onset of stomatitis and other adverse events.

The importance of a multidisciplinary approach

Multidisciplinary management has mounting importance in breast cancer. In fact, optimal patient care and outcomes depend on the participation and dialogue between specialists in imaging, pathologic and molecular diagnostic, surgery, radiation oncology, and medical oncology [12]. In everolimus-treated patients, a close cooperation of different specialists is crucial to optimize clinical outcomes. For instance, dentists and oral cavity specialists may allow a better management of stomatitis. If the patient presents with respiratory symptoms, a radiologist and pulmonologist consultation is recommended to detect early radiological signs of noninfectious pneumonitis and to facilitate differential diagnosis. In addition, nurses may educate patients on potential adverse events and their prevention and management [13].

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Conclusion

Everolimus represents a relatively new therapy in the complex treatment scenario of breast cancer. In order to prolong treatment duration, to avoid dose discontinuations and, therefore, maximize the clinical benefit and outcomes, an early monitoring for the potential onset of adverse events should be instituted; at the same time, patients should be educated to report any symptoms experienced during therapy and to apply some preventive measures.

The multidisciplinary management of each single breast cancer case, based on the involvement of several medical specialists dedicated to cancer treatment, together with the continuous communication with breast cancer patients, may further improve patient's compliance to the administered treatment and, therefore, the management of everolimus-based therapy in clinical practice.

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