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Adverse Event Management of mTOR Inhibitors During Treatment of Hormone Receptor–Positive Advanced Breast Cancer: Considerations for Oncologists

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Abstract

Breast cancer (BC) is diagnosed in nearly 1 in 3 women with cancer in the United States (US); one-third have regional lymph node metastases at the time of diagnosis. The 5-year survival rate of patients with metastatic BC is very low, and approximately 40,000 women were expected to die of the disease in 2013. About 75% of patients with BC have hormone receptor–positive disease, which is often managed with endocrine therapy; however, most patients eventually develop resistance to these therapies. Recently, the mammalian target of rapamycin (mTOR) inhibitor everolimus, in combination with exemestane, improved progression-free survival of patients with advanced BC, leading to its approval by the US Food and Drug Administration. Because adverse events (AEs) associated with everolimus might differ from AEs that oncologists who treat BC patients are more familiar with, everolimus AEs and their effective management are reviewed herein. Possible dose adjustments of everolimus for patients with renal or hepatic impairment and strategies for minimizing potential interactions of everolimus with other drugs and food are also discussed.

Keywords: Advanced breast cancer, Adverse events, Everolimus, Infection, mTOR, Noninfectious pneumonitis, Rash, Stomatitis

Introduction

Breast cancer (BC) is the second most common type of cancer worldwide.[1] At the time of diagnosis, BC is localized in 60% of patients; in 33% it has spread to regional lymph nodes and to distant metastatic sites in approximately 5%.[2] The 5-year relative survival rate for patients with metastatic BC is 23.3%, compared with 98.6% for those with localized disease.[2] In 2013, approximately 232,000 new cases of women with BC will be diagnosed.[3] Approximately 40,000 women are expected to die of the disease,[3] and approximately 90% of these individuals will be ≥50 years old.[4]

Approximately three-quarters of patients diagnosed with advanced BC have hormone receptor–positive (HR+) disease,[5, 6] and estrogen receptor (ER) positivity is associated with postmenopausal status.[6] Consistently, patients with HR+ advanced BC typically respond well to endocrine therapies. Several pharmacologic and nonpharmacologic strategies might be considered to manage patients with HR+ advanced BC. The nonsteroidal aromatase inhibitors (NSAIs) anastrozole and letrozole and the steroidal aromatase inhibitor exemestane[7-9] are the first-line treatment of choice for postmenopausal women with HR+ advanced BC.[10, 11] In addition to AIs, tamoxifen—an oral, nonsteroidal, selective ER modulator (SERM)—and toremifene—a chlorinated derivative of tamoxifen—are also approved for managing HR+ metastatic BC in postmenopausal women.[12, 13] Although clinical trial data have shown that fulvestrant, a selective ER down-regulator (SERD), is as effective as tamoxifen[14] and anastrozole in the first-line setting[15] in managing advanced BC in postmenopausal women, it is only indicated for treatment of HR+ metastatic BC after antiestrogen therapy failure.[16] Disease

progression as a result of de novo or acquired resistance to endocrine therapies used in the first-line setting has highlighted the need for second and subsequent lines of treatment.[17, 18] Second-line hormonal therapy could include tamoxifen or AIs (if not used as first line), the SERD fulvestrant, megestrol acetate, or androgens.[10, 12] Shorter durations of clinical benefit and lower response rates characterize second and subsequent lines of therapies, compared with first-line therapy.[19] Understanding some key regulatory pathways in the development of hormone therapy resistance has led to the discovery and development of novel targeted therapies that inhibit intracellular signaling pathways that are downstream of HRs.

mTOR Pathway and a Role for Everolimus in Breast Cancer

The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling cascade, which is downstream of the ER,[20] is dysregulated in several human cancers.[21] Mutations in the catalytic domain of PI3K and reduced expression of phosphatase and tensin homolog (PTEN), an inhibitor of the PI3K/AKT/mTOR pathway known to occur in ER+ BC,[22] activate the PI3K signaling cascade,[22, 23] resulting in ligand-independent activation of the ER.[20, 24-26] In patients receiving endocrine therapy, phosphorylated AKT (activated form) has been associated with reduced clinical benefit.[26] These observations suggest that overactivation of the PI3K/AKT/mTOR pathway can lead to resistance to endocrine therapies.

The protein kinase mTOR regulates cell growth and proliferation and plays a vital role in the PI3K/AKT/mTOR pathway.[27] It has been hypothesized that mTOR inhibitors can

partially restore sensitivity in patients with acquired resistance and might delay the onset of resistance when used in combination with current therapies.[28, 29] Consistent with this hypothesis, results from 2 randomized, phase II studies showed that the addition of oral everolimus to endocrine therapy improved clinical response rates.[30, 31] The results from Breast Cancer Trials of Oral Everolimus (BOLERO-2), a phase III trial of postmenopausal patients with HR+ human epidermal growth factor receptor 2–negative (HER2–) advanced BC that progressed while receiving anastrozole or letrozole, also showed that everolimus in combination with exemestane improved median progression-free survival (PFS) based on a central assessment to 10.6 months, compared with 4.1 months with exemestane alone (hazard ratio = 0.36; 95% confidence interval [CI]: 0.27-0.47; $P < .001$).[32] For the 18-month follow-up data for BOLERO-2, the PFS for everolimus plus exemestane versus exemestane alone (central review) was 11.0 versus 4.1 months, respectively (hazard ratio = 0.38; 95% CI = 0.31-0.48; $P < 0.001$).[33] Consequently, everolimus has been approved in combination with exemestane for treating patients with HR+, HER2– advanced BC.[34] Post hoc analysis of the quality of life (QOL) of patients enrolled in this trial showed that there was no difference between the 2 arms, indicating that the QOL of patients treated with everolimus was not compromised.[35]

Everolimus in Breast Cancer: Adverse Events

Lack of appropriate management of toxicity might undermine the therapeutic effectiveness of the anticancer agent everolimus and can result in decreased patient QOL, decreased adherence to therapy, and increased cost associated with management of these

issues. Thus, prompt, accurate recognition and management of adverse events (AEs) associated with specific cancer therapies is crucial for improving overall patient outcomes. As a novel therapy and the only approved mTOR inhibitor for managing patients with HR+ advanced BC whose disease is progressing while on an NSAI, oncologists and their treatment teams must be cognizant of the unique adverse event profile as a result of the addition of everolimus to exemestane. Hence, the most commonly observed everolimus-associated AEs and strategies for their optimal management will be reviewed. Everolimus-associated AEs in patients with BC will briefly be compared with the AEs observed with monotherapy use of everolimus in renal cell carcinoma (RCC), pancreatic neuroendocrine tumor (pNET), tuberous sclerosis complex (TSC) associated with subependymal giant cell astrocytoma (SEGA), and angiomyolipoma (AML).

Many of the AEs observed with everolimus represent a class effect of mTOR inhibitors and, therefore, have also been reported to occur with other investigational and approved mTOR inhibitors such as temsirolimus in patients with RCC[36, 37]; ridaforolimus (formerly called deforolimus),[38, 39] which is currently undergoing clinical trials for the management of HR+ HER2– postmenopausal patients with metastatic or locally advanced BC (ClinicalTrials.gov identifiers: NCT01234857, NCT01605396); and sirolimus in renal transplant recipients.[40, 41]

Most Common Adverse Events Associated With Everolimus Therapy

Everolimus has been approved and widely used for a number of years for treating patients with various cancers or conditions. For oncologists treating patients with BC, everolimus has been a welcome recent addition to the therapeutic armory, accompanied by an awareness of some unique adverse events this class of drugs can bring to the treatment of patients with BC. Knowing the signs and symptoms of AEs associated with everolimus therapy (Table 1[33, 42-46]), when to expect an AE, how to manage the AE if it occurs, and when to make dose modifications are all important to preserve patient QOL and to improve overall patient outcome. Knowledge and awareness of these symptoms will enable physicians to individualize treatment plans and, perhaps, incorporate supportive management strategies sooner, including plans to monitor and manage symptoms. Implementation of these strategies might help to minimize the occurrence of AEs and, thus, increase patient adherence to the full course of therapy. In addition, awareness of the occurrence of these events in relation to initiation of everolimus will enable clinicians to better educate patients and other physician specialists about these AEs and their approximate time of onset. Through a better understanding of the timing and the management of everolimus AEs, support staff, patients, and other specialists can be better equipped with effective strategies to manage AEs efficiently.

Management of Everolimus-Associated AEs

Stomatitis

Although mouth ulcerations associated with the use of mTOR inhibitors have been defined as mucositis, based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, version 3.0, it has been suggested that the

ulcers caused by mTOR inhibition are distinct from the mucositis commonly observed with chemotherapy.[47] Stomatitis, the mucosal shallow-based, discrete ulcers associated with mTOR inhibitors, are well demarcated and nonconfluent, and typically localized to the movable mucosa of the mouth and oropharynx but not in the more keratinized mucosa of the palate, gingiva, or dorsal surface of the tongue (Figure 1A).[47] In contrast, chemotherapy-induced mucositis typically has a nonuniform shape and depth, often accompanied by a fibrinous pseudomembrane with cellular debris without peripheral erythema, and is more commonly confluent and not limited to the oral cavity but is associated with a diffuse gastrointestinal tract mucosal injury pattern.[47] Furthermore, the underlying pathoetiology of the ulcerations associated with mTOR inhibitors and chemotherapy differs. Therefore, management strategies to prevent or treat mTOR inhibitor–induced stomatitis should be differentiated from those used to treat chemotherapy-induced mucositis.

Stomatitis is the most common AE associated with everolimus. Results from the BOLERO-2 trial, at a median follow-up of 7.1 months, reported that all grades of stomatitis occurred in 56% of patients in the everolimus plus exemestane arm, compared with 11% in the exemestane plus placebo arm.[32] There were no grade 4 events in either arm; grade 3 stomatitis was reported in 8% of patients in the exemestane plus everolimus arm, compared with 1% in the comparator arm.[32] These results are comparable with those reported from the TAMRAD phase II study, which compared everolimus plus tamoxifen, compared versus tamoxifen alone, also in HR+ HER2– metastatic BC after previous AI exposure. Any-grade stomatitis occurred in 56% of patients receiving tamoxifen plus

everolimus,[31] with grade 3 or 4 events present in 11% of treated patients.[31] The risk for stomatitis at any grade with everolimus plus exemestane at 18-month median follow-up in the BOLERO-2 trial was 59%, compared with 12% with placebo plus exemestane.[33, 48] Grade 3 stomatitis occurred in 8% of patients treated with everolimus plus exemestane; there were no grade 4 events.[33, 48] The majority of patients (98%; n = 121) with grade 2 stomatitis and related events in the everolimus plus exemestane arm experienced complete resolution at a median of 16 days.[48] Results from other everolimus clinical trials in various tumor types and conditions indicate that stomatitis was the most frequently reported AE, with an overall incidence ranging from 31% to 56% (Table 1) and an incidence of grade 3 or 4 stomatitis between 1% and 8%.[33, 42-46] In the RAD001 Expanded Access Clinical Trial in RCC (REACT)–1 involving a heterogeneous group of patients with RCC, including those who might not be eligible to enroll in clinical trials, the overall incidence of any-grade stomatitis was approximately 10%.[49]

The median onset of everolimus- and ridaforolimus-associated stomatitis in patients with various solid tumors is 10 days (range, 4-25 days).[50] The median time to onset for everolimus-associated grade ≥2 stomatitis and related events was 15 days in the BOLERO-2 trial.[48] A retrospective analysis of 6 everolimus phase I and II trials, including 1 BC trial and 5 exploratory lung cancer trials, showed that patients who had received prior chemotherapy, compared with those who were chemonaive, as well as patients receiving everolimus in combination with other antineoplastic agents, compared with everolimus monotherapy, experienced a higher incidence of stomatitis.[51] This observation highlights the differences in experiences with everolimus among the different

indications and various tumor subtypes in which the use of chemotherapy might greatly differ from one indication to another. Therefore, oncologists and their treatment teams must critically assess the risk factors of patients, including previous or concurrent use of chemotherapy, before initiating everolimus therapy.

Oncologists and their treatment teams are strongly encouraged to teach and improve patient awareness of the risk for everolimus-associated stomatitis.[45] Clinicians are advised to reinforce good oral hygiene, including regular brushing with a soft toothbrush and mild toothpaste, flossing, and frequent rinsing of the mouth with sterile water, saline, or a sodium bicarbonate solution.[52, 53] Patients should also be strongly advised to avoid agents that contain alcohol, hydrogen peroxide, iodine, and thyme derivatives.[45] If necessary, the patient should be advised about diet modification,[45] such as avoiding spicy, hot, hard, or acidic foods and beverages.[53] Although specific strategies to prevent and/or manage everolimus-associated stomatitis are not well documented, the use of specific oral steroid rinses (eg, dexamethasone solution) and steroid-based mouthwashes (eg, “miracle mouthwash” or “magic mouthwash” formulations) has been suggested for preventing and treating mTOR inhibitor-associated stomatitis (Table 2).[52-54] Previous reports have suggested that stomatitis can be mitigated with the use of a 5% dexamethasone oral rinse.[50, 55] Additionally, the use of a steroid mouth rinse is currently being evaluated to treat stomatitis as a secondary end point in the BOLERO-4 study as well as to prevent stomatitis in a phase II trial of everolimus plus exemestane in HR+/HER– advanced breast cancer (ClinicalTrials.gov identifier: NCT02069093). Data from a small study evaluated the clinical presentation and management of stomatitis in 17

patients treated with an mTOR inhibitor, and most of the patients were treated with topical corticosteroids that included an oral dexamethasone solution that was rinsed and expectorated.[50] Clinical improvement was noted in more than 85% of corticosteroid-treated patients.[50] In the BOLERO-2 trial, treatment discontinuation as a result of stomatitis and related events occurred in 3% of patients in the everolimus plus exemestane arm[48]; hence, to minimize the severity of stomatitis and improve outcomes, effective management of this AE is recommended (Table 3).[45, 54, 56-59] To minimize the risk for potential drug-drug interactions with everolimus in patients who might need an antifungal treatment, it is recommended that a mouthwash containing an antifungal such as nystatin be used, unless there is a need for systemic antifungal therapy.[54]

Noninfectious pneumonitis

Noninfectious pneumonitis (NIP), a nonmalignant inflammation of the lungs (Figure 1B) has occurred in 8% to 16% of everolimus-treated patients in phase III oncology trials, whereas only 1% of patients with TSC with SEGA or AML experienced NIP (Table 1).[33, 42-46] In the BOLERO-2 trial at the median follow-up of 18 months, NIP occurred in 16% of patients treated with everolimus plus exemestane, and 3% of patients had grade 3 NIP.[33, 60] Of 20 patients with grade 3/4 NIP and related events in the exemestane plus everolimus arm, 16 (80%) experienced resolution to grade ≤ 1 at a median of 3.8 weeks, whereas 15 patients (75%) had complete resolution at a median of 5.4 weeks.[60] Complete resolution of grade 2 NIP occurred in 29 of 35 patients, and the median time to resolution was 5.1 weeks.[60] In the TAMRAD study, NIP occurred in 17% of patients in the tamoxifen plus everolimus arm, with 2% of patients experiencing a grade 3 or 4 event.[31]

At 18-month median follow-up in the BOLERO-2 trial, 7% of patients treated with everolimus plus exemestane discontinued the study drug because of NIP.[60]

Results from a phase II trial in patients with recurrent or metastatic BC showed that the median time to onset of NIP was 51 days for patients receiving daily everolimus therapy,[61] whereas the onset was within 2 to 6 months in the Renal Cell cancer treatment with Oral RAD001 given Daily (RECORD-1) trial with RCC patients.[54] Results from the BOLERO-2 trial, at 18-month median follow-up, showed that the cumulative probability of experiencing grade ≥ 2 NIP and related events in patients treated with everolimus plus exemestane at 24 and 48 weeks was 10% and 16%, respectively.[60] Identification of patients with mTOR inhibitor–induced NIP might be complicated because underreporting might have occurred in asymptomatic patients or those with nonspecific respiratory signs and symptoms such as hypoxia, pleural effusion, cough, and dyspnea that may have been attributed to a potential drug-mediated cause.[54] To assist clinicians in making an appropriate diagnosis of NIP, a panel of international experts recommended that clinicians obtain and carefully consider the pulmonary history of the patient before initiating everolimus therapy.[54] With regard to pulmonary history, pulmonary function tests (PFTs) at screening and baseline should be considered (particularly in patients with significant lung disorders), and an assessment of diffusion capacity and single breath transfer factor ($T_{L,CO}$) (also known as lung diffusion capacity testing [D_{LCO}] in the United States) should be conducted; caution should be exercised in patients with a diffusion capacity of < 20%, and PFTs should be repeated in patients with T_L,CO < 40% of the predicted value.[54] More important, if NIP is suspected, the panel recommended that

infection as a result of *Legionella* or *Pneumocystis carinii* should be ruled out, and, in some cases, clinicians are advised to consider obtaining a pulmonary consultation.[54] In patients with RCC or advanced non–small cell lung cancer, NIP associated with the use of everolimus has been observed radiologically as a ground-glass opacity and focal consolidation in the lower lobe of the lung,[54, 62] suggesting that radiologic determination of NIP might be a useful adjunctive tool. Although the pneumonitis observed with everolimus therapy is noninfectious, some patients have also had fever. Because patients might also be easily immunocompromised, coinfection with pulmonary pathogens might occur, and the clinician must be aware of this.[54] In such patients, the expert panel recommended that it is critical that an infectious cause of pneumonitis be ruled out.[54] It might be prudent to check the white blood cell count to rule out an infectious cause of pneumonitis.

The panel recommended that the withholding of everolimus treatment should be considered in patients with carbon monoxide transfer factor ($T_{L,CO}$) < 40% of the predicted value until lung function normalizes.[54] In patients with multiple lung metastases or with respiratory symptoms at baseline, the panel has suggested that clinicians perform baseline pulmonary function tests and computed tomography before initiating everolimus therapy.[54] Radiographic findings of “ground-glass opacities” or “infiltrates” in asymptomatic patients are suggestive of grade 1 NIP.[54, 56] No intervention or everolimus dose adjustment is required in these patients, but appropriate monitoring should be initiated.[45, 54] In patients with lung metastases, presence of pleural effusion might be confusing because it can be a result of the NIP associated with everolimus treatment or a

result of progression of the disease, or both. Hence, the panel has recommended that, in such cases, everolimus treatment should be discontinued initially, and corticosteroid treatment should be initiated because this strategy would resolve non–tumor-associated NIP.[54] Corticosteroid administration, everolimus dose reduction, or everolimus discontinuation (Table 3) resulted in symptom reversal in patients suspected of having NIP in the BOLERO-2 trial[60] and in patients with RCC from the RECORD-1 trial,[63] lending support to the idea that everolimus-associated NIP might be reversible with appropriate management. Finally, in patients with severe chronic obstructive pulmonary disease or significant pulmonary fibrosis, the expert panel recommended that the use of everolimus be avoided.[54]

Oncologists and their treatment teams should educate patients about the possibility of NIP and signs and symptoms of NIP, and advise them to promptly report any early new or worsening respiratory symptoms, so that the potential for NIP represented by these symptoms can be investigated sooner and interventions can be instituted early and managed appropriately, with minimal disruption to treatment.[45, 54]

Infection

Everolimus, similar to other mTOR inhibitors, blocks cytokine-mediated T-cell proliferation and activation by inducing a G_1-S cell-cycle arrest, resulting in immunosuppression.[64] Consistent with the suppression of T-cell–mediated response, use of mTOR inhibitors results in higher rates of infection. As described in the package insert, infection occurred in 50% of patients (Table 1) treated with exemestane plus

everolimus, compared with 25% of patients treated with exemestane alone.[45] In the BOLERO-2 trial, the rate at 18-month median follow-up was 54% with everolimus plus exemestane, with 5% and 1.5% of patients experiencing grade 3 and 4 events, respectively.[65] The rates of infection observed in phase III trials with everolimus were between 10% and 72% (Table 1).[33, 42-46] BC patients treated with tamoxifen plus everolimus in the TAMRAD trial experienced a 35% rate of infection of any grade, compared with 19% of patients treated with tamoxifen alone.[31] Grade 3/4 infection occurred in 7% and 5% of patients treated with tamoxifen plus everolimus and tamoxifen alone, respectively.[31] Death attributed to pneumonia and sepsis occurred in 1 patient and 2 patients, respectively, in the exemestane plus everolimus arm of the BOLERO-2 trial.[32]

Reactivation of preexisting infection such as fungal infection, hepatitis B virus (HBV) infection, or hepatitis C virus (HCV) infection is a risk for any patient undergoing cytotoxic chemotherapy or immunosuppressive therapy.[66] In fact, in hepatocellular carcinoma (HCC), a disease in which previous HBV and HCV infections are risk factors, results from a phase I trial with everolimus in HCC patients showed that reactivation of HBV infection occurred in 5 patients and HCV flare-up occurred in 1 patient.[67] However, in subsequent phase I and II trials in HCC in which HBV-positive patients were proactively screened and administered anti-HBV therapy while receiving everolimus, no reactivation of HBV was observed.[68] Everolimus-associated reactivation of HBV was observed in 1 patient with pNET in the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3), and 2 patients had everolimus-associated infection consisting

of pulmonary tuberculosis (TB) and bronchopulmonary aspergillosis, each occurring in 1 patient respectively.[42]

Together, these observations highlight the importance of obtaining a patient's thorough medical history before initiating any antineoplastic treatment, including everolimus therapy, and the need for vigilant monitoring of patients for signs and symptoms of new infections (Table 3).[45, 54, 56-59] The expert panel recommended that clinicians assess the potential for a latent TB infection, especially in patients from countries where TB is endemic.[54] The panel has also recommended the use of preventive therapy in patients with HBV (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb] positive) to block reactivation.[54] According to the panel, determining the antibody status of patients for toxoplasma, cytomegalovirus, herpes simplex virus, Epstein-Barr virus, and so forth, before initiating everolimus therapy, might also be useful.[54] A recent report indicated that liver function test results and viral load of patients with HBV or HCV infection should be closely monitored.[68] The expert panel indicated that it may also be beneficial to consult an infectious disease specialist while managing patients with HBV or HCV infections to improve outcomes and minimize liver damage.[54]

Rash

Results both from BOLERO-2 at 7.1-month median follow-up and from the TAMRAD study showed that 36% and 44% of patients in the everolimus treatment arms had a rash, but only 1% and 4% were grade 3/4, respectively.[31, 32] At 18-month median follow-up of the BOLERO-2 trial, the risk was 39%, and only 1% of patients experienced a grade 3

rash.[33, 65] The occurrence of any grade of rash with the use of everolimus in various other phase III clinical trials (Table 1)[33, 42-46] ranged from 12% to 49%. At 18-month median follow-up in the BOLERO-2 trial, 1.7% of all patients managed with use of everolimus plus exemestane discontinued the study drugs because of the development of rash.[65]

Rash—described as maculopapular or acneiform lesions, often with pruritus—induced by mTOR inhibitors is histologically and clinically distinct from that of other targeted agents.[57] Rash associated with mTOR inhibitors occurs primarily in sebaceous gland–rich areas, such as the trunk, scalp, face, and neck, although the extremities are also commonly involved.[57] In general, maculopapular exanthema induced by temsirolimus and everolimus has typically occurred within the first month of therapy.[57]

Use of topical low- to moderate-strength steroids and topical antibiotics has been recommended for treating patients with grade 1 papulopustular rash (Table 3). Although guideline recommendations on the use of specific antibiotic treatment options for everolimus-associated rash have not been established, previous clinical experiences in patients with mTOR inhibitor-associated rash have suggested the initial use of topical antibiotics, such as clindamycin or erythromycin, followed by systemic treatment with oral antibiotics, such as doxycycline or minocycline, if symptoms worsen or persist despite initial topical measures.[57, 69] Clinicians are advised to use low- to moderate-strength steroids, along with oral antihistamines, in patients with grade 1 maculopapular rash.[57] To manage grade 2 or 3 rash, use of oral antibiotics for 2 to 4 weeks, use of oral steroids, and interruption or modification of the everolimus dose are recommended.[57]

Similar to the strategies for managing other AEs, patients should be educated about the possibility of rash during treatment with everolimus. Clinicians should advise patients about the need to promptly report a rash to the treatment team, so that it can be managed effectively, with minimal possibility of therapy discontinuation.[56] Clinicians should encourage patients to use good skin care (eg, frequent moisturization using an alcohol-free cream; bathing or showering in lukewarm water using a moisturizing, fragrance-free soap; using a high sun-protective-factor sunscreen) and to carefully dry skin after bathing.[56, 70]

Hyperglycemia

Hyperglycemia is an AE associated with treatment with use of inhibitors of the PI3K/AKT/mTOR pathway, including mTOR inhibitors.[71] Consistent with this, results from the BOLERO-2 trial, reported at 7.1-month median follow-up, in patients with advanced BC showed that hyperglycemia occurred in 13% of patients treated with exemestane plus everolimus, compared with 2% of those treated with exemestane alone.[32] Among these patients treated with everolimus plus exemestane, hyperglycemia was grade 3 in 4% and grade 4 in < 1%.[32] The risk for hyperglycemia at any grade at 18-month median follow-up was 14%.[33, 65] In 5% of patients, hyperglycemia was a grade 3 event, and, in 0.4% of patients, it was a grade 4 event.[65] Of 20 patients with grade ≥ 3 hyperglycemia/new-onset diabetes mellitus in the everolimus plus exemestane arm, 13 (65%) experienced resolution to grade ≤ 1 at a median of 11.0 weeks.[65] Rates of

hyperglycemia between 13% and 50% were reported in other phase III everolimus trials (Table 1).[33, 42-46]

Because most cases of hyperglycemia in patients treated with everolimus occurred in those who had abnormal fasting glucose levels before treatment initiation, the expert panel recommended that clinicians achieve optimal glycemic control and stability in patients before initiating everolimus therapy.[54] In addition, clinicians are also advised to monitor fasting glucose levels periodically during treatment with everolimus.[54] In patients with no history of diabetes who are treated with a PI3K/AKT/mTOR pathway inhibitor, an NCI task force recommended that clinicians check random glucose levels or, preferably, fasting glucose levels at baseline and at every patient visit.[71] However, obtaining a fasting glucose level at every visit might not be practical for some patients, especially if they travel great distances or are seeing an oncologist later in the day. To circumvent such situations, patients can be strongly encouraged to self-monitor blood glucose level using any of the in-home blood glucose monitors and to report the findings to their clinicians.

The expert panel also advised clinicians to follow the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus guidelines[72] in managing grade 2, 3, or 4 hyperglycemia (Table 3) in patients receiving everolimus therapy.[54] Although lifestyle interventions that decrease body weight and increase physical activity, in addition to medical management, are a vital part the ADA/EASD recommendations,[72] the guidelines may not be practical for a patient with

cancer because no oncology-specific guidelines and interventions are listed. Therefore, oncologists and their treatment teams are left with making a decision regarding what lifestyle interventions might be appropriate or possible for their respective patients with cancer disease. Alternatively, oncologists can involve a diabetes educator in the overall management of hyperglycemia in their patients and particularly in those who might require steroids for management of treatment-related AE or disease- or treatment-related symptom management.[73] The ADA/EASD guidelines recommend, in patients with inadequate glycemic control, addition of antihyperglycemic agents such as metformin as initial therapy and alteration with additional therapy as needed thereafter as appropriate.[72]

Oncologists and their treatment teams are advised to teach their patients about the risk for hyperglycemia during everolimus therapy and to encourage them to promptly report any signs or symptoms to the treatment team.[54] The NCI task force recommended that patients who do not have diabetes but who have risk factors such as abnormal fasting glucose levels > 100 mg/dL, have abnormal random glucose levels > 140 mg/dL, have a family history of diabetes, and who are overweight (body mass index > 25 kg/m^2) perform home blood glucose monitoring once daily, alternating times before breakfast, before lunch, and before dinner during the first week of cycle 1.[71] This task force also recommended that during cycles 2 and 3, home blood glucose monitoring should be done 2 or 3 times per week because some therapeutic agents that affect the PI3K/AKT/mTOR pathway have not been reported to cause hyperglycemia until cycle 2 or 3.[71] Based on this guidance, oncologists and their treatment teams can educate their high-risk patients on how to perform self-monitoring of blood glucose level and encourage them to adhere

to the recommendations of the NCI task force. However, because these patients might not be accustomed to this level of monitoring and might find it overwhelming, it might be more prudent to observe blood glucose levels over time to determine the level of guidance a patient might need.

Hyperlipidemia

In 70% of advanced BC patients treated with everolimus plus exemestane in BOLERO-2, an increase in cholesterol level was noted, and in 50% of patients an increase in triglycerides was seen; grade 3 or 4 events were < 1%.[45] In the phase III cancer trials (Table 1), the observed percentage of patients with an increase in cholesterol level was 66% to 77%, and the increase in triglyceride level was 39% to 73%, mostly grade 1 or 2.[33, 42-46]

Similar to the recommendations for management of hyperglycemia, no intervention strategies are advised to manage a grade 1 increase in cholesterol or triglyceride level.[45, 54] For treatment of patients with higher grade increases in cholesterol or triglyceride level, the expert panel recommended that clinicians adhere to the standard guidelines (Table 3) such as the National Cholesterol Education Program–Adult Treatment Panel III guideline, the Canadian guidelines for the management of dyslipidemia and preventing cardiovascular disease, or the European Society of Cardiology/European Atherosclerosis Society Guidelines for the management of dyslipidemia.[54, 74-76] Furthermore, the panel recommended that oncologists and their treatment teams inform patients already receiving lipid-lowering therapy that a higher dose of that therapy might be necessary if

everolimus treatment increases lipid levels further.[54] Clinicians are also advised to investigate other potential causes of hyperlipidemia and, more important, to normalize serum triglyceride levels in their patients before initiating everolimus therapy.[54] The NCI task force guidelines take into account appropriate management goals that are predicated on life expectancy, with recommendations that patients with a life expectancy > 1 year should have target levels for low-density lipoprotein (LDL) cholesterol and triglycerides of < 190 mg/dL and < 300 mg/dL, respectively.[71] In patients with a life expectancy < 1 year, the target level for triglycerides should be < 500 mg/dL.[71] The task force also recommended that, in patients with triglyceride levels between 200 and 500 mg/dL, statin therapy to lower LDL cholesterol levels should be initiated because this lowers patient risk for cardiovascular events.[71] If LDL is at the target level, the panel recommended the addition of therapies to decrease triglyceride levels, such as fibrate therapy.[71] The task force also recommended that, in patients with diabetes or cardiovascular risks who receive everolimus therapy, strong consideration be given to managing hyperlipidemia.[71]

In addition to actively managing hyperlipidemia in patients, oncologists and their treatment teams are advised to educate patients on the need for therapeutic lifestyle changes that include diet.[71] Furthermore, the task force recommended that patients be encouraged to consume foods such that their saturated fat intake is < 7% of daily calories and cholesterol intake is < 200 mg/day.[71]

Hematologic Adverse Events

mTOR inhibitors have caused hematologic AEs; for example, use of sirolimus in transplant recipients has increased the risk for anemia, leukopenia, and thrombocytopenia.[77] Treatment with everolimus has increased the occurrence of hematologic AEs in patients in phase III trials; however, overall grade 3 or 4 events were infrequent (Table 1).[33, 42-46] To optimally treat patients receiving everolimus therapy, clinicians are advised to not only obtain a complete blood chemistry but also a hematology panel before initiating therapy with everolimus and, more important, to monitor the hematologic parameters periodically thereafter.[45]

Results from the BOLERO-2 trial in patients with advanced BC showed that 21% of patients treated with exemestane plus everolimus had anemia, with 7% and < 1% of patients experiencing grade 3 and 4 events, respectively.[33] Thrombocytopenia occurred in 12% of patients; however, grade 3 or 4 events were uncommon, with only 2% of grade 3 and 1% of grade 4 events.[32] Decrease in neutrophil count was observed in 31% of patients, with only 2% of patients experiencing grade 3 events. There were no grade 4 events.[45] Everolimus-associated decreases in lymphocyte count were observed in 54% of patients, with 11% and 0.6% of patients experiencing grade 3 and 4 events, respectively.[45]

Additional Considerations

Drug Interactions

In addition to AEs, and perhaps of growing equal importance, is the consideration for oncologists and their teams of the potential for a drug interaction between prescription

medications, over-the-counter medications, or dietary supplements and everolimus, as well as other novel biologics. Everolimus is a substrate of cytochrome P450 (CYP) 3A4, CYP3A5, CYP2C8, and multidrug efflux pump P-glycoprotein (PgP), and most of the metabolism of everolimus has occurred in the liver and gut.[45, 78] Everolimus is also a moderate inhibitor of PgP, a mixed inhibitor of CYP2D6, and a competitive inhibitor of CYP3A4.[45] Hence, drugs and dietary supplements metabolized or transported by the CYP family members or PgP are expected to cause drug-drug and drug-food interactions with everolimus.

Because of the potential for an interaction between everolimus and other drugs, clinicians are advised to avoid using strong CYP3A4 inhibitors such as ritonavir and ketoconazole or strong CYP3A4 inducers such as phenytoin and phenobarbital in patients receiving everolimus (Table 4).[45, 56] If patients require coadministration of a strong CYP3A4 inducer, clinicians might consider increasing the everolimus dose from 10 mg/day to 20 mg/day in 5-mg increments.[45, 56] While using moderate inhibitors of CYP3A4 or PgP such as erythromycin and verapamil, clinicians are advised to use caution, to lower the dose of everolimus by 50%, and to individualize subsequent doses.[45] Coadministration of everolimus with exemestane in the BOLERO-2 study increased the minimum concentration of exemestane by 45%; however, this did not increase the number of exemestane-related AEs.[45] Because grapefruit, Seville oranges and star fruits are inhibitors of CYP3A4 and PgP, clinicians are instructed to advise patients to avoid these fruits and their juices/extracts while taking everolimus.[45, 56] Therefore, a thorough review of the list of medications and supplements that patients may be taking before initiating

therapy with everolimus is advised. In addition, patients should be taught the critical importance of informing and obtaining clearance from the cancer management team regarding any therapies or supplements that they may begin during everolimus therapy.[56] Patients should also be advised of the need to inform their other health care professionals that they are receiving everolimus therapy, so the potential for a drug-drug or drug-food interaction can be minimized.[56]

Hepatic Impairment

The level of hepatic impairment can have a significant impact on the exposure levels of various drugs. Hence, it is important that clinicians assess, using specific tools, the presence and the level of hepatic impairment in patients before initiating therapy, so that AEs can be minimized. The Child-Pugh classification system is one such assessment tool that enables clinicians to follow the progression of hepatic impairment in patients with liver dysfunction.[79] Determining the score using the 5 clinical/biochemical indicators (Table 5)[79] allows clinicians to classify the disease as mild (class A), moderate (class B), or severe (class C) and adjust the dose of drugs appropriately.[79]

Results from a small study in patients with impaired hepatic function revealed that everolimus exposure was increased by 1.8-fold in patients classified as Child-Pugh class A, compared with subjects with normal hepatic function.[45] The same study also showed that everolimus exposure was 3.2-fold higher in those classified as Child-Pugh class B, while the exposure was 3.6-fold higher in those classified as Child-Pugh class C.[45] In another study, the average exposure of everolimus was determined to be twice as much in

subjects with hepatic impairment classified as Child-Pugh class B, compared with subjects with normal hepatic function.[45]

Because of the possibility of increased exposure of everolimus in patients with varying degrees of hepatic impairment, clinicians are advised to use everolimus at a dose of 7.5 mg/day in patients with Child-Pugh class A impairment.[45] In patients unable to tolerate this dose, the recommendation is to lower the dose to 5 mg/day.[45] In patients with Child-Pugh class B impairment, the recommended dose is 5 mg/day, and, in patients unable to tolerate this dose, the recommendation is to lower the dose to 2.5 mg/day.[45] In patients with Child-Pugh class C impairment, the recommended dose is 2.5 mg/day if the desired benefit outweighs the risk.[45] In patients with severe hepatic impairment, clinicians are strongly advised not to exceed the 2.5 mg/day dose.[45] It is also recommended that clinicians continuously monitor the hepatic status of the patient undergoing treatment and make appropriate dose adjustments.[45]

Renal Impairment

Pharmacokinetics studies have shown that only 5% of everolimus is renally excreted and, in a population-based study of 170 patients with advanced cancer, oral clearance of everolimus was not influenced by varying creatinine clearance (28–175 mL/min).[45] These observations suggest that everolimus excretion and drug exposure are not influenced by renal impairment. Hence, no dose adjustment of everolimus has been recommended in patients with renal impairment.[45] However, because elevations in serum creatinine and proteinuria levels have been observed in everolimus clinical trials, clinicians are advised

to monitor renal function with tests such as serum creatinine clearance, urinary protein, and blood urea nitrogen before initiating therapy with everolimus and periodically thereafter throughout treatment.[45]

Renal failure has also been observed in clinical trials with everolimus and, in BOLERO-2, renal failure was the cause of death of 1 patient in the exemestane plus everolimus arm.[32] Hence, oncologists and their treatment teams are instructed to advise patients about the risk for renal failure with everolimus therapy.[45] In addition to vigilantly monitoring patient renal function, it is critical that the team teach patients about the signs and symptoms of renal impairment, such as nausea and vomiting, itching, poor appetite, cramps, restless legs, and fluid retention (swollen ankles). Additionally, patients should be educated regarding the importance of informing the team promptly about such symptoms so AEs can be minimized.

Conclusions

Despite advances in screening, detection, and treatment, BC is a significant cause of death and disease in women. Several endocrine therapies, including AIs, SERMs, and SERDs, are used to treat patients with HR+ advanced BC; however, most patients with HR+ disease eventually become resistant to endocrine therapies. Everolimus, an mTOR inhibitor that blocks the PI3K/AKT/mTOR signaling cascade downstream of the ER, was recently shown to improve PFS when used in combination with exemestane in postmenopausal patients with HR+ HER2– advanced BC, leading to its approval by the US Food and Drug Administration. A clear understanding of the AEs associated with

everolimus therapy and an awareness of the strategies to effectively manage them is critical for successful treatment of patients whose disease progressed while receiving previous endocrine therapies. This knowledge will allow clinicians to take appropriate precautions to minimize everolimus-associated AEs in patients and, if AEs do occur, to manage them promptly and appropriately. Routine implementation of these strategies will also help preserve patient QOL, improve adherence to therapy, and maximize overall treatment outcomes.

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Table 1. Incidence of Key All-Grade Adverse Events and Abnormalities Reported With Everolimus Treatment in Oncology[32,33, 42-46]

Adverse Event, %	ABC[a] BOLERO-2[33, 45] (n = 485)	pNET[a] RADIANT-3 (n = 204)[42, 45]	mRCC[a] RECORD-1 (n = 269)[c,43, 45]	SEGA[b] EXIST-1 (n = 78)[44]	AML[a] EXIST-2 (n = 79)[46]
Stomatitis	59	53	40[d]	31	48
Infections	50[e,f]	23[g]	10[g]	72	65
Rash	39	49	25	12	NA
Noninfectious pneumonitis	16	12	8[h]	1	1
Laboratory Abnormalities					
Anemia	21	17	91	NA	13
Thrombocytopenia	12[i]	13	20	NA	19[e]
Neutrophils decreased	31[e]	30[e]	14[e]	NA	NA
Lymphocytes decreased	54[e]	45[e]	51[e]	NA	NA

Hyperglycemia	14	13	50	NA	NA
Cholesterol increased	70[e]	66[e]	77[e]	NA	NA
Triglycerides increased	50[e]	39[e]	73[e]	NA	NA

Abbreviations: ABC = advanced BC; AML = angiomyolipoma; BOLERO = Breast Cancer Trials of Oral Everolimus; EXIST = Examining Everolimus in a Study of TSC; mRCC = metastatic renal cell carcinoma; NA = data not available; pNET = pancreatic neuroendocrine tumor; RADIANT = RAD001 in Advanced Neuroendocrine Tumors; RECORD = Renal Cell Cancer Treatment With Oral RAD001 Given Daily; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

[a]10 mg/day dose of everolimus was administered in these trials.

[b]A starting dose of 4.5 mg/m² body surface area per day of everolimus was used in patients ≤ 65 years old with SEGA, and dose was subsequently adjusted to attain blood trough concentrations of 5 to 15 ng/mL.

[c] The n reported in the prescribing information (n = 274) is different than the results published (n = 269).

[d] Includes stomatitis, aphthous stomatitis, and mouth ulceration.

[e] Data reported are from the prescribing information.

[f] Includes all preferred terms within the “infections and infestations” system organ class, the most common being nasopharyngitis (10%), urinary tract infection (10%), upper respiratory tract infection (5%), pneumonia (4%), bronchitis (4%), cystitis (3%), sinusitis (3%), including candidiasis (< 1%), and sepsis (< 1%), and hepatitis C (< 1%).

[g] Includes all types of infections.

[h] Includes interstitial lung disease, lung infiltration, pneumonitis, pulmonary alveolar hemorrhage, and pulmonary toxicity.

[i] From Baselga et al.[32]

Table 2. Summary of Oral Steroid Mouth Rinse Options for the Prevention/Treatment of Mammalian Target of Rapamycin (mTOR) Inhibitor–Associated Stomatitis (mIAS)[52-54]

	Ingredients	**Schedule**
Oral steroid rinses	Dexamethasone 0.5 mg/5 mL	5–10 mL swished/held 4–5 minutes, spit out; repeat 3–6 times daily
	Clobetasol gel 0.05%	Apply to oral ulcers on a gauze pad, hold in place 5–10 minutes twice daily
	Prednisolone oral solution 15 mg/5 mL	5 mL twice daily (swish and spit)
Steroid-based mouthwash rinse[a] (also known as "miracle mouthwash" or "magic mouthwash")	320 mL of diphenhydramine oral solution 2 g of tetracycline powder 80 mg of hydrocortisone (four 20-mg tablets crushed and added to solution) 40 mL of nystatin suspension Dilute with water to 450 mL	Apply 10 mL solution 4 times a day (swish and spit)

[a]Several formulations of this mouthwash rinse are available; the formulation indicated here was successfully utilized in clinical experiences from a single center in the United States.[52]

Table 3. Everolimus Dose Adjustment and Management Recommendations for Adverse Reactions[45, 54, 56-59]

Adverse Event		Severity			
		Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Stomatitis	Definition	Minimal symptoms, normal diet	Symptomatic but can eat and swallow modified diet	Symptomatic and unable to eat and drink	Symptoms associated with life-threatening consequences
	Dose adjustment	None	Temporary dose interruption until recovery to grade ≤ 1, reinitiate at same dose If symptom recurs at grade 2, interrupt dose until recovery to grade ≤ 1, then reintroduce everolimus at lower dose	Temporary dose interruption until recovery to grade ≤ 1, reinitiate at a lower dose	Discontinue everolimus

	Management[a]	Nonalcoholic or 0.9% salt water mouthwash several times daily	Topical analgesic mouth treatments (eg, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids (ie, triamcinolone oral paste) Avoid agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives		Appropriate medical therapy
Noninfectious pneumonitis	Definition	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADLs	Symptomatic, interfering with ADLs; oxygen indicated	Life-threatening, ventilator support indicated
	Dose adjustment	None	Temporary dose interruption until recovery to grade ≤ 1, reinitiate at a lower dose Discontinue if patient does not recover within 4 weeks	Temporary dose interruption until recovery to grade ≤ 1, consider reinitiating at a lower dose If toxicity recurs at grade 3, consider	Everolimus discontinuation

				discontinuation	
	Management	Initiate appropriate monitoring	Rule out infection Consider corticosteroid treatment		
Infections	Definition	No infection	Localized infection	Systemic infection	Life-threatening
	Dose adjustment	None	Maintain dose if possible, or temporary dose interruption until recovery to grade ≤ 1, reinitiate at same dose If symptom recurs at grade 2, interrupt dose until symptoms subside to grade ≤ 1, then reintroduce everolimus at lower dose	Temporary dose interruption until recovery to grade ≤ 1 Consider reinitiating at a lower dose. If symptom recurs at grade 3, consider discontinuation	Discontinue everolimus
	Management	Initiate treatment with antibiotics as appropriate Perform culture and assess for atypical infection		Intravenous antibiotic, antifungal,[b] or antiviral	Appropriate standard therapy, as for

		In patients who test positive for hepatitis B surface antigen, consider prophylaxis with entecavir or tenofovir		therapy; additional interventions as for grade 1	grades 1–3
Rash	Definition	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% of BSA	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering ≥ 50% BSA	Generalized exfoliative, ulcerative, or bullous dermatitis
	Dose adjustment	None	Maintain dose if possible, or temporary dose interruption until recovery to grade ≤ 1, reinitiate at same dose If symptom recurs,	Temporary dose interruption until recovery to grade ≤ 1, Consider reinitiating at a lower dose. If symptom recurs at grade	Discontinue everolimus

			interrupt dose until symptoms subside, then reintroduce everolimus at lower dose	3, consider discontinuation	
	Management	Mild lesions might resolve spontaneously; no specific therapy is recommended	Use topical treatment initially with product containing benzoyl peroxide and antibiotic		
Hyperglycemia	Definition	> ULN–160 mg/dL	> 160–250 mg/dL	> 250–500 mg/dL	> 500 mg/dL
	Dose adjustment	None	None	Temporary dose interruption; reinitiate at a lower dose	Discontinue everolimus
	Management	None	Manage with appropriate medical therapy and monitor		Treat with appropriate medical therapy

Hyperlipidemia	Definition	HCE: > ULN–300 mg/dL HT: > ULN–2.5 × ULN	HCE: > 300–400 mg/dL HT: > 2.5–5.0 × ULN	HCE: > 400–500 mg/dL HT: > 5.0–10 × ULN	HCE: > 500 mg/dL HT: > 10 × ULN
	Dose adjustment	None	None	Temporary dose interruption; reinitiate at a lower dose	Discontinue everolimus
	Management		Manage with appropriate medical therapy and monitor		Treat with appropriate medical therapy[c]

Abbreviations: ADA = American Diabetes Association; ADL = activity of daily living; BSA = body surface area; HCE = hypercholesterolemia; HT = hypertriglyceridemia; ULN = upper limit of normal.

[a] Antifungals should not be used unless fungal infection has been diagnosed.

[b] If diagnosis of invasive systemic fungal infection is made, everolimus therapy should be promptly discontinued. Avoid coadministration of everolimus with strong cytochrome P450 3A4 inhibitors.

[c] Triglyceride level ≥ 500 mg/dL: increased risk for pancreatitis; treat promptly with fibrates

Table 4. Notable Drug-Drug Interactions With Everolimus[45, 56]

	Everolimus
CYP3A4 inhibitors (increase plasma levels of everolimus)	Avoid use of strong inhibitors, and consider reducing the dose of everolimus to 2.5 mg/day for coadministration with moderate inhibitors
Antibiotics: erythromycin, clarithromycin, telithromycin	
Antidepressant: nefazodone	
Antiemetic: aprepitant	
Antifungals: fluconazole, ketoconazole, itraconazole, voriconazole	
Calcium channel blockers: diltiazem, verapamil	
Human immunodeficiency virus protease inhibitors: amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir	
Other: delavirdine, grapefruit Seville oranges, star fruit	
CYP3A4 inducers (decrease plasma levels of everolimus)	Avoid use of strong inducers when possible, or consider increasing the everolimus dose from 10 mg/day to 20 mg/day in 5-mg increments
Antibiotics: rifampin, rifapentine, rifabutin	
Anticonvulsants: phenytoin, carbamazepine, phenobarbital	
Steroid hormone: dexamethasone	
Other: St John's wort	

Table 5. Child-Pugh Classification and Scoring of the Severity of Liver Disease[79]

Clinical/Biochemical Indicator	*1 Point*	*2 Points*	*3 Points*
Serum bilirubin, mg/dL	< 2	2–3	> 3
Serum albumin, g/dL	> 3.5	2.8–3.5	< 2.8
Prothrombin time, s > control	< 4	4-6	> 6
Encephalopathy, grade	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate

Points are summed, and the total score is classified according to severity as follows: 5–6 points = group A (mild), 7–9 points = group B (moderate), 10–15 points = group C (severe).

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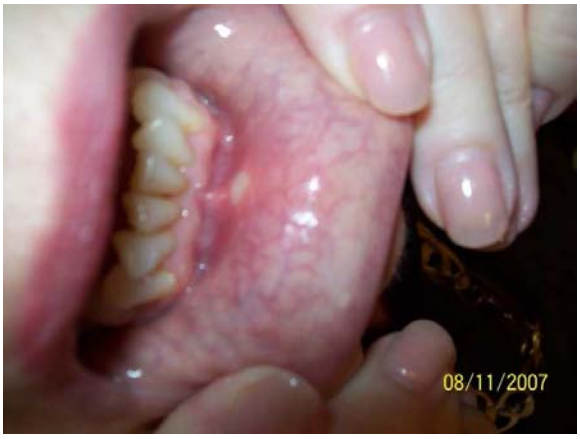
Figure 1. Depiction of everolimus-induced adverse events. (A) Stomatitis. (B) Noninfectious pneumonitis.

A



B