Updates in the Use of the mTOR Inhibitor Everolimus in Advanced Breast Cancer

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Abstract

The inhibitors of mammalian target or rapamycin (mTOR) exhibit antitumor activity via disruption of various signaling pathways and have shown activity when used in combination with hormonal therapy in breast cancer. A review of the role of the efficacy and management of adverse effects of everolimus in combination with exemestane in advanced breast cancer was previously reported by Ng and colleagues. The purpose of this review is to provide an update on the efficacy and safety of everolimus in advanced breast cancer, as well as explore the prognostic role of biomarkers. Since 2012, there has been an update on the efficacy of BOLERO-2 as well as an examination of biomarkers. Additionally, everolimus has been investigated in other settings for advanced breast cancer. An update on the adverse effect profile and management of stomatitis associated with everolimus is also provided.

Introduction

Breast cancer is the most common cancer in women in the US, with approximately 85% of breast cancers being hormone positive (HR+), and 20% being HER2+ [1,2]. Prior to 2012, there were limited options for women diagnosed with HR+ advanced breast cancers. Hormonal options included aromatase inhibitors and fulvestrant. The approval of everolimus in combination with exemestane introduced a novel mechanism of action to overcome anti-hormone therapy resistance, and demonstrated efficacy in the second line setting. This approval was based on the Breast cancer trials of Oral EveROlimus-2 (BOLERO-2) trial, which showed that the addition of everolimus to exemestane doubled progression free survival in pre-treated HR+, HER2-breast cancer patients. Additionally, since the publication of BOLERO-2 in 2012, the concept of predictive biomarkers has come into play, both in the setting of HR+ and HER2+ advanced breast cancers.

The effect of everolimus is mediated through its inhibition of mammalian target of rapamycin (mTOR), a serine-threonine protein kinase that mediates cell growth, proliferation, differentiation, and angiogenesis via multiple signaling transduction pathways [3]. Two complexes of mTOR, mTORC1 and mTORC2 exist. Upstream of this pathway, phosphatidylinositol 3-kinase (PI3K) and protein kinase b (AKT) regulate the activity of mTORC1. In breast cancer, the PI3K/Akt/mTOR signal transduction cascade is active and associated with tumor progression and resistance to estrogen receptor therapy. Everolimus binds intracellular FK506 protein 12 (FKBP12) receptors and allosterically inhibits mTORC1, thereby disrupting downstream phosphorylation and leading to cell cycle arrest and tumor suppression. Everolimus is thought to be specifically helpful in hormone resistant breast cancer, because there is signaling independent of the estrogen receptor pathway driving resistance. The introduction of everolimus is thought to overcome resistance [4]. The mTOR pathway is also implicated in other cancers. Everolimus is also approved for the treatment of advanced renal cell carcinoma, advanced neuroendocrine tumors of pancreatic origin (NET), and subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) [5].

Update of Efficacy

Update on overall survival: BOLERO-2

The role of everolimus in HR+ advanced breast cancer was previously reported in BOLERO-2 [6]. The study compared exemestane 25 mg/day in combination with everolimus 10 mg/day or exemestane 25 mg/day alone as second-line therapy in 724 post-menopausal women with HR+, HER2-breast cancer who had progressed on prior non-steroidal aromatase inhibitor (AI) therapy. The patients in this study were heavily pre-treated, with approximately 50% of the patients having three or more prior therapies, 30% having 2 and about 20% having 1 prior therapy. The patients also had heavy disease burden, with 56% having visceral involvement. Despite the burden of disease and exposure to multiple lines of therapy, adding everolimus to exemestane improved PFS twofold. Median progression free survival (PFS) was 6.9 months with everolimus plus exemestane *vs* 2.8 months with exemestane alone (HR 0.43, 95% CI 0.35-0.54). At this time, the standard PFS for regimens without chemotherapy was 3 months; therefore this represented a clinically significant benefit [2]. It is especially important for patients in whom we want to avoid traditional chemotherapy.

The original BOLERO-2 publication did not include overall survival (OS); however, an update in 2014 in the Annals of Oncology provided the OS results [7]. Unfortunately, although we anticipated to see a statistically significant OS benefit, given the impressive PFS benefit, the 4 month OS benefit provided by adding everolimus to exemestane was not statistically significant (31 months with everolimus plus exemestane *vs* 26.6 months with exemestane alone, p=0.14). Examining the trial design, there are several reasons that could explain why the OS benefit was not statistically significant. The study was

aggressively powered based on an 8 month survival advantage despite the fact that most second-line treatments are associated with a 4-5 month survival advantage [2]. Additionally, as often happens in advanced breast cancer, patients in both groups went on to receive post-study treatments (84% in the everolimus plus exemestane group *vs* 90% in the exemestane alone group), with more patients in the exemestane alone group receiving chemotherapy compared to patients who had received everolimus. (53% in everolimus plus exemestane arm *vs* 63% in exemestane alone arm) [7]. Despite the disappointing OS results, everolimus is still an important option in patients with HR+ advanced breast cancer in whom we want to spare chemotherapy, and is category 2a in the 2016 NCCN Breast Cancer guidelines [2].

Additionally, current endocrine therapies, including monotherapy endocrine agents such as fulvestrant and exemestane for HR+ advanced breast cancer lack overall survival data. The CONFIRM trial randomized patients with HR+ advanced breast cancer who had progressed on an antiestrogen or an AI to fulvestrant 500 mg IM day 0, 14, and 28 every 28 days *vs* 250 mg IM every 28 days [8]. A follow-up found that there was a 4.1 month OS advantage with fulvestrant 500 mg (26.4 mos for fulvestrant 500 mg *vs* 22.3 mos for fulvestrant 250 mg; p=0.02). However, as in the BOLERO-2 study, the 4 month OS difference was not statistically significant [9]. Exemestane was investigated in the EFECT study, which compared exemestane 25 mg daily with fulvestrant 500 mg day 1 followed by 250 mg on days 14 and 28 every 28 days in patients with HR+ advanced breast cancer that had progressed on a nonsteroidal AI. This study found no significant difference in time to progression, overall response rate, clinical benefit rate, and median duration of clinical benefit. OS was not analysed [9]. Most recently, the PALOMA 3 trial explored the addition of palbociclib to fulvestrant in patients with HR+ advanced breast cancer that had progressed on prior endocrine therapy. Postmenopausal women were required to have progressed on AI therapy, and premenopausal women were required to have progressed on tamoxifen. The combination of palbociclib and fulvestrant was associated with a longer PFS (9.2 *vs* 3.8 mos, p<0.001), but OS is not yet available [10]. We await the follow-up of PALOMA 3 to reveal whether the addition of palbociclib will provide OS benefit.

Given the available data, combination therapy consisting of endocrine therapy and novel agent is associated with a better PFS than monotherapy endocrine therapies. While the choice of therapy remains chemotherapy for patients with symptomatic visceral disease, for patients with non-symptomatic visceral disease, delaying chemotherapy is an option. A combination of endocrine therapy and a novel agent is an attractive option for patients with non-symptomatic visceral disease. With the lack of OS data and head-to-head trials with these novel combinations we must use the toxicity profiles to select the best agent for patients. For example, palbociclib is associated with hematologic toxicities, while stomatitis is a dose-limiting toxicity of everolimus. Access to pharmaceuticals from a financial standpoint may also guide these decisions. Additionally, exposure to previous therapies will guide future therapies.

Potential predictive value of ESR1 mutations in BOLERO-2

Another update in BOLERO-2 was to investigate the use of estrogen receptor mutations as indicators of prognosis [11]. Mutations in the ligand-binding domain of the estrogen receptor have been linked to breast cancers resistant to anti-hormonal agents. The mutation causes a ligand-free constitutively activated receptor, and also allows for estrogen receptor gene activation and further growth of the tumor [12].

A retrospective post-hoc analysis of BOLERO-2 identified mutations in the estrogen receptor 1 gene (ESR1) in 28.8% of patients [13]. Two mutations in particular, D538G and Y537S, may be a negative prognostic factor. The post-hoc analysis found that the median overall survival was reduced in patients with one or more mutation (median OS 26 mos D538G, 20 mos Y537S, 15.2 mos both mutations). Interestingly, patients with D538G mutation still derived a benefit from the addition of exemestane (PFS 8.5 mos for WT *vs* 5.8 mos for D538G mutation), however, patients with Y537S mutation did not derived a PFS benefit (median PFS 4.2 mos). The value of these mutations in regards to its implications on second-line treatment is still being investigated. Currently, there is an ongoing trial to determine the frequency and onset of ESR1 mutations in patients with metastatic breast cancer who are on AI treatment [14]. Additionally, the PETREMAC trial is investigating utilizing multiple gene mutations, including ESR1 to provide personalized therapy for patients [15]. Enhanced knowledge of the role of ESR1 and its implications on therapy selection will help guide us as we move further into the realm of personalized medicine.

Efficacy of second-line everolimus monotherapy in HR+ HER2- advanced breast cancer: BOLERO-6

Based on the knowledge that mTOR inhibition can provide overcome resistance to anti-hormone therapy and success in BOLERO-2, everolimus is being investigated as second-line monotherapy in HR+ HER2-advanced breast cancer who have progressed on a prior AI in BOLERO-6 [16]. In this ongoing study, which includes an oral chemotherapy arm, 300 patients will be randomized to everolimus 10 mg/day plus exemestane 25 mg/day combination therapy, or everolimus 10 mg/day alone, or capecitabine 1250 mg/m^2 twice daily for 14 days of a 3-week cycle alone. The primary endpoint is PFS with everolimus plus exemestane *vs* everolimus monotherapy. The secondary endpoints include PFS compared to capecitabine monotherapy, OS, quality of life, and patient satisfaction with treatment. It will be interesting to see the results of this study, particularly in regards to the tolerability of the capecitabine dose, as it is more aggressive than we typically use in practice.

Efficacy of everolimus plus letrozole for first line ER+ HER2- breast cancer: BOLERO-4

Due to promise of everolimus in the second line setting via its provision of efficacy and a tolerable chemotherapy-free regimen, BOLERO-4 investigates the use of everolimus in the first-line setting [17]. BOLERO-4 is an ongoing phase II study of everolimus plus letrozole in first-line therapy in ER+ HER2-metastatic breast cancer. The study is also investigating the potential benefits of continuing this therapy beyond progression. In this single-arm study, 200 postmenopausal women with ER+HER2-metastatic or locally advanced breast cancer without prior therapy for advanced disease will receive everolimus 10 mg/day and letrozole 2.5 mg daily until first disease progression. Upon disease progression patients who continue the trial will receive everolimus 10 mg/day with exemestane 25 mg/day until further disease progression. The primary endpoint is PFS in the first line setting, with a secondary endpoint of PFS in the second-line setting.

Efficacy of everolimus in HER2+ advanced breast cancer

In addition to providing benefit in HR+ advanced breast cancer, mTOR inhibitors have demonstrated activity in breast cancer that may have resistance to targeted therapies such as trastuzumab [18]. Two studies have investigated the use of everolimus in HER2+ advanced breast cancer: BOLERO-1 and BOLERO-3. Once again, as in HR+ advanced breast cancer, we see that biomarkers could be useful in predicting response to everolimus-containing regimens.

Efficacy of everolimus for recurrent HER2+ breast cancer: BOLERO-3

Resistance in both HR+ and HER2+ breast cancer can be mediated via hyperactivation of the PI3K/AKT/mTOR intracellular pathway [19,20]. Resistance to anti-HER2+ therapies has been associated with the loss of PTEN, a tumor suppressor gene. Loss of PTEN results in activation of mTOR, which regulates transcription and translation of proteins including 40S ribosomal protein S6, allowing progression of breast cancer independently of estrogen and HER2. Trastuzumab resistance may be reversed by mTOR inhibition. Based on this theory, the benefit of everolimus in patients who have progressed on trastuzumab was investigated in the BOLERO-3 study [21]. This was a phase 3 trial that randomized 569 women with HER2+, trastuzumab-resistant, advanced breast cancer who had previously received taxane therapy. Trastuzumab resistance was defined as recurrence during or within 12 months of adjuvant treatment or progression during or within 4 weeks of treatment for advance disease. Patients were randomized to receive everolimus 5mg/day or placebo in combination with trastuzumab 4 mg/kg loading dose cycle 1, followed by 2 mg/kg/week and vinorelbine 25 mg/m^2 every 3 weeks. Of note, the dose of everolimus is lower than the approved dose of 10 mg based on BOLERO-2, however, the dose of 5 mg was based on a phase 1b dose-escalation study of everolimus in combination with trastuzumab and vinorelbine in HER2+ pre-treated patients by Jerusalem and colleagues [22]. Similar to BOLERO-2, this study enrolled heavily pre-treated patients, with the mean total previous regimens in the metastatic setting being 3.4, including prior trastuzumab-containing regimens. Unlike other randomized trials in the setting of trastuzumab resistance, patients in BOLERO-3 could have previously received lapatinib. Patients had a heavy disease burden, with 75% of patients in each group having visceral disease. Again, as in BOLERO-2, despite the heavily pre-treated population, everolimus did provide PFS benefit, albeit not as impressive as in BOLERO-2. In BOLERO-3, median PFS was approximately 1 month longer in the everolimus group (7 mos with everolimus + trastuzumab+ vinorelbine vs 5.78 mos with placebo + trastuzumab + vinorelbine p=0.0067). Separation of the Kaplan Meier curves occurred early in treatment, suggesting potential reversal of trastuzumab resistance. Interestingly, a subset analysis showed a significant improvement in PFS in patients with HR- cancers but not with HR+ cancers. We do have evidence that there is communication between the ER and HER2 pathways that allows ER to act as an escape pathway when HER2 is blocked and ER is left available [23]. In terms of comparison of benefit to other trials, median PFS in other trials of trastuzumab-resistance advanced breast cancer ranged from 8.1 to 15.3 weeks for lapatinib and 4.6 to 14.2 months for trastuzumab emtansine [2]. The additional PFS benefit in the BOLERO-3 trial must be weighed against increased toxicity. The rates of grade 3-4 adverse events including neutropenia (73% vs 62%), stomatitis (13% vs 0%), anemia (19% vs 7%), leucopenia (38% vs 29%), fatigue (13% vs 4%), and febrile neutropenia (16% vs 3%) were greater in the group of patients receiving everolimus, and the ability to maintain dose intensity in the group of patients receiving everolimus was lower (0.64 vs 0.73). Surprisingly, there was an increase in hematologic toxicity with the addition of everolimus. In this regimen, hematologic toxicity is most associated with vinorelbine. It has been hypothesized that a drug-drug interaction via competition for CYP3A4 between everolimus and vinorelbine, leading to an increased exposure to the drugs, may be responsible for this increased toxicity; however, pharmacokinetic data does not support this [24,25]. Thus far, this regimen has not been incorporated into NCCN, and therefore it is unlikely that insurance companies will pay for everolimus off-label, particularly in light of the existence of other, less toxic options.

Efficacy of everolimus as first-line treatment for HER2+ advanced breast cancer: BOLERO-1

The efficacy of everolimus was also explored as first-line treatment for HER2+ advanced breast cancer in the BOLERO-1 study [26]. This study was a phase III trial that randomized 719 patients to everolimus 10 mg/day or placebo, in combination with weekly trastuzumab 4 mg/kg loading dose day 1 with subsequent weekly doses of 2 mg/kg plus paclitaxel 80 mg/m^2 intravenously on days 1, 8, and 15 of a 28 day cycle. Median follow-up was 41.3 months. Unfortunately, in the overall population, the addition of everolimus did not add a statistically significant benefit in terms of median PFS (14.95 months with everolimus group vs 14.49 months with trastuzumab and paclitaxel alone, p=0.1166). However, as in the BOLERO-3 study, HR- patients tended to have more benefit, with a PFS of 20.27 vs 13.08 mos (p=0.0049), however, this did not quite meet the pre-defined statistical significance for the study (p=0.0044). Nonetheless, the benefit seen in HR- patients may warrant further study. Currently, NCCN recommends trastuzumab, pertuzumab, and docetaxel per the CLEOPATRA trial in the first line due to superior efficacy data which is unmatched by this regimen [2,27]. A summary of the BOLERO trials can be found in Table 1.

Trial	Population	Interventions	Efficacy	Safety	Pearls
BOLERO-2 [7,27]	HR+, HER2- advanced breast cancer, progressed on non-steroidal AI therapy	Exemestane 25 mg/day + everolimus 10 mg/day vs exemestane 25 mg daily alone	PFS 6.9 mos with everolimus + exemestane vs 2.8 mos exemestane alone (HR 0.43, 95% CI 0.35-0.54) OS 31 mos everolimus + exemestane vs 26.6	Most common grade ¾ AEs with addition of everolimus stomatitis, anemia, dyspnea, fatigue, pneumonitis	Power based on 8 months survival advantage; patients in both groups received post-study treatments FDA approved for second line treatment of HR+, HER2- advanced breast cancer in combination with exemestane

			mos exemestane alone, p=0.14		
BOLERO-1 [26]	HER2+ advanced breast cancer, have not received trastuzumab	Trastuzumab 4 mg/kg load, then 2 mg/kg/week + paclitaxel 80 mg/m^2 D1, 8, 15 + everolimus 10 mg daily *vs* trastuzumab 4 mg/kg load, then 2 mg/kg/week + paclitaxel 80 mg/m^2 D1, 8, 15 + placebo	PFS 14.95 mos in everolimus group *vs* 14.49 mos, p=0.116	Dose interruption in 86% of everolimus *vs* 74%; stomatitis, diarrhea, alopecia more common in everolimus group	More benefit in HR-patients, PFS 20.27 mos with everolimus *vs* 13.08 mos; p=0.027 Not FDA approved for HER2+ advanced breast cancer
BOLERO-3 [21]	HER2+, trastuzumab-resistant advance breast cancer, previous taxane therapy	Trastuzumab 4 mg/kg load then 2 mg/kg/week + vinorelbine 25 mg/m^2 q 3 weeks + everolimus 5 mg/kg/day *vs* trastuzumab 4 mg/kg load then 2 mg/kg/week + vinorelbine 25 mg/m^2 q 3 weeks	PFS 7 mos with everolimus + trastuzumab + vinorelbine *vs* 5.78 mos placebo + trastuzumab + vinorelbine; p=0.0067	Grade ¾ toxicities higher in everolimus group neutropenia, stomatitis, anemia, leucopenia, fatigue, febrile neutropenia	Patients could have previously received lapatinib Subset analysis showed significant improvement in PFS in patients with HR- cancers but not HR+ cancers Not FDA approved for HER2+ advanced breast cancer
BOLERO-4 (ongoing) [17]	ER+, HER2- advanced breast cancer without prior therapy	Everolimus 10 mg/day + letrozole 2.5 mg/day; followed by everolimus 10 mg/day + exemestane 25 mg/day upon progression	Primary endpoint PFS	N/A	Not FDA approved for ER+, HER2- as first line treatment
BOLERO-6 (ongoing) [16]	HR+, HER2- advanced breast cancer, have progressed on prior AI	Everolimus 10 mg/day + exemestane 25 mg/day *vs* everolimus 10 mg/day alone *vs* capecitabine 1250 mg/m^2 BID x 14 days of 21 day cycle	Primary endpoint PFS	N/A	FDA approved for second line treatment of HR+, HER2- advanced breast cancer in combination with exemestane

Table 1: BOLERO Trials of Everolimus in Advanced Breast Cancer

Prognostic value of biomarkers of hyperactive PI3K pathway

Similar to BOLERO-2, an investigation of the predictive value of biomarkers was also performed for the BOLERO-1 and BOLERO-3 trials [28]. Five hundred and sixty-one archival tumor samples were analyzed for hyperactive PI3K pathway, which was defined as low PTEN or known PIK3CA or AKT1 E17K mutation. In 45% of the samples, there were PI3K pathway gene alterations identified. A trend toward greater benefit from everolimus was observed in patients with PI3K pathway activation in each individual trial. In the combined analysis from both trials, patients with PIK3CA mutations or low PTEN derived more benefit from everolimus, and a multivariate analysis showed that the interaction between PI3K status and treatment effect was statistically significant (p=0.016). Thus far, this is an area of exploration limited to clinical trials which needs to be continued to be investigated.

Update on Toxicities

Stomatitis

Stomatitis is a well-known adverse effect of everolimus [1]. In contrast to chemotherapy-induced stomatitis, the clinical presentation of mTOR associated stomatitis is characterized by superficial, well-demarcated, erythematous, and ulcerative painful lesions which are similar to apthous ulcers or canker sores limited to the oral cavity. Oral lesions typically occur within 1 month of everolimus initiation, and can occur as early as two weeks into treatment, with the median onset in BOLERO-2 being 15 days [29]. Stomatitis can occur further out into treatment as well. This adverse effect is thought to be a reversible, dose-dependent reaction mediated by T cells; therefore dose reduction, treatment interruption, and the use of high potency topical corticosteroids are used to manage the toxicity.

The majority of patients on everolimus will experience stomatitis. In BOLERO-2, 64% of patients in the everolimus plus exemestane developed stomatitis, with 8% developing grade 3 stomatitis [6]. The everolimus dose was reduced for 34% of patients in BOLERO-2 [29].

In terms of the onset of stomatitis, in BOLERO-2, more than one-third of all stomatitis events grade ≥ 2 occurred in the first 2 weeks of therapy, corresponding with a cumulative risk of 14%. The cumulative risk of stomatitis was 26% at 6 weeks and 37% at 48 weeks. For the patients who had grade ≥ 3 stomatitis, 97% experienced resolution to grade ≤ 1 following dose interruption and/or reduction after a median of 3.1 weeks and 82% had compete resolution after a median of 7.4 weeks. Overall a minimal number of patients experienced stomatitis that led to discontinuation of everolimus, with 2.7% of patients discontinuing in BOLERO-2, and 0.8% of these patients having grade 3 /4 stomatitis.

Currently, the recommendations for the prevention and management of stomatitis include prophylactic mouth rinses, and treatment via dose interruption and topical nonsteroidal anti-inflammatory paste [5]. The prophylactic mouth rinses recommended include a baking soda/ salt mouth rinse, and a miracle mouthwash composed of diphenhydramine, tetracycline, hydrocortisone, nystatin, and water as per the experience at Texas Oncology-Baylor Charles A. Sammons Cancer Center [30]. Treatment and management of stomatitis once it occurs is dependent on the severity [5]. Per the package insert, for grade 1, conservative measures such as non-alcoholic, salt water, baking soda/salt or miracle mouthwash should be used. Starting at grade 2, the dose of everolimus is interrupted until resolution to grade ≤ 1, in conjunction with topical analgesic mouth treatments with or without topical corticosteroids. For grade 3, the package insert recommends a topical nonsteroidal anti-inflammatory paste (Amlexanox 5%) in addition to interrupting therapy. For recurrent grade 2 or grade 3 toxicity, everolimus should be re-initiated at a lower dose. Everolimus should be discontinued for grade 4 stomatitis.

Given the high rates of stomatitis in the patient population treated with everolimus, there are several ongoing trials investigating the use of prophylactic mouthwashes. Because everolimus-associated stomatitis is believed to be T-cell mediated, steroids are the backbone of prophylactic mouthwashes. Studies have shown preliminary success with the use of prophylactic mouthwashes. The results of a phase II trial of miracle mouthwash plus hydrocortisone versus prednisolone mouth rinses as prophylaxis for everolimus-associated stomatitis were presented at the 2015 San Antonio Breast Cancer Symposium [31]. In this study, patients with HR+ metastatic breast cancer who were receiving an AI plus everolimus 10 mg/day were randomized to either miracle mouthwash (320 mL oral diphenhydramine, 2 grams tetracycline, 80 mg hydrocortisone, 40 mL nystatin suspension in water) or prednisolone 15 mg/5mL solution. Patients swished and expectorated 10 mL of the rinse four times daily starting on day 1 of everolimus treatment for 12 weeks. At interim analysis, 17% of patients developed grade 1 stomatitis, 8% developed grade 2, and there were no grade 3 events. The mouthwashes were well tolerated, with only one patient thus far developing oral candidiasis while on the steroid mouth rinse. Another trial is currently underway to explore the utility of steroid containing prophylactic mouthwashes as well [32]. This phase II study is comparing the incidence of stomatitis in patients using prophylactic steroid mouthwash (alcohol-free dexamethasone 0.5 mg/5mL) with BOLERO-2 historical controls in postmenopausal women with advanced or metastatic HR+ breast cancer.

The prevention of stomatitis is also being incorporated into trials of efficacy for everolimus. In the BOLERO-4 trial, one of the secondary objectives of the study is to assess the efficacy of oral dexamethasone solution in reducing the severity and/or duration of stomatitis as assessed using the Oral Stomatitis Daily Questionnaire (ODMQ) [17]. Given the preliminary data presented at the 2015 San Antonio Breast Cancer Symposium, it is expected that this steroid-based prophylactic mouth rinse will reduce the incidence of stomatitis in comparison to BOLERO-2.

Label update: angioedema

Since the approval of everolimus in 2012, there has been a warning added to the labeling for angioedema with concomitant use of angiotensin-converting enzyme inhibitors [5]. This warning stemmed from the results of a pooled analysis of randomized double-blind oncology clinical trials. The results of this analysis found that the incidence of angioedema in patients taking everolimus with an ACE inhibitor was greater than the control arm with an ACE inhibitor (6.8% vs 1.3%). This prompted the addition of this warning to the everolimus labeling. The package insert does not recommend against the concomitant use of these agents. In clinical practice, medication reconciliation should be done, and patients on concomitant ACE inhibitors should be counseled on this risk. Alternatively, patients may be switched to an angiotensin receptor blocker. The mechanism of this interaction is not well defined, but it has been described in solid organ transplant patients concomitantly receiving an ACE inhibitor and an mTOR inhibitor [33]. The mechanism of the interaction may be mediated through an increase in the propensity of ACE inhibitors to cause an increase in bradykinin, via inhibition of bradykinin breakdown. Increased levels of bradykinin may cause vasodilation, increased tissue permeability and edema.

Conclusion

In our constant quest to discover novel agents to overcome resistance in cancer, targeting the mTOR pathway has shown success in several cancers, including breast cancer. Thus far, everolimus has demonstrated efficacy in the second line treatment of HR+ advanced breast cancer. Currently, everolimus has a limited role in the treatment of HER2+ advanced breast cancer; however, this role could evolve if studies select HR- populations in an attempt to confirm the benefits seen in this population in BOLERO-3 and BOLERO-1. In line with the movement toward biomarker-based, patient-specific therapy, there is preliminary data to support that mutations in the estrogen receptor as well as hyperactivity of the PI3K pathway may have a prognostic role that has yet to be defined. Advancing knowledge of prognostic biomarkers will continue to shape the exploration and development of novel targeted therapies to overcome resistance and identify the subset of patients who will likely benefit from everolimus therapy. While everolimus can be used as part of a more tolerable chemotherapy – sparing regimen, the incidence of stomatitis is high, and investigations of prophylactic steroid-containing mouthwashes are underway. As we await the results of these trials, there are other novel mTOR inhibitors, PI3K inhibitors, and dual mTOR/ PI3K kinase inhibitors in development, which will continue to reshape the ever-changing landscape of treatment of advanced breast cancer.

Conflicts of Interest

Dr. Cuellar is on the speaker bureau for Novartis Oncology.

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