Dosing and Safety Implications for Oncologists When Administering Everolimus to Patients With Hormone Receptor-Positive Breast Cancer

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Abstract

Aberrations in the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin pathway are common abnormalities in breast cancer and are associated with the development of resistance to endocrine- and human epidermal growth factor receptor (HER)2-targeted therapies. Because of the significant improvement in progression-free survival for everolimus plus exemestane compared with exemestane plus placebo, everolimus, an mTOR inhibitor, was approved in the United States for the treatment of patients with hormone receptor-positive (HR+), HER-negative, advanced breast cancer whose disease had progressed while receiving letrozole or anastrozole. To provide optimal prevention and management strategies, it is crucial that clinicians are aware of the adverse events (AEs) associated with mTOR inhibition. Understanding the appropriate dose modifications will help reduce toxicity and improve drug tolerance, thus achieving the optimal benefit from everolimus. Analyses of data from the Breast Cancer Trials of Oral Everolimus 2 trial have shown that, despite a greater frequency of AEs in the everolimus plus exemestane treatment arm, the AEs were effectively managed with temporary dose reductions or interruptions. In some cases, the full dose of everolimus could be resumed. Despite a lower mean dose and duration of exposure in patients aged ≥ 70 versus < 70 years, everolimus plus exemestane was similarly efficacious, suggesting that appropriate dose reductions for toxicity will not adversely impact efficacy. Appropriate modification of the everolimus dose and dose delay according to the severity of AEs, with resumption of the optimal dose of everolimus when toxicity has improved, will positively affect patient outcomes in HR+ advanced breast cancer.

Clinical Breast Cancer, Vol. 16, No. 1, 18-22

Keywords: Exemestane, Hormone receptor positive advanced breast cancer, mTOR inhibition, Pneumonitis, Stomatitis

Introduction

Breast cancer is the second most common cancer (age-standardized incidence rate, 76.0 per 100,000) and the second-leading cause of cancer-related death (age-standardized mortality rate, 14.7 per 100,000) among US adults.[1] In the United States in 2015, > 230,000 women will have been diagnosed with breast cancer and approximately 40,000 will have died of their disease.[2] Approximately 60% to 75% of patients with invasive breast cancer have hormone receptor-positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative disease.[3,4] These cancers are commonly managed with endocrine therapies such as aromatase inhibitors (eg, anastrozole, letrozole, and exemestane), selective estrogen receptor modulators (eg, tamoxifen and toremifene), and, in the advanced setting, the estrogen receptor downregulator fulvestrant.[5]

Aberrations in the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway are common in breast cancer,[6-9] with activating mutations in PIK3CA present in one quarter to one half of HR+ breast tumors.[7,8] Current data suggest that the frequency of abnormalities in this pathway is more common in metastatic than in primary tumors.[10] Also, increased signaling through this pathway has been associated with resistance to endocrine and HER2-targeted therapies.[11-14] Thus, targeting the PI3K/AKT/mTOR pathway is an appealing treatment strategy.

Several mTOR inhibitors have been investigated as antitumor therapies, with 2 agents (everolimus and temsirolimus) currently approved by the US Food and Drug Administration (FDA) for the treatment of various cancers.[15,16] Upstream pathway inhibitors

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Submitted: Jun 16, 2015; Accepted: Sep 11, 2015; Epub: Sep 29, 2015

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targeting PI3K are under evaluation, with several now being tested in the clinic.[17] The cyclin-dependent kinase (CDK) 4/6 inhibitor palbociclib, which targets the cell cycle, recently received accelerated FDA approval for the treatment of HR+ advanced breast cancer combined with letrozole based on the results of a recent phase II study, which demonstrated a significant improvement in progression-free survival (PFS) with this combination.[18] Agents targeting other pathways and other CDK 4/6 inhibitors are under investigation in breast cancer clinical trials in combination with hormone therapies.[19]

Everolimus is the only mTOR inhibitor indicated with approval for use combined with exemestane for the treatment of patients with HR+ HER2− advanced breast cancer whose disease has progressed during treatment with letrozole or anastrozole.[15] This approval was based on the results from interim and final analyses of the robust phase III Breast Cancer Trials of Oral Everolimus 2 (BOLERO-2) study in which everolimus plus exemestane was associated with a significant improvement in investigator-determined PFS (primary endpoint) compared with exemestane plus placebo in postmenopausal women with HR+ advanced breast cancer who had experienced recurrence or progression during or soon after nonsteroidal aromatase inhibitor (NSAI) therapy.[20,21] At a median follow-up period of 18 months, PFS had more than doubled among those receiving everolimus plus exemestane versus those receiving exemestane plus placebo (7.8 vs. 3.2 months; hazard ratio, 0.45; 95% confidence interval, 0.38-0.54; $P < .0001$).[21] In addition, the relative reduction in risk of PFS events with the addition of everolimus to exemestane was evident in both younger and older age groups (56% and 55% in those aged < 70 and ≥ 70 years, respectively).[22]

In the overall survival (OS) analyses, the addition of everolimus to exemestane resulted in the longest OS reported to date in the post-NSAI setting[23-25]; however, a statistically significant survival benefit compared with exemestane alone was lacking (31.0 vs. 26.6 months; hazard ratio, 0.89; 95% confidence interval, 0.73-1.10; $P = .14$).[23] This lack of significance could have resulted from several factors. First, BOLERO-2 was not sufficiently powered to detect an OS advantage of less than an optimistic 8 months. Second, differences existed between the study arms with respect to the post-study use of salvage chemotherapy, making survival effects difficult to demonstrate. In addition, it has been historically challenging to demonstrate a survival benefit in patients with HR+ advanced breast cancer receiving endocrine therapy. Significant OS benefits have been restricted to trials of first-line therapies for advanced disease.[23] However, despite these potential confounding factors, a lower proportion of deaths in BOLERO-2 occurred in the everolimus plus exemestane group than in the exemestane plus placebo group (55.1% vs. 59.8%, respectively), suggesting a possible survival benefit with the concurrent use of everolimus.[23]

The class-effect toxicities associated with mTOR inhibitors are well characterized and include epithelial-cutaneous adverse events (AEs; eg, stomatitis, rash), pulmonary dysfunction (eg, noninfectious pneumonitis), metabolic AEs (eg, hyperglycemia, hyperlipidemia), and fatigue.[26] The lack, or inappropriate management, of these toxicities can potentially compromise the therapeutic effectiveness of mTOR inhibitors, such as everolimus.[26] Everolimus is generally well tolerated in the treatment of advanced breast cancer, with its most common AEs stomatitis, infections, rash, noninfectious pneumonitis, fatigue, hyperglycemia, hyperlipidemia, and myelosuppression. Most of these AEs are not life-threatening and can be resolved by dose interruptions or adjustments.[26,27] This point was supported for stomatitis, in particular, through a recent meta-analysis of randomized, controlled, phase III trials in patients with advanced solid tumors, including trials of advanced breast cancer, advanced pancreatic neuroendocrine tumor, and advanced renal cell carcinoma. This demonstrated that the efficacy of everolimus (in regard to PFS) was maintained despite the development of stomatitis and the need for dose reductions or interruptions to manage this common everolimus-related toxicity.[28]

To provide the most effective prevention and management strategies, it is important that practitioners and patients are familiar with the AEs associated with mTOR inhibition. Optimal dosing is important to achieve maximum therapeutic efficacy with appropriate drug exposure and maintain patient quality of life. The present report reviews the implications of currently available BOLERO-2 data on everolimus dose intensity, exposure, and safety in treating patients with advanced breast cancer.

Dose Intensity and Exposure

In the BOLERO-2 trial, the median duration of exposure to everolimus was 23.9 weeks (range, 1.0-123.3 weeks) at a median follow-up period of 18 months,[21] and the median dose intensity of everolimus was 8.6 mg/day.[29] Drug exposure was affected by age. Compared with patients aged < 70 years, the median dose intensity of everolimus when administered with exemestane was lower for patients aged ≥ 70 years (8.9 vs. 7.2 mg/day), with a decrease in the mean duration of exposure of both everolimus (33.8 vs. 23.2 weeks) and exemestane (36.1 vs. 27.4 weeks) when these drugs were administered in combination.[22] Overall, 46.1% of patients in the everolimus plus exemestane treatment arm had a relative everolimus dose intensity of 0.9 to < 1.1, 18.9% had a relative dose intensity of 0.7 to < 0.9, and 17.0% had a relative dose intensity of 0.5 to < 0.7.[30]

Dose Reductions and Interruptions Because of AEs

AEs of any grade were more common in patients treated with everolimus plus exemestane than in those treated with exemestane plus placebo (100% vs. 91%), as were grade 3 AEs (44% vs. 23%). However, grade 4 AEs (9% vs. 6%) were uncommon, regardless of the assigned treatment.[29] In the everolimus plus exemestane arm, the most common AEs of any grade were stomatitis (59%), rash (39%), fatigue (37%), diarrhea (34%), nausea (31%), and decreased appetite (31%). The most common grade 3 events were stomatitis (8%), anemia (7%), dyspnea (5%), an increase in gamma-glutamyl transferase (5%), hyperglycemia (5%), and fatigue (4%).[21] Pneumonitis was also more common in everolimus plus exemestane arm than in the exemestane plus placebo arms (all grades, 16% vs. 0%; grade 3, 3% vs. 0%).[21]

Dose reductions or interruptions were required in 301 patients (62%) treated with everolimus plus exemestane and in 28 patients (12%) treated with exemestane plus placebo.[29] A total of 1065 everolimus dose-interruption or dose-reduction events were reported in the BOLERO-2 trial, with 44% of these events resolving and allowing resumption of full-dose everolimus (10 mg/day) and 76% 1 within 2 weeks (Table 1).[29] For everolimus, 705 dose interruptions and 360 dose reductions were required.[29] The median duration of dose reduction for everolimus was 29 days (range, 1-672

Table 1 Dose Reductions and Interruptions Due to Adverse Events in the BOLERO-2 Trial[29]

Variable	EVE + EXE (n = 482)			PBO + EXE (n = 238)		
	Total (n)	EVE	EXE	Total (n)	PBO	EXE
≥1 Dose reduction						
Patients aged <65 years	290	101 (35)	0	158	4 (3)	0
Patients aged 65-69 years	74	35 (47)	0	37	1 (3)	0
Patients aged ≥70 years	118	45 (38)	1 (<1)	43	2 (5)	0
Previous chemotherapy	29	8 (28)	1 (3)	14	1 (7)	0
Previous endocrine therapy	434	166 (38)	0	214	6 (3)	0
≥1 Dose interruption						
Patients aged <65 years	290	159 (55)	35 (12)	158	16 (10)	7 (4)
Patients aged 65-69 years	74	42 (57)	10 (14)	37	5 (14)	3 (8)
Patients aged ≥70 years	118	68 (58)	28 (24)	43	3 (7)	3 (7)
Previous chemotherapy	29	17 (59)	5 (17)	14	1 (7)	0
Previous endocrine therapy	434	240 (55)	63 (15)	214	22 (10)	12 (6)

Data presented as n or n (%).
Abbreviations: BOLERO-2 = Breast Cancer Trials of Oral Everolimus-2; EVE = everolimus; EXE = exemestane; PBO = placebo.

days), and the median duration of dose interruption for everolimus was 7 days (range, 1-41 days).[29] For patients receiving everolimus plus exemestane, ≥ 1 dose interruption for AEs was required for everolimus in 56% and for exemestane in 15%. The corresponding proportions were 10% and 5% for placebo and exemestane.[29] Patient age, previous exposure to chemotherapy, and previous endocrine therapy did not influence the requirement for dose interruptions or reductions (Table 2).[29]

In general, a dose interruption has been recommended for grade 3 toxicities, with resumption of treatment either at a lower dose or at the same dose (depending on the specific toxicity) after recovery to grade ≤ 1. Class-effect AEs in the everolimus plus exemestane treatment arm generally resolved quickly and completely after dose interruption or reduction. Thus, 38 of 39 patients (97%) with grade ≥ 3 stomatitis experienced resolution to grade ≤ 1 after a median of 3.1 weeks, and 82% experienced complete resolution after a median of 7.4 weeks.[29] Also, 23 of 32 patients (72%) with grade ≥ 3 fatigue experienced resolution to grade ≤ 1 after a median of 8.0 weeks, and 56% experienced complete resolution after a median of 18.7 weeks.[29] Finally, 27 of 32 patients (84%) with grade ≥ 3 infections experienced resolution to grade ≤ 1 after a median of 3.0 weeks.[29]

Pneumonitis is another less common but potentially serious class toxicity associated with everolimus.[15] Dose interruption with resumption of treatment at a lower dose should be considered for patients treated with everolimus who experience grade ≥ 2 pneumonitis.[15,29] In the BOLERO-2 trial, 20 patients (4.1%) experienced grade 3 pneumonitis, and 16 (80%) of these 20 patients experienced resolution to grade ≤ 1 after a median of 3.8 weeks. Finally, 75% of the patients with grade ≥ 3 pneumonitis experienced complete resolution after a median of 5.4 weeks.[29] Grade ≥ 3 hyperglycemia or new-onset diabetes mellitus developed in 28 patients (5.8%) receiving everolimus in the BOLERO-2 trial.[29] Of the patients with grade ≥ 3 hyperglycemia or new-onset diabetes mellitus, 46% experienced

Table 2 Interval to Resumption of Full Drug Dose in Patients With Dose Reductions or Dose Interruptions of Any Cause in the BOLERO-2 Trial[29]

Variable	EVE + EXE (n = 482)		PBO + EXE (n = 238)	
	EVE	EXE	PBO	EXE
Dose reduction or interruption events (n)	1065	224	114	65
Interval resumption (% of events)				
≤1 wk	47	69	85	87
>1 but ≤2 wk	29	20	9	10
>2 but ≤3 wk	12	6	4	3
>3 wk	12	5	2	0
Interval to resumption of full dose[a] (days)				
Median	8	3	2	2
Range	2-333	2-48	2-27	2-21

Abbreviations: BOLERO-2 = Breast Cancer Trials of Oral Everolimus 2; EVE = everolimus; EXE = exemestane; PBO = placebo.
[a]For patients able to resume the study drug.

resolution to grade ≤ 1 after a median of 29.1 weeks.[29] Although dose reductions were not required for hyperglycemia in the BOLERO-2 trial,[29] temporary dose interruptions are indicated for grade 3 glycemic AEs.[15] For grade 1 and 2 glycemic AEs, no adjustments are indicated.[15] Management recommendations include dose interruption followed by resumption of the same dose without reduction, depending on the patient's glucose control.

Re-escalation to the full dose of everolimus after everolimus dose reductions for AEs was allowed on the basis of the safety findings. Of the 181 patients with ≥ 1 everolimus dose reduction, 13 (7.2%) were able to resume full-dose everolimus.[29] Of the 13 patients who were able to re-escalate to full-dose everolimus, 2 had required an initial dose reduction because of pneumonitis. Of these 2 patients, 1 experienced a recurrence of this event after dose re-escalation, resulting in discontinuation of everolimus.[29] Another 4 of the 13 patients were able re-escalate to full-dose everolimus after initial dose reductions because of stomatitis, with 2 experiencing a recurrence of stomatitis after dose re-escalation.[29] One of the 13 patients underwent a dose reduction because of a pruritic rash, which recurred after dose re-escalation and necessitated discontinuation of everolimus therapy.[29] Of the 13 patients, 1 developed recurrence of pneumonia and 1 recurrence of upper respiratory tract infection after everolimus dose re-escalation.[29] One patient initially underwent a dose reduction because of vomiting and diarrhea but was discontinued from treatment at a later date because of acute renal and respiratory failure. Finally, 4 of the 13 patients who had received an initial dose reduction for unclear reasons subsequently were able to re-escalate to their full dose of everolimus.[29]

These analyses suggest that the grade 3 toxicities associated with everolimus can be effectively managed by temporary dose interruptions, with resumption of treatment at either a lower dose or the same dose, depending on the specific toxicity. However, a few of the patients with everolimus dose reduction because of grade 3 AEs will be able to re-escalate to the full dose of this drug. Those with everolimus dose re-escalation should be carefully monitored for toxicity recurrence. However, re-escalation of the everolimus dose after grade 3 pneumonitis is not recommended.

In clinical practice, dose interruptions, followed by dose reductions as necessary, for specific grade 2 toxicities, such as stomatitis and pneumonitis, might allow for earlier resumption of therapy and reduce the overall severity of the AE. It has been recommended that everolimus be withheld for grade 2 stomatitis until resolution to grade 1, with dose reductions used for recurrent grade 2 stomatitis. Ongoing studies, including the BOLERO-4 study (ClinicalTrials.gov identifier, NCT02069093), are evaluating the use of a prophylactic steroid mouthwash to treat everolimus-induced stomatitis.[31-33]

Discontinuations Because of AEs

A greater proportion of patients treated with everolimus plus exemestane (26% for everolimus; 9% for exemestane) than with exemestane plus placebo (3% for exemestane; 5% for placebo) discontinued treatment of ≥ 1 study drug because of AEs.[29] The most common all-grade AEs leading to discontinuation in the everolimus plus exemestane treatment arm were pneumonitis (n = 27; 5.6%), stomatitis (n = 13; 2.7%), dyspnea (n = 11; 2.3%), fatigue (n = 9; 1.9%), and rash (n = 8; 1.7%).[29] The grade 3 or 4 AEs leading to discontinuation were pneumonitis (1.9%), dyspnea (1.5%), stomatitis (0.8%), fatigue (0.8%), rash (0.6%), asthenia (0.4%), and hyperglycemia (0.2%) in the everolimus plus exemestane treatment arm and stomatitis (n = 1; 0.4%) and lung infection (n = 1; 0.4%) in the exemestane plus placebo arm.[29]

Conclusion

Although the incidence of grade 1 to 2 AEs in the BOLERO-2 trial was greater for patients treated with everolimus plus exemestane than for those who received exemestane plus placebo, the median dose intensity of everolimus was 8.6 mg/day in patients treated with everolimus plus exemestane despite the dose reductions and interruptions.[29] Although the mean dose and duration of exposure were lower for patients aged ≥ 70 years than for those aged < 70 years, everolimus plus exemestane retained similar efficacy in both groups.[22]

All grade 3 toxicities associated with everolimus should be managed by dose interruption.[26] In general, on resumption, the dose should be reduced. Certain grade 2 toxicities, including stomatitis and pneumonitis, should be managed by dose interruption; the resumption of full dosing rather than dose reduction in these cases must be determined by the severity of the event and time to recovery. Dose reductions for AEs can be re-escalated in some cases, although this must be undertaken with caution and is not recommended for pneumonitis. Where possible, prevention strategies should be considered, including baseline assessment of glucose control. A number of clinical trials are also evaluating the use of steroid mouthwashes to treat and prevent stomatitis.

Altogether, these data suggest that oncologists treating patients with advanced breast cancer should assess and modify the dose of everolimus appropriately according to the severity of the observed AE. Efficacy can be maintained despite everolimus dose reductions required to manage toxicities, such as stomatitis.[28] Provider and patient education are critical for early detection and management of toxicity. The appropriate management of AEs will improve patient exposure to the drug, maximize potential efficacy, and control toxicity.

Acknowledgments

Andrea Bothwell and Matthew Grzywacz, PhD, of Apothecom, Yardley, PA, provided editorial and technical support in the development of the present report, with funding provided by Novartis Pharmaceuticals Corporation. Dr Rugo received research support from Novartis, Pfizer, and Lilly in the form of funding paid to her institution.

Disclosure

The authors have stated that they have no conflicts of interest.

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