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Breast Cancer

Everolimus Plus Exemestane in Advanced Breast Cancer: Safety Results of the BALLET Study on Patients Previously Treated Without and with Chemotherapy in the Metastatic Setting

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Key Words. Advanced breast cancer · Safety · Everolimus · Hormone-receptor positive · Real life

Abstract

Background. The BALLET study was an open-label, multicenter, expanded access study designed to allow treatment with everolimus plus exemestane in postmenopausal women with hormone receptor-positive metastatic breast cancer progressed following prior endocrine therapy. A post hoc analysis to evaluate if previous chemotherapy in the metastatic setting affects the safety profile of the combination regimen of everolimus and exemestane was conducted on the Italian subset, as it represented the major part of the patients enrolled (54%).

Patients and Methods. One thousand one hundred and fifty-one Italian patients were included in the present post hoc analysis, which focused on two sets of patients: patients who never received chemotherapy in the metastatic setting (36.1%) and patients who received at least one chemotherapy treatment in the metastatic setting (63.9%).

Results. One thousand one hundred and sixteen patients (97.0%) prematurely discontinued the study drug, and the main reasons reported were disease progression (39.1%), local reimbursement of everolimus (31.1%), and adverse events (AEs) (16.1%). The median duration of study treatment exposure was 139.5 days for exemestane and 135.0 days for everolimus. At least one AE was experienced by 92.5% of patients. The incidence of everolimus-related AEs was higher (83.9%) when compared with those that occurred with exemestane (29.1%), and the most commonly reported everolimus-related AE was stomatitis (51.3%). However, no significant difference in terms of safety related to the combination occurred between patients without and with chemotherapy in the metastatic setting.

Conclusion. Real-life data of the Italian patients BALLET-related cohort were an adequate setting to state that previous chemotherapy did not affect the safety profile of the combination regimen of everolimus and exemestane. ***The Oncologist*** 2017;22:648–654

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Implications for Practice: With the advent of new targeted agents for advanced or metastatic breast cancer, multiple lines of therapy may be possible, and components of the combined regimens can overlap from one line to another. Thus, it is important to assess even the potential of cumulative and additive toxic effects among the drugs. Previous chemotherapy did not affect the safety profile of the combination regimen of everolimus and exemestane. The continuous monitoring of the safety signals of this drug combination from general clinical practice is important, in particular for stomatitis.

Introduction

Endocrine therapy is an important class of target-directed therapy blocking the growth-promoting effects of estrogen via estrogen receptors (ER) [1]. Although endocrine therapy continues to be the cornerstone of effective treatment of ER-positive (ER+) breast cancer (BC), the emergence of the resistance to endocrine therapy is frequent [2]. Intensive research has identified a number of potentially targetable pathways that interact with ER signaling in BC leading to cancer progression beyond endocrine receptor blockade [3–6]; one mechanism implicated in endocrine resistance in BC is the activation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (mTOR) signal transduction pathway [7, 8]. Based on this hypothesis, the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) phase III study had been conceived to evaluate the efficacy and the safety of the combination of everolimus (an mTOR inhibitor) and exemestane (steroidal aromatase inhibitor) in patients with ER+ BC progressed to nonsteroidal aromatase inhibitors (NSAIs) [9]. The BOLERO-2 results showed that the addition of everolimus to endocrine therapy leads to an improved clinical outcome with significant PFS benefit. Conclusions also stated that careful monitoring of patients and increased physician awareness of the safety profile of everolimus-based therapy were warranted.

The BALLET study was a European open-label, multicenter, expanded access study designed to allow treatment with everolimus plus exemestane in postmenopausal women with ER+ locally advanced or metastatic BC who have progressed following prior NSAIs. Safety results of this study, recently published, enabled further investigation of this drug combination in a clinical setting mimicking the real world [10]. The aim of the present report is to present and discuss the post hoc analysis performed on Italian patients enrolled in the BALLET study (1,153 out of 2,131 of the whole study population), reporting results in everyday clinical practice evaluating the possible differences on the cumulative toxicity of everolimus plus exemestane in patients who previously received or did not received chemotherapy in the metastatic setting.

Materials and Methods

The BALLET study was a European, multicenter, open-label, single-arm, phase III b, expanded access study focused on the use of everolimus/exemestane combination in postmenopausal women with ER+ locally advanced or metastatic BC after recurrence or progression following NSAIs treatment (EudraCT Number: 2012-000073-23, CRAD001YIC04). Complete inclusion/exclusion criteria list, study design, and treatment were already reported [10]. Everolimus was provided from May 2012 until the drug was locally reimbursed for this indication or until 31 January 2014. The global study enrolled 2,131 patients, of whom 1,153 (54.1%) were Italian (128 cancer centers). Local reimbursement in Italy has been granted since July 2013.

The primary study objective was to evaluate safety of everolimus plus exemestane in postmenopausal women with ER+ locally advanced or metastatic BC after recurrence or progression following NSAIs treatment. The assessment of safety was based mainly on the frequency of adverse events (AEs) and on the number of laboratory values that were new or worsening. Vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and physical examination were also assessed during the study period. The secondary objective was to evaluate grade 3 and 4 AEs during treatment with everolimus and exemestane in the routine clinical practice (frequency of AEs recorded as grade $\geq$3 or as serious A E [SAE]). Stomatitis and pneumonitis were considered events of particular interest as the most frequent infections reported in the BOLERO-2 trial and the most frequently reported AEs that led to permanent treatment discontinuation in the BALLET study [9, 10]. The BALLET study did not employee stomatitis prevention methodology.

The present analysis performed on the Italian cohort of the BALLET study was focused on the following two subpopulations: patients without initial chemotherapy treatment prior to everolimus/exemestane combination ("without-chemo group") and patients with initial chemotherapy treatment prior to everolimus/exemestane combination ("with-chemo group"). In particular, the subpopulation with no initial chemotherapy included only patients who never received chemotherapy in the metastatic setting, whereas the subpopulation with initial chemotherapy included only patients who received at least one chemotherapy treatment in the metastatic setting, whatever the line of treatment.

The safety population included all patients who received at least one dose of everolimus and exemestane and had at least one post-baseline safety assessment. The mean cumulative dose (the total dose given during the study treatment exposure), the mean dose intensity (the ratio between cumulative dose and duration of exposure), and compliance to dose regimen planned by protocol (relative dose intensity, i.e., the ratio between the actual dose intensity and the planned dose intensity) were calculated. All the AEs were assessed by the Common Terminology Criteria (CTCAE), version 4.03.

The study was approved by the ethical committee at each site and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All the patients provided written informed consent.

Patients

One thousand two hundred and seventy-nine (1,279) female Italian patients were screened, 1,153 (90.1% of the screened

Table 1. Baseline and disease characteristics

Characteristic	*n* = 1,151
Median age (range), years	64.0 (33–85)
Age categories	
<70 years, *n* (%)	817 (70.9)
≥70 years, *n* (%)	334 (29.1)
Median BMI (range), kg/m^2	25.3 (15.7–54.6)
ECOG PS, n (%)	
0	828 (71.9)
1	295 (25.6)
2	19 (1.7)
Missing	9 (0.8)
Current disease status, *n* (%)	
Metastatic	967 (84.0)
Locally advanced	184 (16.0)
Metastatic site, *n* (%)	
Bone only	310 (26.9)
Visceral	648 (56.3)
Visceral only	106 (9.2)
Bone and visceral	467 (40.6)
Others	411 (35.7)
Number of metastatic site, *n* (%)	
≥5	221 (19.2)
4	144 (12.5)
3	255 (22.2)
2	279 (24.2)
1	252 (21.9)
Current extent of disease, *n* (%)	
Bone	886 (77.0)
Liver	393 (34.1)
Lymph nodes	345 (30.0)
Lung	326 (28.3)
CNS	30 (2.6)
Other	363 (31.5)

Abbreviations: BMI, body mass index; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status.

set) of these were enrolled, and 1,151 (90.0% of the screened set) were included in the present analysis. Two patients were excluded due to lack of baseline data. Patients who never received chemotherapy in the metastatic setting were 416 (36.1%) and those who received at least one chemotherapy treatment in the metastatic setting were 735 patients (63.9%).

Patients' baseline characteristics are summarized in Table 1. Briefly, median age at treatment was 64 years (range 33–85 years), 47.9% were aged ≥65 years, and 29.1% were aged ≥70 years; 98.7% were white and 97.5% had an ECOG performance status ≤1. Body mass index was 26.1 kg/m^2 on average.

Seventy-seven percent of study population (*n* = 886) had an extent of disease involving bone and 34.1% (*n* = 393) involving liver. The majority of the patients of both groups had a metastatic cancer (85.1% in the without-chemo group versus 83.4% in the with-chemo group). For both groups, the most frequent metastatic site of cancer was visceral (43.8% in the without-chemo group versus 63.4% in the with-chemo group); 49.3% of the patients in the without-chemo group and 56.5% of the patients in the with-chemo group had at least three metastatic sites of cancer involved.

Mean time elapsed from diagnosis to the informed consent signature was approximately 10 years. Prior antineoplastic medications were administered mainly in therapeutic (88.0%) and adjuvant (79.0%) settings. One hundred twenty-five patients (10.9%) received prior antineoplastic medications in the adjuvant setting only, while 23.5% underwent at maximum until first line of treatment in advance setting, 21.3% until second line, 15.9% until third line, 10.5% until fourth line, and 17.8% until fifth line or over.

Treatment

The mean duration of study treatment exposure was 158.3 ± 106.8 days (median 139.5) for exemestane and 153.9 ± 108.5 days (median 135.0) for everolimus, ranging between 1 and 706 days. Two hundred forty-five (21.3%) and 712 (61.9%) patients temporary interrupted exemestane and everolimus, respectively, for an average of 14.1 days for exemestane and 24.2 days for everolimus. Three hundred thirty (28.7%) patients took everolimus at a 5-mg dose for a mean of 99.8 days, and almost all patients (1,149, 99.8%) took everolimus at the prescribed 10-mg dose for a mean of 113.7 days.

The mean cumulative dose was 3,900.4 ± 2,644.6 mg for exemestane and 1,279.3 ± 919.7 mg for everolimus, while the mean dose intensity was 24.6 ± 1.2 mg/day for exemestane and 8.6 ± 1.8 mg/day for everolimus. Relative dose intensity (patients'compliance) resulted on average 0.98 ± 0.05 for exemestane and 0.86 ± 0.18 for everolimus. Treatment compliance was higher on exemestane than everolimus; the percentage of patients with compliance higher than 90% was 94.4% and 58.6% for exemestane and everolimus, respectively; the percentage of patients with compliance lower than 60% was 0.1% and 15.1% for exemestane and everolimus, respectively. No difference in treatment exposure was noticed between the two subgroups.

One thousand twenty-nine (89.4%) took at least one concomitant medication/significant nondrug therapy administered during the study and for up to 28 days after study drug discontinuation. The most reported concomitant medication was zoledronic acid (390 patients, 33.9%).

Sixty-two percent of patients were administered at least one antineoplastic medication since discontinuation of study drug (64.4% in the without-chemo group versus 60.0% in the with-chemo group). The most reported antineoplastic medication was exemestane (292 patients, 25.4%).

Safety

Sixty-nine patients (6.0%) died during the study or within 28 days after last study treatment dose. The main causes of deaths were disease or tumor progression (*n* = 31), (S)AEs (*n* = 17), worsening of general conditions (*n* = 7), sudden death (*n* = 7), and other causes (*n* = 7).

In terms of serious/clinically significant AEs, 209 patients (18.2%) experienced at least one SAE (0.2% experienced a SAE leading to hospitalization or prolongation of hospitalization) and 155 (13.5%) experienced at least one AE leading to discontinuation of everolimus or exemestane. The incidence of fatal

Table 2. Incidence of adverse events in either group (at least 10%)

Adverse event	Without-chemo group, *n* = 416 (%)	With-chemo group, *n* = 735 (%)	Total, *n* = 1,151 (%)
Stomatitis	221 (53.1%)	370 (50.3%)	591 (51.3%)
Asthenia	98 (23.6%)	169 (23.0%)	267 (23.2%)
Pyrexia	73 (17.5%)	141 (19.2%)	214 (18.6%)
Anemia	59 (14.2%)	110 (15.0%)	169 (14.7%)
Rash	56 (13.5%)	100 (13.6%)	156 (13.6%)
Diarrhea	69 (16.6%)	79 (10.7%)	148 (12.9%)
Hyperglycemia	56 (13.5%)	92 (12.5%)	148 (12.9%)
Hypercoholesterolemia	36 (8.7%)	107 (14.6%)	143 (12.4%)
Peripheral edema	44 (10.6%)	79 (10.7%)	123 (10.7%)
Decreased appetite	50 (12.0%)	72 (9.8%)	122 (10.6%)
Cough	47 (11.3%)	74 (10.1%)	121 (10.5%)
Fatigue	47 (11.3%)	70 (9.5%)	117 (10.2%)
Nausea	29 (7.0%)	74 (10.1%)	103 (8.9%)

Table 3. Incidence and severity of stomatitis and pneumonitis

Adverse event	Without-chemo group, *n* = 416 (%)	With-chemo group, *n* = 735, (%)	Total, *n* = 1,151 (%)
Stomatitis	221 (53.1%)	370 (50.3%)	591 (51.39%)
Grade 1	101 (24.3%)	158 (21.5%)	259 (22.5%)
Grade 2	76 (18.3%)	133 (18.1%)	209 (18.2%)
Grade 3	44 (10.6%)	77 (10.5%)	121 (10.5%)
Grade 4	0 (0%)	2 (0.3%)	2 (0.2%)
Pneumonitis	23 (5.5%)	64 (8.7%)	87 (7.6%)
Grade 1	3 (0.7%)	14 (1.9%)	17 (1.5%)
Grade 2	17 (4.1%)	37 (5.0%)	54 (4.7%)
Grade 3	2 (0.5%)	10 (1.4%)	12 (1.0%)
Grade 4	1 (0.2%)	3 (0.4%)	4 (0.3%)

and significant AE was slightly higher—but not statistically significant—in the group of patients with chemotherapy in the metastatic setting compared with the group of patients without chemotherapy in the metastatic setting, in particular 8.0% versus 2.4% for deaths, 20.4% versus 14.2% for SAEs, and 14.6% versus 11.5% for AEs leading to treatment discontinuation, respectively.

Incidence of grade 3 and 4 AEs leading to permanent discontinuation of study treatment was 11.0% (9.6% in the without-chemo group versus 11.8% in the with-chemo group in the metastatic setting). The most frequent grade 3 and 4 events leading to permanent discontinuation of treatment were stomatitis (2.8%), anemia (1.7%), hyperglycemia (1.1%), and asthenia (1.0%).

The most reported grade 3 or 4 toxicities were observed for hematologic parameters in absolute lymphocytes, which decreased for 50 patients (4.3%), and in WBC, which decreased for 10 patients (0.9%), and for biochemistry parameters, for 123 patients in gamma glutamyltransferase (10.7%) and for 64 patients in glucose (5.6%). Overall, 93% of patients experienced at least one AE, in particular 91.1% of patients without chemotherapy in the metastatic setting and 93.3% of patients with chemotherapy in the metastatic setting without significant difference in the two subgroups (Table 2).

The most reported AE was stomatitis (51.3%). The observed incidence of stomatitis by severity was 22.5% for CTCAE grade 1, 18.2% for grade 2, 10.5% for grade 3, and 0.2% for grade 4. Pneumonitis had a lower incidence: 7.6% of patients experienced at least one event (1.5%, 4.7%, 1.0%, and 0.3% split by CTCAE grades 1, 2, 3, and 4, respectively; Table 3). The probability of experiencing stomatitis at 6 months from the start of treatment was approximately 50%, slightly less than the 10% probability for pneumonitis.

The incidence of everolimus-related AEs was higher compared with the occurrence of exemestane-related events; 83.9% of patients (both in without- and with-chemo groups) experienced at least one AE related to everolimus, whereas 29.1% (26.7% versus 30.5% in without- and with-chemo groups) experienced at least one AE related to exemestane. The most reported AE related to everolimus was stomatitis, which was experienced at least once by approximately half (49.7%) of the patients overall.

Weight loss (defined as decrease from baseline of ≥10%) was the most frequent physical abnormality, which occurred in 160 patients (13.9% overall and 12.7% versus 14.6% in without- and with-chemo groups, respectively). No statistically relevant difference was observed between the safety profiles of the two patient subgroups without and with chemotherapy in the metastatic setting.

Discussion

The pivotal BOLERO-2 trial showed that dual-blockade based on the association of everolimus plus exemestane doubled the median progression-free survival versus exemestane alone in patients with hormone receptor-positive (HR+)/human epidermal growth receptor 2-negative (HER2−) metastatic BC recurring/progressing on prior NSAIs. It also stated the importance of diligent monitoring, proactive communication, early detection, and implementation of appropriate AE management strategies [9] in those patients receiving the combination. In this scenario, the BALLET study has been initiated as the expanded access program focused on the safety profile of the combination. To our knowledge, it is the largest reported safety dataset on a patient population outside the restrictive criteria of a clinical trial of patients with HR+/HER2− BC progressing on prior NSAIs [10]; showing even the patients were more heavily pretreated, the safety profile of everolimus plus exemestane was consistent with the BOLERO-2.

The current practice of the therapy of advanced/metastatic BC is based on sequential administration of different regimens that are considered as lines of treatment [2]. With the advent of new targeted agents, multiple lines of targeted therapy may be possible, and components of the combined regimens can overlap from one line to another. Noteworthy, a recent network meta-analysis showed that combination as first- or second-line therapy in HR+/HER− metastatic BC is more efficacious than several chemotherapy regimens that were reported in the literature along with favorable toxicities for the combination in most instances [11]. Thus, it is important to assess even the potential of cumulative and additive toxic effects among the drugs. With the increasingly widespread use of everolimus in the management of metastatic BC, more experience has to be accumulated on the safety in patient subgroups characterized by metastatic sites, prior and subsequent therapies including cytotoxic agents or radiation, and comorbidities.

The post hoc safety analysis, herein reported, revealed no statistically significant difference in the occurrence of AEs and SAEs between the two subgroups (namely, patients who never previously received chemotherapy in the metastatic setting and patients who previously received at least one chemotherapy treatment in the metastatic setting). The combination regimen of everolimus and exemestane, the only regimen currently registered with an mTOR inhibitor in this setting, represents a valid alternative to the harmful toxicity profile of cytotoxic chemotherapy, confirming what was previously reported [10, 11].

Furthermore, the present analyses relating to real-world practice in Italy confirmed the side effects of the everolimus/exemestane combination are mainly confined to the toxicity profile of everolimus [2]. Data are consistent with overall European population, addressing the clinicians to pay particular attention to its administration in the first months [10].

The long-term management of women with HR+ BC remains a challenge. Suboptimal response in some patients and relapse during or after therapy highlight the medical need of a better knowledge of the pathogenic mechanism along with a deeper understanding of the resistance to therapy itself. From the perspective of medical oncology, everolimus is a relatively new drug in the treatment of BC targeting the mTOR signaling involved in the endocrine resistance process. Although the data on safety and efficacy of everolimus are rapidly accumulating in patients with BC, the safety profile of everolimus is mostly consistent across all clinical trials [2], and there is an important need of continuous safety monitoring in the everyday clinical practice.

Stomatitis was the most frequent (51.3%) and relevant AE to be clinically focused on, in particular, with 53.1% in without- and 50.3% in with-chemo group, without any significant difference. Prophylactic methodology might be a way to improve the stomatitis rate in these patients. In fact, recently published analysis (after the BALLET study was completed) suggests a correlation between stomatitis and efficacy of everolimus in patients with solid tumors, including metastatic BC, and a careful monitoring of patients is warranted [12]. The other commonly reported AE with everolimus is pneumonitis (interstitial lung disease), which occurred in 7.6% of the present study population (5.5% in without- and 8.7% in with-chemo group, respectively) [13]. The reason for a lower incidence of pneumonitis compared with the previous reports [14] could be related to the increased awareness of the clinicians to possible initial symptoms, such as dyspnea, dry cough, fatigue, etc., and thus to their ability in an early diagnosis and management [13, 15]. Furthermore, the majority of pneumonitis and stomatitis in the present analysis were grade ≤2: 79.2% (468 out of 591) for stomatitis and 81.6 (71 out of 87) for pneumonitis, respectively.

Conclusion

The outcome of patients with advanced/metastatic BC is continuously improving because of the availability of new active agents. The combination of everolimus and exemestane in treating metastatic BC is a solid treatment option now largely used in Italy. This post hoc analysis of the BALLET study showed that previous chemotherapy did not affect the safety profile of the combination regimen based on everolimus and exemestane. Safety data on the Italian subset were representative of real-world evidence and were consistent with both the overall European data and clinical trial results. However, new safety issues may emerge in long-term survivors receiving the everolimus/exemestane therapy: it is important to continuously evaluate the safety data from everyday clinical practice.

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