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EFFICACY AND SAFETY OF EVEROLIMUS-EXEMESTANE COMBINATION IN BREAST CANCER PATIENTS

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Abstract

Breast cancer is the second leading cause of cancer death in women worldwide. In Lebanon, hormone positive patients resistant to endocrine treatments account for most of the cases. These two facts directed the attention to evaluate everolimus-exemestane use in hormonal receptor positive metastatic breast cancer patients, in Lebanon. A multi-center, observational, retrospective cohort study was carried out by screening 69 metastatic breast cancer patient's files in order to determine the progression free survival (PFS), overall survival (OS) and side effects of everolimus. This study revealed that across different therapy lines, the median PFS for patients on everolimus-exemestane combination was 5.87 ± 10.84 months at a median follow up of 5.135 ± 6.375, and the median survival was 23.83 months with minimum and maximum survival, at 0.26 months and 30.5 months, respectively. Everolimus-exemestane has been shown to be effective in overcoming hormonal resistance in Lebanese breast cancer patients. Stomatitis, as a side effect of everolimus, accounted for 30.84% of the cases. Medical intervention, dose modification, dose postponing, drug discontinuation, and spontaneous resolution were used to manage all side effects. In comparison to previous studies, the current work demonstrated lower stomatitis percentages reflecting the preventives measures taken by oncologists. As a conclusion, everolimus-exemestane co-administration has proven to be an effective combination in overcoming hormonal resistance in Lebanon and a better tolerance is attributed to preventive measures in order to control drugs side effects.

Keywords

Breast cancer, Everolimus, Progression free survival, Overall survival, Metastasis

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ABSTRACT: *Breast cancer is the second leading cause of cancer death in women worldwide. In Lebanon, hormone positive patients resistant to endocrine treatments account for most of the cases. These two facts directed the attention to evaluate everolimus-exemestane use in hormonal receptor positive metastatic breast cancer patients, in Lebanon. A multi-center, observational, retrospective cohort study was carried out by screening 69 metastatic breast cancer patient's files in order to determine the progression free survival (PFS), overall survival (OS) and side effects of everolimus. This study revealed that across different therapy lines, the median PFS for patients on everolimus-exemestane combination was 5.87 ± 10.84 months at a median follow up of 5.135 ± 6.375, and the median survival was 23.83 months with minimum and maximum survival, at 0.26 months and 30.5 months, respectively. Everolimus-exemestane has been shown to be effective in overcoming hormonal resistance in Lebanese breast cancer patients. Stomatitis, as a side effect of everolimus, accounted for 30.84% of the cases. Medical intervention, dose modification, dose postponing, drug discontinuation, and spontaneous resolution were used to manage all side effects. In comparison to previous studies, the current work demonstrated lower stomatitis percentages reflecting the preventives measures taken by oncologists. As a conclusion, everolimus-exemestane co-administration has proven to be an effective combination in overcoming hormonal resistance in Lebanon and a better tolerance is attributed to preventive measures in order to control drugs side effects.*

KEYWORDS: *Breast cancer, Everolimus, Progression free survival, Overall survival, Metastasis*

1. INTRODUCTION

Breast cancer is the most common type of cancer (1) and the second leading cause of cancer mortality in women worldwide (2). According to the International Agency for Research on Cancer (IARC), the worldwide incidence of all types of cancer was estimated at 14.1 million in 2012, and the global burden was projected to grow to 21.7 million new cancer cases by 2030 (3).

Five main intrinsic subtypes of breast tumors are identified and classified according to the genes expressed, namely: luminal A, luminal B, triple-negative/basal-like, human epidermal growth factor receptor type 2-enriched (HER2), and normal-like. Seventy-five percent of breast cancer patients are estrogen receptor positive (4). Endocrine therapy is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is a concern or proof of endocrine resistance or a rapidly progressing disease (3). In advanced hormone positive breast cancer, up to 70% of cases develop a mutation in PI3K/Akt/mTOR pathway, and hyperactivation of this pathway can lead to endocrine resistance (5). Metastatic patients are treated either with hormonal therapy (endocrine therapy), targeted therapy, chemotherapy or a combination of these, depending on breast cancer type.

Everolimus is a macrolide immunosuppressant and a first generation mammalian target of rapamycin inhibitor. In 2009, everolimus was shown to significantly increase letrozole efficacy in neoadjuvant therapy for patients with estrogen receptor positive breast cancer (6).

In 2012, everolimus was FDA approved for the treatment of advanced hormone receptor positive, and HER2-negative breast cancer, in combination with exemestane (7). Furthermore, everolimus was also approved as first line setting, in combination with exemestane, during or within 12 months following adjuvant treatment of

metastatic stage after progression (8); other studies as well were recently conducted in a metastatic setting. Additionally, everolimus was studied in HER-2 positive breast cancer (9), and current studies were conducted in HER-2 positive breast cancer as well as in triple negative breast cancer.

Several side effects were indicated in everolimus treated patients, predominantly gastrointestinal disorders such as stomatitis. Other frequently encountered side effects were endocrine and metabolic disorders, mostly hyperglycemia and hyperlipidemia, respiratory side effects, mostly non-infectious pneumonitis, dermatologic, hematologic, hepatic, renal, central nervous system, neuromuscular and skeletal disorders, and infections (10).

A Lebanese study, evaluating the efficacy of everolimus-exemestane co-therapy in reversing hormone resistance in Lebanese breast cancer patients, showed a progression free survival (PFS) of 5.2 months (11). This value is lower than 6.9 months, the value shown in BOLERO-2 trial that appraised the progression-free survival of everolimus combined with an aromatase inhibitor in patients with hormone-receptor–positive advanced breast cancer previously treated with non-steroidal aromatase inhibitors (8). Consequently, the current study was conducted to assess the response, progression free survival and overall survival of everolimus-exemestane combination and side effects of everolimus.

2. METHODS

2.1 Study Design

This is a retrospective, observational, multi-center, cohort study conducted in Lebanon, and based on data collected from five oncology clinics, geographically distributed over different areas in Lebanon from May 2015 through August 2015.

2.2 Inclusion and Exclusion Criteria

All Lebanese female adult patients, presenting to oncology clinics with histologically and pathologically confirmed hormone receptor positive metastatic breast cancer were included in the study and treated with a combination of everolimus (10 mg) and exemestane (25mg) daily. The exclusion criteria comprised patient diagnosed with cancer other than breast cancer and male patient.

2.3 Data Collection

Patients' medical profiles were reviewed and a survey form was filled. Socio-demographics, risk factors, family history, medical history, prognosis, treatment, compliance to treatment, reasons for non-compliance, side effects were retrieved. Progression free survival defined as time from initiation of index therapy to disease progression or death was calculated. Overall survival defined as the time from initiation of index of therapy to death from any cause was also documented. Patients without recorded death were censored at last follow-up date.

2.4 Ethical Consideration

Prior to data collection, verbal consent was taken from treating physicians in all oncology clinics included in the study. Patients were referred to by their identification number for confidentiality purposes.

2.5 Statistical Analysis

Data was statistically analyzed using SPSS version 20 program, and median +/- SD (interquartile range) were calculated for continuous data, while frequencies and percentages were calculated for nominal data.

Kaplan-Meier (K-M) analyses were used for comparison of progression free survival (PFS) between everolimus-based therapy in first, second, third, and fourth line and later lines metastatic stage; and also for overall survival estimation after everolimus-based therapy in first, second, third, fourth line, and in all other lines use. Log rank test was used to assess significance. Results were considered significant at $p\text{-value} < 0.05$.

3. RESULTS

Data on 69 female patients with hormone positive metastatic breast cancer were collected from five oncology clinics in different regions. At diagnosis of breast cancer, the mean age of participants was 52.54 ± 11.44 years, and postmenopausal females constituted 50.73%. The median age of everolimus-exemestane combination initiation was $60.36\% \pm 10.56$ years. Twenty-five percent had family history of breast cancer. Forty eight point seventy seven percent of the cases were either overweight or obese. Moreover, 19.04% of the patients had hypertension, 14.28% had hyperlipidemia, 9.52% had diabetes and 9.52% had thyroid problems. Stage IIIC and metastatic stage constituted 52.39% of cases at diagnosis (Table 1).

Table 1: Demographic information of the studied sample

Age at Diagnosis (Mean ± SD)		52.54±11.44
Starting everolimus age (Median ± IQR)		60.36±10.56
		Frequency (percentage)
Menopausal state at diagnosis of breast cancer		
	Premenopausal	34 (49.27%)
	Postmenopausal	35 (50.73%)
Region of residency		
	Mount Lebanon	28 (47.45%)
	Beirut	14 (23.72%)
	North	11 (18.64%)
	South	4 (6.77%)
	Bekaa	2 (3.38%)
Family History of Breast cancer		
	First Degree	1 (3.57%)
	Second degree	4 (14.28%)
	First and second degree	2 (7.14%)
	No Family history	21 (75%)
Smoking		
	Smoker	10 (21.27%)
	Non-smoker	34 (72.34%)
	Ex-smoker	3 (6.38%)
Co-morbidities		
	No comorbidities	22 (34.92%)
	Hypertension	12 (19.04%)
	Hyperlipidemia	9 (14.28%)
	Thyroid disorders	6 (9.52%)
	Diabetes mellitus	6 (9.52%)
	Cardiovascular disease	3 (4.76%)
	Kidney disease	3 (4.76%)
	Metabolic	1 (1.58%)
	Other	1 (1.58%)
Body Mass Index		
	Underweight	1 (2.43%)
	Normal	20 (48.78%)
	Overweight	15 (36.58%)
	Obese	5 (12.19%)

In this study, the major site of metastasis before everolimus-exemestane combination administration was bones (46%) followed by visceral metastasis including both liver and lungs (58%). The last medication preceding everolimus-exemestane combination use in first and second lines were for non-steroidal aromatase inhibitors in a percentage of 72.7% and 80%, respectively. On the other hand, this study showed increased chemotherapy use preceding everolimus-exemestane combination in second (13.3%), third (15%), fourth (75%) and fifth (100%) everolimus line therapies (Fig. 1).

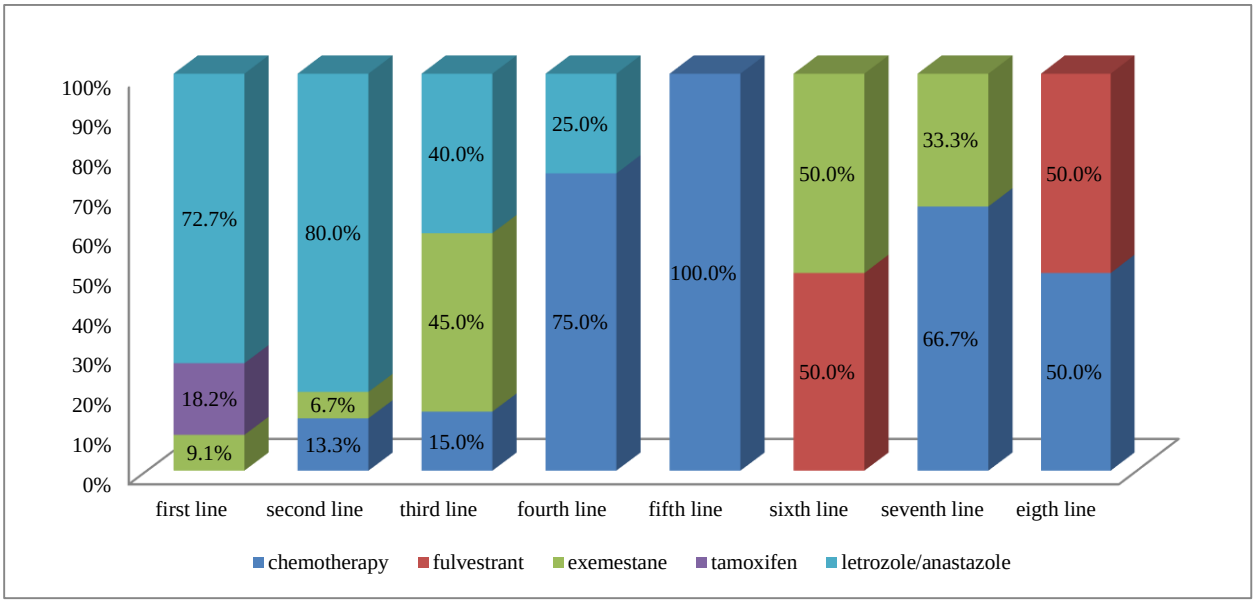

Fig. 1 Last medication before starting everolimus-exemestane combination

Median progression free survival for everolimus-exemestane co-therapy was determined by the Kaplan-Meier method at a median follow up of 5.135 ± 6.735 months. Across all therapy lines of everolimus-exemestane co-therapy, median PFS was 5.87 ± 10.84 months. In addition, median progression free survival for everolimus-exemestane co-therapy in first, second, third, fourth and later line therapies were 4.94, 6.17 and 9.14, respectively with no significant difference, log rank, or p-value=0.7418 (Fig. 2).

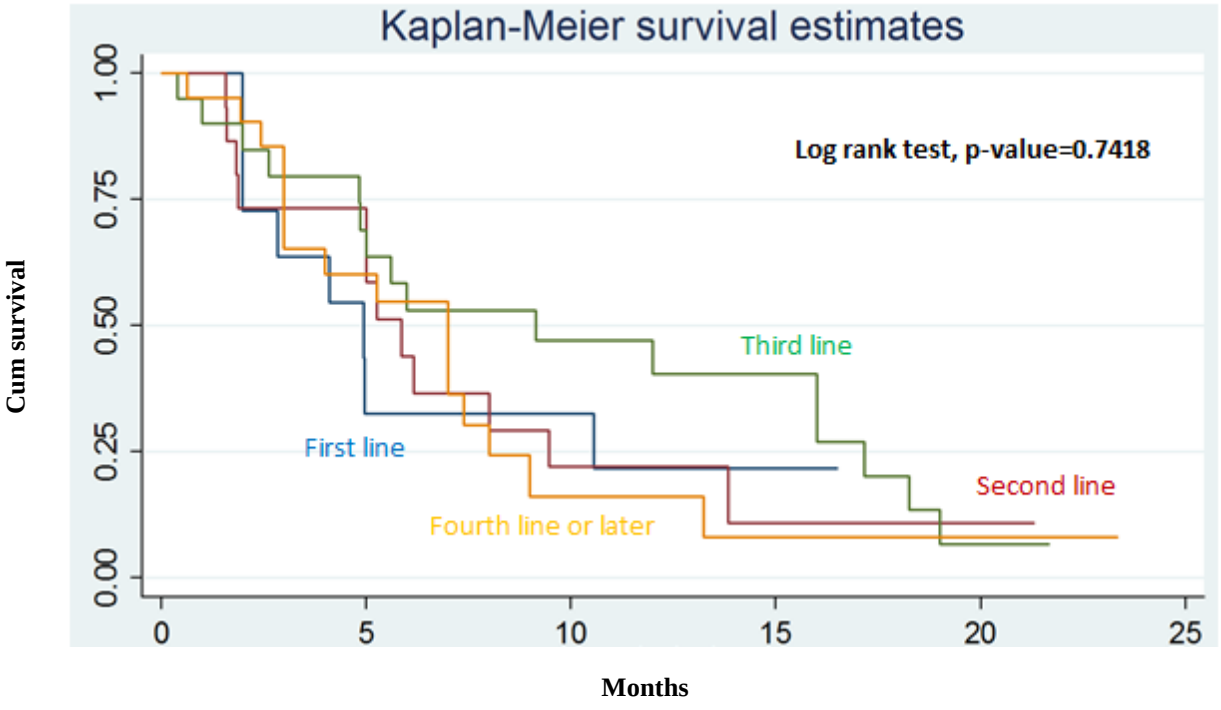

Fig. 2 Kaplan-Meier curves of progression free survival after all lines of everolimus-exemestane co-therapy

Comparing first, second, third, fourth and later everolimus-exemestane line therapies, no significant difference were found in median survival, p-value=0.5227. Median survival after everolimus in this research was 23.83 months with minimum and maximum survival, 0.26 months and 30.5 months, respectively (Fig. 3).

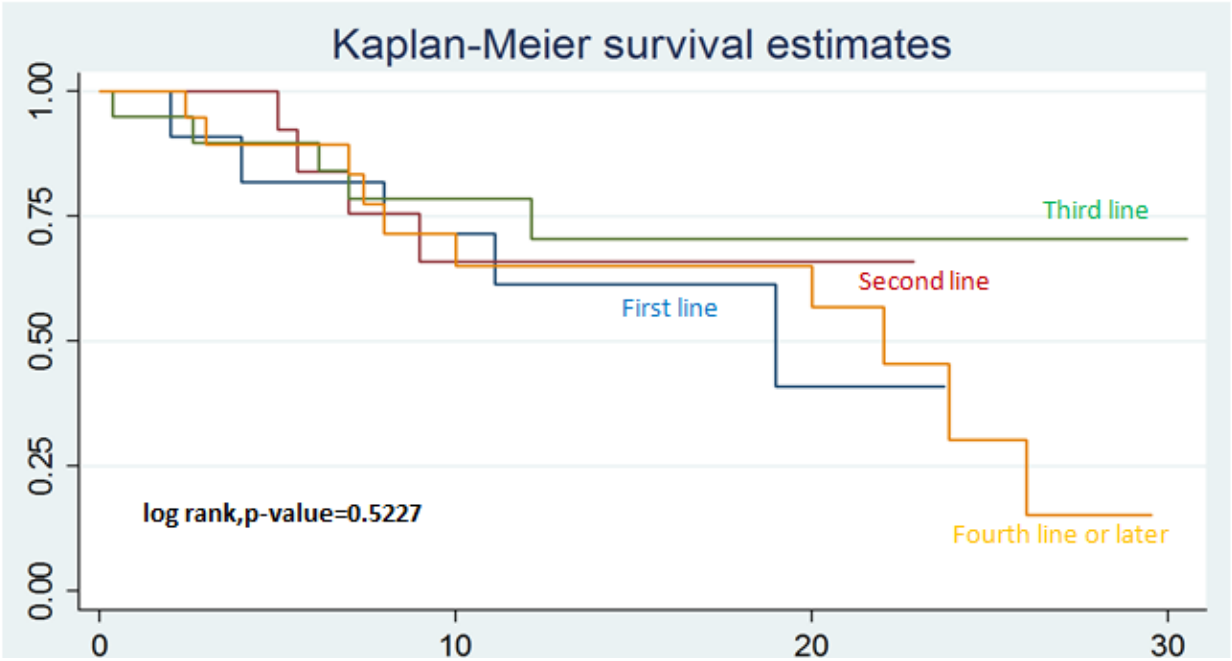

Fig. 3 Kaplan-Meier curves of overall survival after all lines of everolimus-exemestane co-therapy

Lower median PFS was obtained in patients who were chemotherapy naïve (5.27 vs. 7 months) (Fig. 4), and higher median PFS was noted in patients with non-bone metastasis (7 vs. 5.27 months) (Fig. 5).

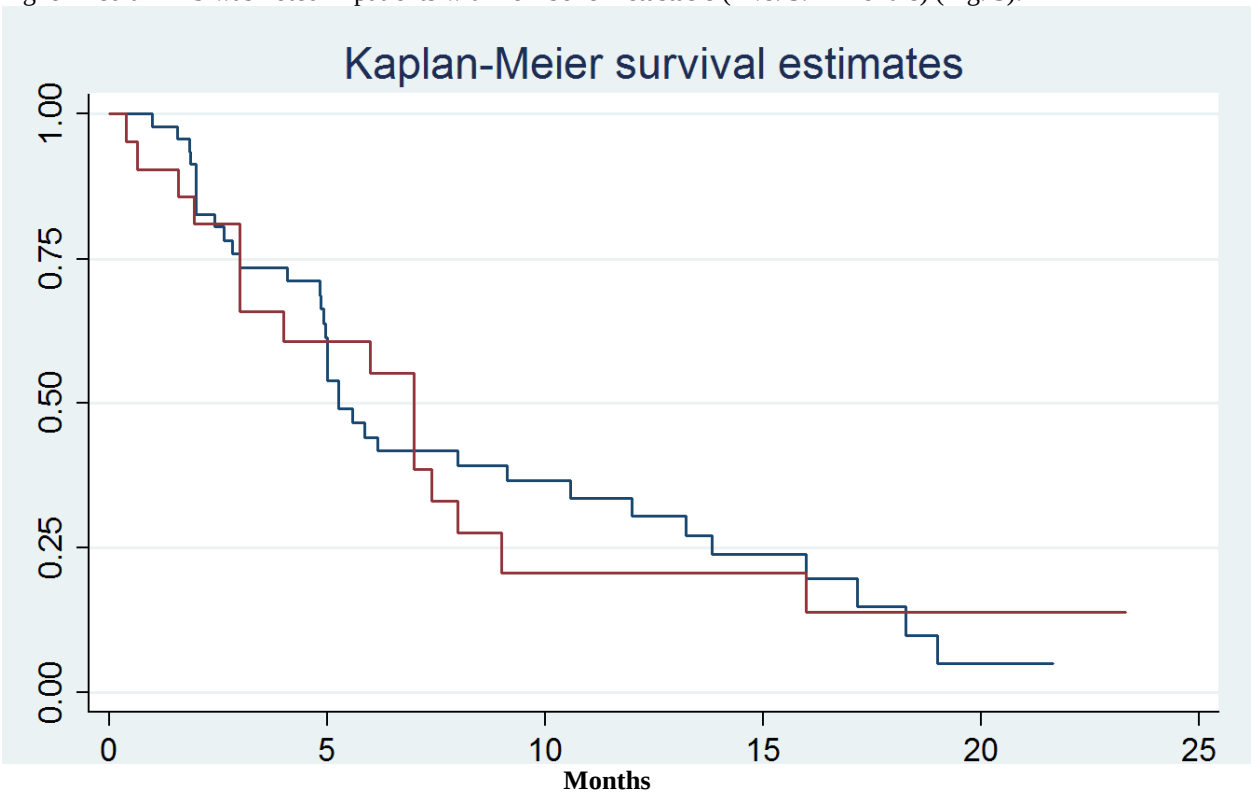

Fig. 4 Progression free survival of everolimus-exemestane combination regarding the last medication before starting everolimus

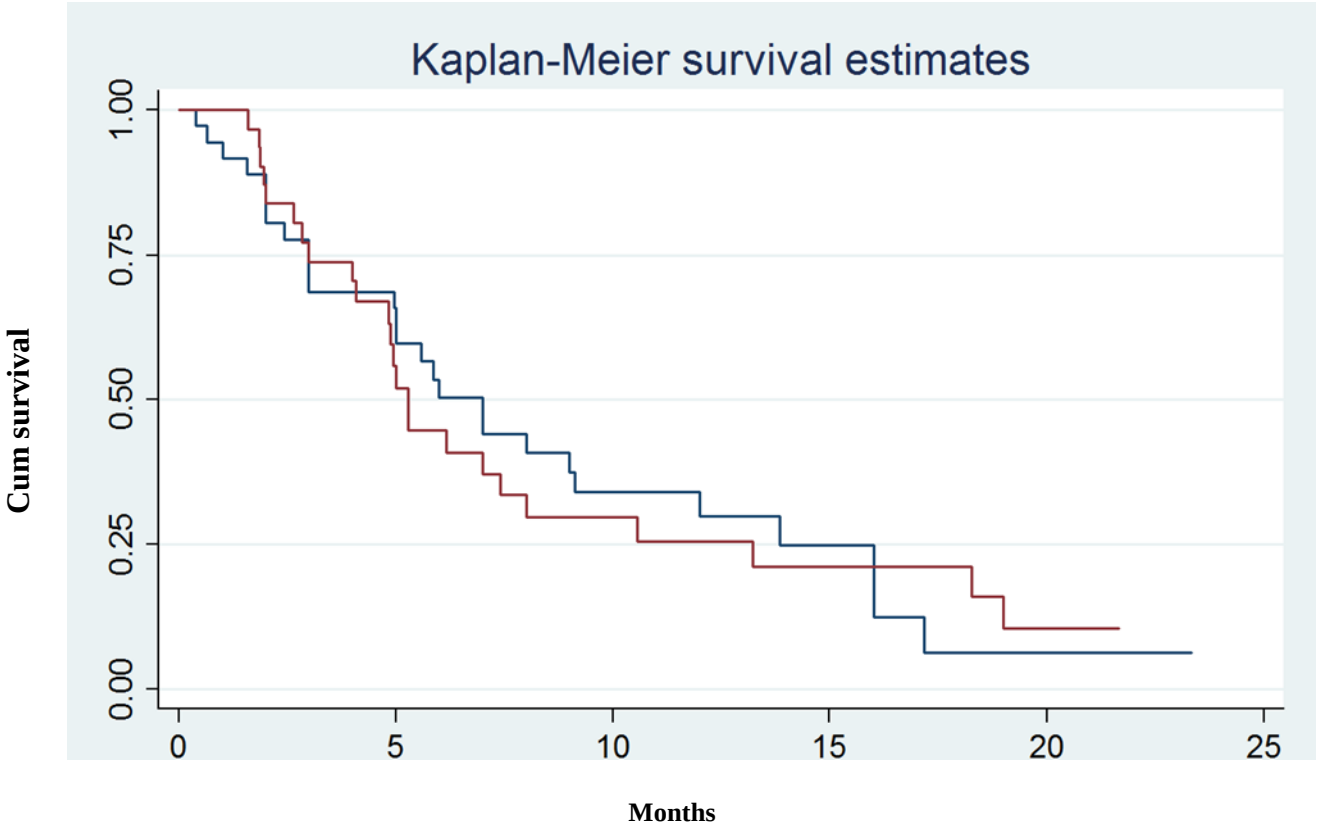

Fig. 5 Progression free survival of everolimus-exemestane combination according to the type of metastasis before everolimus use (Bone vs. non-bone)

Several everolimus side effects were reported by patients most prominently stomatitis of any grade presenting 30.84% (Fig. 6).

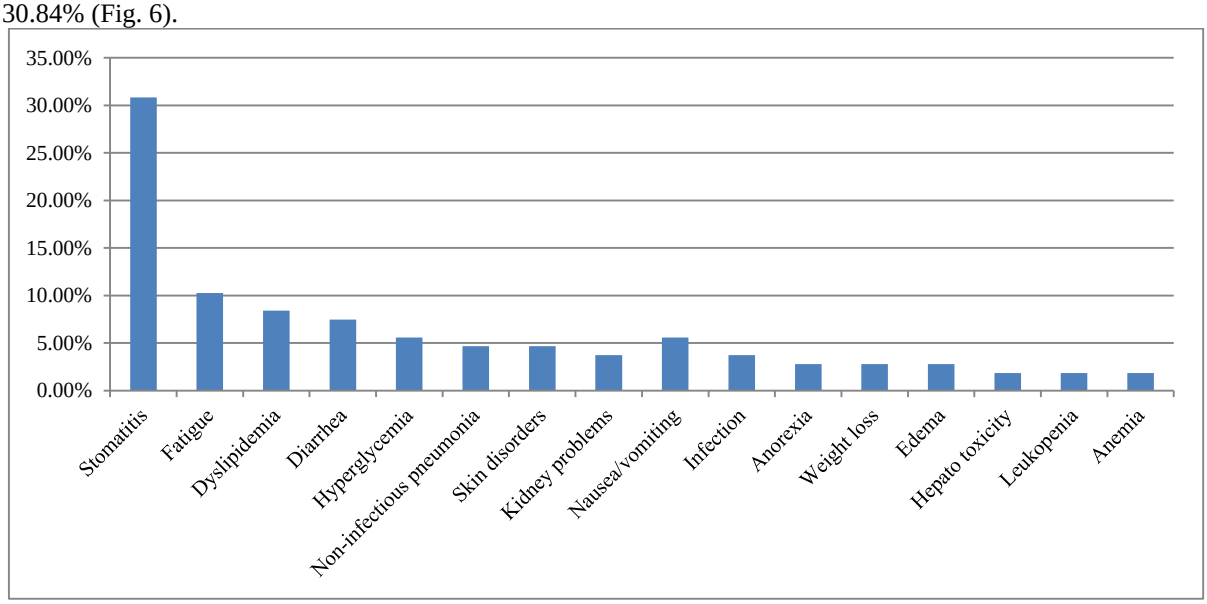

Fig. 6 Side effects of everolimus encountered by the patients

During the course of the study, everolimus side effects were managed either by medical intervention in 45.2% of cases, dose modification in 21.9%, dose postponing in 15.06%, drug discontinuation in 9.58%, or finally spontaneous resolution in 8.21% (Fig. 7).

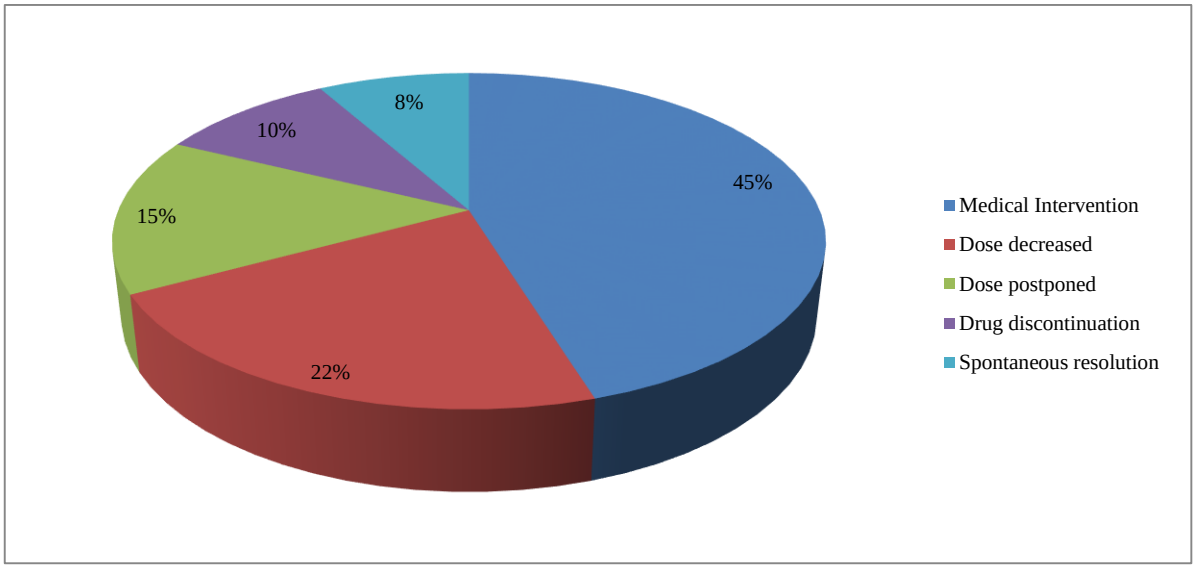

Fig. 7 Side effects of everolimus management

A high percentage (77%) of patients in this research discontinued their treatment. Seventy-percent of patients who discontinued everolimus did so due to progression, 17% due to side effects, 11.3% due to death and 1.88% due to cost (Fig. 8).

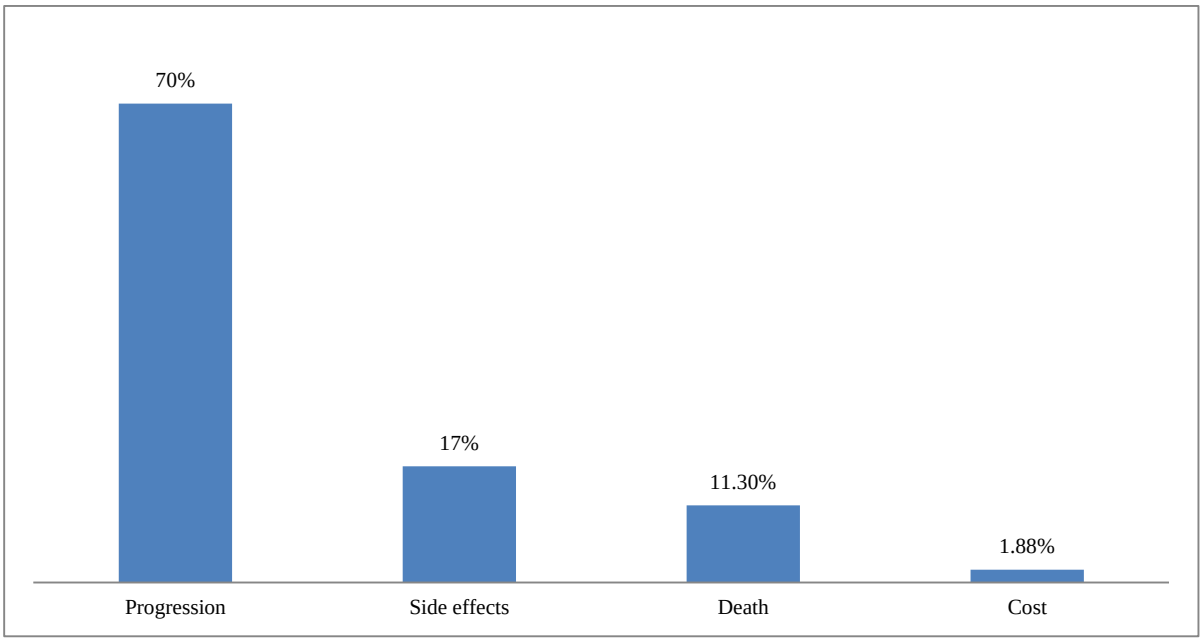

Fig. 8 Reasons of everolimus discontinuation

4. DISCUSSION

Family history of breast cancer is a major risk especially in females having one or more affected first-degree relatives (3). This is reflected in the studied sample where 24.99% of the participants had one or more first or second degree relatives or both with breast cancer. Age is another risk factor of breast cancer. In the current study, the median age of everolimus-exemestane combination initiation (60.36% ± 10.56 years) was near the median age reported by other studies (10). Considering obesity as an associated factor with increased risk of breast cancer,

48.77% of cases were either overweight or obese in this study (13). As such, regular exercise, weight loss and a healthy diet are crucial in order to maintain an adequate BMI.

Stage IIIC and metastatic stage constituted 52.39% of cases at diagnosis. This finding imposes better awareness among the Lebanese females in order to detect breast cancer in its early stages. Moreover, the bone was shown to be the major site of metastasis (46.4%) followed by visceral metastasis including liver and lungs (58%) before initiation of everolimus-exemestane combination comparably to cases in previous studies published by Baselda et. al., Thaddeus et al. and others (7-8, 14-16).

Non-steroidal aromatase inhibitors accounted mostly as the last medication preceding everolimus-exemestane co-therapy in the first and second lines similar to the results of BRAWO trial (14-16). This study showed increased chemotherapy use preceding everolimus-exemestane combination as identified also by previous studies (14-16). In fact, these matched results demonstrated a reflection of the level of common practice in Lebanon. Although NCCN guidelines recommended consecutively using three lines of endocrine therapy before switching to chemotherapy, some physicians in community-based oncology practices in Lebanon reserved everolimus-exemestane combination till after chemotherapy failure.

Across all therapy lines of everolimus-exemestane co-therapy, median progression-free survival (PFS) was 5.87 ± 10.84 months similar to Assi et al results which showed a median PFS of 5.2 months since the initiation of therapy (11). On the other hand, the median PFS was different from other median PFS found by Baselda et. al., Thaddeus et al. and others (7-8, 14-17). In fact, results identified by previous studies showed higher values in first and second line therapies and lower values in third and fourth line therapies (14-16). Furthermore, no specific line of everolimus-based therapy was powered over another in terms of survival. Median survival, in this study, was inferior to that of BOLERO-2 trial which showed a median survival of 31 months (18), but was within median survival of individuals with metastatic breast cancer that varied between 18 and 24 months (19); and this might be related to the exclusions done in ECOG 3 trial as well as in the BOLERO-2 trial, resulting in higher survival. Contrasting the findings obtained by the study conducted by Assi et al (11), lower median PFS was obtained in patients who were chemotherapy naïve (5.27 vs. 7 months). These results strengthen the susceptibility that physicians in community-based oncology practices reserved everolimus until chemotherapy failure. In accordance with the study conducted by Assi et al (11), higher median PFS was noted in patients with non-bone metastasis (7 vs. 5.27 months). As a result, everolimus-exemestane combination could be a good option for patients with metastasis other than bone.

Stomatitis percentage in this study is lower than those cited in the literature (7, 14-16), and they were due to the impact of prophylactic measures and careful monitoring during treatment. In fact, good side effects management played a key role in reducing everolimus discontinuation. Nevertheless, the major reason for everolimus discontinuation was progression followed by side effects as stated by the literature (7).

5. CONCLUSIONS

Everolimus-exemestane co-therapy has proven to be an effective combination in overcoming hormonal resistance in Lebanese breast cancer patients with results slightly inferior to those reported in the BOLERO-2 population. Good tolerance of the drug could be attributed to a control of the drug's side effects via adapted and preventive effective strategies. Further prospective study is needed to assure these findings.

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