Everolimus with endocrine therapy as a treatment option in ER + MBC failing at least one line of endocrine therapy: a single institute experience

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Abstract

75% of MBC are hormone receptor positive; on ET the responders eventually will acquire resistance. One of the suggestive mechanisms for this resistance is the activation of the mTOR pathway.
In the BOLERO-2 study, the addition of everolimus to exemestane was associated with a significant improvement in PFS.
Purpose and Methods: To evaluate the response rate in heavily pretreated population and the safety of the drug in different genetic/ethnic backgrounds.
We performed a retrospective analysis of all ER+, MBC who received everolimus during a period of 6 months.
A few cases were reported based on their interesting findings.
Results: 19 patients, Median age was 58, 26% were pre-menopause.
The combination was used after failure of at least one line of ET (1-4), 17 patients had it with exemestane and 2 with tamoxifen.
The median duration of the treatment was 20 weeks. 8 had it for ≤4weeks. The reasons were poor patient selection (PS ≥3), poor tolerance or progressive disease. Response assessment, 10 had PR, 2 SD, 1 PD, in 6 patients no evaluation was possible for premature stoppage of the therapy.
Toxicities: mucositis 78%. Less frequently hyperglycemia, weight loss, infection and non-infectious pneumonitis.
Dose interruptions and adjustments were frequently reported >70%.
Conclusions: Everolimus combination was associated with a high RR, it may be less toxic than chemotherapy, but patients who are poor candidates for chemotherapy may not be a good candidates for this combination as well, Educating patients and physicians experience reduce the treatment toxicity and improve the tolerability.)

Background

75% of metastatic breast cancers are hormone receptor positive but not all patients will respond to endocrine therapy[1]. In fact, a small proportion is primary refractory while the others eventually will acquire resistance to endocrine treatment (secondary resistance). One of the suggestive mechanisms for this acquired resistance is associated with activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway. In early pre-clinical and clinical studies, the addition of the mTOR inhibitor everolimus to endocrine therapy showed antitumor activity[3,4].
In the BOLERO-2 study, the addition of everolimus to exemestane was associated with a significant improvement in progression-free survival, with observed medians of 6.9 and 2.8 months[5]. This corresponded to a 57% reduction in the hazard ratio[5].

Objectives

- To evaluate the response rate in a heavily pretreated population, which differs from patients usually included in a clinical trail.
- To elaborate on the safety profile of the drug in patients who have worse PS and different genetic/ethnic backgrounds.

Methods

- We performed a retrospective analysis of all hormone receptor positive MBC who received everolimus as a combination with endocrine therapy during a period 6 months. 19 patients were included in this analysis.
- We reported the response rate which was defined by either radiological response according to (RECIST) criteria or a drop in tumor marker, as well as the median duration of treatment, Everolimus dosing, treatment interruptions, side effects, as well as other demographic data.
- A few cases were reported based on their interesting findings.

Results

Nineteen patients were eligible for evaluation. The median age was 58, (38 - 75 years). 5 patients (26%) were pre-menopause. (Fig. 1)
All patients received the combination after failure of at least one line of hormonal therapy. Three patients received the combination as 1st line palliative hormonal treatment after failing adjuvant hormonal therapy, while 8 patients received it as

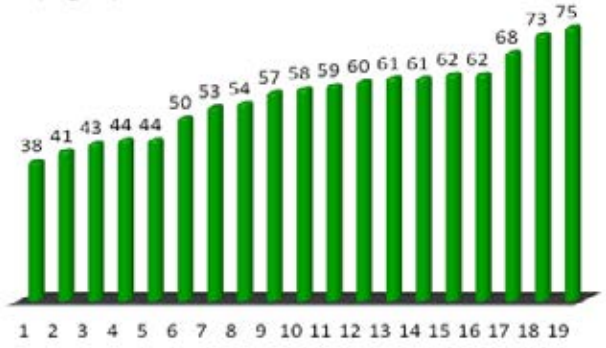
2nd line therapy. Five patients received treatment as 3rd line, 2 patients as 4th line and 1 patient received it as 5th line hormonal treatment. (Fig. 2, table 1)

The everolimus combination was with exemestane in 17 patients and with tamoxifen in 2 patients.

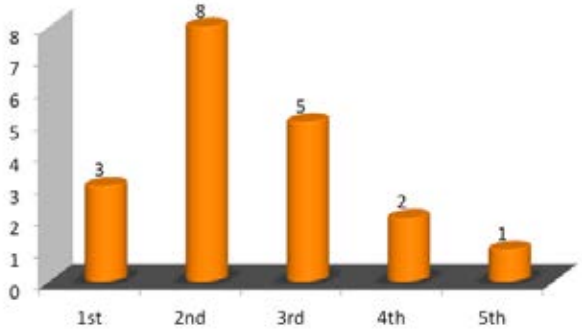
In 41% of the 1st group, the exemestane was considered a re-challenge and in 1 of the 2 tamoxifen cases, the patient was progressing and everolimus was added to the tamoxifen. (fig. 3, table 2)

Patient exposure to endocrine therapy before the combination ranged from (1 to 4) drugs with an average of 2.3.

(fig 1)



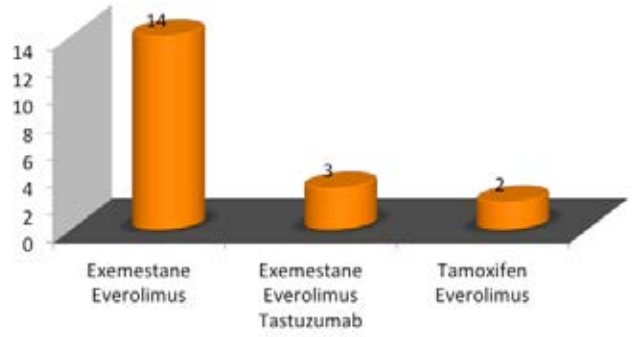
(fig 2)



(table 1)

	Prior hormonal treatment in palliative setting
1	0
2	Letrozole
3	Tamoxifen, Letrozole
4	Letrozole, Tamoxifen,
5	Letrozole, Exemestane, Tamoxifen, Fulvastran
6	Tamoxifen, Letrozole, Fulvastran
7	Tamoxifen
8	0
9	0
10	Letrozole, Exemestane
11	Letrozole
12	Anastrazole, Exemestane
13	Anastrazole, Exemestane
14	Exemestane
15	Exemestane, Tamoxiifen, Letrozole
16	Letrozole
17	Exemestane
18	Tamoxifen
19	Letrozole

(fig 3)



(table 2)

		Prior exposure	
Exemestane Everolimus	17	7	41%
Tamoxifen Everolimus	2	1	50%

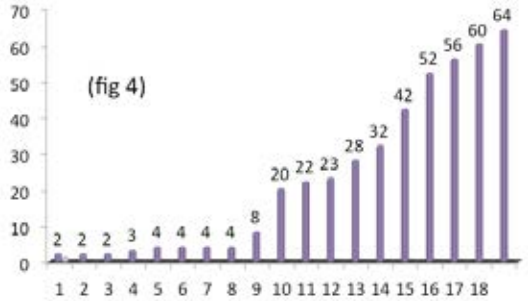
The median duration of the combination treatment was 20 weeks, ranging from 2-64 weeks. Eight patients had treatment duration of ≤4weeks. The main reason for this short duration was poor patient selection (poor PS ≥3) in 3 patients, 4 patients had poor tolerance and one patient had progressive disease. Eventually In all patients, the treatment was stopped for either progressive disease or poor tolerance (fig. 4, 5).

Response assessment (1st assessment) was available for 13 patients. Ten had PR, 2 SD, 1 PD, in 6 patients no evaluation was possible for premature stoppage of the therapy, (Table 3).

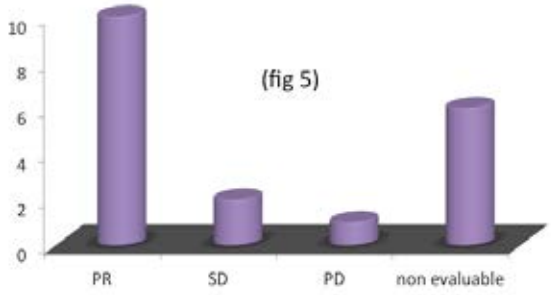
The toxicities reported were: mucositis (all grades) in 78% (fig 6). Less frequent Side effects included hyperglycemia, weight loss, infection (skin, UTI and URTI); two cases had non-infectious pneumonitis, which resolved with medical treatment. One of them the treatment was resumed at a lower dose.

Dose interruptions and dose adjustments were frequently reported >70%.

(fig 4)

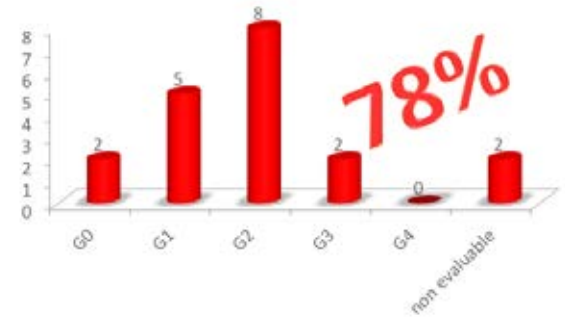


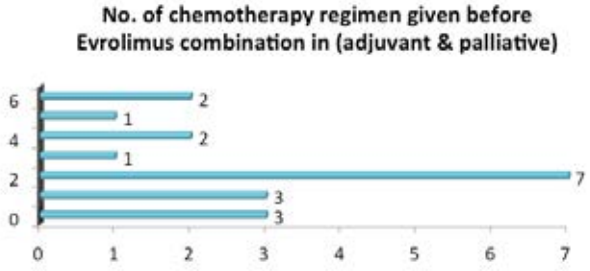
(fig 5)



(table 3)

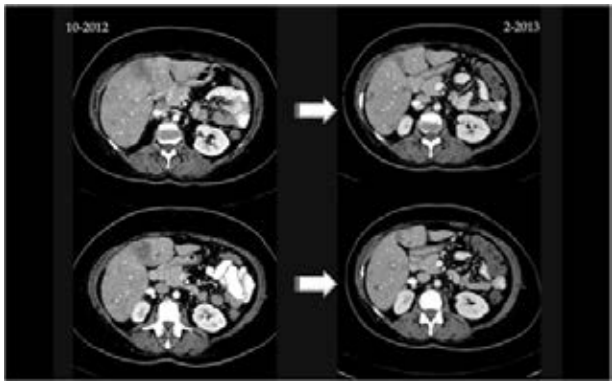
No. of pts	response
10	PR
2	SD
1	PD
6	non evaluable

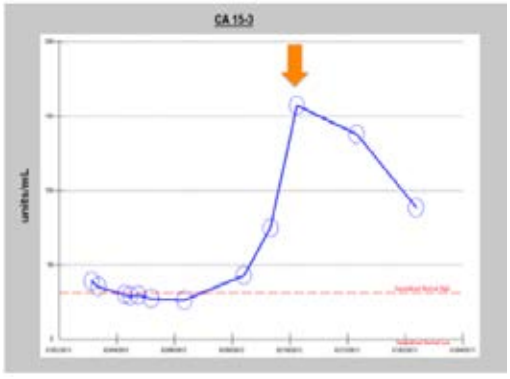




No. of pts	Reasons for early discontinuation
4	Referred to palliative care initial PS ≥3
1	Progressive Disease
1	Lost F/U
1	Still on treatment
1	poor tolerance

Line of R	Type of treatment	started	completed	Duration of response
1st Hormonal	Tamoxifen	Apr 2008	October 2010	30
2nd Hormonal	Letrozole	Octo 2010	October 2011	12
1st Chemo	Nab-Paclitaxel	Octo 2011	June 2012	
3rd Hormonal	Fulvestrant	June 2012	October 2012	4
4th Hormonal	Everolimus & Exemestane	Octo-2012	October 2013	12





Cases

Case 1

42 y/o patient diagnosed in 2000 with right breast cancer, underwent Rt MRM, staged as pT1b, N1 +1/12 LN, M0, ER (+), PR (+). She received adjuvant chemotherapy with 6 cycles of CEF followed by adjuvant endocrine therapy consisting of tamoxifen for 3 years only cause patient became pregnant.

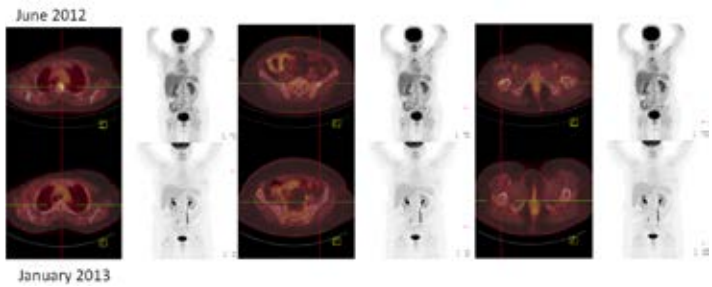
In March of 2008, she developed hip pain. Evaluation revealed diffuse bone metastases. She received palliative radiotherapy to pelvis and to D1-L2 spine. Cerb2 receptors were done on the initial breast tissue and this was negative. She was restarted on endocrine therapy with tamoxifen and goserelin, as well as zoledronic acid. Re-evaluation in January of 2010 revealed stable disease. In October of 2010, she developed progressive bone disease without visceral involvement. She was then switched to letrozole and continued on goserelin and zoledronic acid. A year later in October of 2011, CT scan revealed multiple liver metastases.

1st line palliative chemotherapy with nab-paclitaxel was given between October 2011 and June 2012. This was followed by 3rd line hormonal treatment fulvestrant 500mg. She was maintained on goserelin, and zoledronic acid was changed to denosumab. She continued to progress with increasing liver lesions. Liver biopsy revealed metastatic breast cancer, ER (+80%) PR (+50%) Cerb 2 (0). 4th line hormonal treatment was exemestane and everolimus was started in October of 2012. This was maintained for one year until October of 2013.

Case 2

49 y/o premenopausal female diagnosed in May of 2010 with right breast cancer. PET-CT revealed multiple bone lesions with no visceral metasteses.

1st line chemotherapy was paclitaxel + UFT + folinic acid and bevacizumab. She had 4 cycles between May2010 and Sept. 2010. Follow up PET-CT showed partial response. She underwent Rt MRM in October 2010. Histopathology revealed invasive ductal carcinoma, ER (+), PR (+), Cerb2 (0). 1st line hormonal treatment consisted of tamoxifen. She was also maintained on monthly injections of zoledronic acid. In January of 2012, she presented with back pain radiating to the left leg. MRI of the spine revealed progressive disease without cord or nerve root compression. Ovarian function assessment was consistent with post-menopausal state. She was switched to letrozole. Follow up PET-CT in June of 2012 revealed progressive bone metastases. Exemestane was started as 3rd line endocrine therapy. With no improvement in symptoms, Everolimus was added to exemestane in September of 2012. This lead to a clinical and radiological improvement of 14 months.



Conclusions

- The combination treatment of exemestane and everolimus is associated with a high response rate in fit patients.
- This treatment may be less toxic than chemotherapy, but patients who are poor candidates for chemotherapy may not be good candidates for this combination as well.
- Education and experience of both parties (patients and physicians), will help in reducing the everolimus toxicity and improve the tolerability to this treatment.

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