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Efficacy of Rapamycin Therapy in the Women with Metastatic Breast Cancer in West Iran

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Abstract **Background:** Mammalian target of rapamycin (mTOR) is one of the serine-threonine protein kinases and plays an important regulatory role in cell growth. Several randomized trials have shown that the use of mTOR inhibitors could improve patient outcome with hormone receptor-positive or Her2 positive breast cancer. The aim of study is to evaluation of efficacy of rapamycin therapy on the OS in metastatic breast cancer (mBC) patients in West Iran for the first time. **Materials and Methods:** Between of 2010 to 2014, sixty women with mBC referred to our Clinic. All of them after metastasis were treated with rapamycin (1 mg/day). Forty-three patients were treated for at least one year to three years (mean, 18 months) with rapamycin, that these patients were interred to our study. **Results:** The mean age for the patients at diagnosis of BC was 42 years (±9.9), 100% women. All of the patients had metastasis. For comparison of survival, we divide patients to 3 groups. Group 1: Patients with ER, PR positive and Her2 negative, Group 2: Patients with ER, PR and Her2 positive and Group 3: Patients with ER, PR and Her2 negative. The 5-year overall survival for mBC patients in group 1 was 93.3%, group 2 was 42.8% and group 3 was 72.7%. **Conclusions:** Rapamycin combination to hormone therapy increases the OS in the patients with mBC, but Rapamycin combination to trastizumab therapy reduces the OS.

Keywords: *metastatic breast cancer, overall survival, rapamycin*

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1. Introduction

Breast Cancer (BC) is the most common cancer (27% of all cancers) and common cause of death (16%) which occurs due to cancers among women, either in developed or developing countries [1]. The mean age in Iran for the patients with BC is more between of 50 – 70 years [2]. Up to 75% of breast cancers express the estrogen receptor (ER)α and/or the progesterone receptor (PR). Patients with hormone receptor-positive metastatic breast cancer (mBC) are typically treated with endocrine therapy. Yet, not all patients with mBC respond to endocrine treatments and are considered to have primary (de novo) resistance [3]. For patients who are estrogen and/or progesterone receptor positive, endocrine therapies offer treatments that interfere with the signaling pathway involved in cell growth and proliferation. Two targeted therapeutic examples include aromatase inhibitors, which interfere with estrogen production, and tamoxifen, which interferes with estrogen binding to the receptor. For patients who are Human epidermal growth factor receptor2 (HER-2) positive, targeted therapies with HER2 antibodies, such as trastuzumab and lapatinib, offer possible treatment options [4]. Rapamycin (sirolimus) was discovered more than thirty years ago from a soil sample from the island of Rapa Nui. It was isolated from Streptomyces hygroscopicus and initial characterization focused on its antifungal activities. Subsequent characterization showed that it has immunosuppressive properties and has been used successfully to reduce organ rejection with kidney transplantation. Rapamycin has proven to be a versatile compound with several seemingly unrelated properties, including antifungal, immunosuppressive, and anticancer. The National Cancer Institute (NCI) Developmental Therapeutics Program demonstrated that rapamycin inhibited cell growth in tumor cell lines [5].

The aim of study is to evaluation of efficacy of rapamycin therapy on the OS in mBC patients in West Iran for the first time.

2. Materials and Methods

2.1. Patients

Between of 2010 to 2014, sixty women with mBC referred to our Clinic. All of them after metastasis were treated with rapamycin. Forty-three patients were treated

for at least one year to three years (mean, 18 months) with rapamycin (1 mg/day), that these patients were interred to our study. We surveyed age, site of metastasis, grade, type of treatment and survival in the patients.

2.2. Statistic Analysis

IBM SPSS software version 19 was used for calculating of mean age and also GraphPad Prism 5 software for comparison of survival in the patients with differentiated treatments. P≤0.05 is statistically significant.

3. Results

The mean age for the patients at diagnosis of BC was 42 years (±9.9), 100% women. All of the patients had metastasis. 25 patients (58.1%) had metastasis to bone, 8 patients (18.6%) to liver, 6 patients (14%) to lung and 4 patients to brain. 5 patients (11.6%) were in grade I, 29 patients (67.4%) in grade II and 9 patients (21%) in grade III. Out of 43 patients, 32 patients (74.4%) got radiation, 34 patients (79.1%) were treated with tamoxifen, 24 patients (55.8%) with letrozole, 12 patients (28%) with trastizumab (Herceptin) and all of patients with *Rapamycin*.

Table 1. The clinical variables in the patients with metastatic breast cancer and invasive ductal carcinoma (n=43)

Clinical Variables	n(%) Mean±SD
Age(year)	42±9.9
Metastasis	
Yes	43(100)
No	0(0)
Site of Metastasis	
Bone	25(58.1)
Liver	8(18.6)
Lung	6(14.0)
Brain	4(9.3)
Grade	
I	5(11.6)
II	29(67.4)
III	9(21.0)
Type of treatment	
Radiation	32(74.4)
Tamoxifen	34(79.1)
Letrozole	24(55.8)
Trastizumab	12(28.0)
Rapamycin	43(100)

For comparison of survival, we divide patients to 3 groups:

Group 1: Patients with ER, PR positive and Her2 negative that were treated with hormone therapy (tamoxifen or letrozole or both), rapamycin and a number of patients with radiation.

Group 2: Patients with ER, PR and Her2 positive that were treated with hormone therapy (tamoxifen or letrozole or both), trastizumab, rapamycin and a number of patients with radiation.

Group 3: Patients with ER, PR and Her2 negative that were treated with hormone therapy (tamoxifen or letrozole or both), rapamycin and a number of patients with radiation.

The Figure 1 shows the 5-year survival for mBC patients in group 1 compared to group 2. The survival rate for group 1 was 93.3% but in group 2 was 42.8% that statistically this comparison was significant (P=0.006).

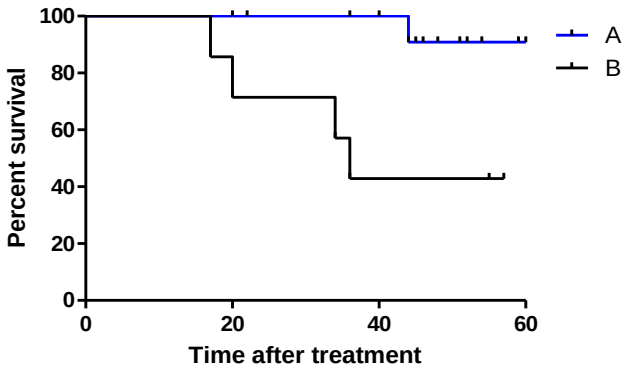

Figure 1. the 5-year overall survival for metastasis breast cancer patients with (A) ER, PR positive and Her2 negative compared to (B) ER, PR and Her2 positive

The Figure 2 shows the 5-year survival for mBC patients in group 1 compared to group 3. The survival rate in group 1 was 93.3% but for group 3 was 72.7% that statistically this comparison was significant (P=0.03).

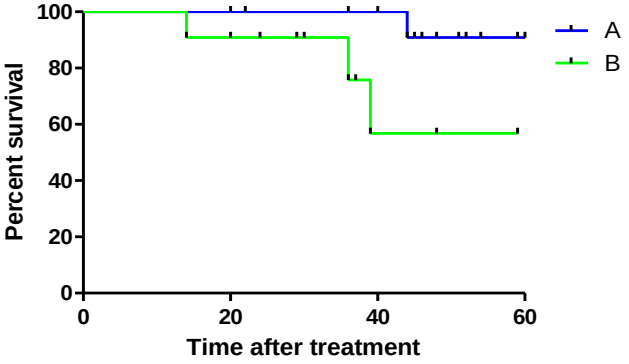

Figure 2. the 5-year overall survival for metastasis breast cancer patients with (A) ER, PR positive and Her2 negative compared to (B) ER, PR and Her2 negative

The Figure 3 shows the 5-year survival for mBC patients in group 2 compared to group 3. The survival rate in group 2 was 42.8% but for group 3 was 72.7% that statistically this comparison was no significant (P=0.3).

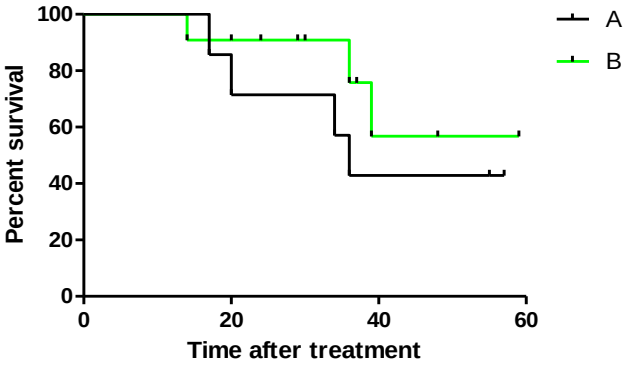

Figure 3. The 5-year overall survival for metastasis breast cancer patients with (A) ER, PR and Her2 positive compared to (B) ER, PR and Her2 negative

4. Discussion

BC is the most frequent malignancy among women that can be a leading cause of death through middle-aged women [6] that in Asia the maximum incidence is in 40 –

50 age groups. In Contrast, in western countries the increase in incidence continues as the age increases [7]. HER2 overexpression or gene amplification occurs in approximately 25 % of all breast cancers, and is associated with decreased the OS [8]. Mammalian target of rapamycin (mTOR) is one of the serine-threonine protein kinases and plays an important regulatory role in cell growth [9]. Several randomized trials have shown that the use of mTOR inhibitors could improve patient outcome with hormone receptor-positive or Her2 positive BC [10]. A study [11] reported that the combination of rapamycin with trastuzumab appears to be well tolerated with promising clinical benefit rate in patients with metastatic HER2-positive BC after progression on prior trastuzumab therapy. Therefore, mTOR inhibition may overcome resistance to trastuzumab in some HER2-positive tumors. In our study the 5-year overall survival for mBC patients in group 1(ER, PR positive and Her2 negative) was 93.3% compared to group 2(ER, PR and Her2 positive) was 42.8%. This difference in results shows that probably combination of hormone therapy with Trastizumab affect on worse treatment with rapamycin. mTOR activation was shown to mediate resistance to endocrine therapy in preclinical models and mTOR was described as a mechanism facilitating escape of long-term estrogen deprivation. Also, the addition of mTOR inhibitors to endocrine treatment has been investigated in phase II and III studies, including patients with hormone receptor-positive and HER2 negative BC [12]. Rapamycin has been shown to inhibit the growth of estrogen positive breast cancer. However, TNBC is resistant to rapamycin treatment in vitro [13]. In our study, the OS for group 1(93.3%) was better than TNBC group (72.7%) and this was better than group 2(42.8%). Therefore, we can result that rapamycin inhibits the growth of estrogen positive breast cancer, but trastuzumab therapy for group 2 causes that the OS be lower than TNBC group. Group 2(ER, PR and Her2 positive) is more resistant to rapamycin treatment compared to TNBC.

Chang et al. [14] suggested that rapamycin may be an effective treatment for ER-positive breast cancer, either alone or in combination with tamoxifen, and also may be a potential therapy for tamoxifen-resistant cancers. Even the mTOR inhibitor everolimus, in combination with hormonal treatments, has led to excellent results in progression-free survival in patients with mBC resistant to hormone therapies [15].

5. Conclusions

Rapamycin in combination to hormone therapy increases the OS in the patients with mBC, but Rapamycin in combination to trastizumab therapy reduces the OS. For a more definitive result, it needs more researches on rapamycin therapy with more mBC patients and with emphasis on tumor markers.

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