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Role of progesterone receptor status in determining treatment response among premenopausal breast cancer Libyan patients.

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Highlights

- **Breast cancer is the most common type of cancer affecting Libyan women.**
- **Despite recent advances in drug treatment, recurrence and distant metastasis are still major concerns.**
- **Identifying some biological factors such as receptor status has become a major prognostic factor for treatment outcomes.**

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ABSTRACT

Breast cancer is the most common type of cancer affecting women in Libya. Treatment strategy for premenopausal women involves Tamoxifen as an anti-estrogen in estrogen receptor-positive tumors. Many factors have been identified as predictors of treatment response, such as the receptor status of the tumor. In relation to progesterone receptors, a small number of studies have been performed regarding targeting progesterone receptors in cases of breast cancer.

Subject &Methods: a case series study of 46 premenopausal breast cancer females. A retrospective hospital record-based study of the clinicopathological features of premenopausal breast cancer cases admitted to the oncology department in the Benghazi medical center (BMC) Benghazi, Libya during two years, 2010 and 2013.

Results: The mean age of the study sample is 39.9×5.6 years, 56.5% of cases were in stage II at diagnosis, 47% of cases were infiltrating ductal carcinoma, 84.8% had positive progesterone receptor, 89.1% of the cases received Chemotherapy, 95.7% had radiotherapy, 28.3 had a history of either local recurrence or distant metastasis during the five years follow up period. Although approximately 92% of the relapsed cases were PR positive, this study revealed no statically significant relationship between progesterone receptor status and the treatment outcome in premenopausal breast cancer cases admitted to BMC at Benghazi ($x^2 19 = 4.7$ & $P=0.74$).

Conclusion: The study concluded that there was no clear role of the progesterone receptors in the tamoxifen treatment response, and further advanced research needed to understand the role of progesterone receptors in determining responders from non-responders to Tamoxifen treatment.

1. Introduction

Internationally, about a fifth of cancer deaths is attributed to breast cancer. It has been found that the most common type of cancer affecting women in the eastern part of Libya is breast cancer (Bodalal *et al.*, 2014). A previous study done in Libya involved about 234 patients with breast cancer, who were admitted to the oncology institute in Sabratha, Libya between the years 2002 and 2006; 68.4% of the cases were found to be premenopausal (Boder *et al.*, 2011). Tamoxifen has been proved to be the drug of choice for the treatment of estrogen receptor-positive tumors especially in premenopausal women ("Tamoxifen for early breast cancer: an overview of the randomised trials," 1998). Furthermore, Tamoxifen showed a good prophylactic effect against breast cancer in high-risk women (Powles *et al.*, 2007). Despite the advances in therapeutic strategies in breast cancer, drug resistance, and recurrence of malignancy with distant metastasis remain major problems (Li *et al.*, 2008). Many factors are considered as predictors for response to adjuvant endocrine therapy. One of these factors is progesterone receptor status. It has been shown that tumors with high progesterone receptor (PR) expression showed better responses to tamoxifen adjuvant therapy than those with PR negative tumors (Stendahl *et al.*, 2006). Furthermore, PR negative tumors tend to show higher expression levels of HER-1 and HER-2 receptors (Bardou *et al.*, 2003; Kim *et al.*, 2006; Osborne *et al.*, 2005). Overexpression of HER-1 and HER-2 receptors was shown to be related to tamoxifen resistance among ER-positive breast cancer patients (Huang *et al.*, 2005). Limited studies had been performed in relation to targeting progesterone receptors in cases of breast cancer.

According to the literature, progesterone receptor status is a strong predictor for response to tamoxifen (Purdie *et al.*, 2014; Stendahl *et al.*, 2006). It has been shown that ER activation by estradiol results in the induction of synthesis of PR in the breast (Horwitz and McGuire, 1978). Another important observation is that the downstream signaling pathways activated by the binding of progesterone to its receptors have been identified to be carcinogenic in mice mammary tissue (Brisken, 2013; Gonzalez-Suarez *et al.*, 2010). Based on these contradictory multiple pieces of evidence, PR seems to be of prognostic value in cases of breast cancer (Rojas *et al.*, 2017). Their absence has been linked to resistance to

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treatment, on the other hand, their expression showed an oncogenic effect in animal models of breast cancer. Furthermore, massive research emphasized the significance of progesterone receptor expression levels as a determinant to treatment response, and it should be accurately measured (Bardou *et al.*, 2003). Two isoforms of progesterone receptors, PRA and PRB were first described by Sherman et al., in 1970 (Bamberger *et al.*, 2000; Sherman *et al.*, 1970). Determination of PR isoforms as a predictor of treatment response has been highlighted in some studies (Hopp *et al.*, 2004). The differential expression of both isoforms is vitally correlated with clinical outcomes and tamoxifen response (Hopp *et al.*, 2004; Mote *et al.*, 2002). It has been elucidated that the majority of progesterone receptor-positive breast tumors express a higher level of the PR-A subtype (Bamberger *et al.*, 2000). Moreover, breast tumors with a higher PR-A/PR-B ratio have been linked to poorer outcomes (Singhal *et al.*, 2018). Many studies have provided clear evidence of the benefits of using progesterone antagonists in repressing the ER-mediated transcriptional activity in vitro (Lala *et al.*, 2019; Singhal *et al.*, 2018). However, PR action in breast cancer is grossly understudied and remains controversial (Lange and Yee, 2008).

The impact of prognostic/predictive biomarkers on the outcome of patients treated with appropriate standard systemic treatment has been considered by the American Joint Committee on Cancer (AJCC) (Dieci *et al.*, 2019). Staging System panel in the update of the breast cancer staging. Based on the incorporation of biologic factors (histologic grade, estrogen receptor, progesterone receptor, HER2, and multigene panels) to the classic anatomic stage, the 8th edition of the AJCC breast cancer staging system has introduced the prognostic stage, which was developed using data from patients identified in the National Cancer Database (2010–2011) and then validated in large cohorts of patients from the MD Anderson Cancer Center and the California Cancer Registry (Dieci *et al.*, 2019). Several studies, all conducted in retrospective patient cohorts, have been reported in the last couple of years. Overall corroborating the prognostic stage as a more accurate discriminator of breast cancer patients' outcome as compared to the anatomic stage (Dieci *et al.*, 2019).

2. Aims of the study

To assess the role of progesterone receptor and response to tamoxifen therapy among female Libyan patients from the eastern part of Libya.

3. Subjects and Method

A case series study was carried out. A retrospective hospital record study based on the clinicopathological features of breast cancer in females and the relation between progesterone receptor status and response to tamoxifen therapy among patients from the eastern part of Libya was investigated. The total number of breast cancer cases was 180 cases collected throughout one month from the oncology department in BMC during two years, 2010 and 2013. Oncology records for the years 2011 and 2012 were missed from the hospital. All cases were from the eastern part of Libya. 46 cases out of 180 were selected according to the follow-up period, estrogen receptor status, and age. All selected cases were premenopausal and had regular five years follow-up. All were estrogen receptors positive and received tamoxifen during their follow-up period.

3.1 Selection criteria

- Estrogen receptor status
- Age ≤ 50years
- premenopausal
- Had five years fellow up

3.2 Exclusion criteria

- Age >50 &menopause
- Negative estrogen receptors

3.3 Data collection

Many personal, clinical, and biological data were collected by the use of proforma filled from patients' files. The data were included: age, residency, family history of breast cancer, stages and types of the tumor at diagnosis, other receptor status, tumor markers, type of surgery, and chemotherapy regimen they received.

3.4 Data analysis

Data were coded and analyzed as frequencies, percentage, or as range and mean and some tests of significance were carried out at 95% degree of confidence and probability P=>0.05. The analysis was performed using SPSS software version 25.

Ethical approval was signed and obtained from the research ethics committee in Benghazi medical center.

3.5 Limitations

No electronic computerized health information system is available, and poor manual medical records with a lot of missing information for patient's treatment and complications which were resulted from irregular follow up and the patients were treated in many places in and outside Libya. In addition, mortality data were missing in many cases.

4. Results

The present study reported 46 premenopausal women out of 180 women diagnosed by histopathology as breast cancer cases during the years 2010 and 2013. In the present study premenopausal breast cancer represents 25.6% of all cases. The mean age of cases was 39.9+5.6 years; the minimum 22 years and the maximum 50 years. 25 (54.4%) of cases were in their 40-50 years, 25 (54.3%) of cases from outside Benghazi, 8 (17.4%) had a family history of breast cancer (Table 1).

Table1

Demographic characteristics of premenopausal breast cancer cases at Benghazi medical center (BMC)

Characteristics	Number	Percent
1. Residency		
• **Benghazi**	21	45.7
• **Outside Benghazi**	25	54.3
2. Age		
• **20<30y**	2	4.3
• **30<40y**	19	41.3
• **40-50y**	25	54.4
3. family history		
• **positive**	8	17.4
• **unknown**	6	13.0
• **No family history**	32	69.6

The current study reported that 26 (56.5%) cases at stage II (TNM staging), 11 (23.9%) at stage III, 7 (15.2%) at stage I, and 1 (2.2) at stage 0 and stage IV as shown in (Fig.1).

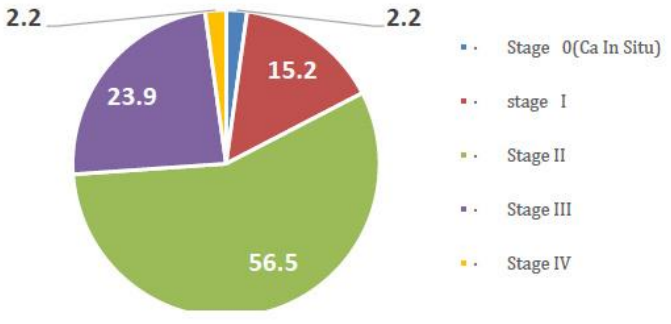

Fig. 1. Stage Distribution of premenopausal breast cancer cases admitted to BMC, Benghazi Libya

Table 2, showed that 40 (47%) cases infiltrating ductal carcinoma, 4 (8.7%) infiltrating lobular carcinoma, and 2 (4.3%) ductal carcinoma in situ.

Table 2

Distribution of premenopausal breast cancer cases according to types and management

Items	Number	Percent
1. Tumor type		
• Inf. Duct.ca	40	87.0
• Duct carcinoma in situ	2	4.3
• inf.lob.ca	4	8.7
2. Progesterone Receptors		
• positive	39	84.8
• Negative	7	15.2
3. Estrogen Receptors		
• positive	46	100.0
4. HER-2 receptors*		
• positive	11	23.9
• Negative	35	76.1
5. Radiotherapy		
• Yes	44	95.7
• No	2	4.3
6. Surgery		
• SMAC**	21	45.7
• Lumpectomy	19	41.3
• MRM***	5	10.9
• missing	1	2.2
7. Tumor marker		
• Normal	33	71.7
• Increased	7	15.2
• Nil	6	13.0
8. Chemotherapy		
• FEC based****	35	76.1
• FAC based*****	2	4.3
• others	5	10.9
• missing	4	8.7
9. Metastasis		
• Yes	13	28.3
• No	33	71.7
Total	46	100.0

**HER: human epidermal growth factor receptor, **SMAC: simple mastectomy with axillary clearance, ***MRM: modified radical mastectomy ****FEC:5-fluorouracil epirubicin cyclophosphamide, *****FAC: 5-fluorouracil Adriamycin cyclophosphamide. TNM(T=tumor, N= node , M= metastasis.

The present study reported that progesterone receptors were positive in 39 (84.8%), estrogen receptors were positive in all cases and only 11 (23.9%) were HER2 receptors positive (Table 2). The current study reported that 44 (95.7%) had radiotherapy, (45.7%) had a simple mastectomy with axillary clearance (SMAC), 19 (41.3%) had a lumpectomy, and 5 (10.9%) had modified radical mastectomy (MRM). 89.1% of the cases received chemotherapy, 35 (76.1%) treated with 5-fluorouracil epirubicin cyclophosphamide (FEC based), and 2 (4.3%) were treated with 5-fluorouracil adriamycin cyclophosphamide (FAC based). The present study reported that 13 (28.3%) had recurrence metastasis (Table 2).

This study showed the distribution of types of premenopausal breast cancer according to family history, estrogen receptor, progesterone receptors, and HER2 receptors. There is no significant relationship between the type of cancer and family history, progesterone receptors and HER2 receptors where ($X^2 4 = 6.4$ & P=0.168), ($X^2 2=0.657$ & P=0.720), and ($X^2 2=2.169$ & P=0.338) respectively. Also, family history was positive in 6 (15.4%) of infiltrating ductal carcinoma, 2 (50%)of ductal ca. in situ, and 8 (17.8%) of infiltrating lobular cancer. The positive progesterone receptors were reported in 34 (85%) of infiltrating ductal carcinoma cases, 2 (100%) of ductal ca in situ, and 3 (75%) of inf. lob. ca. (Fig. 2).

The present study reported no significant relationship between progesterone receptors and treatment outcome in premenopausal breast cancer cases admitted to BMC at Benghazi ($x^2 19=14.7$ & P=0 .74).

5 Discussion

This study included only premenopausal patients with positive estrogen receptor expression. Among patients treated with Tamoxifen, some cases may show primary resistance, while others may develop secondary resistance (Clarke *et al*., 2001). Most of the studied resistance mechanisms are related to either loss of ER, altered expression of ER, or mutation of ER (Lykkesfeldt, 1996). In this study sample, 13 out of 46 (28.2%) of patients experienced recurrence and distant metastasis. This indicates that some cases showed resistance to tamoxifen despite regular treatment and follow-up over five years. Approximately, 92% of the relapsed cases were PR positive, but this relation failed to show statistically significant evidence. This could be due to the small sample number. Considering this result may contradict the previous studies about the positive role of PR in improving treatment outcomes, and this could imply that cases with PR-positive tumors are not good responders to tamoxifen therapy. It is evident that differential expression of progesterone receptor subtypes A and B is strongly related to cancer development in the mammary tissue (Richer *et al*., 2002).

Moreover, the higher expression of the PR-A subtype has been linked to poor treatment outcomes (Singhal *et al*., 2018). However, many of the available antiprogesterones like lonaparisan and mefiprestone failed to improve treatment outcomes in humans, and a drug like onapristone has been proved to be hepatotoxic (Jonat *et al*., 2013; Lala *et al*., 2019).

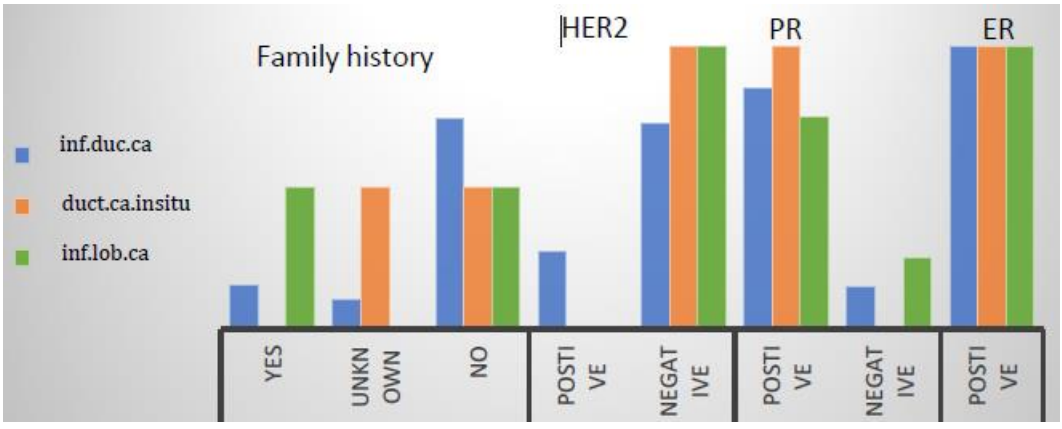

Fig. 2. Distribution of types premenopausal breast cancer according to family history and hormonal receptors

A randomized placebo-controlled phase II trial using telapristone acetate, a selective negative progesterone receptor modulator, in treating early breast cancer was recently performed. It has been shown that this drug can produce an anti-proliferative signal by repressing HER2 amplification genes, so reducing the expression of HER2 which is one of the suggested mechanisms of Tamoxifen resistance (Lee *et al*., 2020).

6. Conclusion

The researchers concluded that no significant role of progesterone receptor in tamoxifen response in premenopausal breast cancer cases with positive PR in the BMC, Benghazi Libya. As the evidence from the literature seems controversial, further advanced studies are required to determine responders from non-responders. Moreover, developing drugs with selective PR-A subtype blocking activity, as well as further analysis and genotyping tests could be an additional strategy in the management of premenopausal breast cancer women.

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