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Quality of Life in Relation to Hormonal Therapy in Breast Cancer Patients- an Evidence Based Review

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Abstract

Antihormonal treatment is currently the mainstay therapy in hormone receptor positive breast cancer patients after adjuvant chemotherapy or after surgical resection. However long term use of antihormonal therapy can lead to various side effects which may affect patient's daily activities. This study was done to assess certain parameters on quality of life in day to day activities of the breast cancer patients who were on hormonal therapy based on recently published articles. This was an evidence based review of published studies on quality of life related to various side effects of hormonal therapy in breast cancer patients. Literature search was done based on English language, full text freely available journal articles indexed in PUBMED database over last 5 years. MeSH terms used for retrieving the articles were hormonal therapy, quality of life, breast cancer through Boolean method. Thirty articles were identified out of which seven articles were selected according to inclusion criteria and are discussed in this review. Data on the quality of life related to commonly reported side effects with different hormonal therapies were collected from these articles. Different scales were used by different authors in those published studies. The commonality of adverse events was found to be on musculoskeletal system, vasomotor symptoms and sexual function in these studies and is discussed in this review.

Keywords: Hormonal therapy; Quality of life; Breast cancer

Introduction

Breast cancer is now the most common cancer among females worldwide and one of the leading cause related to cancer mortality [1]. 1.67 million New breast cancer cases were diagnosed in 2012 worldwide including 144,937 from India [2]. Antihormonal treatment is currently the main stay therapy in hormone receptor positive breast cancer patients after surgical resection or adjuvant chemotherapy. Currently, selective estrogen receptor modulators and Aromatase Inhibitors (AIs) are two major groups used in antiestrogen therapy for hormone sensitive breast cancer. Some recent studies indicated that patients with breast cancer derive some additional benefit, in terms of disease-free survival, overall survival, and decrease in contralateral breast cancer risk, if tamoxifen is taken for up to 10 years or AIs are continued for 5-10 years after completion of 5 years of tamoxifen [3]. However long term use of antihormonal therapy can lead to various side effects related to vasomotor symptoms, musculoskeletal symptoms, sexual disorders etc [3]. So there is a need to understand the long term impact of hormonal therapy in breast cancer patients on their quality of life. This study was done to assess a few parameters on quality of life in day to day activities of the breast cancer patients who were on hormonal therapy based on a few recently published articles.

Materials and Methods

This was an evidence based review of published studies on quality of life related to various side effects of hormonal therapy in breast cancer patients. Literature search was done based on English language, full text freely available journal articles indexed in PUBMED database over last 5 years. MeSH terms used for retrieving the articles were hormonal therapy, quality of life, breast cancer through Boolean method. Thirty articles were identified out of which seven articles were selected according to inclusion criteria and discussed in this review. Studies on quality of life of patients on non hormonal chemotherapy, surgical and radiotherapy and published in other indices were excluded. Data on the quality of life related to commonly reported side effects with different hormonal therapies were collected from these articles. These were assessed in order to identify their relation to quality of life in those patients. The findings were expressed according to published data.

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Table 1: Impact of Hormonal Treatment on Musculoskeletal Symptoms.

Study	Design	Sample Size	Tool	Result
Seber [4]	Cross-sectional survey	78	Health Assessment Questionnaire (HAQ) VAS SF-36	Higher incidence of antihormonal treatment related musculoskeletal pain in Letrozole group compared to tamoxifen plus LHRH group (p=0.062). Thirty-seven (47.4%) patients were found to have musculoskeletal symptoms associated with antihormonal treatment
Ganz [5]	Observational cohort study	186	BCPT symptom scale	Musculoskeletal symptoms were significantly higher in aromatase inhibitor group *vs.* no endocrine treatment group (p=0.02) at 12 months
Ganz [6]	Randomized, double blind phase 3 clinical trial	1193	BCPT symptom scale	Severity of musculoskeletal pain (1.50 *vs.* 1.72; p=0.0006) was significantly higher in anastrozole group than in tamoxifen group
Yagata [7]	Randomized open-label, multicenter trial	330	SF-36 EuroQol EQ-5D-3L	Joint pain and joint stiffness were reported by 61.6% and 59.1% of patients respectively taking anastrozole. Joint pain was reported in the knee by 61.0% of patients and in the hand by 36.0% of patients.

Table 2: Impact of Hormonal Treatment on Vasomotor Symptoms.

Study	Design	Sample Size	Tool	Result
Ribi [8]	Randomized phase 3 trial	1722	Breast Cancer Study Group QoL Core Form Trial-specific module	Treatment differences for vasomotor symptoms like hot flushes and sweats were significantly more in patients receiving tamoxifen plus ovarian function suppression than patients on tamoxifen alone at 6 and 24 months
Ganz [5]	Observational cohort study	186	BCPT symptom scale	hot flash symptom severity, and adjusted group means were significantly higher with the two endocrine groups i.e tamoxifen and aromatase inhibitor at 6 months (P=0.009) and at 12 months (P=0.003)
Ganz [6]	Randomized, double blind phase 3 clinical trial	1193	BCPT symptom scale	Vasomotor symptoms (1.33 *vs.* 1·17; p=0.011), were significantly more severe in tamoxifen group than anastrozole group. Younger age was significantly associated with more severe vasomotor symptoms (mean severity score 1·45 for age <60 years *vs.* 0·65 for age ≥60 years; p=0·0006
Taira [9]	Randomized, open label, parallel group study	497	FACT B	Symptoms of hot flush increased significantly from 6.5% at baseline to 11.3% (p=0.0125) after 4 weeks and 10.3% (p=0.0451) at 16 weeks with letrozole

Results

Data of adverse effects of hormonal therapy were collected from seven published articles. Different scales were used by different authors in those published studies. The commonalities of adverse events were found to be on musculoskeletal system, vasomotor symptoms and sexual function and the data were categorized accordingly in this study.

Musculoskeletal symptoms

The musculoskeletal symptoms associated with hormonal therapy in breast cancer patients has lead to an interest in studying the long term effect of adjuvant hormonal therapy on breast cancer patients. Details of these studies are given in Table1. Most of these studies have reported worsening of musculoskeletal symptoms with use of aromatase inhibitors as adjuvant treatment in breast cancer patients. Results from a cross sectional survey by Seber et al. suggested that antihormonal treatment related musculoskeletal pain was more in patients receiving letrozole therapy when compared with patients receiving tamoxifen plus LHRH agonist, although the difference in two groups didn't reach statistical significance (p=0.062) [4]. Similar worsening of musculoskeletal symptoms with aromatase inhibitors was reported in two other studies [5,6]. Outcomes from an observational cohort study suggested that musculoskeletal symptoms were significantly higher in aromatase inhibitor group *vs.* no endocrine treatment group (p=0.02) [5]. Whereas results from a randomized phase 3 clinical trial suggested that severity of musculoskeletal pain (1.50 *vs.* 1.72; p=0.0006) was significantly greater in anastrozole group than in tamoxifen group [6]. In another randomized open label study, which studied joint symptoms in postmenopausal breast cancer patients who completed five years of treatment with anastrozole, reported that joint pain and joint stiffness were reported by 61.6% and 59.1% of patients respectively taking anastrozole [7]. In this study most common site for joint pain reported were knee and hand by 61.0% and 36.0% of patients respectively whereas most common site of joint stiffness was the hand (67.9%), followed by the knee (33.1%), the foot (24.1%), the shoulder (23.0%), the elbow (10.2%), and the wrist (23.0%).

Vasomotor symptoms

Details of studies are given in table 2. Results from a randomized control trial by Ribi et al. suggested that treatment differences for vasomotor symptoms like hot flushes and sweats were significantly more in patients receiving tamoxifen plus ovarian function suppression than patients on tamoxifen alone at 6 and 24 months [8]. However these differences were not present at 60 months. Outcomes from an observational cohort study by Ganz et al. [5] suggested that hot flash symptom severity, and adjusted group means were significantly higher with the two endocrine groups i.e. tamoxifen and aromatase inhibitor at 6 months (p=0.009) and at 12 months (p=0.003). Pair wise comparisons in this study suggested a statistically significant differences at 6 months and 12 months between tamoxifen and the no-Endocrine Treatment(ET) group (p=0.008 and p=0.002 for respective time points) and between AI and no ET (P=0.02 and p=0.02 for respective time points) [5]. Similarly results from a randomized phase 3 trial by Ganz et al. [6] suggested that vasomotor symptoms (1.33 *vs.* 1·17; p=0.011), were significantly more severe in tamoxifen group than anastrozole group. Results from this study also suggested that younger age was significantly associated with more severe vasomotor symptoms (mean severity score 1·45 for age <60 years *vs.* 0·65 for age ≥60 years; p=0·0006 [6]. Results from an another study by Taira et al. which studied response of letrozole in postmenopausal breast cancer patients suggested that symptoms of hot flushes increased significantly from 6.5% at baseline to 11.3% (p=0.0125) after 4 weeks and 10.3% (p=0.0451) at 16 weeks [9].

Sexual functioning

Details of studies are given in table 3. Results from a study by Ribi et al. suggested that patients reported a continuous decline in sexual interest over the whole treatment period in both groups, with a clinically meaningful decrease observed between months 6 and 60 (range, -8 to-11) in patients on tamoxifen plus OFS, and after

Table 3: Impact of Hormonal Treatment on Sexual Functioning.

Study	Design	Sample Size	Tool	Result
Ribi [8]	Randomized phase 3 trial	1722	Breast Cancer Study Group QoL Core Form Trial-specific module	Decline in sexual interest over whole treatment period in both groups, with a clinically meaningful decrease observed between months 6 and 60 (range, -8 to-11) in patients on tamoxifen plus OFS, and after 36months (-9 at month 36 and -9 at month 60) in patients on tamoxifen.
Ganz [6]	Randomized, double blind phase 3 clinical trial	1193	Four-item Medical Outcomes Study (MOS) Sexual Problems Scale to measure sexual functioning	Decline in mean sexual functioning scores in both tamoxifen and anastrozole groups. However difference in two groups was not statistically significant (mean score 43.65 for the tamoxifen group *vs.* 45.29 in the anastrozole group; p=0.56)

36months (-9 at month 36 and 9 at month 60) in patients on tamoxifen [8]. Similarly results from a randomized control by Teevarwerk et al. reported decline in sexual activity among women receiving tamoxifen plus OFS compared with women receiving tamoxifen alone at all follow-up time points after month 6 and differences were statistically significant [10]. Outcomes from a randomized control trial by Ganz et al. [6] reported decline in mean sexual functioning scores in both tamoxifen and anastrozole groups. However difference in two groups was not statistically significant, mean score 43.65 for the tamoxifen group *vs.* 45.29 in the anastrozole group; p=0.56 [6].

Discussion

Patients of breast cancer on aromatase inhibitors have higher incidence of musculoskeletal symptoms like symptomatic arthralgia, joint pains and joint stiffness in this review. This can be explained through depletion of estrogen caused by aromatase inhibitors which results in loss of bone mineral density and increased risk of fractures [3]. It typically occurs within 3 months after initiation of AI treatment and higher prevalence is observed at around 6 months [11]. Arthralgic symptoms can have an impact on treatment adherence and daily activities in patients on aromatase inhibitors. In an observational study by Boonstra et al. all patients with arthralgia symptoms experienced an impact on their daily activities and mean PDI was 20.0 (SD, 17.8), indicating a major impact limiting daily activities [11]. However in study by Yagata et al. 325 patients reported joint pain but this didn't affect the activities of daily living in (96%) most of patients [7].

Vasomotor symptoms were reported to be present with both tamoxifen and aromatase inhibitors in this review. Hot flushes are one of the common antihormonal treatment related vasomotor side effect. They are characterized by episodic sensations of heat, intense sweating including night sweats, and flushing affecting the face and chest, which are often accompanied by palpitations and anxiety [12]. They can have a negative impact on women's quality of life by causing decreased sleep quality and increased levels of fatigue and depression [13]. In healthy women treatment with hormonal replacement therapy is effective in reducing hot flushes, however in patients of breast cancer, hormonal replacement therapy is contraindicated due to risk of disease recurrence [12,13].

Decline in sexual acivity was reported to be more with patients on tamoxifen plus ovarian function suppression in two studies (Ribi et al. and Tevaarwerk et al.), when compared to tamoxifen alone [8,9]. Sexual dysfunction can lead to emotional distress, including sadness/depression, issues related to personal appearance, stigma, and can have negative impacts on personal relationships [14]. In a survey conducted by Live strong 2010, that included over 3,000 people (24% with breast cancer, 41% one to five years post-treatment), sexual functioning and satisfaction were ranked the third most frequently reported concern [14-15]. Most of the above studies were based on western context however there is a need to assess the similar parameters globally with different socio cultural context in order to identify the variability on quality of life.

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