

Post Treatment Monitoring of Localized Breast Cancer in Tunisia

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Abstract

Background: Therapeutic advances in breast cancer resulted in an increase in survival, which had resulted in a dilemma in how to manage these patients after cancer treatment. The aim of our study was to report post therapeutic monitoring features of breast cancer in Tunisia in comparison with international guidelines and particularities of post treatment toxicity management.

Methods: We conducted a retrospective study including 50 breast cancer survivors in the department of medical oncology in The Military Hospital of Tunis between January 2012 and December 2013.

Results: All patients were clinically monitored by specialists every 3 months the first two years and 6 months the 3 following years. Mammography and ultrasound were done every year. Chest X-ray, abdominal ultrasound and CA 15-3 were systematically done every 6 months. Local recurrence occurred in 1 patient (2%) and metastatic recurrence in 12 patients (24%). Breast reconstruction was made in 5/37 mastectomy. Fatigue grade I-II was treated by cognitive behavioral therapy and correction of anemia in 40/47 patients. Peripheral neuropathy was treated in 10/10 cases. Weight monitoring was performed in 80% of patients and lifestyle dietary advice was provided in 70% of cases. Sexuality problems were considered using psychotherapy in 21/30 patients receiving hormonal therapy. Psychological disorders were treated by psychotherapy in 26/32 patients. Cognitive disorders were not treated. One third of women with menopausal symptoms were treated.

Conclusion: High priority should be given to improve quality of monitoring and late treatment toxicity management of breast cancer survivors in Tunisia.

Introduction

Earlier detection and treatment of breast cancer (BC), combined with recent advances in treatment, contributed to survivors living longer with cancer with a 5-year survival rate of almost 90%; thus, addressing survivors' unique post-treatment needs is critical to providing quality health care (1,2). Many studies highlighted the importance of surveillance, health promotion, and assessing and managing the myriad of physical, psychological, spiritual, social, and practical long-term and late effects faced by many cancer survivors after completing active treatment. Recent publications affirm the importance of addressing health, wellness, and quality of life (QoL) concerns of post-treatment cancer survivors. In recognition of the increasing need for information to support primary care clinicians who care for BC survivors, these guidelines were developed to provide recommendations to enhance the quality of clinical follow-up care after surgery, radiotherapy (RT), hormonal therapy (HT) and chemotherapy (CT). Although many evidence-based clinical guidelines exist for diagnosis and treatment, there are few evidence-based clinical care guidelines addressing life-long follow up care for survivors by cancer type (2). We studied post therapeutic monitoring features of BC in Tunisia in comparison with international guidelines and particularities of post treatment toxicity management.

Methods

We conducted a retrospective descriptive study in the department of medical oncology in the military hospital of Tunis on 50 patients with non-metastatic BC at diagnosis and who have completed surgery, CT, HT and RT. Patients were included between January 2012 and December 2013. We studied epidemiological, clinical and therapeutic features of our population and we focused on frequency of monitoring, physical examina-

tion, laboratory tests and imaging for the detection of BC recurrence in the adjuvant setting after curative-intent primary therapy and compared our practice with ASCO guidelines. We also studied our performance in management of common long-term and late treatment toxicities. Toxicity was evaluated according to WHO toxicity scale. Statistical analysis was performed with SPSS version 18.

Results

The mean age was 51.3 years (34-77 years). 13 patients had a lumpectomy and axillary dissection (26%) and 36 patients had a mastectomy (72%). Histological stage was pT1 in 18%, pT2 in 52%, pT3 in 20% and pT4 in 10% of cases. Lymph node status was pN0 in 38%, pN1 in 28%, pN2 in 8% and pN3 in 26%. 30 tumors (60%) were hormone receptor positive (HR +) and 12 tumors (24%) overexpressed HER (Table 1). Neoadjuvant CT was performed in 7 cases (14%). Histological response was stage 4 according to Chevalier classification in 4 cases, stage 3 in 2 cases and stage 2 in 1 case. All patients had adjuvant CT: Sequential CT with 3-4 FEC cycles (5FU-Epirubicin-Cyclophosphamide) followed by 3-4 Docetaxel or Paclitaxel cycles in 68% of cases, 6 FEC in 20% of cases and 3-4 Docetaxel in 12% of cases after poor pathologic response to neoadjuvant FEC chemotherapy. 47 patients had RT (94%): 50 gray in 40 cases and 60 Gray in 7 cases. 30 patients had HT: 18 started with tamoxifen and 12 with aromatase-inhibitors. All patients whose tumors overexpressed HER2 received Trastuzumab. In order to seek recurrence, a detailed cancer-related history and physical examination were done every 3 months the first 2 years and every 6 months the following 3 years, a mammogram and breast ultrasound were done every year and a chest radiograph and abdomino-pelvic ultrasound were done every 6 months. CA15-3 was done every 6 months. Metastatic recurrence was suspected because of clinical examination in 13 patients (26%) reporting bone or abdominal pain or persistent headache or cough. Recurrence was suspected by biological and radiological tests in 36 patients (72%) including CA 15-3 increase in 29 cases, chest radiograph in 21 cases, abdominal ultrasound in 17 cases, bone scintigraphy in 13 cases and CT-scan in 11 cases. Finally, after a median follow up of 24 months, one patient had local recurrence (2%) and 12 patients had metastatic relapse (24%).

Concerning long-term and late treatment toxicities (Table 2), postoperative sequelae were keloid scar in 4 patients and breast asymmetry in 6 of 13 patients who underwent conservative surgery. After radical surgery (37 patients), skin dysesthesia was observed in 21 patients. A lymphedema occurred in 18 patients (36%) and functional impairment of the shoulder in 33 cases (66%). Breast reconstruction in case of mastectomy was done in 5 out of 37 cases. 25 patients with lymphedema or functional impairment were referred to physical therapist. After CT, 47 of patients reported grade I-II fatigue (94%) treated by cognitive behavioral therapy and correction of anemia in 40 patients. 8 patients had (16%) edema in the lower extremities. Onycholysis was observed in 23 patients (46%) and skin and nails hyperpigmentation in 19 patients (38%). Post CT amenor-

Table 1. Demographic characteristics of patients at baseline

Characteristics	No. (%)
Age-years	
Mean	51.3
Range	34-77
Age (%)	
<40	7 (14)
40-59	32 (64)
60-69	7 (14)
≥70	4 (8)
Family history of breast cancer	6 (12)
Postmenopausal status	24 (48)
Surgery	
Lumpectomy and axillary dissection	13 (26)
Mastectomy	36 (74)
Pathological features	
Tumor size >2 cm	42 (84)
Histological stage	
pT1	9 (18)
pT2	26 (52)
pT3	10 (20)
pT4	5 (10)
pN0	19 (38)
pN1	14 (28)
pN2	4 (8)
pN3	13 (26)
SBR I	9 (18)
SBR II	25 (50)
SBR III	16 (32)
Vascular tumor emboli	8 (16)
HR (+)	30 (60)
Her2 overexpressed	12 (24)
CA15-3 elevated	8 (16)

rhea occurred in 23 patients (46%). Peripheral neuropathy reminded after CT in 10 cases (20%) and was of grade II in 8 cases and grade III in 2 cases. Serotonin-norepinephrine reuptake inhibitors were delivered in all cases and tricyclic antidepressants was added in 2 cases. Neuropathy has decreased gradually after the end of treatment after a median of 5 months. RT complications were essentially hyperpigmentation in 19 patients (38%). HT toxicities were essentially a weight gain in 22/30 cases, hot flashes in 24 cases, dyspareunia in 11 cases, vaginal discharge in 2 cases, decreased libido in 25 patients, arthralgia in 4 cases and dyslipidemia in 3 cases. Sexuality problems were considered using psychotherapy in 21 out of 30 patients receiving HT, dyspareunia was treated in 5 cases using water based lubricants and moisturizers for vaginal dryness and hot flashes were treated in 7 cases. One young patient was referred to a specialist in reproductive endocrinology and infertility and was pregnant after treatment. Psychologi-

Table 2. Long term treatment toxicity

	No. (%)
Surgery	
Keloid scar	4 (8)
Breast asymmetry after conservative surgery	6 out of 13 pt
Skin dysesthesia	21 (42)
Lymphedema	18 (36)
Functional impairment of the shoulder	33 (66)
Chemotherapy	
Asthenia	47 (94)
Edema	8 (16)
Onycholysis	23 (46)
Skin and nails hyperpigmentation	19 (38)
Post chemotherapy amenorrhea	23 (46)
Peripheral neuropathy	10 (20)
Grade II	8
Grade III	2
Hormone therapy (30 patients)	
Weight gain	22
Hot flashes	24
Dyspareunia	11
Vaginal discharge	2
Joint pain and aches	4
Dyslipidemia	3
Psychological disorders and cognitive Impairment	
Anxiety or depression	32 (64)
Sleep disturbances	24 (48)
Cognitive disorders	10 (20)
Problems with concentration	15 (30)
Memory problems	27 (54)

cal disorders (anxiety or depression) were noted in 32 cases (64%) and sleep disturbances in 24 cases (48%) and only one patient received anxiety and depression medication, 26 patients were referred to psychotherapist. Executive function impairment was noted in 10 cases (20%), problems with concentration in 15 cases (30%) and memory problems in 27 cases (54%). 5 among 10 patients returned to work after the end of CT and RT. Median overall survival was 24 months and median disease-free survival was 22.5 months.

Discussion

Our study evaluated the monitoring features of non-metastatic BC in Tunisia in comparison to ASCO guidelines and particularities of post treatment toxicity management through the experience of medical oncology department of the military hospital in Tunis. The ASCO clinical practice guidelines provide comprehensive, holistic recommendations specific to post-treatment BC clinical care to better manage potential long-term and late effects of treatment and to provide appropriate surveillance improving the overall health and quality of life of BC survivors (2). These recommendations focused on surveillance for tumor recurrence, screening for second primary cancers, management of physical and psychosocial long-term

and late effects of BC and treatment, health promotion, care coordination and practice implications (2).

The risk of BC recurrence continues through 15 years after primary treatment and beyond. Follow-up by multiple specialists after initial therapy is costly, represent duplication of effort and has not been shown to improve outcome. Monitoring by a primary care physician (PCP) informed of the appropriate follow-up and management strategy seems to lead to the same health outcomes as specialist follow-up with good patient satisfaction. It is recommended that PCP should consult with the cancer treatment team and obtain a treatment summary and survivorship care plan to ensure care is evidence based and well coordinated (2). Our patients were monitored by their surgeons, radiotherapists and medical oncologists. No one was discharged to his PCP for ongoing follow-up. This may be because of anxiety of patients and oncologists considering PCP inappropriate for monitoring and lack of communication and cooperation and PCP information about follow-up strategies.

Monitoring frequency of our patients was similar to ASCO guidelines indicating clinical monitoring every 3 to 6 months the first 2 years, every 6 to 12 months the next 3 years and annually thereafter (2,3). Mammography and breast ultrasound were done every year for all our patients. Annual mammography is recommended to screen for local recurrence or a new primary BC (2). Screening with breast MRI is not recommended unless the patient meets high-risk criteria for increased BC surveillance (lifetime risk of primary BC more than 20%, BRCA1/BRCA2 mutation or a very strong family history of BC) (2). The benefit of breast ultrasound in early diagnosis of recurrence compared to mammography is not established and ultrasound is not recommended in BC monitoring. However, it could be done to better individualize local or contralateral recurrence (4). The estimated risk of local recurrence is 1% per year in the literature (5). In our series, local recurrence occurred in one case (2%) 29 months after treatment. Metastatic recurrence was systematically screened by abdominopelvic ultrasound, chest X-ray and CA 15-3 every 6 months the first five years. Brain and thoraco-abdomino-pelvic CT-scan and bone scintigraphy were done if symptoms identified. Contrary to our practice, no scientific society recommends systematic diagnostic tests to detect recurrence (2,6). A physical examination and additional complementary tests oriented according to symptoms are recommended. No benefit of intensive surveillance in terms of overall survival, event free survival or quality of life were attributed to systematic request of additional tests (2, 7, 8, 9). Tunisian society of clinical oncology doesn't support intensive surveillance, but systematic prescription of laboratory tests or imaging by our oncologists may be explained by doctor and patient anxiety and metastatic recurrence frequency in our population secondary to advanced stages at diagnosis and frequency of young patients with high risk tumors.

Post treatment toxicity management included surgery, CT, RT and HT complications.

Conservative treatment was associated with more aesthetic and morphological sequelae than reported in the literature

ranging from 15 to 20%. Breast-reconstructive surgery is recommended after lumpectomy or mastectomy. Breast prostheses are options after mastectomy. Patients who have body image concerns that are not corrected by the above options are referred for psychosocial care (2,10).

In our series, breast reconstruction was made only in 5 cases with good patient satisfaction. This could be due to lack of patient information and financial insurance problems.

Lymphedema was observed in 36% of cases similarly to the literature reporting a frequency of 2 to 56%. It is recommended to inform patients about preventive measures like weight control, daily physical activity, early rehabilitation of the shoulder and scar rubbing to avoid adhesions and to refer patient to physical therapist or lymphedema specialist for lymphedema treatment (2,11). This has not been applied by the majority of our patients because of lack of information. Lymphedema physiotherapy was done in 12 out of 18 patients with partial improvement. Functional impairment of the upper extremity and shoulder pain were treated by physiotherapy in 15 out of 33 cases with partial improvement. This lack of access to physiotherapy was secondary to the carelessness of the patient and physician in some cases.

Regarding chemotherapy toxicity, peripheral neuropathy was predominantly of low grade in accordance with the literature and was essentially secondary to taxanes. The serotonin-norepinephrine reuptake inhibitor duloxetine decreases neuropathic pain and was used for our patients having grade II-III neuropathy. Antidepressants and anticonvulsants have not demonstrated consistent significant improvements in symptoms (2,12).

Cognitive Impairment including problems with concentration, executive function, and memory can lead to distress and impaired QoL in BC survivors and have detrimental effects on the survivor's role within the family, in the workplace, and in society. 35% of BC patients report cognitive impairment after treatment. The treatment of cognitive impairment in the BC survivor is not well established. A few studies have shown some success with pharmaceuticals, such as modafinil. Cognitive rehabilitation strategies, including the practice of group cognitive training has been found to be helpful at reducing cognitive impairment in BC survivors (2, 13). Concentration and memory disorders were more frequent in our population, but not treated because of lack of information about possibility of treatment.

BC related fatigue is very common with an estimated prevalence of 28% to 91%. It is recommended to assess for fatigue and treat any causative factors including anemia, thyroid dysfunction, and cardiac dysfunction, mood disorders, sleep disturbance and pain, engage regular physical activity and refer for cognitive behavioral therapy as appropriate (2, 14). Our patients had a low to moderate grade fatigue in 94% of cases. Partial improvement occurred after correction of anemia, prescription of multivitamin treatment and cognitive behavioral therapy.

Women can experience menopausal symptoms after CT or HT with vasomotor symptoms typically more severe in young

women because of the abrupt change in hormones and could impact on QoL. 50% to 70% will likely experience hot flashes while on tamoxifen. It is recommended to offer venlafaxine, selective serotonin reuptake inhibitors, gabapentin, lifestyle modifications and environmental modifications (rhythmic breathing, vitamins, exercise, avoiding spicy foods, caffeine, and alcohol, cool rooms and dressing in layers) to help mitigate vasomotor symptoms of premature menopausal symptoms (2,15,16). In our series, only one third of women with hot flashes were treated.

Approximately 62% of BC survivors are overweight or obese versus 73% of patients receiving HT in our series. It's recommended to achieve or maintain a healthy weight and refer patients to multicomponent obesity treatment programs (2). In our series, a weight monitoring was performed in 80% of patients and lifestyle dietary advice was provided in 70% of cases.

BC patients younger than 40 years represented 14% of our population. Infertility is a potential long-term toxicity that could have a profound impact on physical and psychosocial QoL. It is recommended to refer survivors of childbearing age who experience infertility to a specialist in reproductive endocrinology and infertility as soon as possible (2). It was done in one young patient in our series, other patients didn't desire pregnancy.

Sexual complaints (decreased libido, arousal or lubrication concerns, orgasmic concerns, dyspareunia) are a common problem among BC survivors that should be assessed. It is recommended to offer non hormonal, water-based lubricants and moisturizers for vaginal dryness and refer patients for psycho-educational support, group therapy, sexual counseling, marital counseling, or intensive psychotherapy when appropriate (2). Psychotherapy was the most used treatment in our series with moderate satisfaction.

Annual gynecologic follow-up is recommended for women receiving tamoxifen because of increased risk of endometrial cancer (2,8). Gynecologic follow-up including clinical and radiological monitoring of our patients was done every 6 months because of doctor and patient anxiety. No patient had endometrial cancer.

Up to 50% of women receiving treatment with aromatase inhibitor report arthralgias and myalgias that are severe enough in 20% of women to lead to treatment discontinuation. Symptoms are often not responsive to nonsteroidal anti-inflammatory drugs or acetaminophen. Acupuncture and exercise have been demonstrated to improve symptoms (2). In our series, 4 patients who experienced polyarthralgia were treated with nonsteroidal anti-inflammatory treatment with improvement in all cases.

The prevalence of depression and anxiety specifically among BC survivors was 22% (13-56%) using the Center for

Epidemiologic Studies for Depression, 22% (17-48%) using the Beck Depression Inventory and 10% (1-22%) using the Hospital Anxiety and Depression Scale. It's recommended to assess patients for depression, and anxiety, conduct a more probing assessment for patients at a higher risk of depression (young age, prior psychiatric disease, low socioeconomic status), offer pharmacotherapy and refer to appropriate psycho-oncology and mental health resources (2). In our study, psychological disorders were noted in 32 cases (64%) and only one patient received anxiety and depression medication, 26 patients were referred to psychotherapist. Anxiety and depression scales were rarely used by our oncologists, making our results very subjective. Psychotherapy was preferred and pharmacotherapy was rarely indicated with good satisfaction in 19 cases.

Conclusion

High priority should be given to improve quality of monitoring of BC survivors in Tunisia including less intensive surveillance following national guidelines of Tunisian Society of Medical Oncology and international guidelines. Participation of PCP in BC monitoring, maintaining communication with the oncology team throughout the patient's diagnosis, treatment, and post-treatment care to ensure care is evidence-based and well-coordinated, establishing educational programs tailored to the specific concerns of PCPs regarding appropriate surveillance testing and long-term effects of cancer and its treatment are important measures to reduce monitoring cost and improve patient satisfaction. Assessment and management of physical and psychosocial long-term and late effects of BC and treatment should be more considered and standardized by Tunisian oncologist to improve patient QoL.

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