Review Article

Late effects of cancer treatment in breast cancer survivors

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Abstract

Postoperative radiation therapy (RT) and chemotherapy,both reduces the risk of local recurrence and extends overall survival in patients with breast cancer (BC). Concerns have, however, been raised about the risk of acute and chronic side effects in breast cancer survivors as the number of treated individuals is large and their expected survival is long compared to most patients with other malignant diseases. Cardiac toxicity, reproductive dysfunction, pneumonitis (RP),arm lymph edema, neuropathy, skin changes are examples of the wide range of complications that has been associated with adjuvant treatment.

Key words: Breast cancer survivors, cancer treatment, late effects

Introduction

In the US, 64% of adults whose cancer is diagnosed today can expect to be alive in 5 years out of which, breast cancer survivors make up the largest group of cancer survivors (22%) followed by prostate cancer survivors (17%) and colo-rectal cancer survivors (11%).[1] The actuarial survival data of Indian breast cancer patients with early stage disease at 10 years in is 77%.[2] It is therefore important to address late effects of cancer treatment and devise methods to curtail them. Late effects of cancer treatment in breast cancer can be attributed to both chemotherapy and radiotherapy (RT).

Cardiac Morbidity

Chemotherapy-induced cardiovascular toxicity may include cardiomyopathy with or without overt congestive heart failure (CHF), endothelial dysfunction, and arrhythmias. RT-induced cardiovascular toxicity may include coronary artery disease (CAD), valvular disease, chronic pericardial disease, arrhythmias and conduction disturbances, cardiomyopathy, or carotid artery stenosis. Trastuzumab therapy is associated with a specific type of cardiac dysfunction, which differs in many respects from anthracycline-induced myocardial damage. Anthracycline cardiomyopathy is characterized by a dose dependent progressive decrease in systolic left ventricular function often resulting in CHF.[3] In the adult survivor, it is clinically indistinguishable from CHF due to other causes. Several factors increase the risk of developing CHF are extremes of age, pre-existing cardiac disease, pregnancy, athletes, dose beyond 300 mg/m^2 doxorubicin or epirubicin beyond 600 mg/m^2, longer duration of survival. There is also evidence that the risk can be reduced but not eliminated with cardioprotective drug use (dexrazoxane) and with the use of epirubicin and pegylated preparations. It can also be reduced by alterations in administration schedule (e.g., once per week υ once every 3 weeks) or continuous infusion schedules. Echocardiography is the most widely used noninvasive tool to evaluate cardiac function. Primary parameters of systolic function are represented by measurements of ejection fraction (EF) and fractional shortening (FS). The treatment approach for this entity is the same as for non-anthracycline-induced dilated cardiomyopathy. Trastuzumab-related cardiac dysfunction differs from anthracycline-induced myocardial damage in that it rarely causes death, is not dose related, and in most instances, it is reversible with improvement in cardiac function when the drug is discontinued and/or the patient is treated with cardiac medications.[4] Concurrent administration of trastuzumab and doxorubicin leads to an unacceptable rate of symptomatic CHF and should not be used. In the four large adjuvant trastuzumab trials, symptomatic CHF occurred in 1-4% of patients depending on whether they received prior anthracycline or a non-anthracycline adjuvant regimen, and whether they received trastuzumab concurrently with or sequentially after the chemotherapy.

Radiation treatment remains a critical component of comprehensive breast cancer treatment, providing a substantial reduction in local and regional recurrence rates for early-stage and locally advanced breast cancers and contributing to improvements in overall survival. Over the past several decades, breast conservation treatment has become more widely used and the indications for post-mastectomy radiation have expanded, resulting in more patients receiving post-operative irradiation. Simultaneous refinements in the delivery of radiation to the breast or chest wall have evolved. The oldest radiation techniques exposed large volumes of the heart to excessive dose, but as this technique was recognized as harmful to the heart, the more contemporary technique of tangential irradiation was developed and widely adopted.[5] Long-term outcome

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data in the era of tangential radiation have become available; these data show more subtle effects on the heart, demonstrating that the changes in technique were beneficial. In studies published before 1990, reflecting pre-modern radiation oncology, the risk of radiation-induced CAD was thought to be increased in patients with left-sided breast cancer compared with right-sided, exceeding the risk reduction gained by adjuvant radiation therapy. More recent meta-analyses have shown a survival benefit for radiation treatment after surgery (mainly breast conserving), and with modern techniques, and the incidence of cardiac disease for left and right breast radiation therapy is similar.[6] The surveillance epidemiology and end results (SEER) study examined the risk of cardiac death in 27,283 women in three periods of radiation therapy reflecting the transition to modern RT: 1973-1979, 1980-1984, and 1985-1989. This study confirmed the lack of laterality in the incidence of ischemic heart disease that grew from changing radiation treatment delivery technique and showed that the risk of death substantially decreased over time from approximately 13% in 1973 to 1979 to 5.5% in 1985 to 1989.[7] Data regarding the interaction of left breast irradiation and cardiotoxic systemic therapies, such as doxorubicin and trastuzumab, are limited since these agents have been in use a shorter time. Several studies have demonstrated a higher risk of cardiac disease when the internal mammary nodes were included in the treatment fields. Those who believe these nodes should be covered in order to maximize the treatment benefits, utilize 3D CT-based treatment planning in order to precisely target the area with any of several available techniques, dictated by the patient's individual anatomy. Internal mammary nodes should not be treated with 2D techniques in which the cardiac dose volumes cannot be measured.

Radiation-induced late pericardial disease (months to years after treatment) may be silent, with the incidental discovery of asymptomatic pericardial effusions, or may present with hemodynamic compromise secondary to a reduction in ventricular filling and cardiac output. There is no evidence that interventions can alter the course of clinically silent effusions. There is evidence that the incidence of pericardial disease can be decreased from 20% to 2.5% with the use of modern techniques. Radiation-induced myocardial disease presents with diastolic disease and restrictive hemodynamics. Modern techniques have reduced the risk of systolic dysfunction but have not changed the course of restrictive disease.

Reproductive Function

Ovarian dysfunction following chemotherapy for breast cancer is related to patient age, to ovarian function at the time of treatment and to the specific agents used, particularly the dose of alkylating agents such as cyclophosphamide. Chemotherapy causes depletion of the primordial follicle pool in a drug- and dose-dependent manner.[8] For those who do resume normal menstrual cycles, ovarian damage due to chemotherapy can still be identified. Declining ovarian reserve is reflected in lower circulating levels of estradiol, inhibin B and AMH produced by the granulosa cells of the ovarian follicle and reduced numbers of antral follicles. Breast cancer patients who have not started or completed their families may wish to consider available options to try and increase the chances of successful pregnancy following chemotherapy. Currently, there are no treatments, which are guaranteed to preserve fertility. For women with breast cancer, the issue of fertility preservation is more complex than in other cancers with concerns that fertility preservation strategies and/or subsequent pregnancy may increase the risk of cancer recurrence, particularly in women with hormone-receptor positive disease. Fertility preservation options can be divided into those which aim to reduce the impact of chemotherapy on ovarian function, those which aim to remove and preserve ovarian tissue before starting chemotherapy and those which aim to produce mature oocytes or fertilized embryos for future use.

Bone Health

In addition to the negative effect that adjuvant cancer therapy can have on ovarian function in premenopausal women with breast cancer, much of the evidence strongly suggests that there is also a negative effect on bone. Cancer treatment-induced bone loss (CTIBL) has been measured in a significant proportion of patients who become temporarily or permanently amenorrheic following chemotherapy. Trials examining the influence of adjuvant therapy on bone mineral densitometry (BMD) in premenopausal women with breast cancer have consistently shown a significant decrease in BMD within the 1st year after initiation of therapy.[9] Bone loss may be attributed to concomitant corticosteroid therapy as well.[10] A single-digit BMD loss in a patient with normal BMD does not require any therapy while that in a woman with osteopenia requires active therapy. Ovarian function suppression with LHRH agonists, such as goserelin, can be used in combination with tamoxifen in premenopausal women with estrogen receptor-positive breast cancer. It is evident that patients who develop chemotherapy induced ovarian failure (CIOF) have an increased risk for CTIBL; therefore, using markers (anti-Müllerian hormone) that predict CIOF could help to identify patients who should receive anti-resorptive therapy. Among premenopausal women who retain ovarian function during therapy, lifestyle advice and calcium and vitamin D supplementation are adequate measures to maintain bone health, and no additional interventions are required until there is a change in menopausal status. Because BMD loss is more pronounced in women who experience amenorrhea, these women should receive a baseline BMD scan and regular follow-up scans to assess bone health. One should consider non-validated risk factors like smoking, excess alcohol consumption, and family history of hip fracture in clinical guidance, when assessing overall fracture risk on a case by-case

basis. Premenopausal women with a *Z*-score lower than -2.0 or a *Z*-score of -1.0 or lower and/or an annual decrease in BMD of 5-10% should receive bisphosphonate therapy plus calcium (1,000 mg/day) and vitamin D (1,000-2,000 IU/day) supplementation. Oral bisphosphonates might be a reasonable alternative in some patients. Denosumab (60 mg every 6 months) is an anti-resorptive therapy approved in the United States and Europe for the treatment of patients with postmenopausal osteoporosis at high risk for fracture (i.e., with prior osteoporotic fracture, or multiple risk factors for fracture, or who failed or are intolerant of another anti-resorptive therapy). Osteoporosis in postmenopausal women is seen with both non-steroidal (letrozole or anastrazole) and steroidal (exemestane) aromatase inhibitors (AIs).[11,12] After completion of treatment, fracture rates return to normal. A decrease in BMD is a risk factor for fractures and remains the current gold standard method of assessment for osteoporosis and prediction of future fracture risk. The American Society of Clinical Oncology, among others, has published guidelines for the bone health evaluation of postmenopausal women who are receiving AIs.[13] These guidelines recommend a baseline BMD before initiation of AIs as well as annual screening. Pharmacologic intervention is suggested for women with BMD *T*-scores of -2.5 or less. Annual BMD screening is recommended for patients with BMD *T*-scores greater than -2.5.

Pulmonary

Radiation pneumonitis in irradiated breast cancer patients has been reported in literature in 1980-1995, before the usage of three DCRT techniques, which can effectively shield lungs lying in the trajectory of the tangential beams. The incidence of radiation pneumonitis during that period ranged from 0% to 14%, except for one report in 1985 of incidence of radiation pneumonitis as 29%. Radiation pneumonitis after RT for BC has been reported to be related to the following factors: The amount of lungs irradiated within the tangential fields, the use of an additional supraclavicular (SC) field, prior exposure to chemotherapy, concurrent tamoxifen medication, smoking habits. In a single institutional experience of 613 breast cancer patients, there was an increased incidence of radiation pneumonitis among patients treated with local-regional RT (4.1%) versus those receiving local RT only (0.9%) and among patients receiving chemotherapy (3.9%) versus those not treated with chemotherapy (1.4%). According to multivariate analysis, only the use of nodal RT remained independently associated with radiation pneumonitis. There was a statistically non-significant trend for increasing rates of radiation pneumonitis with grouped average long distances: Below 2 cm (4% RP rate), between 2 and 3 cm (6%), and above 3 cm (14%).[14]

Breast Cosmesis

The rate of poor or fair cosmetic outcome in most series is 15-20% or less.[15] Surgical factors as the extent of breast tissue removed and scar orientation impact, mostly on breast appearance and cosmetic outcome.[16] The use of chemotherapy and patient factors such as breast size, older age and race have also been associated with more frequent co smetic failures. However, several radiation treatment factors are associated with poorer cosmetic outcomes as well. The effect of the radiation technique on the cosmetic result was demonstrated by de la Rochefordiere *et al*.[17] They found that the use of >2 fields, a boost given with interstitial brachytherapy, a boost dose >18 Gy, and a breast dose >50 Gy were associated with poorer cosmetic outcomes. The cosmetic results were significantly better with newer, contemporary irradiation techniques. Breast cancer patients can experience pain in the irradiated breast, nodal regions or chest wall for years after treatment. Pain after breast cancer surgery can result from injury to muscle and ligaments and is more likely to be transient as compared to persistent neuropathic pain due to damage to the nerve tissue. Skin thickening or fibrosis of the breast or chest wall is observed in about 1/3 of patients.[18] However, moderate or severe fibrosies are found in less than 5% of patients. The prevalence of lymphedema following local therapies is observed in 15-25% 1-5 years after diagnosis. The primary treatment factors contributing to arm edema are the extent of axillary node dissection and nodal irradiation. Until recently, axillary node dissection was a standard part of the surgical management of invasive breast cancer, regardless of tumor size and nodal involvement. The incidence of subsequent lymphedema in different studies after surgery alone averages about 13%. Sentinel lymph node biopsy has resulted in significantly less morbidity, with estimates of subsequent lymphedema of <1-3%.[19] The addition of SC and/or axillary radiation fields following dissection results in a higher incidence of lymphedema ranging from 9% to 58%. Breast irradiation alone after lumpectomy and axillary node dissection has a negligible effect on the incidence of lymphedema. The prevalence of impaired arm and shoulder mobility varies from less than 10% to almost 70%, depending on the method of assessment (measured or self-reported), time since treatment, and type of surgery, with greater impairment for mastectomy than lumpectomy and RT versus no RT. Treatment techniques, total dose and concomitant chemotherapy are the risk-factors.

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Dr. Lalit Kumar MD, DM: He is presently Professor and Head of Medical Oncology at the All India Institute of Medical Sciences (AIIMS) , New Delhi (India). He studied medicine at the SN Medical College, Agra, India and completed DM (fellowship) in Medical Oncology at the Cancer Institute (WIA) Chennai (India). He undertook a post-doctoral fellowship at the Leukaemia Unit of Hammersmith Hospital, Royal Post-graduate Medical school London, UK. He has contributed to the development of Medical Oncology discipline at AIIMS and has developed a cost effective and sustained bone marrow/stem cell transplantation program. His areas of interest include- Multiple Myeloma and Gynaecological malignancies. A fellow of the Indian Academy of Sciences (FASc.) and of the National Academy of Medical Sciences of India (FAMS), he is also the recipient of Dr BC Roy National Award, Ranbaxy Science Foundation award, Commonwealth Scholarship and the Indian Council of Medical Research award.

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