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Evolving Concepts in Breast Cancer Management : A Review

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SUMMARY

The magnitude of the problem of breast cancer is on the rise in our country. The last century has witnessed several landmark changes in the approach to patients wih breast cancer. Till recently, women had to under go extirpation of the entire breast resulting in significant physical and psychological trauma. The current trend is to go for a figure-conserving procedure. Tumour biologists have unraveled many mysteries about cancer cell growth. Most notable among these is the identification of estrogen receptors and tamoxifen. Next breakthrough was the demonstration of the effectiveness of combination chemotherapy in premenopausal women and tamoxifen in the postmenopausal women. The current treatment policy is one of the spectacular examples of *"Evidence based medicine"* where sound scientific proof of effectiveness has been gathered through very large multicentric randomized trials and meta-analyses on well over 75,000 women across the globe.

Key words : Breast cancer, Treatment policy, Surgery, Hormone therapy, Chemotherapy.

INTRODUCTION

Breast cancer is the commonest cancer among middle aged women in developed [western] countries. Its incidence has been increasing in India and now it is the second most common cancer in Indian women as per the reports of National Cancer Registry Project (1, 2). It has been estimated that annually about 52,000 women develop breast cancer in India and as a result of increasing population and longevity alone, this figure would increase to 86,000 by the turn of this century (3). Most patients (90%) in India present to the physician with advanced disease (4). The reasons for this delay are poor awareness among women, illiteracy, socio-economic factors, inadequate distribution of health care system in rural and semi-urban areas and improper training of doctors to diagnose early cancer.

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Epidemiology

Almost one third (32%) of all new cases and 18% of cancer deaths in women are related to breast cancer. The cause of mammary cancer remains obscure but insight continues through epidemiologic, genetic and animal research. The patterns of risk are complex and suggest that both hereditary and environmental factors are influential. It has been estimated that approximately 25% of all breast cancers can be explained by currently recognized somatic risk factors viz., age above 40 years, nulliparity [Relative risk; RR 1.4], history of breast cancer [RR 1.2 to 1.5], family history [RR 1.7 to 2.5], early menarche and late menopause, irradiation, obesity [RR 1.8], alcoholism (RR 1.5) and estrogen pills (RR 1.7 - 4.1). Moreover patients with benign breast disease demonstrating histological atypia have a RR of 5 (5, 6). It has been hypothesized that psychological factors also play a role in the development of breast cancer (7). Recognition of these factors has helped define women at risk, on whom screening test could be applied to improve early detection and outcome. Patients with very early breast cancer have a ten-year survival of around 90%. Early detection can be easily accomplished by breast self-examination (BSE), physician examination and mammography (8).

Breast cancer has long been regarded as a local disease with an orderly sequence of progression from breast parenchyma to the regional nodes and eventually to the blood stream *(Halstedian concept).* The originator of this belief, William Stuart Halsted developed the first radical mastectomy in 1882 (9). Since then millions of women across the globe have undergone this procedure for breast cancer.

Despite local aggressive treatment with radical mastectomy and radiotherapy, many women with breast cancer still succumb to systemic metastases. Therefore, in early seventies a new concept was propounded which enunciated that breast cancer was a systemic disease soon after its inception (10). This paved way to the development of limited surgery and systemic therapy even for early disease. In the eighties European surgeons performed breast conservation surgery and demonstrated its effectiveness to be at par with the radical procedure. Incidentally, this coincided with the Women's Liberation movement, with consumers demanding a figure conserving operation. The next revolutionary step in the management of breast cancer was the introduction of anti-estrogen-tamoxifen. Almost at the same time, G. Bonadonna of Milan, Italy described the famous chemotherapy [CT] combination of cyclophosphamide, methotrexate and 5-fluorouracil [CMF] which is one of the most widely tested and effective regimens in Oncology (10).

The foundations of systemic adjuvant chemotherapy were derived from the facts that (10): [i] by the time tumor becomes clinically detectable, it is advanced and has many opportunities to establish micro-metastases; [ii] neoplastic cell dissemination is both by lymphatic and blood vascular system and is interrelated; and [iii] surgical 'cure' rates drop

as tumor size and axillary lymph node metastasis increase.

Modern Surgical Procedures for Invasive Breast Cancer

Both clinical presentation and surgical approach to breast cancer have changed dramatically over the last century. In 1882, Halsted performed the first radical mastectomy, and this was the standard for therapy about 75 years. Realization that 90% of treatment failures are systemic metastases has led the surgical oncologist to explore alternatives to radical mastec-tomy as an initial approach to operable breast cancer (11). The surgical practice changed in the mid seventies from radical mastectomy [RM] to modified radical mastectomy [MRM].

Radical and Extended Radical Mastectomy

The breast and the underlying pectoral muscles are sacrificed leaving a bare chest wall. Regional lymph nodes along the axillary vein up to the costoclavicular ligament are removed with the breast specimen. This procedure often requires a skin graft or a flap repair. Prosthetic reconstruction is difficult unless the muscle flaps are mobilized. The extended radical mastectomy is standard RM along with the removal of internal mammary nodes. Breast reconstruction in such women is difficult.

Modified Radical Mastectomy

David Patey of the Middlesex Hospital in London developed a procedure bearing his name that preserves pectoralis major and sacrifices pectoralis minor in order to remove level 1, 2 and 3. This is currently the most widely used procedure for locally advanced disease and refers to combining total mastectomy with removal of axillary lymph nodes. Since it leaves the pectoral muscle, the defect is well suited to prosthetic reconstruction. The 10-year survival among axillary node negative women was 82% and with positive nodes, it dropped to 48% (12). Thus, the long-term survival is similar to radical mastectomy but cosmetic and functional results are far superior to radical mastectomy.

Local excision and primary radiotherapy

Excision of the primary tumor with preservation of the breast has been referred to by many terms such as partial mastectomy, segmentectomy, tylectomy or lumpectomy. In essence, this procedure entails wide local excision of the primary tumor together with axillary node dissection followed by whole breast irradiation (13).

HORMONAL THERAPY

Estrogen and progesterone receptors

Constant effort by the tumor biologists to unravel the mysteries of cancer growth led to the understanding of estrogen receptors and other growth factors which influence the breast cancer metastasis. The number of estrogen receptors [ER] in the breast cancer cells can be high, intermediate or absent. This quantitative grading of ER is predictive of response to hormonal manipulations

viz., oophorectomy or tamoxifen. Seventy percent of the tumors with positive estrogen receptors regress after hormonal manipulation whereas only 5% of negative tumours respond to these procedures. The highest response rates are observed in patients with tumors containing both estrogen and progesterone receptors. On the whole, cancers with high levels of estrogen receptors have a better prognosis than those with intermediate levels or no receptors. Laboratory medicine continues to play an important role in the management of the patients with cancer breast. Investigations in the past decades have provided bio-chemical and clinical evidence that estrogen and progesterone receptors, EGF receptor, the protein product of the C-erb B-2 Oncogene and Cathepsin D represent a panel of bio-clinical markers that are useful for ascertaining the biological aggressiveness of a carcinoma (14).

Tamoxifen

Tamoxifen (15-18) is a non-steroidal anti-estrogen. It appears to exert its main anti-proliferative effect by competing with estrogen for binding to estrogen receptor proteins. Estrogen receptor complex inhibits gene transcription and protein synthesis of factors important to tumour growth. After binding to the ER tamoxifen antagonizes many of the cellular events affected by estrogen. The predominant effect of tamoxifen is cytostatic. Although tamoxifen behaves primarily as an estrogen antagonist, it may act as a partial agonist for some organs. The anti-estrogen properties of tamoxifen usually are not sufficient to suppress ovarian function. The long term use of tamoxifen continues to result in increased steroido-genesis in pre-menopausal women. The ovulation continues and there is a possibility of pregnancy. The standard therapeutic dose is 20mg orally daily. Very large world-wide randomized trials on women receiving tamoxifen as an adjunct to surgery and radiation therapy have demonstrated improved 5 year survival and reduced local recurrence. Moreover, it reduces the incidence of cancer in the opposite breast. Therefore, it is being tried for the chemoprevention of breast cancer in high-risk women. These benefits have been observed in both pre-menopausal as well as postmenopausal women. The drug is well tolerated by most women and the toxicity is minimal and transient. The frequency of nausea and vomiting, weight gain, vaginal bleeding, skin rash, edema and abnormal liver function is < 3%. Transient ocular disturbances of the eyes due to damage of retina and optic nerve are rare (< 1%) (19). Thrombocytopenia, tumour flare and hypercalcemia may ocur in 5% of cases. Other newer anti-estrogens are trioxifen, zindoxifen and torenifene. A randomized trial of 2 vs. 5 year of adjuvant tamoxifen showed that 5 years of tamoxifien is more beneficial than 2 years (20). Although tamoxifen has been used for periods longer than 5 years with some extra lives saved in some trials, the finding is not consistent across the studies. Moreover ther is an increased incidence of endometrial cancer in these patients.

Therefore, Richard Peto and others are trying to find the optimum duration of tamoxifen therapy through a large multi-national trial [ATLAS trial].

Surgical oophorectomy

Oophorectomy improves 10-year survival in women under 50 years. Oophorectomy is indicated in pre-menopausal women with slow growing metastatic disease, a long disease free interval, and age over thirty-five years. In a meta-analysis of 75,000 women, the Early Breast Cancer Trialists Collaborative group demonstrated a proportional reduction in annual mortality of 28% with ovarian ablation compared to no ablation (21).

Formestane - the new endocrine alternative

Formestane is a highly specific aromatase inhibitor, the key enzyme in estrogen biosynthesis which significantly suppresses estrogen levels in post menopausal women with advanced breast cancer. It has a long duration of response (13 to 33 months). The usual dosage is 250 mg administered intramuscularly at weekly intervals. It produces an objective response in 25% of women after relapse or failure of previous hormone therapy. It is relatively non-toxic and is used as a second line drug (22).

Modern Adjuvant Chemotherapy

The first randomized trials were performed by NSABP and National Cancer Institute, Italy using patients with positive axillary lymph nodes. NSABP used single agent chemotheraphy in the adjuvant situation and hence became the standard approach. The fifteen-year results of the CMF (12 cycles) trial showed a 10% survival benefit in the CMF treated women compared to the control (36% vs. 26%). The significant survival benefit observed in pre-menopausal women was not observed in post-menopausal women. A second trial compared the effectiveness of 6 vs. 12 cycles of CMF for node positive patients. At 14 years, both relapse free and total survival rates between the two groups remain similar. Henceforth only 6 cycles of CMF have been recommended in the adjuvant setting. All premenopausal women receive chemotherapy regardless of the nodal status. For a post-menopausal patient the hormone receptor status decides the approach. In the presence of positive ER, with unfavorable prognostic indicators [poor histological grading, aneuploidy, high tumor cell proliferative activity, more than 3 positive nodes etc] and negative receptor status adjuvant CT is beneficial (10).

The Treatment of Stage I Node Negative Breast Cancer

Approximately 20-25% women with stage 1 breast cancer eventually develop disseminated disease. A comprehensive meta-analysis of adjuvant chemotherapy was reported based on 133 randomized trials involving 75,000 women including both poly-chemotherapy and adjuvant hormonal manipulations. The results of this meta-analysis are depicted in Table 1

Table 1 : *Reduction in annual odds of recurrence and death. Data based on Meta-analysis of 11,000 women (see reference-21)*

Age group (years)	No. of cases & controls	Recurrence*	Death*
<50 (pre-menopausal)	3138	36 (5)	25 (6)
<50 (post-menopausal)	225	37 (19)	†
50-59 (pre-menopausal)	911	25 (9)	23 (9)
50-59 (post-menopausal)	3128	29 (5)	13 (7)
60-69	3774	20 (5)	10 (6)

Data based on meta-analysis of 11,000 women (reference 21)
* Data shown as % [SD]
† There are very few patients in this group; therefore, the estimate is imprecise.

(21). This data indicated that there was both reduced recurrence and improved survival for node positive and node negative patients. The greatest benefit was seen in younger patients with at least 6 months combined chemotherapy. Patients with tumours less than 1 cm have an excellent prognosis and do not require adjuvant systemic chemotherapy.

The Treatment of Stage II Node Positive Cancers

Prognosis is directly related to the number of nodes histologically involved with metastasis. After surgery, women with 1-3 positive nodes have a 10-year survival of 38% - 63% and with four or more nodes that are positive have a survival rate of 13% - 27% (23,24,25,26). Thus, a sizable proportion of women in stage II cancer succumb to systemic disease. Hence, adjuvant CT aims at killing any remaining breast cancer cells thereby increasing the disease free survival and cure.

The anthracycline derivative doxorubicin remains the single most effective drug in the treatment of advanced breast cancer. Initially the drug did not gain much popularity due to its potential for myocardial damage after prolonged treatment. Combination CT regimens with doxorubicin or its analogue eqirubicin have shown to induce a higher response rate in patients with more than three positive axillary lymph nodes in stage II cancer, locally advanced or clinically disseminated breast cancer than those that do not contain an anthracycline.

Primary Chemotherapy in Stage III Disease

Combination chemotherapy is necessary to improve survival of patients with Stage III disease (27). Advantages of anterior chemotherapy are :

[i] sub-clinical metastasis as well as primary disease can be treated and may facilitate later resection; [ii] drug delivery may be more consistent if tumor vasculature is unaltered by surgery or radiation; [iii] the sensitivity to the chemotherapy can be established and the tumor response can be observed.

Patients treated with combination chemotherapy with CAF followed by local therapy and then resuming chemotherapy had a five-year disease free survival of 40%. Because of the poor prognosis of stage III, recently high dose chemotherapy with bone marrow support is under trial.

Newer Chemotherapeutic Agents

Docetaxel (28) is a member of the toxoid class of antineoplastic agents. Its mechanism of action is primarily related to its ability to enhance microtuble assembly and to stabilize microtubules by preventing their depolymerisation thus disrupting normal cell division. It has been investigated in the treatment of patients with advanced and / or metastatic breast cancers. As first line treatment, monotherapy with docetaxel was associated with complete response rate of 5%-16% and partial response rate of 19%-53% with an overall response rate of 54% - 68%. It has also shown impressive activity as second line treatment. Vinorelbine, a new semisynthetic vinca alkaloid is also showing promise in advanced breast cancer.

Conclusion

The burden of breast cancer as a cause of morbidity and mortality in the Indian women is on the rise. In order to improve the present gloomy statistics we need to launch public health programmes for early detection through media and schoolgirl education, physician examination and mammographic screening. This, together with an improvement in the standard to surgical and radiation therapy across the country would brighten the picture.

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