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Advanced Breast Cancer : Current Status in Management – a Personal Experience in Indian Scenario

Anand Kumar

Professor of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005.

INTRODUCTION

It is a privilege and honour to me to have been awarded this prestigious Glaxo Oration of the National Academy of Medical Sciences for the year 1997. I am grateful to the Governing body of the Academy for the confidence bestowed on me to deliver the oration on one of the common problems of the country as well as of the globe i.e., advanced breast cancer. I have been involved in the study of various aspects of this disease and would like to highlight on the following issues.

Advanced breast cancer - its definition, scenario of beast cancer in Indian population with emphasis on clinical presentation, its problems, management objectives, management options i.e., various protocols, extent of surgery and the results, management problems e.g., cost vs. benefit, newer drugs vs. conventional drug.

When to treat, how long to treat and how to treat or not to treat at all.

Personal experiences of treating locally advanced breast cancer, quality of life assessment, thrombasthenia, a new side effect of cancer chemotherapy and assessment of prognostic parameter in Indian patients.

Advanced breast cancer incorporates:

1. Locally advanced breast cancer [LABC]
2. Inflammatory breast cancer
3. Metastatic breast cancer
4. Recurrent breast cancer

Stage wise, it is IIIa-IIIb, inflammatory carcinoma and stage IV disease. The classification incorporates different therapies from such groups of advanced breast carcinoma with varying prognosis. Stage IV disease is referred to as metastatic breast cancer and has different management policy than LABC. Recurrent breast cancer may be grouped with metastatic breast cancer. Similarly, though inflammatory breast carcinoma has certain peculiarities with reference to diagnosis and prognosis, it has been grouped in LABC.

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Correspondence: Prof Anand Kumar, MS, FAMS, Professor of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi - 221 005.

EPIDEMOLOGY

Nearly 75-80% cases of breast carcinoma in developing countries are advanced at the time of presentation contrary to developed countries (1). The overall incidence of breast carcinoma is 30% of all female malignancies and it accounts for 10% of all cancer deaths in females. In western population, the observation that 1 in 9 women are likely to develop breast cancer during their life time, suggests the magnitude of the problem. Nearly 48% new cases are likely to occur in patients more than 65 year of age. Screening for breast cancer is associated with early detection and better prognosis. But according to NIH Survey [1992], 27% of elderly women in advanced countries did not have adequate screening. The patients denied screening are likely to develop breast cancer, of which 50% had either stage III or IV disease (2). Another remarkable fact in this reference has been that the relapse after adjuvant treatment is more aggressive and carry a poor prognosis (3).

Bloom et al (4) quoted the survival statistics of untreated patients. Mean survival is reported as 38.7 months. Fifty per cent of patients die by 2.7 years, 82% die by 5 years and 96% by 10 years. Nearly 75% of patient had ulcerated lesion at death and 25% had chest wall erosion. Early detection causes 40% reduction in advanced cases and 30% increase in survival.

Unfortunately statistics in our country are sparse and the age adjusted reported incidence is 28/100000 new cases per year (5). Seventy five per cent of these cases are either locally advanced or disseminated. In Banaras, the hospital statistics suggest that breast cancer accounts for 11-15/1000 admissions. The various factors for the cases to have advanced disease at presentation include ignorance, fear, denial, socio-economic factors and illiteracy. The worst factor has been the practice of various systems of medicine actively being practiced in the country. The myths and beliefs of practice of such medicine need to be addressed at all levels so as to bring down the incidence of advanced disease at presentation. Lack of screening programmes, health education are also accountable for such problems in the country.

Besides the epidemiological problems, the patients in this country face the overwhelming problem of adequate treatment even for those presenting at a relatively early stage. The concept of multimodal treatment though known to medical fraternity, is not being practiced or offered to patients for several reasons. One of the important factor has been non-availability of resources and the cost of the treatment. Neither the agencies involved in patients care nor the patients at large can afford the cost of adequate treatment, and are responsible for relapse, advanced disease and high mortality.

MANAGEMENT OBJECTIVES

Advanced breast cancer has a different objectives as regards its treatment. Broadly the objectives are classified as:

a. Palliation [*not cure*] including improvement in quality of life
b. Increased disease free survival
c. Balancing effect of treatment versus toxicity

The questions "whether to treat or not to treat at all", if "yes" how much and how long to treat? should also be addressed. The philosophy of treatment ought to be more subjective and should be more individualised than generalised in third world countries. The treatment should be directed towards comprehensive care and not towards terminal care. The phenomenon of comprehensive care demands contributions from family, fraternity [medical], friends and ignorance on anybody's part would lead to failure of management objectives.

Increase in disease free survival

Five-year survival in stage III disease before the concept of neoadjuvant therapy was only 30%. The break-up of disease free survival [DFS] with the advent of neoadjuvant chemotherapy has been shown in Table 1.

Table 1. *Break-up of disease free survival with the advent of neoadjuvant chemotherapy*

DFS	Stage IIIa	Stage IIIb
5-year DFS (%)	80	45
10-year DFS (%)	64	28

DFS = disease free survival

Let me address the philosophy of treatment in advanced breast cancer. Though multimodality treatment has been advocated using anthracycline based chemotherapy with above quoted response, in India, in my personal experience, only 10% of the patients could afford or accept the anthracycline based chemotherapy. The fate of the remaining 90% patients remains still gloomy. The aim is to treat as best as possible considering cost vs. effective therapy. In this regard CMF combination seems appropriate in the Indian setting, though response is nearly 10%-15% less than anthracycline based chemotherapy. The treatment is affordable, acceptable and has appropriate response.

Question of how much to treat is totally governed by several clinical and investigatory parameters and should be purely individualised. No strict general policy could be adopted in the Indian setting. The treatment with a rational approach which fulfills the objectives of management is advocated for Indian patients.

Palliation and not cure

Cure in breast cancer is only known for patients detected and treated in early stage. In advanced breast carcinoma the objective is not to cure the disease but to provide relief from symptoms, make the patient acceptable to society and rehabilitation. Palliation virtually is the major objective of management of advanced breast cancer. It is agreed that survival longevity without comforts and function would not be tenable. In order to have an effective palliation, the initial assessment of symptomatic sites of disease involvement is essental. Mangement of ulcers in LABC, local pain, painful or unstable weight bearing bones, hypercalcaemia, cord compression, neurological changes seen in metastatic breast disease are important aspects of management. The initial assessment of symptoms are supplemented with desired investigations which ultimately become the

monitoring parameters for the assessment of response. The common problems associated with breast cancer patients in India are fungation, foul smelling ulcer, anaemia, pleural effusion. These problem could be alleviated with systemic chemotherapy, local surgery, graded analgesics and intra-cavitary instillation of cytotoxics. Improvement in quality of life becoming increasingly important in the treatment of advanced cancer. The parameters accountable are [i] disease related symptoms and toxic effects of treatment; [ii] functional status; and [iii] psychological status. Psychological aspects assumes different dimension depending on local socio-cultural beliefs and economic factors.

Management options in Advanced Breast Cancer

Systemic therapy/chemotherapy/ hormone therapy/biologic therapy are the main stay of therapy for advanced breast cancer. Local treatment i.e., surgery and radiotherapy is always adjuvant to systemic therapy. Till 1970 only loco-regional therapy was advocated and 5-year and 10-year survival following radical mastectomy were 30%-45% and 20%-30% respectively. Similarly for stage IIIb the corresponding results was 2%-28% and 0%-10% respectively. Surgery if performed alone leads to 60% local treatment failure, hence is not the only treatment. The best ultimate results are achieved through combined modality treatment. Houston (6) observed 2 times more response in patients receiving adjuvant treatment for the first time than those who received treatment without adjuvant treatment.

Role of surgery

Role of surgery dates back to Hippocratic era [400 BC]. Anatole Francis quotes *"Let us not cast aside things that belongs to the past for only with the past can we weave the fabric of the future."* As early as 30 BC- 38 AD Celsus opposed surgery and cautery for advanced breast cancer. Galen [181-203 AD] stated that once a breast malignant mass grows to a noticeable size, no one has cured it with surgery alone. Rhazes [841-966 AD] warned not to incise and advised complete removal of the breast. Ambrose Pare [1510-1590] opposed all the philosophers of local excision for large ulcerative lesions of breast. These historical data holds true even today and the role of local surgery alone for advanced breast carcinoma is very limited.

Indications for surgery in advanced breast carcinoma has been in conjunction with chemotherapy/radiotherapy for specific indications like local, invasion, extensive axilliary disease, extensive bulky disease and inflammatory carcinoma (7-9).

Radiotherapy

This modality of treatment has been purely loco-regional. Five years survival for LABC varies from 10%-30% and local failure ranges from 25%-72%. Radiotherapy when compared to surgery alone as a method of treatment, was difficult to compare because of different inclusion criteria of patients in both the groups. Veronesi (10) in his series reported 42% 10-year survival following surgery and excluded T4, N2, supraclavicular lymph node [SCLN] cases. Pierquin (11) reported similar results following radiotherapy using

the same exclusion criteria. Most of the series edge towards less favourable outcomes after radiotherapy. Though there are reports of long time survival with radiotherapy in the treatment of LABC (11,12) considerable toxic and unacceptable long term side effects have been observed(13).

Next milestone in treatment of LABC has been combination of surgery with pre-operative or post-operative radiotherapy. This modality though has a better local control but did not add to survival benefits and systemic failure (14). Role of radiation has been significant in the management of localised bony metastasis, cerebral metastasis and spinal bone compression. It provides best palliation when used in conjunction with chemotherapy and surgery.

Systemic Therapy

Systemic therapy comprises of hormone therapy and chemotherapy (15). It has been employed in the management of breast cancer since 1970. Various factors are being analysed towards their use. These are age and menopausal status, stage of the disease, performance status, hormone receptor status, histology, tumour grade, oncogenes expression, aneuploidy and sites of metastases. These have a significant effect on disease-free survival (3,16). Use of systemic therapy has improved the overall prognosis in advanced breast carcinoma particularly LABC.

Hormone Therapy

Hormone therapy includes opherectomy, LHRH analogues, adrenalectomy, aromatase inhibitors, antiestrogen [tamoxifen] and progestins. It is used alone and in combination with local therapies for LABC. Used alone it has achieved objective regression in breast tumours [upto 56% in LABC] but without any added advantage as regards overall survival. When used as an adjuvant treatment after loco-regional treatment, it did not contribute towards overall survival. However synchronised chemo-hormone therapy achieved 82% response as compared to 43% for chemotherpy alone (17).

Hormone therapy options for advanced breast cancer are classified as *ablative* [oopherectomy, LHRH analogues or medical oopherectomy, adrenalectomy and aromatase inhibitors or medical adrenalectomy], *additive* [progestins, oestrogens and androgens]; *antagonistic* [antioestrogens and antiprogesterone]. These are best indicated in patients without visceral crisis and with either positive or unknown hormone status. Primary hormone therapy has been grouped as oopherectomy and LHRH analogues for pre-menopausal patients, antioestrogens for pre- and post-menopausal patients.

Subsequent hormone therapy is required are antioestrogens, aromatase, inhibitors, progestins, oestrogens for post-menopausal women and LHRH analogues, progestins and antioestrogens for pre-menopausal patients.

Tamoxifen is the initial choice for hormone therapy. Ten mg twice a day for 5 years is the dose recommended for hormone responsive advanced breast cancer. Tamoxifen in addition to oopherectomy has beneficial effects (18). The side effects are

minimal and treatment is cost-effective. Response ranges from 30%-75% (19). Response varies according to site of metastasis, [soft tissue > bone > visceral and duration varies from >2 years > 1 year < 1 year respectively] and absoute value of hormone receptors. Tamoxifen has proven to be as effective as any other form of hormone therapy (3, 20). Another important aspect about initial hormone therapy is, it does not compromise any delay in chemotherapy (21). Major advantage of hormone therapy has been 25% reduction in death hazards in long term follow-up (14).

Magesrol acetate [progestins] is an alternative to tamoxifen with similar response. It is preferred as second line therapy particularly in the high doses. It is relatively more toxic and expensive than tamoxifen. Aminoglutethimide [aromatase inhibitor] is the third line choice of hormone therapy for metastatic breast cancer.

There are no reports of randomised clinical trials on this subject from India. However considering the availability, affordability, assessment of duration of response and non-availability of hormone receptor status, oopherectomy tamoxifen still is the most cost effective hormone therapy for advanced breast cancer for Indian patients [Figure 1 and Table 2].

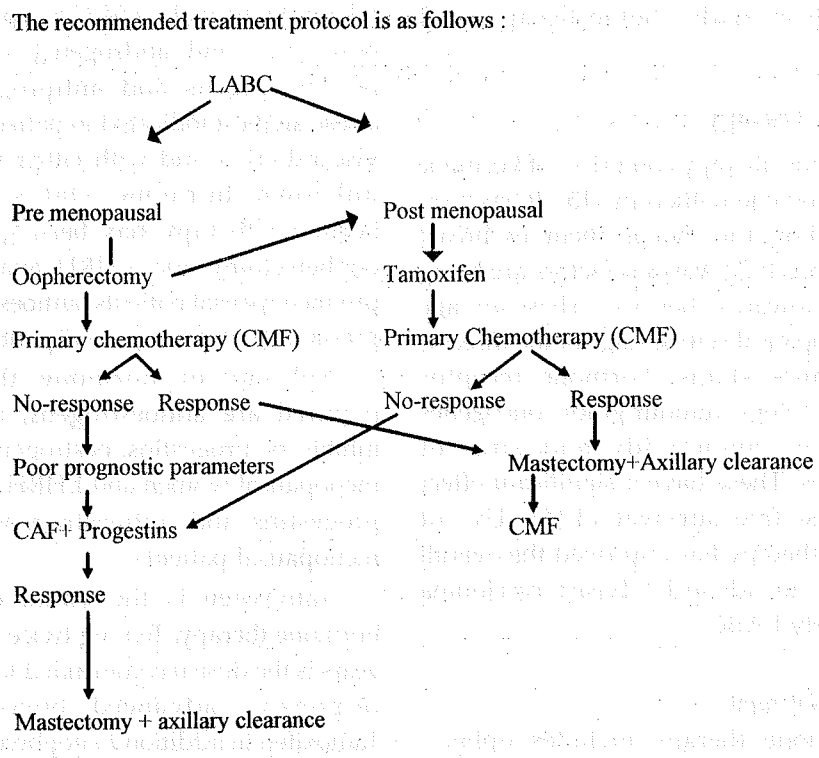

Figure 1. Recommended treatment protocol

Table 2. *Hormone therapy options for advanced breast cancer*

Therapy	Menopausal status	Treatment sequence		
Ablative				
Oopherectomy	Pre	+++	++	–
LHRH analogues	Pre	–	–	–
[Medical oopherectomy]				
Aromatase inhibitor [Medical	Post	+	++	+++
adrenalectomy]	Pre	–	+	++
Additive				
Progestins	Pre	–	+	++
Oestrogens	Post	++	+++	++
Androgens	Post	–	+	+
Antagonists				
Antioestrogens	Pre	++	+++	+++
	Post	+++	++	++
Antiprogestins	Pre	?	?	?
	Post	?	?	?

Chemotherapy

Before 1970 loco-regional treatment was the only treatment for advanced breast cancer and systemic therapy was added only if local recurrence or distant metastasis occurred. For a better overall survival and disease free survival the role of systemic chemotherapy was then recognised and introduction of adjuvant chemotherapy produced 60% response as compared to 25% by radiation alone (15). Chemotherapy was used in combination and various combinations were used. With the realisation of advantage of systemic chemotherapy over loco-regional treatment, chemotherapy was used as primary treatment for advanced breast cancer and 5-year and 10-year survival figures quoted for stage IIIa are 80% and 64%; and for IIIb are 45% and 28% respectively. This was in contrast to < 30% survival at 5 years without chemotherapy.

Table 3. *Use of chemotherapeutic protocols and their results*

Drugs	% Response	% CR	Duration response
CMF	40-70	8-15	6-10 months
CMF±V±P	30-80	7-25	6-14 months
CMFVP	46	11	9 months
CA	41-78	2-22	10-12 months
CAV	52-53	0-8	7-8 months

C = cyclophosphamide, M = methotrexate, F = 5-fluorouracil, V = vincristine, p = prednisone

The various chemotherapeutic protocols in use and their results are shown in Table 3. The mainstay of chemotherapy is still adriamycin and cyclophosphamide based regimens. Two common combinations are CAF and CMF. CAF has nearly 10%-15% advantage in terms of reponse than CMF but with added cost. When corrected for the prognostic factors there would appear to be only minor differences in the chemotherapeutic regimens at least as applied to advanced disease. There has been an explosion in new chemotherapeutic drugs [Table 4] which include traxol, navelbine, camptoghecin [CPT-II] with response around 35% when used alone and 25%-80% in combination.

Table 4. *Newer drug regimens and their response*

Drug regimens	% Response
AV	25
AM_{MC}	40
$FAVM_{MC}$	54
$VACL_{E}$	78

A = adriamycin, V = vincristine, M_{MC} = mitomycin C, F = 5-flurouracil, L_E = Leucovorine

Considering the response, there had been minimum variation, which raises certain ethical issues regarding the selection of combination chemotherapy regimes for advanced breast cancer. The issues involved are what should be an optimal regimen? [CMF vs. CAF vs. newer agents], dose of chemotherapy, duration of chemotherapy?

Tormey (22) and Aisner (23) compared the various combinations and concluded that adriamycin based combinations are better than any other combinations for the treatment of advanced breast cancer. There have been attempts to increase the response by several methods e.g.; dose intensification, use of GM-CSF and ABMT.

Honkoop (24) observed 82% response after dose intensification with GM-CSF and 83% response with 24% CR using a combination of adriamycin and paclitaxel. Bishop (25) compared the results following use of paclitaxel and CMFP [Table 5].

Table 5. *Comparison of results using CMFP and paclitaxel*

	CMFP	PACLITAXEL
Overall response (%)	35	31
Time to progression (months)	6.4	5.5
Neutropenia (%)	63	64
Mucositis (%)	27	13

Based on reference 26

The newer agents, though comparable and at times more effective, raise issues for Indian patients such as:

Are these cost effective and what is cost benefit ratio?

Henceforth the management of advanced breast cancer in Indian patients needs to be re-evaluated considering the applicability, affordability, availability and acceptability.

MANAGEMENT OF ADVANCED BREAST CANCER IN INDIAN SCENARIO-A PERSONAL EXPERIENCE

Considering the background of management of advanced breast cancer and the advances in chemotherapy, the

Indian patients have a few more ethical considerations. These are economy, cost vs. benefit in terms of quality and quantity of life, feasibility, evaluation of prognostic markers, drug related toxicity and follow-up. In a study conducted at the Institute of Medical Sciences, Banaras Hindu University, a combination of cyclophosphamide, methotrexate, 5-fluorouracil and prednisone was used to treat patients with advanced breast cancer. CMFP regimen has the advantage of being cost-effective, is well tolerated and results in 64% disease free survival for 18 months. The drugs used could be administered on domiciliary basis and nearly 90% patients did not need hospitalisation. Approximately 10% patient shaving dose limiting toxicity needed hospital admissions. This has been one of the major advantage of CMFP combination (26). Gastrointestinal, bone marrow toxicity and alopecia was observed in 44%, 12% and 14% cases respectively. In the same study it was highlighted that patients who received radiotherapy prior to chemotherapy had significant poor response [35% vs 70% respectively]. Patients with soft tissue metastasis responded better than visceral or osseous metastasis.

This study was extended to locally advanced breast carcinoma and fungating breast carcinoma in particular using CMFP (27). In this study, 26.7% patients had complete response and 33.3% cases had partial response. Nearly 83% patients were made operable using CMFP as primary chemotherapy for such cases [2 cycles preoperatiely and 7 cycles post-operatively. Advantage of primary chemotherapy had been the healing of malignant ulcer, mobility of lymph nodes and mobility of primary tumour making tumours operable. Mastectomy and axillary clearance which were not possible initially were only possible after primary chemotherapy. Clinical response was confirmed histologically in the form of tumour necrosis, smudging of cells, lymphocytic infiltration, stromal oedema and fibrosis. Major and minor toxicities were the same as reported earlier. The cases were followed up for 5 years and 16.6% cases were disease free while 28% had local failure and 52% had systemic failure. The results were comparable to current approaches for treatment of stage IIIb breast carcinoma (28).

The choice of current treatment for advanced breast cancer is based on study of prognostic indices e.g., receptor status, tumour grades, oncogenes, aneuploidy besides the clinical parameters of age, menopausal status, site of metastasis and lymph nodes. One of the current cost effective prognostic parameter studied has been argyrophilic nucleolar organizer regions [AgNOR].

AgNOR and their significance as prognostic parameter

AgNOR count determines the nuclear activity and a high count is associated with poor prognosis (29). These are loops of ribosomal DNA [rDNA] located on the short arm of the acrocentric chromosomes 13,14,15,21 and 22. These are identified by silver nitrate stains in paraffin section. High count is found in paients with advanced stage, > 4 metastatic nodes and distant metastasis. The clinical application of this study is, patients with higher AgNOR count

are prone to develop local and systemic failures and should be treated with aggressive combined modality for a favourable outcome. AgNOR count in benign breast disease and malignant breast tumors were 1.88 and 6.65 respectively [p<0.001]. The study suggests that any tumour with AgNOR>3 count is highly suggestive of malignancy. AgNOR count increases with increase in tumour size. The study sugests the value of AgNOR in predicting high risk patients and also an indicator of aggressiveness.

Quality of life assessment in Indian patients with advanced breast cancer

Quality of life [QoL] assessment is an important consideration in patients with cancer. The relevant measurement of quality of life can be established on the basis of expected impact of the treatment on quality of life, the expected impact of the treatment on survival and the health state of patients before initiation of treatment. In advanced breast cancer it is considered critical when it is one of the major objective of the treatment. Four domains of QoL, are ideal to study:

- The physical [symptoms/distress, activity leve/functional status]
- The psychological [symptoms/distress, or anxiety and depression and positive effect].
- The social [the quality of social interactions and relations]
- Financial concomitants of the disease and treatment

Considering the above domains of QoL patients with advanced breast cancer being treated with various therapeutic arms were evaluated. Following CMF therapy, patients with advanced breast cancer had improvement in their physical symptom score [73.68%, 90.93% and 81.8% over 6,9 and 12 months]. The improvement in physical symptoms are better than chemo-radiation group. Similarly daily functional status worsened in chemo-radiation group [80%] than in chemotherapy alone [36.6%] at 1 year. Job related social and overall functional status also had similar pattern of response. The study suggests that chemotherapy alone provide a better quality of life than chemo-radiation. Hormone therapy had the least deleterious effect on QoL. Eighty per cent patients in this group improved in their physical score.

Breast reconstruction has been reported to reduce the distress of mastectomy and to have a positive effect on life style, sexual and social relations. Cosmetic disfigurement by mastectomy causes less psychological concern to our patients than in western hemisphere. Since the dress and conservative life style managed to bypass these areas of cosmetic concern, their worries about the disease decreased from 84.2% to 57.9% during therapy and after treatment it declined to 39.5% [Unpublished data]. Worry about the cost of therapy and disruption of the economic structure of the family seen in 63.2% during treatment and 60.5% after treatment is an important consideration. This might rise if newer modalities of treatment are adopted. If financial concerns are addressed, the quality of life could be improved further if NGOs and consolidation of family resources support the patient. Counselling is an important aspect of patient management

with reference to QoL. This aspect has been lacking in this sub-continent.

One important aspect of CMF therapy has been study of toxicity. Though the major toxicity has been seen only 10% cases, the combinations of drugs were tolerated well. A new side effect with CMF combination was observed and reported i.e., aggregation defects in platelets responsible for clinical symptoms of mucositis and haemorrhage without thrombocytopenia (30-32). CMF or CMFP is a combination which has comparable toxic effect and with almost similar response is considered to be effective chemotherapy for advanced breast carcinoma in the Indian subcontinent.

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