Review Article

Recent Advances in the Management of Metastatic Breast Cancer

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Management of cancer rests on a multidisciplinary team effort involving basic researchers, radiologists, pathologists, surgeons, radiotherapists, medical oncologists, nurses and psychologists. The above disciplines are currently evolving and contributing to the improved management of breast cancer. Despite advances in the primary and adjuvant systemic therapy in non-metastatic breast cancer, 20-30% of these, present on follow-up with systemic relapse. 1 to 5% of patients are diagnosed to have metastatic disease at presentation[1], although the incidence is slightly higher in India. Some form of active treatment for advanced breast cancer has been available for more than a century, rendering prospective randomized clinical trial of therapy compared to observation alone unethical[2]. Despite more than three decades of research with the therapeutic modalities, metastatic breast cancer (MBC) remains essentially incurable, with a median survival time of approximate 2 years from the documentation of the metastasis. The median survival is more in patients having bone and soft tissue metastasis compared to those having visceral metastasis. A small percentage of patients even do not relapse for a decade or longer after therapy.

Newly introduced therapies may improve the odds of survival over time for patients with MBC. Several new chemotherapeutic agents have shown response in advanced disease that is resistant to standard medications namely taxanes, capecitabine and vinorelbine. The introductions of potent and selective aromatase inhibitors (SAI) have resulted in some additional survival[3]. As years of research has failed to cure or show any survival benefit in patients with MBC, the focus is on quality of life (QOL), which is often achieved by the judicious application of both local and systemic therapies.

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PATTERN OF METASTASIS:

Patients with short disease free interval have more of visceral metastasis where as bony metastasis predominates in patients with a longer disease free interval. Invasive lobular cancer is more likely to spread to peritoneum, pleura, adrenal gland, uterus and ovary while those with invasive cancer are more likely to spread to liver, lungs and bone. Patients with ER-positive tumors may have a more indolent clinical course, with slower progression of disease and longer survival. In contrast, patient with ER-negative tumors may have a more aggressive disease, with a shorter disease free interval, more rapid spread and a higher incidence of visceral metastasis with a shorter duration of survival.

TREATMENT:

Local: Metastasis at a single site can be treated with local therapies like surgery or radiation. More extensive tumors are either difficult to resect or to include in one radiation field, thereby rendering them more likely to recur[4]. The efficacy of external RT is well established in dosage ranging from 800-1000cGy(single fraction) to 3000cGy(10 fractions) in the relief of pain due to bony metastasis. Patients with disseminated bony disease can also receive hemibody irradiation. A RTOG trial using 600 cGy for upper hemibody and 800 cGy for the

lower half attained a pain relief in 70% of patients[5]. Studies conducted with hemi-body irradiation have also documented a delay in TTP. Radiotherapy has a established role in MBC with metastasis to the brain, spinal cord compression from vertebral body lesions and carcinomatous meningitis. Laminectomy and decompression of a spinal metastasis is indicated in few cases of MBC who have progressive neurological compromise, intractable pain and recurrence of cord compromise following local irradiation. Fracture of long bones can be stabilised with intramedullary nails or prosthesis may be indicated in patients of MBC with massive osteolysis in weight bearing bones. In contrast if there are multiple sites of metastasis, systemic therapy remains the lone option for the patient.

HORMONAL:

Though a majority of MBC expresses Estrogen receptor/Progesterone receptor (ER/PR), only 20-40% of patients with hormone responsive breast cancer undergo major tumour regression following endocrine therapy, with an additional 20-30% remaining stable for periods exceeding 6 months6. Tamoxifen has been the gold standard of receptor-positive breast cancer for over 2 decades. Over the years, tamoxifen has been compared to ovarian ablation, megestrol acetate, toremefene and Diethyl Stilbesterol among other agents, with none proven superior to tamoxifen.

The development of third generation Aromatase inhibitors has changed the algorithm for the treatment of postmenopausal MBC[7]. In 1990, the SAI's replaced amino-gluthemide and megestrol acetate as the preferred second line hormonal therapy[3,8,9]. Further phase III randomised trials have shown superiority of anastrozole and letrozole over tamoxifen for post - menopausal hormone sensitive MBC[10-13] leading to its approval as first line therapy in this setting. Pooled results of 2 double-blinded randomized trials have shown anastrozole to prolong time to progression (TTP) in sub group of patients with known positive hormone receptors (HR)[10,12]. In another smaller, double blinded phase II randomised study, confined to women with HR+ve disease, an increased survival for the anastrozole arm was found[13]. Letrozole also showed superiority over tamoxifen with regards to response rate (RR), TTP and survival (upto 2 years) in a single, large, randomised, double blind trial[11]. Letrozole is known to be more potent compared to anastrozole in inhibiting aromatase activity both in vivo and in vitro. A randomised trial comparing the two in advanced breast cancer failing anti-estrogen therapy showed letrozole arm to have a higher RR (19.1% to 12.3%; $p<0.013$) with statistically insignificant TTP and OS[14]. A comparative phase II study favoring exemestane over tamoxifen has prompted the investigators to extend the study to phase III, the results of which are awaited[15].

Table 1: Randomized trials of tamoxifen and aromatase inhibitors as first line therapy for MBC

Trial/Author (Ref)	Treatments RR (%)	Time to Progression (Months)
TARGET[10]	Tamoxifen 33 Anastrozole 33(p-NS)	8.3m 8.2m (p-NS)
Smith et al[11]	Tamoxifen 21 Letrozole 32 (p<0.0002)	6 m 9.4 m (p-<0.0001)
North] American[12	Tamoxifen 17 Anastrozole 21 (p-NS)	5.6 m 11.1 m (p<0.005)
Milla-Santos[13]	Tamoxifen 23 Anastrozole 34 (p-not reported)	-5 m -9 m (p-<0.05)
EORTC[15]	Tamoxifen 14 Exemestane 44 (p-<0.05)	

RR-Response rate, Ref- Reference

TARGET-Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability Study, EORTC-European Organization for Research and Treatment of Cancer, NS-Not Significant

The above studies have made tamoxifen the second line therapy of choice in postmenopausal hormone sensitive MBC. Fulvestrant, a newer anti-estrogen, has been approved in tamoxifen resistant postmenopausal MBC, after phase III studies showed its equivalence to anastrozole; with fulvestrant demonstrating 30% longer mean duration of response. Fulvestrant was well tolerated and the estrogen receptor down regulation with its use did not preclude response to subsequent hormonal therapy[16,17]. Studies are ongoing for biological agents like Iressa, to delay or prevent the onset of hormone resistance[18].

Hormone sensitive pre-menopausal women with MBC should be treated with tamoxifen with or without ovarian ablation (i.e. oophorectomy or leutinizing hormone receptor (LH-RH)agonists like goserelin). Recent focus has shifted towards treating premenopausal women with the combination of tamoxifen and leutinizing hormone receptor agonist (LHRH-a). A meta-analysis of 4 trials suggested the combination to be more effective than single agent LHRH-a in terms of RR (39% VS 30%, $p<0.03$) progression free survival (PFS) (8.7 VS 5.4 months, $p<0.003$) & overall survival (OS) (2.9 VS 2.5 years, p-0.02)[19]. In a small pharmacokinetics study, the SAI vorozole suppressed estrogen levels beyond those achieved by goserelin alone without any significant rise in androgen[20]. Premenopausal patients with MBC, resistant to tamoxifen and LHRH-a should be treated with megestrol acetate. SAI's are not an option as on date for premenopausal women with MBC outside trial setting. Non steroidal benzothiophene selective estrogen receptor modulator, arzoxifene (LY353381) has been tried in a phase II randomized study in two different dosages (20 and 50mg) with response rates varying from 10-25% as per the patient profile[21].

Table 2-Randomized phase III trials of taxanes in MBC with minimal or no previous anthracycline exposure

Study (Ref)	Treatments	RR (p value)	TTP (p value)	OS (pvalue)
		Single-agent		
Chan 1999 [24]	D A	47.8% 33.3%(0.008)	26 w 21 w	15 m 14 m
Bishop 1999 [25]	P	29% CMFp 13.9m (0.068)	5.3 m 35% (0.37)	17.3 m 6.4 m (0.25)
Paridaens	P A	25% 41%(0.003)	4.2 m 7.5m (<0.001)	15.6 m 18.3m (0.38
Sledge 2003[27]	P A AP	34% 36% 47%(,0.0-07)	6.0 m 5.8 m 8.0m(,0.009)	22.2 m 18.9 m 22.0 m
		Combination		
Nabholtz 1999[28]	AD AC	59% 47%(0.009	37.3w 31.9 w(0.015)	3% difference in both arms (NS)
Mackey 2002[29]	DAC FAC	55% 44% (0.023)	31 w 29 w (0.51)	21 m 22 m (0.93)

D, docetaxel; P, paclitaxel; A, doxorubicin; C, cyclophosphamide; M, methotrexate; F, 5-fluorouracil;p-prednisone; NA, not available; w, weeks; m, months; RR, rerponse rate; TTP, time to progression; OS, overall survival.

Chemotherapy (CT): Doxorubicin is considered the most active cytotoxic agent in the treatment of breast cancer. Its popular use in adjuvant setting has increased the likelihood of anthracycline-resistant MBC. In the above setting taxanes have become the current choice of therapy[22]. Taxanes have been used as a single agent or in combination in MBC.Of the two, docetaxel has proven superior to paclitaxel in a randomised trial[23].Docetaxel as a single agent has been compared with Doxorubicin alone in 326 anthracycline naïve patients in a phase III randomized trial. Although docetaxel yielded a higher RR the difference in the median TTP, QOL and median OS were not significant[24]. The combination of docetaxel with doxorubicin has been compared with other combination regimen.(**table 2)**.

Studies involving paclitaxel monotherapy as first line therapy for MBC have shown conflicting results. A study comparing paclitaxel (175mg/m2 over 3 hours) with doxorubicin (75mg/m2) showed better RR and TTP in favour of doxorubicin, with no benefit in OS[26]. In contrast, a phase III intergroup trial involving paclitaxel and doxorubicin showed equal OS, although the combination showed better RR & TTP[27]. Another study by Bishop et al comparing paclitaxel to a non-anthracycline combination regimen (CMFp)[25] showed improved OS with no difference in the RR(**table 2**). Paclitaxel in the dosage of 80mg/m2/wk was shown to be well tolerated, feasible and effective in a phase II trial for MBC (RR of 40.5%, median TTP of 4.8 months and median OS of 15.8%)[30]. The advantage of the weekly regimen is the low incidence of myelouppression.

In patients previously treated with anthracycline, docetaxel has been compared as a single agent and in combination with capecitabine[31-34]. As a single agent, in 2 of the 3 studies, it showed statistically significant RR, TTP and OS. Docetaxel and capecitabine combination has been shown to be superior to docetaxel alone in terms of RR, TTP and OS with no difference in QOL(**table 3**). There are no available paclitaxel-based phase III trials following anthracycline failure.

Table3-Randomized phase III Trials of taxanes in MBC after anthracycline failure

Study	Treatments	RR (p value)	TTP (p value)	OS (p value)
Single-agent				
Nabholtz 1999[31]	D Mito+VBL	30% 11% (,0.0001)	19w 11w (0.001)	11.4 m 8.7m (0.0097)
Sjostrom 1999[32]	D M F	42% 21% (<0.001>	6.3 m 3.0 m (<0.001)	10.4 m 11.1m (0.79)
Bonneterre 2002[33]	D FUN	43% 38.8% (0.69)	6.5m 5.1m	16m 15 m
Combination				
O'Shaugnessy 2002[34]	D+Cape D	41.6% 29.7% (0.006)	6.1 m 4.2 m (0.0001)	14.5 m 11.5m (0.0126)

D, docetaxel; Mito, mitomycin; VBL, vinblastine; M, methotrexate; F, 5-fluorouracil; N, vinorelbine; Cape, capecitabine; NA, not available; w, weeks; m, months; FUN, 5-fluorouracil and vinorelbine.

The impact of CT on survival and QOL in anthracycline-taxane failure is still debated and under evaluation. These regimens either as single agent or in combination have been consistently associated with fewer responses without any effect on median survival. Hence no standard regimen has evolved[35]. Capecitabine, an oral pro-drug of 5-Fluorouracil, in two studies exceeding 130 heavily pretreated patients showed response rates of 18-20% and disease stabilization in 43-48%[36-37]. Capecitabine in the dosage of 2.5gm/m2/day has been approved as a third line option for MBC failing anthracycline and taxane. Vinorelbine as a single agent given weekly has shown RR of 20-40%. It has also been tried in combination with 5FU, trastuzumab, anthracycline and cisplatin without any encouraging results in MBC[38-40].A phase II study of oral vinorelbine at dosage of 60-80mg/m2/week showed a RR of 31%. It was found to be an effective, convenient and well tolerated promising alternative to the parenteral therapy[41]. Irinotecan as a single agent has shown some activity in patients previously treated with doxorubicin and taxanes[42].Liposomal doxorubicin appears to be efficacious and less cardiotoxic than conventional doxorubicin allowing its combination with trastuzumab[43].The combination has shown little or no activity in patients with anthracycline resistant disease[44].

Gemcitabine as a monotherapy in MBC has shown responses varying from 37% as a first line therapy to 18% as third line therapy. It has been approved in MBC in combination with paclitaxel as second line therapy. The study comparing gemcitabine alone to its combination with paclitaxel showed RR of 39.3% and 25.6%(p<0.0007) and TTP of 5.4 and 3.5 months (p-0.0013) respectively, the QOL indices favoring the combination[45]. Oxaliplatin combined with 5-FU in a small phase II study showed a RR of 33% with 36% of the patients showing stable disease[46]. A number of newer cytotoxic agents are under evaluation in MBC, such as the multitargeted antifolate Premetrexed (Alimta)[47] and the epothilones, a new promising class of antitubilin agent that seems to lack cross resistance with taxane[48].

The other areas of debate are regarding the schedule of administration of drugs(as sequential or simultaneous combination therapy) and optimal duration of CT. No conclusion has been reached on these vital issues. The advantages of single agent sequential therapy include administration of each drug at its maximum tolerated dose and avoiding the overlapping toxicity seen with combination regimen. The phase III, 3 arm study comparing sequential scheduling of paclitaxel and doxorubicin, with the combination of both drugs concluded that, although the combination had better RR and median time to treatment failure, it did not improve the survival or the QOL compared to either of the sequential therapy[27]. However simultaneous combination therapy may be appropriate for symptomatic patients with massive tumour burden, in whom better and quick response may be worth the increased toxicity.

CT can be given till best response and then discontinued, to be restarted at the time of progression. It may also be administered on a continual basis till there is progression of the disease or toxicity precludes further therapy. There are advocates of both these approaches. A recent meta-analysis of 4 trials in MBC showed a 23% increase in median OS in women randomised to longer duration of CT[49].The final decision regarding the schedule and duration of therapy should be taken after discussion with the patient. The concept of metronomic CT is to administer the cytotoxic drugs at relatively low doses, which is thought to optimize the

Table 4- Trastuzumab and CT for HER-2 overexpressing advanced breast cancer

	CT alone	CT + Trastuzumab	*p* value
Median survival	20.3months	25.1months	0.046
1 year survival	68%	79%	0.008
TTP	4.6months	7.4months	<0.001
RR %	32	50	<0.001
TTP Time to Progression			
RR Response rate			
CT Chemotherapy			

Table 5 Some of the new biological agents with clinical potential in breast cancer.

Agent	Class	Target	Current status
ZD1839 (Iressa)	Tyrosine kinase inhibitor	EGFR	Phase II evaluation
Tak 165	Tyrosine kinase inhibitor	Her-2	Phase I evaluation
R-115777 (Zarnestra)	RAS farnesyl transferase inhibitor	RAS and other fernesylaated proteins	Activity seen in phase II trials, phase III trials starting
RhuMAB VEGF	Monoclonal	VEGF antibody	Modest activity in Phase II
PS-341	Proteosome inhibitor	Proteosome	Activity in Phase I/II trial as single agent
ZD 6474	Tyrosine kinase inhibitor	VEGFR	Phase I Study
BAY 43-9006	RAF kinase inhibitor	RAF	Phase I study

angiogenic effect of CT. It might be a reasonable option in patients with relatively indolent disease for whom toxicity is the main concern[50]. The role of high dose chemotherapy (HDCT) with autologous stem cell transplantation in the above setting is still a matter of debate. A randomized study comparing HDCT to conventional CT showed no benefit in terms of TTP or OS. The same results were also seen in a French multicentric, randomized study[51]. In contrast, a single center randomized trial has shown survival benefit with HDCT in MBC[52], but the study is under review as part of a misconduct investigation.

BIOLOGICAL THERAPY:

Her-2 over expression or amplification occurs in approximately 20-25% of patients with breast cancer. It is associated with aggressive disease and decreased survival[53-54]. Trastuzumab is a humanized mouse monoclonal antibody against the HER-2 protein and is an active and tolerable drug as a first line therapy for MBC[55]. It is given as a weekly schedule (4-mg/kg of loading dose followed by 2-mg/kg/week). CT when added to trastuzumab has shown increase survival as compared to CT alone in a randomized trial (Table-4)[56], though no randomized trial is available till date to show superiority of the combination over trastuzumab alone. Pharmacokinetics and safety data suggest less frequent administration of a larger dose of trastuzumab (6mg/kg x q3weekly) might be feasible. A Phase II trial evaluating the safety and pharmacokinetics of trastuzumab and paclitaxel as a 3 weekly schedule have shown a similar plasma drug trough levels and RR with those achieved with the standard weekly regimen[57].

Number of biological agents targeting a variety of molecular pathways relevant to the biology of breast cancer cell are being tried, the results of which are still awaited (Table-5). Bexarotene, a retinoid X receptor-selective retinoid with preclinical anti-tumour activity in MBC has been tried in a multicenter phase II study as an oral preparation with a RR of approximately 6%[58].

Bisphosphonates are an integral part in the treatment of women with bone metastases, decreasing the incidence of pathological fractures, pain, and hypercalcemia. Well-conducted, placebo-controlled randomized clinical trials that have demonstrated reduced skeletal morbidity in the bisphosphonate arm. This family continues to grow and the new generation compounds, in view of their increased potency, are expected to be even more efficacious and more convenient to use[59-60]. Zolendronic acid is the most preferred of all bisphosphonates because of its shorter duration of infusion without any compromise on the effect. ASCO 2003 recommends a minimum infusion time of 2 hours for pamidronate and 15 minutes for zolendronic acid with serum creatinine to be monitored before each therapy. Bisphosphonate are not recommended in patients with abnormal bone scan without evidence of bone destruction on imaging. Bisphosphonates given for metastatic pain is recommended along with systemic CT or hormonal therapy[61].

Patients with widespread bony metastasis can be treated either with Phosphorus 32P which has a expected RR of 80% or Strontium(Sr) 89 which has a RR of 83%. Sr is selectively taken up by tumor involved bone with a ratio of 10:1. 32P and 89Sr are the only agents currently approved for bone metastasis. Newer agents like Samarium 153 and Rhenium 186 are also being studied. Supportive care for MBC as on date also includes chest tube drainage and chemical pleurodesis, pleuroperitoneal shunt, pericardiocentesis and chemical pericardiodesis. Rehabilitation of a case of MBC should be addressed to and taken care as per the patient's personal preferences.

The optimal management of MBC till date remains a therapeutic challenge. The choice of therapy depends upon the hormonal status, prior exposure and toxicity profile. Aromatase inhibitors and tamoxifen are the commonly employed hormonal agents with fulvestrant being approved for tamoxifen resistant cases. The choice and schedule of cytotoxic agent(s) depends upon the patient's disease profile and preference. Biological agents such as trastuzumab and bisphosphonates also play an important role in the management of MBC. The future lies in the development and use of the newer biological and hormonal agents. As these novel therapies are integrated into daily practice, the main challenge will be to select those patients who are likely to benefit from a specific schedule with minimal toxicity.

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