Original Article

Practical consensus recommendations regarding the use of hormonal therapy in metastatic breast cancer

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Abstract

Metastatic breast cancer (MBC) is cancer that has spread from the breast to another part of the body or has come back in another distant location. Treatment options for MBC depend on several factors. One of these factors is the levels of hormone receptors (HRs) in the tumor. Cancers with high levels of HRs, called HR-positive, use the hormones estrogen and progesterone to grow and spread. Hormonal therapy is a type of treatment specifically for HR-positive breast cancer. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at these practical consensus recommendations in regards with the use of hormonal therapy and the management of HR-positive MBC for the benefit of community oncologists.

Key words: Aromatase inhibitor, combination, endocrine therapy, ESR1 testing, evorolimus, exemestane, fulvestrant, palbociclib

Introduction

Estrogen receptors (ERs) and progesterone receptors (PRs) are found positive in about 20–45% of Indian breast cancer patients.[1,2] Although metastatic breast cancer is unlikely to be cured, there have been meaningful improvements in survival due to the availability of more effective systemic therapies, including endocrine therapy in the treatment of hormone-sensitive disease.[3-6] The endocrine treatment of breast cancer utilizes strategies that reduce or halt estrogen production, block signalling through the ER, or antagonize ER itself. There are several different types of drugs used in hormonal therapy, which use different ways to keep estrogen from helping the cancer grow.[7] This manuscript was prepared to help community oncologists to use hormonal therapy optimally in hormone receptor positive MBC and provide guidelines regarding the use of the different anti-endocrine drugs.

Expert oncologists from all over India met to discuss and reach a consensus statement to provide community oncologists practical guidelines on the use of hormonal therapy in the management of HR-positive MBC. The discussion was based on published evidence and practical experience in real life management of such patients. The expert group discussions were moderated by Dr Senthil Rajappa. The core expert group consisted of Dr Jyoti Bajpai, Dr Mehboob Basade, Dr Chanchal Goswami, Dr Christopher Twelves, Dr Aditya Murthi and Dr A K Rathi. Members of the panel were also allowed to share their personal experiences and make comments. This manuscript is the outcome of the expert group discussion and consensus arrived at in 2017.

Defining Clinical Cohort and Practice of Expert Group Panel Members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the participating delegates and expert group panel members – on the basis of which this document was prepared. The experts discussed two cases: Case 1: 43 year old premenopausal lady with no co-morbidities and left breast lump. Tumour is found to be cT2N3M1, ER/PR strong positive and HER2 negative. There are 5 metastatic sites in the skeleton and no visceral metastases. Case 2: 47 year old lady diagnosed with T2N1M0 Ca breast 11 years ago. The patient underwent breast conservation surgery, TACx6, radiotherapy and 5 years of tamoxifen/5 years of Anastrozole. No co-morbidities were found. Now shows up with c/o right hip discomfort and has completed AI treatment. Based on these cases, a series of questions were put up for poll upon which the expert group discussed and aimed to reach a consensus. Each question had multiple choice options from which participants were to select the one most appropriate for their clinical practice setting. The expert group then formed the practical consensus recommendations for the community oncologists.

Case 1: Surgery of the primary in hormone receptor-positive metastatic breast cancer patients

To the question as to when would they consider surgery of the primary in a patient with HR-positive MBC, with bone only metastasis, a total of 50% of the polled oncologists were of the opinion that they would not recommend surgery upfront but would go for it later based on the response to therapy. Another 33.33% of the polled oncologists were in support of recommending surgery of the primary upfront while the rest were in support of not recommending surgery at all [Table 1]. The role of locoregional treatment of the primary tumor in patients with stage IV breast cancer is debatable as it is an invasive approach that has not been firmly established to improve outcome. Removal of the primary can induce an angiogenic surge and promote the progression of metastases.[8,9] Other potential disadvantages of surgery of the primary are

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Table 1: Question 1 - When would you consider surgery of the primary in a patient with hormone receptor-positive metastatic breast cancer, with bone only metastasis?

Options	Now	Later	Never
Percentage of polled oncologists	33.33	50	16.67

Expert group consensus: Substantial evidence is not present for locoregional treatment to replace systemic treatment as the standard of care in patients with HR-positive MBC. Upfront locoregional control should not be offered to these patients. HR=Hormone receptor, MBC=Metastatic breast cancer

the possible release of growth factors related to surgical wounding[10] and the immune-suppression caused by surgery and anaesthesia.[11] The panel discussed about a study from India evaluating the effect of locoregional treatment in MBC patients which indicated no evidence to suggest that locoregional treatment of the primary tumour affects overall survival in patients with MBC.[12] Another study called the TBCRC 013[13] was a multicenter prospective registry study evaluating the role of surgery for the primary tumor in de novo Stage IV disease. The study included 112 patients of whom majority were ER + ve (84%) and all the patients received a first line of systemic therapy. The study found no evidence showing that surgery had an effect on the overall survival of the patients irrespective of their tumour subtype. On the other hand, the MF07-01 prospective Turkish trial included 274 women who presented with stage IV breast cancer. Based on the extent of disease, patients received surgery followed average 4 weeks later by systemic therapy (n = 138) or systemic therapy alone (n = 136). At a follow up of 5 years, 41.6% of the surgery group was alive, compared with 24.4% of the systemic therapy group (hazard ratio [HR] =0.66; P =0.005). Median overall survival at that time was 46 months and 37 months, respectively. The greatest benefit was observed in patients with estrogen receptor–positive, HER2-negative disease, patients with solitary bone metastases, and those younger than age 55[14] The panel added that modern systemic therapy has contributed to improved survival in patients with distant metastasis. The expert group concluded that at the moment, substantial evidence is not present for locoregional treatment to replace systemic treatment as the standard of care in patients with HR-positive MBC and did not recommend upfront locoregional control. However, locoregional therapy along with systemic therapy may prolong survival in subsets of patients with ER + disease and solitary bone metastasis (from Turkish study). However, this is based on exploratory analyses. Any decision on locoregional therapy in oligometastatic disease should be individualised to the age, ER status, sites of metastatic disease and most importantly response to therapy.

Treatment Options in Hormone Receptor-positive Metastatic Breast Cancer Patients

To the question as to what would be their preferred treatment for patients with HR-positive MBC, 57.2% of the polled oncologists voted in support of recommending chemotherapy followed by endocrine therapy while the rest were in support of recommending endocrine therapy ± targeted therapy as indicated in Table 2. There is little evidence that concomitant use of endocrine agents plus chemotherapy results in improvements in survival outcomes in women with metastatic breast cancer.[15] The toxicity is also generally worse with chemotherapy and endocrine therapy has been known to have relatively less toxic adverse effects.[16,17] A meta-analysis done to evaluate the effects of chemotherapy and endocrine therapy on HR-positive MBC patients indicated a recommendation of treating these patients first with endocrine therapy rather than chemotherapy.[17] This analysis suggested that neither survival nor quality of life is improved by treating patients with chemotherapy when hormone therapy has a reasonable chance of providing disease control. Recently, ASCO and ESMO (ABC3) have issued guidelines for the use of endocrine therapy in HR-positive MBC patients. Treatment decision need to take consider the following factors: HR and HER-2 status, previous treatment used and their toxicities, disease-free interval, biological fitness of the patient, tumour burden (defined as number and site of metastases), significant co-morbidities, menopausal status, socio-economic and psychological factors, available/feasible therapies in the patient's country and patient preference. However, the preferred treatment for HR positive Her2 negative MBC remains hormonal therapy.[18,19] The Expert Panel acknowledged that there are situations in which chemotherapy is appropriate as initial therapy for HR-positive MBC, including in patients with immediately life-threatening disease, like visceral crisis. It is important to note that according to ABC3 guidelines of ESMO, visceral crisis is different from the mere existence of metastasis in visceral organs. There should exist compromise in such organs sufficient to lead to severe organ dysfunction (on the basis of symptoms, signs and investigations) along with rapid progression of disease. In conclusion, the expert consensus was that endocrine therapy rather than chemotherapy should be offered in patients with HR-positive MBC who are not in visceral crisis.

First Line Hormonal Therapy after Ovarian Ablation for Premenopausal Women

When asked as to what hormonal therapy they would recommend after ovarian ablation, 50% of the polled oncologists were in support of recommending aromatase inhibitors (AIs), 33.33% were in support of recommending letrozole plus palbociclib while the remaining oncologists voted for AIs plus fulvestrant [Table 3]. Aromatase inhibitors have become well established for the treatment of postmenopausal women with HR-positive MBC and for adjuvant hormonal therapy for primary breast cancer. Two randomized, double-blind trials concluded that anastrozole had better outcome in postmenopausal HR-positive advanced breast cancer patients as compared to tamoxifen.[20] Benefit of aromatase inhibition has now been extended to premenopausal women after ovarian ablation.[21] Ovarian ablation by oophorectomy, ovarian radiation or hormonal suppression is the initial recommended treatment for HR-positive MBC in premenopausal women. Ovarian ablation combined with aromatase inhibitors is now being seen as a feasible option of treatment in premenopausal women.[21]

In February 2015, the Food and Drug Administration (FDA) approved palbociclib in combination with letrozole, as initial endocrine-based therapy for postmenopausal women with ER-positive, HER2-negative metastatic breast cancer.[22] The approval was based on the very favorable PFS results of PALOMA 1 clinical trial.[23] A total of 165 postmenopausal females with stage IV breast cancer or inoperable locally recurrent disease who had not received any systemic treatment for advanced disease

were enrolled in the trial. There was a trend toward increased overall survival for the combination arm in comparison to the mono-therapy group (37.5 months vs 33.3 months). The addition of palbociclib to endocrine therapy resulted in improvement in the objective response rate and the clinical benefit rate. Recently, the primary results of a confirmatory Phase III trial, PALOMA-2 were presented; these expand and confirm the significant clinical benefit and safety of the palbociclib–letrozole combination in ER + ve/HER2 − ve advanced breast cancer.[24] The FALCON trial enrolled 524 HR-positive treatment naive MBC patients for evaluating the efficacy of fulvestrant as compared to that of a third generation AI, anastrozole.[25] The study concluded that fulvestrant had a superior PFS as compared to anastrozole. This benefit was confined to patients with bone only metastasis. Though not right to cross compare trials, the benefit of AI plus palbociclib in patients with bone only metastasis was far superior to the fulvestrant arm of the FALCON study. The expert panel concluded that a combination of AIs and palbociclib should be the preferred first line hormonal therapy after ovarian ablation. The panel added that if palbociclib treatment is not feasible, AIs should be offered. In patients with bone only disease, fulvestrant may offer better efficacy than an AI, though one needs to keep in mind the financial implications and the intra muscular administration in both buttocks every month which can impact compliance.

It is important to state that, irrespective of the site of metastasis, the combination of AI plus palbociclib was superior to AI alone. There are no clinical or molecular biomarkers to guide choice of AI with palbociclib versus AI alone.

Case 2: Role of ESR1 mutation testing

Estrogen receptor is a protein encoded by the ESR1 gene. Mutations of the ESR1 gene have been increasingly recognized as an important mechanism of endocrine therapy resistance.[26,27] Given the assumed impact that the presence of ESR1 mutations has on outcome to endocrine therapy, assessing ESR1 mutations in MBC patients may be of significant interest to further individualize treatment for MBC patients. Upon posed with the question regarding the role of ESR1 mutation testing in HR-positive MBC patients, a total of 42.85% answered affirmatively while another 42.85% were indecisive [Table 4]. It was not until 2013 that a series of studies using next-generation sequencing (NGS) of DNA renewed interest in the mutated receptor by demonstrating a high prevalence (11–55%) of ESR1 mutations in metastatic ER-positive breast cancers with prior AI exposure.[27-32] The biggest disadvantage of these studies was that they concerned mostly small, heterogeneously treated, and retrospectively selected patient cohorts. Schiavon *et al*.[33] were the first to present a study in which ESR1 mutations were assessed in a relatively large cohort of MBC patients. The observations by Schiavon *et al*. also suggested that AI treatment in the metastatic setting might cause ESR1 mutations. Addition of palbociclib to letrozole in improving both median PFS and CBR rate is consistent in nearly all subgroups analyzed, as is seen with the overall study population.[34] In fact, Palbociclib benefit is seen irrespective of ESR mutations.[35] Between AI and Fulvestrant, there is no benefit for AI in those with mutation while there is improvement if PFS with fulvestrant.[36]

Preclinical studies have shown differences among ESR1 mutations in terms of sensitivity to endocrine therapies,[30] but clinical analyses have been underpowered and have not yet reached a consensus on this issue.[37-39] The panel opined that the current evidence on ESR1 mutations warrants prospective studies in which patients are randomized and treated according to the ESR1 mutation status. In conclusion, the expert panel was of the view that the presence of ESR1 mutations in patients with ER-positive MBC has high potential for clinical validity and utility but prospective studies in which the exact role of how ESR1 mutations can be used to guide treatment decision-making have to be initiated. At present, the panel does not recommend testing for ESR1 in routine clinical practice.

Second Line Hormonal Therapy

The final question that was asked to the polled oncologists was what would be their preferred therapy for patients who have previously received aromatase inhibitors. To this question, majority of the polled oncologists were in support of recommending a treatment consisting of fulvestrant and palbociclib [Table 5]. On February 19, 2016, palbociclib was approved for use in combination with fulvestrant for treatment of HR–positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.[40,41] The approval was based on results of a double-blind phase III trial (PALOMA3) in which 521 pre-and postmenopausal women with advanced or metastatic disease who had disease progression on or after adjuvant or metastatic endocrine therapy were randomized 2:1 to receive

Table 2: Question 2 - What is your preferred treatment for patients with hormone receptor-positive Metastatic breast cancer?

Options	Chemotherapy	Endocrine therapy (±targeted therapy)	Chemotherapy followed by endocrine therapy
Percentage of polled oncologists	0	42.85	57.15

Expert group consensus: Endocrine therapy rather than chemotherapy should be offered in patients with HR-positive MBC who are not in visceral crisis. Chemotherapy may be offered in patients with life threatening disease and rapid progression. HR=Hormone receptor, MBC=Metastatic breast cancer

Table 3: Question 3 - What is the first choice of hormone therapy after ovarian ablation?

Options	AIs	Tamoxifen	Fulvestrant	Letrozole + palbociclib	AI + fulvestrant
Percentage of polled oncologists	50	0	0	33.33	16.67

Expert group consensus: A combination of AIs and palbociclib should be the preferred first line hormonal therapy after ovarian ablation. If palbociclib treatment is not feasible, AIs should be offered and in patients with bone only disease, fulvestrant may be offered. AIs=Aromatase inhibitors

Table 4: Question 4 - Is there any role for ESR1 testing?

Options	Yes	No	Don't know	Don't waste money
Percentage of polled oncologists	42.85	0	42.85	14.3

Expert group consensus: At present, ESR1 testing is not recommended in routine clinical practice. Further studies required for ESR1 mutation testing to become a standard form of testing

Table 5: Question 5 - What is the preferred therapy for patients who have received aromatase inhibitors previously?

Options	Letrozole + palbociclib	Fulvestrant 500	Fulvestrant + palbociclib	Exemestane + everolimus	Tamoxifen
Percentage of polled oncologists	25	0	75	0	0

Expert group consensus: A combination of fulvestrant and palbociclib should be offered to patients who have received AIs earlier. Exemestane plus everolimus is another option but its toxicity has to be taken into account. AIs=Aromatase inhibitors

oral palbociclib plus fulvestrant (n = 347) or fulvestrant plus placebo (n = 174) until disease progression or unacceptable toxicity.[41,42] The median progression-free survival was found to be 9·5 months in the fulvestrant plus palbociclib group and 4·6 months in the fulvestrant plus placebo group. The study concluded that the combination could be considered as a therapeutic option for patients with recurrent HR-positive, HER2-negative MBC that has progressed on previous endocrine therapy. A meta-analysis was carried out to evaluate the PFS yielded by palbociclib and fulvestrant as opposed to that by endocrine therapy.[43] It was found that the combination of palbociclib and fulvestrant yielded significantly greater PFS than endocrine therapy in treatment-naïve and previously treated patients with advanced/metastatic breast cancer. Palbociclib plus fulvestrant was also associated with significantly less toxicity than everolimus plus exemestane.

A randomized phase-3 trial called the BOLERO-2 was carried out to evaluate the combination of the mTOR inhibitor everolimus with the aromatase inhibitor exemestane.[44] Results showed that the combination of everolimus with exemestane had increased efficacy compared with exemestane plus placebo with respect to progression-free survival in the range of 4–6 months in a patient population of postmenopausal, HR-positive, advanced breast cancer patients. However, the toxicity profile of the combination arm was seen to be increased. Considering all the existing evidence, the expert panel concluded that for patients who have received aromatase inhibitors previously, a combination of fulvestrant and palbociclib should be offered. The panel added that the combination of everolimus and exemestane is also an option however, given the increased toxicity profile of the combination arm of exemestane and everolimus, the prescribing oncologist will need to consider the benefit of the combination against the added toxicity it brings.

Take Home Message

1. Im patients with metastatic breast cancer, available evidence does not support locoregional treatment. The decision should be individualised based on patient and tumor characteristics, site and number of metastasis and response to systemic therapy
2. Endocrine therapy rather than chemotherapy is preferred in patients with HR-positive MBC. Chemotherapy may be offered for those who are highly symptomatic and visceral crisis needing rapid tumor responses
3. A combination of AIs and palbociclib should be the preferred first line hormonal therapy for HR + metastatic breast cancer. Premenopausal women need to undergo ovarian ablation before starting on AI with Palbociclib. If treatment with palbociclib is not feasible, AIs should be offered. In patients with bone only disease, fulvestrant may be offered over AI
4. At present, ESR1 testing is not recommended in routine clinical practice
5. A combination of fulvestrant and palbociclib should be offered to patients who have progressed on an AI. Exemestane plus everolimus is another option

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