ELSEVIER

Critical Reviews in Oncology/Hematology xxx (2011) xxx–xxx

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives

Nagi S. El Saghir[a,*], Arafat Tfayli[a], Hassan A. Hatoum[a], Zahi Nachef[a], Phuong Dinh[b], Ahmad Awada[b]

[a] *Breast Center of Excellence, NK Basile Cancer Institute, American University of Beirut Medical Center, PO Box 11-0236, Riad El-Solh 1107 2020, Beirut, Lebanon*

[b] *Jules Bordet Institute, Brussels, Belgium*

Accepted 18 January 2011

Contents

* Corresponding author. Tel.: +961 1 350 000x5350; fax: +961 1 370 814.
E-mail addresses: nagi.saghir@aub.edu.lb, ns23@aub.edu.lb (N.S. El Saghir), at35@aub.edu.lb (A. Tfayli), hassan.hatoum72@gmail.com (H.A. Hatoum), phuong.dinh@bordet.be (P. Dinh), ahmad.awada@bordet.be (A. Awada).

1040-8428/$ – see front matter
doi:10.1016/j.critrevonc.2011.01.010

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

Abstract

Current treatment of metastatic breast cancer (MBC) aims at achieving meaningful clinical responses, improved quality of life, long-term remissions, prolonged survival, and dares to hope for a cure in a small percentage of cases. This article will discuss both consensus and controversies in the management of MBC in the context of the new evolving breast cancer molecular classification. Hormonal therapy remains the mainstay of management of MBC Luminal A and B. Data is emerging on management of ErbB2-positive HR-positive MBC by combining hormonal manipulation and targeted anti-ErbB2 therapy and has recently received regulatory approval in Europe and USA. The optimal use and duration of single agent or combination chemotherapy is discussed. Data and controversies surrounding the use of newer agents such as nab-paclitaxel, ixabepilone, eribulin, and PARP inhibitors as well as trastuzumab is reviewed. Better understanding of pathophysiology has paved the way for the introduction of newer anti-ErbB2 agents such as lapatinib, pertuzumab, T-DM1 and neratinib. Controversies regarding bevacizumab and anti-angiogenesis are discussed. Bisphosphonates have significantly reduced skeletal related events and made significant improvements in the quality of life of patients with MBC. Newer anti-RANK Ligand antibodies show promising results. Significant advances in the understanding of molecular biology of breast cancer have been made and should lead to an improvement in the outcome of MBC. More possibilities of cure can become an attainable goal in the near future.

Keywords: Metastatic breast cancer; Endocrine treatment; Aromatase inhibitors; Chemotherapy; Anthracyclines; Taxanes; Anti-ErbB2 targeted therapy; Anti-angiogenesis; PARP inhibitors; Anti-EGFR; Bisphosphonates; Anti-RANKL; Palliation; Survival

1. Introduction

Metastatic breast cancer (MBC) remains a major therapeutic challenge either as the first presentation of breast cancer or as recurrence after prior treatment of early stage disease. Median survival of patients with metastatic breast cancer is between 2 and 3 years [1]; it varies according to histological and molecular subtype, as well as age, and it has improved with modern therapy [2,3].

The goal of treatment of MBC remains primarily the achievement of disease control (in terms of PFS) and the palliation of symptoms for as long as possible, with the least possible side effects. These benefits may lead to an additional goal of improved overall survival (OS) and possibly cure. This is more easily achieved in patients with limited recurrent disease and exquisite sensitivity to therapy. Early detection of local recurrences can be treated with local surgery or completion mastectomy in cases of prior breast-conserving surgery, with/without radiation and systemic therapy, and can result in cure [4]. Alongside advances that have been made in surgical and radiotherapeutic options, new chemotherapeutic and targeted agents and formulations have the potential to bring significant clinical benefits and are being rigorously tested in many clinical trials. Advances in multidisciplinary care can result in clinically meaningful benefits and potential cures. For example, in patients with single site or oligometastatic breast cancer, treatment with surgery, radiation therapy where feasible, in addition to systemic therapy has been shown to result in significant improvement of survival [5].

This article will review the current management guidelines and therapeutic strategies in MBC, and include new therapeutic options with molecular oncology and translational research that made significant steps towards cure of breast

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

cancer. We will also discuss the ongoing controversies that warrant future research.

2. Incidence and prediction of disease recurrence

While MBC at presentation is treatment-naïve, most patients with MBC at the time of recurrence would already have had adjuvant chemotherapy and/or hormonal therapy (HT) and/or trastuzumab. More than 50% of recurrences occur after 5 years from diagnosis, with many recurrences reported after 10 or 20 years [6]. Factors that predict early recurrences (within 2–3 years of diagnosis) include advanced stage of the primary tumor, younger age, poorly differentiated histology, negative hormonal receptors (HR), ErbB2 receptor and uPA (urokinase plasminogen activator) overexpression [7], and the type of treatment modality that was applied at the time of initial diagnosis. HER2, triple negative and Luminal B subtypes tend to relapse earlier. Disease-free interval has always been a clinical parameter in treatment decisions. Using molecular sub-types could be seen as simply putting a firmer biological basis on what good clinicians have been doing for years.

In addition, recently developed gene microarray technologies in breast cancer seem to improve the prediction of probability of distant metastasis to selected organs (e.g., bone) as well as that of local recurrence [8–10]. The new technologies open the way for an early use in clinical studies of selective agent such as biophosphonates or anti-RANKL antibodies to prevent dissemination.

3. Tailoring therapy for Metastatic breast cancer (MBC) according to prognostic factors and new molecular subtyping

Tailoring of therapy to each individual patient involves making a choice of therapy based on factors that affect prognosis and predict response/resistance to available drugs and treatments, with the least possible side effects. Those factors include longer vs. shorter disease-free interval, age, menopausal status, site(s) of recurrence (soft tissue and bone vs. visceral), the bulk of recurrent disease, symptomatic disease or not, prior adjuvant therapy, organ functions, performance status, co-morbidities, as well as tumor characteristics such as hormone responsiveness status and ErbB2/HER2-neu receptor expression. Quality of life considerations and less toxic therapy should remain important considerations when clinicians make choices of therapy for palliation of patients with metastatic breast cancer. Treatment strategies according to the currently described molecular subtypes [11] are reviewed. The pace of disease progression and site(s) of relapse dictate such strategies. Additional practical considerations include accessibility to treatment strategies and costs of therapy [12,13], as well as the patient's personal preferences and wishes.

4. Endocrine therapy for Luminal subtypes metastatic breast cancer

Endocrine therapy can lead to disease control, palliation of symptoms and improvement of quality of life in most hormone-receptor positive MBC patients. Endocrine manipulation was first reported in 1896 when oophorectomy was shown to induce regression of extensive chest wall disease in breast cancer patients [14]. Tamoxifen was introduced in the 1970s after the discovery of estrogen receptors [15,16]. The current standard strategy to predict hormonal sensitivity is the detection of ER (estrogen receptors) and/or PR (progesterone receptors) which are present in Luminal A and Luminal B breast cancer. Longer and more dramatic responses to hormonal therapy are seen in low grade tumors with higher percentage and stronger intensity of hormone receptors (HR) expression [16]. Newer molecular technologies may help to better predict the sensitivity or resistance to hormonal therapy by taking into account the interaction between ER, PR, ErbB2 and other signal-transduction pathways such as m-Tor, Pi3 kinase, and insulin growth factor receptors activation [17]. The 21-gene Recurrence Score (Oncotype DX) has been recently approved in the United States to predict and quantify the risk of distant recurrence of adjuvant tamoxifen-treated patients [18] and additional benefit from adjuvant chemotherapy in primary breast cancer. No such data exist yet for MBC.

Endocrine therapy is recommended as primary systemic therapy for patients with MBC and positive HRs. Patients with soft tissue and bone metastases are more likely to have ER positive tumors [19] and better response to HT than those with visceral metastases [20]. In addition to strategies followed in Luminal A patients, high grade Luminal B patients may have ErbB2 overexpression and derive significant benefit from the addition of modern targeted anti-ErbB2 therapy to hormonal therapy (see Section 6.2).

Previously reported small retrospective studies as well as three recent studies support the practice of re-biopsy of metastatic disease for determination of receptor status. This attitude is gaining popularity and now recommended whenever tumor tissue is accessible. A large retrospective study from Karolinska institute looked at 1095 cases between 1997 and 2007 and found that in 486 patients, ER changed in 27% from positive in primary tumor to negative in relapse and 8% changed from negative to positive. In 456 patients PR status changed in 38% from positive in primary tumor to negative in relapse and 5% changed from negative to positive [21]. Another study carried in Canada and the UK showed an overall 38% discordance rate between metastatic tumor and the primary [22]. Most common discordance was seen in hormone receptors with ER changing results in 12.6% of cases (14% gain of ER and 12% loss), a larger change of 34% in PR status (16% gain PR and 47% loss) while HER2 change was seen to a lesser degree of 5.4% only (HER2 gain in 4.6% and loss in 12.5%). Least changes were seen in TNBC. More importantly, change in therapy was reported in a sig-

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

nificant 15% of patients (41/271 cases). A third study from Italy noted a more significant change of receptor status in biopsied liver recurrences with discordance rates of 14.5%, 48.6%, and 13.9% for ER, PgR, and HER2, respectively, between primary tumor and liver metastases [23]. Again, change of therapy was noted in 12.1% of patients (31 out of 255 patients).

Change of tumor biology and/or change of technical methodology could be the explanation for such discordances. Tissue handling, delay and duration of fixation, type and degree of tissue fixation, slicing large tumors before fixing them in formalin, and type of antibody used all influence receptors determination. All pathology laboratories should have standard procedures to allow for proper determination of receptors in order to better guide therapy.

4.1. Choice of hormonal therapies in post-menopausal Luminal MBC

4.1.1. Anti-estrogens

4.1.1.1. Tamoxifen. *Tamoxifen* is a selective estrogen receptor modulator (SERM) and has been the gold standard of endocrine therapy for over 40 years. Tamoxifen saturates the nuclear ER, blocks the interaction of E with ER, and stops the ER-dependant growth of breast cancer cells. Most of the actions of tamoxifen are mediated by its active metabolites 4-OH-tamoxifen and endoxifen which is the product of metabolism of tamoxifen by cytochrome P450 enzyme *CYP2D6*. Endoxifen concentration varies according to *CYP2D6* enzyme activity which is directly related to genetic polymorphism as well as possible concomittent administration of medications that inhibit its activity. Although a new large multicenter study from Germany confirmed an association between *CYP2D6* variation in polymorphism and response to tamoxifen [24], a recent report of the International Tamoxifen Pharmacogenomics Consortium (ITPC) presented at San Antonio Breast Cancer Symposium failed to demonstrate an association of CYP2D6 genotype with Disease-Free Survival or Overall Survival in women with primary breast cancer receiving adjuvant tamoxifen [25]. In the current continuing controversy, it is important to continue research to provide prospective information, and it seems prudent in the clinic to avoid using drugs like fluoxetine and paroxitene which inhibit *CYP2D6* and may render tamoxifen less effective. Venlafaxine does not inhibit CYP2D6 and is considered a safe choice to treat hot flashes induced by tamoxifen [26].

4.1.1.2. Toremifene. *Toremifene* is another SERM that is effective in ER-positive MBC. However, it was found to be cross-resistant to tamoxifen, and therefore has not been widely used in the clinic [27]. However, toremifene is not metabolized by *CYP2D6* and may be an alternative to tamoxifen in patients who are deemed as "poor metabolisers"

4.1.2. Aromatase inhibitors (AI)

Aminogluthetimide (AG) was the first first-generation AI that replaced surgical adrenalectomy [28]. AG is a non-specific AI that suppresses steroidogenesis completely and therefore patients treated with AG require corticosteroid supplementation. Second generation AIs, on the other hand, interfere with the peripheral conversion of androstenedione into estrogens thus suppress the production of estrogens in postmenopausal women. AIs have been shown to be effective and had been used in tamoxifen-resistant patients and may also be useful in the presence of limited visceral disease.

Anastrozole is a non-steroidal AI that results in a clinical benefit rate of 56% (CR + PR + stabilization of > or = 24 weeks), and 32% objective response rate, equivalent to tamoxifen, but with different toxicity profile [29,30].

Letrozole is another non-steroidal AI that has produced a higher overall objective response (32% vs. 21%), higher clinical benefit (49% vs. 38%) and improved overall survival (34 vs. 30 months) compared with tamoxifen [31].

Exemestene is a steroidal AI that produces a response rate of 23% when given to patients who have progressed on tamoxifen [32]. After failure of nonsteroidal AIs (anastrozole and letrozole), exemestene has a definite but limited activity [33] and has been shown to be equivalent to fulvestrant (see section below) with median time to progression of 3.7 months in the EFECT trial [34].

AIs also compare more favorably with megesterol acetate after failure to tamoxifen [35–37]. AIs are now recommended as first line HT in postmenopausal women. Letrozole has been shown to produce more significant aromatase inhibition [38]; however no clinical study yet has shown definitive superiority mainly in terms of survival of one AI agent over the other. The initial report of the MA-27 trial comparing 5 years of adjuvant anastrozole vs. exemestane revealed no significant difference in activity between the 2 agents [39]. Combinations of AIs with targeted therapy are discussed in Section 6.2.

4.1.3. Fulvestrant

Fulvestrant, an anti-estrogen receptor (anti-ER) drug, is a Selective ER DownRegulator (SERD) that destroys ERs and decreases the number of PRs in breast cancer cells [34,40]. Fulvestrant is now approved for tamoxifen-resistant tumors. After failure of nonsteroidal AIs (anastrozole and letrozole), fulvestrant has been shown to be equivalent to exemestane as noted above [34]. However, fulvestrant is a more expensive drug and requires monthly injections, while exemestene is a cheaper and more convenient oral drug. A recent follow-up analysis of the FIRST trial showed advantage of higher dose fulvestrant 500 mg over anastrozole in first line MBC [41].

Like with aromatase inhibitors, recent data has also supported the use of fulvestrant in patients with limited visceral disease, as an additional line of hormonal therapy, before switching to chemotherapy [42].

Combining fulvestrant with anastrozole in FACT phase III trial showed no advantage over single agent anastrozole with almost identical time to progression (median 10.8 vs. 10.2

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

months, HR 0.99, $p = 0.91$) and overall survival (median 37.8 vs. 38.2 months) [43]. This trial, in line with ATAC adjuvant trial indicates that combination of hormonal therapies is not superior to mono-hormonal therapy [43,44] and is not the way to go. On the other hand, combining hormonal therapy with anti-ErbB2 targeted therapy in ErbB2-positive HR-positive metastatic breast cancer is rather a promising strategy (see Section 6.2).

4.1.4. Progestational agents

Progestational agents have also been used after failure to tamoxifen. Synthetic megesterol acetate is the most commonly used agent (at a dose of 40 mg orally four times a day) and produced response rates of at least 12.4% [45]. Megesterol acetate is currently suggested for use after failure to tamoxifen, AIs and before or after fulvestrant.

4.1.5. Estrogens

After failure of above endocrine manipulations, estrogens themselves may still have a place in the treatment of metastatic breast cancer. In addition to previous anecdotal reports, a phase II study showed that the administration of high-dose DES resulted in a 31% response rate when given to 31 patients who have received multiple lines of hormonal therapy [46].

4.2. Choice of HT in premenopausal Luminal MBC

HT is used as first line therapy in premenopausal women with non-visceral, bone disease as well as low-bulk visceral MBC. Ovarian ablation may be achieved either by surgical oophorectomy or irradiation. Ovarian suppression can be more successful than irradiation and, putting costs aside, may be even preferred over surgical oophorectomy. It may be achieved with monthly or 3-monthly depot injections of an LHRH agonist such as goserelin, leuprolide, or triptorelin. These patients should also be given tamoxifen. The combination of LHRHa with tamoxifen has been shown to be better than LHRHa alone with an overall survival of 2.9 years vs. 2.5 years [47]. Patients can be rendered effectively post-menopausal by ovarian ablation or ovarian suppression (OS/OA) and therefore become candidates for aromatase inhibitors; Although many oncologists practice it, data to support this strategy is limited to a small case series [48] and a recent phase 2 study of 45 patients that showed a 71% clinical benefit (CR: 3%, PR: 34%, stable disease over 6 months: 34%), with a median TTP of 8 months (range 2–63 months) and median OS of 26 months (11 to more than 63 months) when OS and AI modalities are combined together [49]. Unlike in postmenopausal women, data on the use of combination anti-estrogen and anti-ErbB2 therapy is not yet available for pre-menopausal women. The presence of positive ErbB2 receptors in some patients and in particular Luminal B subtype lowers the threshold for early use of chemotherapy in combination with anti-ErbB2 therapy, especially in patients with visceral MBC.

4.3. HT combined with molecular-targeted therapies in MBC

The rationale to combine HT with other molecular-targeted therapies inhibiting several transduction pathways is based on preclinical studies in which potent inhibition of cancer cells and delays in drug resistance were observed. Unfortunately, randomized clinical studies combining HT with anti-EGFR, ras inhibitors and m-Tor inhibitors did not lead in clinical practice to a therapeutic breakthrough. Further clinical studies combining HT with PI3K or IGFR inhibitors are ongoing. HT in combination with anti-HER-2 will be discussed in Section 6.2.

The optimal use of all these approaches is a more fundamental question. Whether these drugs should be administered in combination or sequentially merit well designed clinical trials. Better selection of the patients based on tumor gene sequencing is another promising tool in order to improve therapeutic results. Recently designed clinical trials follow this way.

5. Choice of chemotherapy for MBC

5.1. Chemotherapy old and new agents

Chemotherapy is generally used upfront to treat MBC patients with negative hormonal receptors (ErbB2-overexpressive or not) or hormone refractory in Luminal subtype disease, and also in the presence of rapidly proliferative and/or bulky metastatic breast cancer (Fig. 2). Chemotherapy is generally used at regular intervals with cycles that would cause maximal cell kill but acceptable and reversible toxicity on normal tissues. Although dose dense chemotherapy seems to be useful in the adjuvant setting [50], it is not recommended in metastatic disease because this strategy did not show any superiority over every 3-weekly schedules. Recent data indicate that low-dose daily or weekly metronomic chemotherapy may have additional anti-angiogenic mechanisms of action, in addition to its direct anti-tumor activity [51].

Breast cancer is generally considered a chemotherapy-sensitive tumor and the most effective agents include anthracyclines and taxanes. Chemotherapy can give up to 50–70% response rates when used in combination. Other effective agents include 5FU, capecitabine, vinorelbine, cyclophosphamide, gemcitabine, platinum salts [52,53]. Taxanes are particularly useful in patients who have anthracycline-resistant tumors [54]. Recent data have shown that weekly paclitaxel is better than the 3-weekly paclitaxel regimen in terms of more efficacy and lesser toxicity [55,56]. Newer taxanes include the nanoparticle-albumin-bound nab-paclitaxel which produces higher response rates

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

than paclitaxel (33% vs. 19%). Weekly nab-paclitaxel seems to be more active than 3-weekly nab-paclitaxel (median TTP: 9 vs. 7.7 months), does not cause hypersensitivity reactions, but induces more neuropathy [57].

Ixabepilone is a new semisynthetic anti-microtubule epothilone analogue that, when used in combination with capecitabine, produced better objective response rates (35% vs. 14%) and better, though modest, median PFS (5.8 vs. 4.2 months) in pre-treated patients progressing after anthracyclines and taxanes. However, it gives no survival advantage and the combination is more toxic in terms of peripheral neuropathy, fatigue and myalgia [58,59]. Although it has received FDA approval in the USA, in combination with capecitabine, for anthracycline- and taxane-resistant metastatic breast cancer, and as single agent for anthracycline-, taxane-, and capecitabine-resistant MBC, it has not received EMEA approval in Europe because of limited benefit and significant toxicity and the manufacturer has withdrawn its application for marketing authorization in Europe [60,61].

Eribulin (E7289) is a new anti-microtubule halochondrin B analog that showed promising antitumor activity. In a phase II trial of heavily pretreated patients with MBC, eribulin had an objective response rate of 10–14% [62]. A phase III trial (EMBRACE trial) comparing single-agent eribulin to the investigator's choice of chemotherapy regimen, showed in heavily pre-treated MBC patients, a statistically significant improvement in overall survival of 2.5 months, with a manageable safety profile. Interestingly, the observed objective response rate confirmed the data reported in the phase II program as well as the safety profile [63]. The result of EMBRACE trial opens the way to study eribulin in early stage disease.

Cationic liposomal paclitaxel (Endotag) is another new anti-microtubule agent that targets negatively charged tumor endothelial cells. It impairs tumor microvasculature and has shown in a new phase II randomized clinical trial in patients with triple negative breast cancer an improved clinical benefit rate and PFS at week 16 of 59% for the combination, 34% for Endotag alone and 50% for paclitaxel alone. Median PFS was 4.2 months for Endotag plus paclitaxel, 3.4 months for Endotag alone and 3.7 months for paclitaxel alone. This benefit was associated with minimal increased toxicity. Longer follow-up and larger studies will be needed to better determine its role in TNBC as well as in other types of breast cancer [64].

5.2. *Combination vs. single agent chemotherapy in MBC*

Combination chemotherapy include FAC/CAF, CEF, AC or EC, AT, and ET among others. It gives response rates in the ranges of 50–80%, but is rarely curative. Combinations give higher response rates but are generally more toxic than single agent therapy. Combinations have also been compared to each other with variable results. Combination AT vs. AC showed no survival advantage [65]. When taxanes are given with doxorubicin, there is, however, a longer time to progression (TTP) [66]. Triple combination with docetaxel, adriamycin and cyclophosphamide (TAC) result in more significant toxicity particularly myelosuppression and febrile neutropenia [67]. In patients pretreated with anthracyclines, significant improvement in overall response rate (ORR) (42% vs. 30%), and TTP 6.1 vs. 4.2 months, as well as an OS advantage of 14.5 vs. 11.5 months has been reported with combination of docetaxel plus capecitabine vs. single agent docetaxel in a randomized phase III trial [68]. The combination of gemcitabine plus paclitaxel has also been shown to have significantly higher ORR (40.8% vs. 22.2%) and TTP (5.2 vs. 2.9 months) and OS (18.5 vs. 15.8 months) when compared to single agent paclitaxel in another phase III trial [69]. Of note that in these studies, no or few patents in the single agent arm had crossed over to the other drug of the combination arm, which helps explain the observed survival advantage. Gemcitabine combined with vinorelbine compared with single agent vinorelbine in a phase III study of patients refractory to anthracyclines and taxanes with heavy visceral disease showed non-statistically significantly different ORR (36% vs. 26%), significant PFS (6 vs. 4 months), with higher hematological toxicity rate [70].

A recent phase III trial of gemcitabine plus docetaxel (GD) compared to capecitabine plus docetaxel (CD) with planned crossover to the alternate single agent in metastatic breast cancer (MBC). GD and CD had similar efficacy with toxicity profiles consistent with prior clinical experience. Results suggest that the GD to C crossover sequence may provide a clinical benefit over CD to G [71].

Vinorelbine is an effective agent in MBC and has been combined with cisplatin in phase II studies [72]. Platinum compounds are getting more attention for triple negative disease, particularly BRCA-associated breast cancer mainly in the neo-adjuvant setting [73,74]. The results of the BALI trial comparing cisplatinum plus cetuximab to cisplatinum alone as first-line therapy are reviewed in Section 9.

Another trial comparing pegylated liposomal doxorubicin (PLD) plus docetaxel vs. docetaxel alone gave improved response rates but no impact on survival. This combination did not receive regulatory approval because of excessive hand foot syndrome [75].

In summary, combination chemotherapy is generally more active and produces higher response rates and longer time to progression than single agent chemotherapy but at the expense of higher toxicity. Moreover only a few studies have included a planned crossover analysis, such as the study comparing anthracyclines with taxanes in combination or in sequence and did not show an improvement of TTP nor survival [1].

The recommendation for now remains to use combination chemotherapy in the presence of more aggressive disease and bulky visceral involvement, particularly in younger patients who usually have better tolerance and less co-morbidities. Otherwise, sequential administration of drugs at maximal tolerated doses, particularly anthracycline and taxanes is preferred.

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

5.3. Duration of chemotherapy in MBC

When patients are started on chemotherapy, they should be re-evaluated clinically (symptoms and performance status), with tumor markers and with imaging studies at regular intervals. If the patient shows improvement after 2–3 cycles of a particular chemotherapy regimen, then the same regimen is continued for a total of 6–8 cycles. The exact total duration of therapy depends on the response and toxicity profile of the drugs used. For example, anthracyclines administration is limited by their potential cumulative cardiotoxicity and one should never exceed a total dose of 450–550 mg/m^2 of doxorubicin. Dexrazoxane, is an iron chelator that, has been shown to reduce anthracycline-related cardiac toxicity [76] and is approved for patients receiving more than 300 mg/m^2 of doxorubicin and having a continued response to it. Pegylated (liposomal) doxorubicin can be used for longer duration than doxorubicin. As first-line therapy, it has similar results as doxorubicin for ORR, PFS, and OS, has less cardiac toxicity but significant skin toxicity [77].

There is no evidence to support maintenance chemotherapy in MBC and it is generally not recommended. Once patients complete their planned and tolerated therapy, they are placed under observation if they have negative HRs, or placed on HT if they have positive HRs and are still considered hormone-sensitive. We propose this strategy of maintenance hormonal therapy mainly in patients with bulky and aggressive disease at presentation. In fact, when chemotherapy is stopped in this group of patients, the progression-free period is usually very short and consequently maintenance hormonal therapy could prolong the duration of chemotherapy-free interval. If the patients are also receiving targeted therapy, for example trastuzumab, they are continued on it for longer durations (see Section 6.1). For patients with MBC who do not respond to a specific drug or combination, they are generally switched to another drug according to their performance status, tolerance, potential of antitumor activity and the preference of the patient.

6. Treatment of ErbB2-overexpressive breast cancers

6.1. Anti-ErbB2-based therapies

Patients with MBC who benefit from anti-ErbB2 targeted therapy are those whose tumors show overexpression of ErbB2 receptors at cell surface by IHC (three plus: complete staining of more than 30% of cells), or have amplification of the corresponding ErbB2 gene by FISH test (or equivalent technique) when IHC is equivocal.

6.1.1. Trastuzumab

Trastuzumab is a humanized monoclonal antibody that targets the extracellular domain of ErbB2 cell surface receptors. It binds to ErbB2 receptor and prevents heterodimer downstream signaling and activation of proliferation MAPK pathways. Loss of PTEN and mutation of PI3K kinase reduces the effects of trastuzumab. Initial single agent data showed that trastuzumab gives 15% RR in pretreated MBC. Trastuzumab was shown to result in prolonged overall survival as first-line therapy for metastatic breast cancer patients in combination with anthracyclines or paclitaxel [78]. However, excessive cardiac toxicity has been observed when trastuzumab is used with anthracyclines [79,80] and therefore concurrent use with anthracyclines should be avoided. Trastuzumab, however, can be given safely with vinorelbine or taxanes with impressive responses [81,82]. Trastuzumab plus docetaxel resulted in a 73% ORR with a Median time to progression over 10 months in BCIRG 007 trial [82]. Carboplatin gave no further benefit in the arm combining trastuzumab, docetaxel and carboplatin when compared to trastuzumab and docetaxel only [82].

Trastuzumab is generally continued for as long as the patient is responding to treatment, and can be continued with a different chemotherapeutic agent even after disease progression (see below). Trastuzumab safety profile allows for continued administration as long as patients are monitored by repeated echocardiography and left ventricular ejection fraction every 2–3 months. Although cardiac toxicity from prolonged administration of trastuzumab remains unknown, anecdotal and unpublished observations indicate no increased cardiac toxicity after initial one year period. Synergism with chemotherapy and other newer targeted ErbB2 agents is cited as a reason for continuation of trastuzumab beyond progression. Recent trials have shown that trastuzumab, when continued beyond progression in combination with lapatinib, is better than changing over to lapatinib alone. The PFS improved from 8.4 to 12 months with the combination, the response rate increased from 6.9% to 10.3% [83]. Other combinations of trastuzumab plus pertuzumab [84], trastuzumab plus neratinib (irreversible pan-HER inhibitor), or trastuzumab plus HSP-90 inhibitors are currently being investigated. In conclusion, there is enough data to suggest that continued blockade of ErbB2 receptors with trastuzumab, in addition to chemotherapy and newer anti-ErbB2 agents is effective beyond progression [83,85–87]. However, it is proposed to stop trastuzumab when patients become clearly resistant to the chemotherapy/trastuzumab-based therapy or in patients with de novo resistance to trastuzumab (no response at all to trastuzumab-based therapy) [85].

6.1.2. Lapatinib

Lapatinib is an oral 4-anilinoquinazoline derivative, a reversible dual tyrosine kinase inhibitor that affects ErbB1 and ErbB2 receptors and pathways [88,89]. Lapatinib has been shown to be active in trastuzumab-resistant ErbB2-positive cells, including those with truncated Erb-B2 receptors which are present in about 30% of ErbB2 cell lines and tumors [90]. Trastuzumab cannot bind to truncated ErbB2 (p95 ErbB2) because this receptor is missing its extracellular domain while it continues to exert its proliferative signal-

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

ing through its membranous and intracellular portions. High p95erbB2 correlates with extensive nodal involvement and decreased survival [90]. Truncated ErbB2 remains sensitive to lapatinib which inhibits its TK activity [91,92]. Response to trastuzumab is also decreased in the presence P13Kinase mutation or loss of PTEN [93]. As mentioned earlier, a prolongation of Progression Free Survival (PFS) was observed (HR: 0.77; 95% CI: 0.6, 1.0; $p = 0.029$) in women with ErbB2-positive MBC who had received previous trastuzumab with chemotherapy and were treated with lapatinib and trastuzumab. The clinical benefit rate (CR + PR + SD for 6 months) with lapatinib and trastuzumab was 24.7% compared to 12.4% for lapatinib single agent [93,94].

Lapatinib combined with capecitabine was associated with a 51% reduction in the risk of disease progression and a median PFS time of 37 weeks, compared with 18 weeks in the capecitabine single-agent arm in a phase 3 trial [94,95]. ORR for combination therapy group was 23% compared to 14% in monotherapy group ($P = 0.113$). Interestingly, the combination therapy group had a tendency to experience less progressive CNS metastases (11 vs. 4: 2% only vs. 6%). and its effects in reducing CNS metastases has been shown in another phase II trial [95]. Therefore lapatinib is a small oral molecule that is effective in a group of trastuzumab resistant tumors, crosses the blood brain barrier and reduces CNS metastasis. It can be safely combined with trastuzumab or capecitabine, and has a reduced cardiac toxicity profile.

6.1.3. Pertuzumab

Pertuzumab is a new monoclonal antibody that binds to the dimerisation domain of ErbB2 receptor and prevents pairing and homodimerisation of ErbB2 as well as heterodimerisation with the other ErbB receptors ErbB1, ErbB3, and ErbB4, and is a potentially active monoclonal antibody in trastuzumab-resistant ErbB2-positive breast cancer. Recent safety data on the use of pertuzumab in combination with trastuzumab in this category of patients was favorable and evidence of activity (ORR of 18.2% and clinical benefit rate of 39.4% was seen in 33 patients enrolled in a phase II trial [96]. Pertuzumab administered as single agent had limited objective response rate of 7%. A wide clinical development program of pertuzumab is ongoing in breast cancer expressing HER-2.

6.1.4. Neratinib (HKI-272)

Neratinib (HKI-272) is a potent inhibitor of ErbB2 and epidermal growth factor receptor (EGFR) kinase and acts on the proliferation of EGFR-dependent cells. It reduces ErbB2 receptor autophosphorylation in cells at doses consistent with inhibition of cell proliferation and it functions as an irreversible binding inhibitor, most likely by targeting a cysteine residue in the ATP-binding pocket of the receptor. Consequently, neratinib treatment of cells results in inhibition of downstream signal transduction events and cell cycle regulatory pathways resulting in decreased cell proliferation. In vivo, neratinib is active in ErbB2 and EGFR-dependent tumor xenograft models when dosed orally on a once daily schedule. Because of its activity, neratinib has been selected as an antitumor agent in breast and other ErbB2-dependent cancers. Neratinib showed impressive single agent activity in ErbB2-positive patients pretreated with trastuzumab (ORR: 22%) and in patients without prior trastuzumab (ORR: 52%). The main side effect of this agent was diarrhea occurring in 25–30% of patients [97].

Trials combining neratinib with paclitaxel (RR 70%), vinorelbine (RR 43%) or capecitabine were performed. The early results showed promising antitumor activity. Moreover 3 pivotal trials were launched, one in the adjuvant setting and the other two in the metastatic setting. Paclitaxel plus neratinib combination is compared to paclitaxel plus trastuzumab in the first-line setting and neratinib single agent is compared to the combination of capecitabine plus lapatinib in patients progressing on taxane plus trastuzumab.

6.1.5. T-DM1

T-DM1 is an antibody-drug conjugate. The antibody is trastuzumab and the drug is antimicrotubule agent DM1 which is very toxic when administered alone. DM1 is conjugated to trastuzumab via a non-reducible thioether bond to a linker molecule (MCC) [98]. T-DM1 combines the ErbB2-targeting properties of trastuzumab with targeted delivery of a highly potent anti-microtubule derivative, DM1. It is hypothesized that after binding to ErbB2, T-DM1 undergoes receptor-mediated internalization, resulting in intracellular release of DM1. In a phase II study of 112 patients who had received prior trastuzumab, of whom 60% had prior lapatinib and who had a median of three prior chemotherapy regimens, the objective RR according to the investigators was 40% [99].

T-DM1 was combined with pertuzumab, as a second line therapy in patients who had received prior anti-HER2 therapy in a phase II trial that was reported to produce an overall response rate of 35% and a relative safe profile. Although authors noted transient thrombocytopenia and transaminases elevation, they noted a few serious side effects like pneumonia which requires more attention during further development of such combinations. This study does not support the use of pertuzumab in addition to T-DM1 since the ORR is equivalent to what was observed with T-DM1 alone [100].

6.1.6. Hsp90 inhibitors

A recent phase I study examined whether a heat shock protein (Hsp) 90 inhibitor tanespimycin (17-AAG; KOS-953) could be administered safely in combination with trastuzumab at a dose that inhibits Hsp90 function in vivo. Patients were treated with weekly trastuzumab followed by intravenous tanespimycin, assessed in escalating dose levels. Twenty-five patients were enrolled onto four tanespimycin dose levels: 225 ($n = 4$), 300 ($n = 3$), 375 ($n = 8$), and 450 mg/m^2 ($n = 10$). Tanespimycin plus trastuzumab is well tolerated and has antitumor activity in patients with metastatic

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

ErbB2-positive breast cancer whose tumors have progressed during treatment with trastuzumab. These data suggest that Hsp90 function can be inhibited in vivo to a degree sufficient to cause inhibition of tumor growth [101].

6.2. Combination of anti-ErbB2 therapy and aromatase inhibitors

The TAnDem study is a randomized phase III clinical trial where postmenopausal women with ER-positive, ErbB2-positive MBC received treatment with anastrozole or anastrazole plus trastuzumab until disease progression. Median PFS was 4.8 months in the combination arm and 2.4 months in the anastrozole alone arm. ORR was 20.6% in the combination arm vs. 6.8% with anastrazole alone. Median survival was 28.5 months with combination therapy and 23.9 months with monotherapy [102].

Lapatinib plus letrozole vs. letrozole was studied as first line therapy of ER-positive metastatic breast cancer, including patients with visceral disease, in a phase III trial (EGF 30008 study). The median PFS in the ErbB2+ population was significantly increased from 3.0 months in the letrozole group to 8.2 months in the lapatinib + letrozole group [$p = 0.019$]. Overall response rate (ORR) in the ErbB2+ population was significantly increased from 14.8% to 27.9% in the combination group [$p = 0.021$], with a clinical benefit rate (CBR) improvement from 28.7% to 47.7% [$p = 0.003$]. There was no difference in ORR or CBR in the ErbB2-negative population. The combination of letrozole and lapatinib, which has recently received regulatory approval, was well tolerated and no new safety issues were identified [103]. Rash and diarrhea were the main manageable side effects with no additional toxicity with more prolonged follow up [104].

In conclusion, combination targeted therapy with hormonal and ErbB2 manipulation seems the way of the future for Luminal breast cancer tumors with ErbB2 overexpression, a group of patients that is least frequent in clinical practice, and who are not deemed in urgent need for upfront chemotherapy. Although many see the Tandem trial results as rather disappointing with small DFS in both groups and not much of a solid argument, it was a rather early evidence in favor of combining anti-HER2 agents and AIs. The letrozole-lapatinib trial is more confirmatory and more encouraging but it was associated with increased toxicity compared to letrozole alone. The issue of synergy between Anti-HER2 agents and AIs remains unsettled and the effect of prior anti-HER2 exposure remains to be studied.

7. Anti-angiogenic therapy

Anti-angiogenic therapy was mostly tested in ErbB2-negative breast cancer. Data in ErbB2-positive breast cancer is limited although the rational exists. In fact, ErbB2 positive tumors are known to be very angiogenic.

7.1. Bevacizumab

Bevacizumab is a monoclonal antibody to vascular endothelial growth factor that has been tested in four major randomized trials which combined it with chemotherapy. ECOG E2100, a randomized phase III trial, compared bevacizumab + weekly paclitaxel vs. paclitaxel single agent for ErbB2 negative MBC. Patients (722 patients) were randomized to receive either 90 mg/m^2 of paclitaxel alone on days 1, 8, and 15 q 28 days, or with bevacizumab 10 mg/kg on days 1 and 15. The combination significantly prolonged progression-free survival as compared with paclitaxel alone (median, 11.8 vs. 5.9 months) and increased the objective response rate (36.9% vs. 21.2%). Although there was a very significant improvement in response rate and progression free survival, there was no significant difference in overall survival rate between the two groups (median, 26.7 vs. 25.2 months) [105,106]. Bevacizumab, combined with taxol, received regulatory FDA and EMEA approval for metastatic breast cancer based on this trial.

A second randomized trial (AVADO trial) showing the benefit of adding bevacizumab to a taxane (docetaxel) in the first-line treatment of ErbB2-negative metastatic breast cancer has been reported. It showed a significant improvement in progression-free survival, echoing the results of the E2100 study published earlier, though less impressive. The trial compared a high dose of 15 mg/kg (Bev15) and a low dose of 7.5 mg/kg (Bev7.5) of bevacizumab. With a median follow-up of 25 months, comparative median PFS for bevacizumab 7.5 mg/kg vs. placebo arms was 8.1 months vs. 8.1 months, respectively, and for bevacizumab 15 mg/kg vs. placebo arms a significant 10.1 months vs. 8.1 months. ORR for placebo group, Bev7.5 and Bev15 were 46%, 55% and 64%, respectively. OS were 76%, 81% and 84%, respectively. There was no statistical difference in OS [107]. Trial was not designed to compare the two different doses of bevacizumab used.

While E2100 and AVADO investigated bevacizumab as first line therapy in combination with paclitaxel and docetaxel, respectively, a third trial RIBBON-1, tested bevacizumab in combination with different and commonly used chemotherapy regimens in first line metastatic breast cancer therapy. The addition of bevacizumab to capecitabine, taxane; or anthracycline-based chemotherapy regimens used in first line treatment of MBC resulted in statistically significant improvement in PFS with a safety profile comparable to prior phase III studies [108].

A metaanalysis of three trials with upfront bevacizumab combined with chemotherapy was presented at ASCO 2010 [109]. This analysis confirmed an improvement in ORR of 17%, a 36% reduction in risk of progressive disease or death, and a modest 2.5 month improvement in median PFS; however, again no benefit in Overall Survival was seen [109].

RIBBON-2 trial, which investigated bevacizumab, at a dose of 15 mg/kg q3w or 10 mg/kg q2w, in second line MBC therapy, in combination with different chemotherapy regimens, showed an improvement in PFS (7.2 vs. 5 months)

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

with the addition of bevacizumab to chemotherapy [110].

In summary, all four randomized phase III trials with bevacizumab in combination with chemotherapy provided only improvement in response rates and PFS, but with no impact on overall survival. Best results were obtained with weekly paclitaxel while only modest improvement is noted with docetaxel. However, at this time it is not clear who clearly benefits from bevacizumab-based therapy. No predictive markers of sensitivity and/or resistance are available. One reasonable option might be patients with bulky and rapidly progressive disease as usually seen in triple-negative breast tumors. Whether bevacizumab-based therapies are superior to chemotherapy combinations is unknown but clearly the safety profiles as well as the costs are different. More recently, FDA advisory panel voted against the use of bevacizumab in metastatic breast cancer [111] and FDA itself issued its final recommendation in December 2010 to withdraw the indication of bevacizumab use in metastatic breast cancer because data submitted to FDA showed only a small effect on progression-free survival without evidence of an improvement in overall survival or a clinical benefit to patients sufficient to outweigh the risks. The FDA stated its desire for conduction of additional studies of bevacizumab in patients with metastatic breast cancer designed to identify a population of patients in which the drug's benefits exceed the risks [112]. Interestingly, a small recent study of bevacizumab in ovarian cancer noted that serum VEGF levels may have a predictive value for response [113].

This decision stresses the importance of overall survival in evaluating new drugs; however, it forces the medical oncology community to rethink or to better define objectives of clinical trials in patients with metastatic breast cancer who have a relatively long survival and usually get several lines of chemotherapy for metastatic disease, and where the experimental drugs are often given later on to the patients if the trials are positive. In such situations, DFS does not automatically translate into OS; and prospective evaluation of subgroups becomes essential. Finally, the combination of bevacizumab with other molecular-targeted therapies is under clinical evaluation in particular in HER-2 positive tumors.

7.2. Axitinib

Axitinib is an oral inhibitor of the VEGF, PDGF and colony stimulating factor-1 receptor tyrosine kinases. Phase II trials of this agent administered alone or in combination with chemotherapeutic drugs (e.g. docetaxel) were reported in several types of malignancy, with activity observed in breast and other carcinomas. Reported side effects include fatigue, hypertension, diarrhea, hand-foot syndrome and proteinuria [114].

7.3. Sunitinib

Sunitinib is an oral, multitargeted tyrosine kinase inhibitor. It inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor, stem cell factor receptor (KIT), and colony-stimulating factor-1 receptor. Sixty-four patients heavily pretreated MBC with an anthracycline and a taxane received sunitinib 50 mg/d in 6-week cycles (4 weeks on, 2 weeks off) in a phase II trial to assess the objective response rate. Seven patients achieved a partial response (median duration, 19 weeks), giving an overall response rate of 11%. Three additional patients (5%) maintained stable disease for > or = 6 months. Median time to progression and overall survival were 10 and 38 weeks, respectively. Triple negative and ErbB2-positive tumors seem to respond better [115]. On the other hand, sunitinib was compared head to head with capecitabine in another international multicenter randomized open-label phase III study in ErbB2-negative MBC who had prior chemotherapy with anthracyclines and taxanes. Sunitinib was given at a continuous dosing schedule of 37.5 mg/day vs. capecitabine 1000–1250 mg/m^2 orally bid for 14 days of every 21 days. Short PFS rates were observed (2.8 months vs. 4.2 months) in favor of capecitabine. Objective response rates were 11.3% vs. 16.4%, again in favor of capecitabine. OS rates were equivalent [116]. Single agent sunitinib was inferior to capecitabine and should not be used alone in MBC.

Another international phase III study involving 593 patients comparing sunitinib and docetaxel vs. docetaxel alone in HER2 negative metastatic breast cancer again showed no advantage to the combination (PFS 8.6 m vs. 8.3 m and OS 24.8 m vs. 25.5 m) with a significant increase in toxicity [117]. Another phase III study reported at ASCO 2010, randomized 442 patients to sunitinib + capecitabine vs. capecitabine as second or third line therapy again did not show any advantage of adding sunitinib with PFS 5.5 m vs. 5.9 m and OS 16.4 m vs. 16.5 m and increased toxicity in the sunitinib arm [118].

With all those results, it is clear that sunitinib has not shown any success in breast cancer and this is not surprising. In fact, the rationale behind this huge clinical development plan in breast cancer is lacking. The antitumor activity of sunitinib is limited to a small number of patients who remains undefined at the molecular level. Consequently, those trials and others send a clear message that targeted therapy should not be studied in unselected groups of patients. The selection should be based at the molecular level, either a biologic marker known to drive the malignancy or key in the carcinogenesis process, or by defining as early as possible a predictive single or multi-gene profile to predict sensitivity to the new anticancer agent under development.

7.4. Sorafenib

Sorafenib at a dose of 400 mg orally twice a day was combined with oral capecitabine 1000 mg/m^2 twice daily for 14 days every 21 days in the recently reported SOLTI-0701 study in ErbB2 negative MBC and gave a PFS of 6.4 vs. 4.1 months, hence a 42% reduction in the risk of disease progression or death, with an even better PFS in patients given treatment as

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

first line (7.6 vs. 4.1 months); however, there was a significant increase in hand foot syndrome (HFS) in the experimental combination arm. Close monitoring for early symptoms of HFS, dose reduction, and discontinuation of drug, and better management of HFS will be essential in order to move on with further use of this interesting oral combination [119]. A phase III trial to confirm the phase II data will start very soon but this strategy brings the risk of failure if patients included will be from unselected population as mentioned earlier.

8. PARP inhibitors in BRCA-mutated basal-like and in triple negative breast cancer

Recent evidence has suggested that cells that have impaired BRCA1 regulated DNA repair, a process called homologous recombination, are exquisitely sensitive to inhibition of the single strand break and base excision repair enzyme poly (ADP-ribose) polymerase-1 (PARP). This occurs due to synthetic lethality caused by the combination of genetic and drug induced DNA repair defects within tumor cells and not in normal tissues. The PARP enzyme is also responsible for initial steps in the repair of damage to the single stranded DNA template by alkylating agents such as the platinum salts, cyclophosphamide and temozolamide.

8.1. Olaparib

Olaparib is a new potent oral PARPi, that showed significant activity as single agent in BRCA1 and BRCA2 MBC with response rate of 41% in BRCA1 and BRCA2 carriers with advanced breast cancer who has had a median of 3 prior chemotherapy regimens and prior exposure taxanes and anthracyclines. More than 50% of patients had triple negative breast cancer and this subpopulation had a similarly high response rate. The drug was well tolerated with main toxicities of mild nausea and fatigue [120].

8.2. BSI-201

On the other hand, in a phase II study, *BSI-201*, an intravenous PARP inhibitor, was combined with gemcitabine and carboplatin (GCP) chemotherapy and compared with the same chemotherapy (GC) regimen alone in women with advanced first or second relapse triple negative metastatic breast cancer. A significant improvement in response rate (48% vs. 16%), PFS (6.9 vs. 3.3 months) and OS (9.2 vs. 5.7 months) was noted for the PARPi combination arm (GCP) which was well tolerated with no additional toxicities compared with GC [121].

PARP inhibitors seem to be very promising agents in the therapy of well selected groups of MBC and more research is needed to better define their optimal use.

9. Anti-EGFR therapy

Research efforts have not yet uncovered a receptor that could drive tumor growth in triple negative breast cancer, like Luminal and HER2-overexpressive cancers. EGFR is overexpressed in over 50% of TNBC cases and several trials have added anti-EGFR agent cetuximab to chemotherapy in an effort to increase response rates. Randomized phase II BALI-1 trial results were recently presented [122]. Investigators added cetuximab or placebo to cisplatin in 173 patients and reported an overall response rate of 20% for the combination vs. 10.3% for single agent cisplatin (P: 0.11). Progression Free Survival increased significantly from 1.5 months to 3.7 months for the combination cetuximab plus cisplatin. Although this study was not blinded and did not meet its primary objective of achieving an ORR >20%, it gave an encouraging result and clinical trials adding cetuximab to other agents are in order. The role of cetuximab in TNBC will be better defined once the results of biochemical markers from BALI-1 are known.

10. Bisphosphonates and monoclonal antibody targeting RANK ligand

Bisphosphonate therapy should be given for patients with bone metastases. Randomized trials have confirmed the value of pamidronate in decreasing skeletal complications [123]. Zoledronic acid, a newer bisphosphonate has shown superior results over pamidronate for reducing skeletal complications with less side effects and easier administration. Bisphosphonates are recommended for patients with MBC and bone metastases [125]. They reduce skeletal related events (SRE), reduce fracture rates and improve quality of life [124]. Bisphosphonates are given once a month as short intravenous infusions, with adequate hydration and monitoring of renal function.

Denosumab, a fully human monoclonal antibody to RANKL, has been proven to suppress bone resorption in intravenous bisphosphonate (IV BP)-naïve patients with breast cancer-related bone metastases. Two hundred twenty-five eligible women were randomized to 1 of 5 blinded denosumab cohorts or an open-label IV BP cohort. Denosumab was administered subcutaneously every 4 weeks (30, 120, or 180 mg) or every 12 weeks (60 or 180 mg) through 21 weeks. No denosumab-related serious or fatal adverse events occurred. After these results, it was concluded that in IV BP-naïve breast cancer patients with bone metastases, denosumab suppresses bone turnover and seems to reduce SRE risk similarly to IV BPs, with a safety profile consistent with an advanced cancer population receiving systemic therapy [126].

A recent phase III study evaluated the efficacy of denosumab vs. zoledronic acid for control of bony pain in patients with MBC. Patients receiving denosumab had a significantly

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

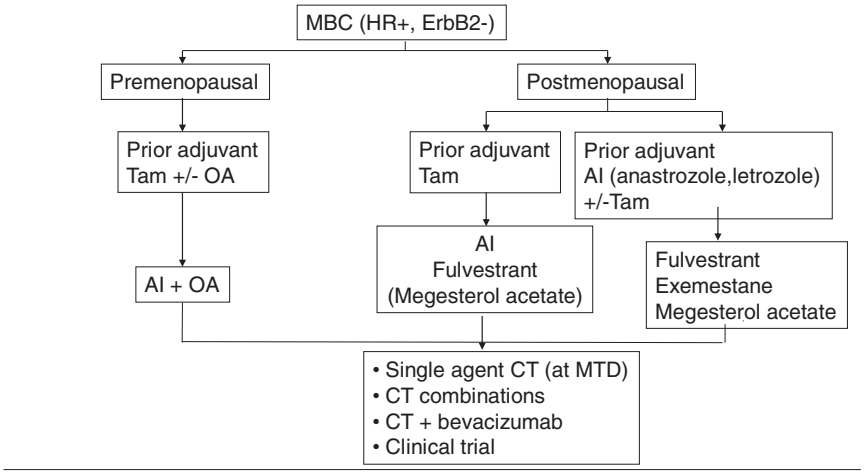

Fig. 1. Overall management of Luminal subtype of metastatic breast cancer (MBC).

longer time with mild or no pain as compared to patients receiving zoledronic acid and were less likely to develop worsening of their pain [127].

11. Radiation therapy in patients with MBC

In patients with widespread metastases, specific complications and painful conditions are treated with local and directed therapy such as radiation therapy to control painful bony lesions and CNS metastases. Patients with resectable brain metastasis are often offered radiation therapy after resection [128]. A small percentage of patients with isolated sites of metastases treated with local therapy may remain disease-free for prolonged periods of time.

12. Surgery in patients with MBC

Surgery and radiation, may be necessary to treat a local recurrence to improve patients' quality of life. Mastectomy, as part of management of MBC has been shown in several retrospective studies to be advantageous mainly in controlling local disease [129–132]. Recent studies have looked at breast stem cells as a potential therapeutic target [132]. Removing the primary tumor may eliminate or further reduce the continuous seeding of breast stem cells with metastatic properties. Although prospective randomized trials are lacking, patients with single site or oligometastases, who are responding to systemic therapy, are considered candidates for mastectomy. Patients with resectable single brain metastasis are best managed by surgery followed by radiation therapy [128].

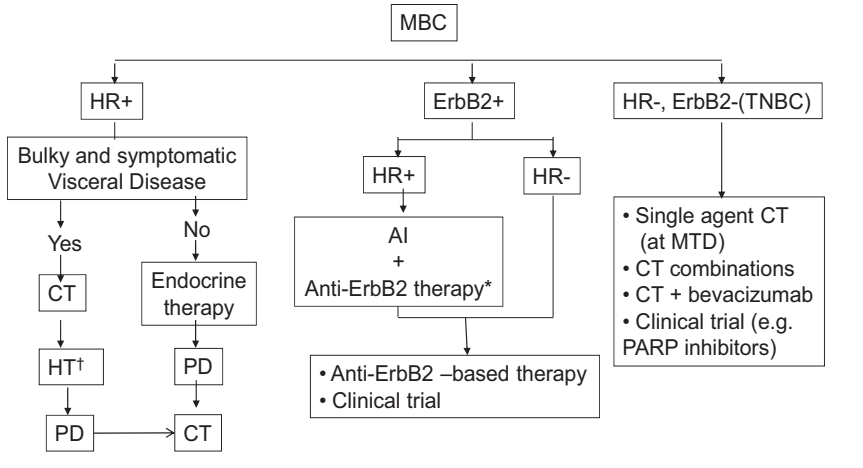

Fig. 2. Overall management of metastatic breast cancer (MBC).

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

13. Conclusions

Hormonal therapy, chemotherapy, targeted anti-ErbB2 therapy, antiangiogenic therapy, anti-DNA repair therapy, and many others options are now available for patients with metastatic breast cancer. The "one size fits all" model should no longer be used in MBC and therapy should be tailored to individual patients according to patient and tumor characteristics, as well as molecular subtypes and targets. Algorithms for management of Luminal MBC and overall management of MBC are provided in Figs. 1 and 2. Significant improvements are seen in response rates and progression-free survivals. Limited, but real improvements are also seen in overall survival in certain groups of patients. Curing patients with metastatic breast cancer remains a hope for only a few but is becoming more real. Advances in the treatment of metastatic breast cancer are being rapidly moved to the neoadjuvant and adjuvant settings where eradicating micrometastases is producing better survival and more cures. Adjuvant trastuzumab is a great example of the success of molecular-targeted therapy moved from the metastatic setting into the adjuvant one.

The variety of treatment choices and the heterogeneity of breast cancer make it imperative that patients with metastatic breast cancer, like patients with early breast cancer, be managed by multidisciplinary teams and breast clinics, or at the least, discussed at tumor board conferences. Participation of bench and bedside researchers in multidisciplinary discussions and subsequent management decisions improves translational research and breast cancer care.

Finally, costs of therapy have become very high. Targeted therapy is expensive and is usually given for prolonged periods of time. It is desired and hoped that costs be contained and prices brought down, so that treatment can be made available for women with breast cancer worldwide [133].

Conflict of interest statement

None.

Reviewers

Professor Jacques Bonneterre, Head of the Breast Unit, Centre Oscar Lambret, Dept. of Medical Oncology, F-Lille, Cedex, France.

Professor David A. Cameron, Cookridge Hospital, NCRN Coordinating Centre, Hospital Lane, Leeds, LS16 6QB, United Kingdom.

References

[1] Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol 2003;21(4 (February)):588–92.

[2] Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving. Cancer 2004;100:44–52.

[3] Hortobagyi GN. Can we cure limited metastatic breast cancer? J Clin Oncol 2002;20(3 (February)):620–3.

[4] Lu WL, Jansen L, Post WJ, Bonnema J, Van de Velde JC, De Bock GH. Impact on survival of early detection of isolated breast recurrences after the primary treatment for breast cancer: a meta-analysis. Breast Cancer Res Treat 2009;114(3 (April)):403–12.

[5] Singletary SE, Walsh G, Vauthey JN, et al. A role for curative surgery in the treatment of selected patients with metastatic breast cancer. Oncologist 2003;8(3):241–51.

[6] Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 1996;14: 2738–46.

[7] De Cremoux P, Grandin L, Dieras V, et al. Urokinase-type plasminogen activator and plasminogen-activator-inhibitor type 1 predict metastases in good prognosis breast cancer patients. Anticancer Res 2009;29(5 (May)):1475–82.

[8] Hayes DF. Prognostic and predictive factors revisited. Breast 2005;14(6 (December)):493–9 [Epub 2005 October 18].

[9] Nuyten DS, Kreike B, Hart AA, et al. Predicting a local recurrence after breast-conserving therapy by gene expression profiling. Breast Cancer Res 2006;8(5):R62.

[10] Driouch K, Landemaine T, Sin S, Wang S, Lidereau R. Gene arrays for diagnosis, prognosis and treatment of breast cancer metastasis. Clin Exp Metastasis 2007;24(8):575–85.

[11] Sorlie T. Molecular portraits of breast cancer: tumour subtypes as distinct disease entities. Eur J Cancer 2004;40(18):2667–75.

[12] Anderson BO, Yip CH, Smith RA, et al. Guideline implementation for breast healthcare in low- and middle income countries: overview of the breast health global initiative summit 2007. Cancer 2008;113(8 Suppl.):2221–42.

[13] Eniu A, Carlson RW, El Saghir NS, et al. Guideline implementation for breast healthcare in low- and middle income countries: treatment resource allocation. Cancer 2008;113(8 Suppl.):2268–80.

[14] Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. Lancet 1869;2:104–7.

[15] Henderson MD, Buroker TR, Samson MK, Mood DW, Baker LH, Vaitkevicius VK. Response of patients with carcinoma of the breast to hormonal therapy and combination chemotherapy. Surg Gynecol Obstet 1975;141(2 (August)):232–4.

[16] Osborne CK, Yochmowitz MG, Knight 3rd WA, McGuire WL. The value of estrogen and progesterone receptors in the treatment of breast cancer. Cancer 1980;46(12 Suppl. (December)):2884–8.

[17] Ingle JN. Sequencing of endocrine therapy in postmenopausal women with advanced breast cancer. Clin Cancer Res 2004;10(1 Pt. 2 (January)):362S–7S.

[18] Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 2004;351(27 (December)):2817–26.

[19] Blanco G, Holli K, Heikkinen M, Kallioniemi OP, Taskinen P. Prognostic factors in recurrent breast cancer: relationships to site of recurrence, disease-free interval, female sex steroid receptors, ploidy and histological malignancy grading. Br J Cancer 1990;62: 142–6.

[20] Howell A, Robertson JF, Vergote I. A review of the efficacy of anastrozole in postmenopausal women with advanced breast cancer with visceral metastases. Breast Cancer Res Treat 2003;82(3 (December)):215–22.

[21] Karlsson E, Lindström LS, Wilking U, Skoog L, Johansson U, Bergh J. Discordance in hormone receptor status in breast cancer during tumor progression. Proc Am Soc Clin Oncol 2010 [Abstract 1009].

[22] Amir E, Clemons M, Freedman OC, et al. Tissue confirmation of disease recurrence in patients with breast cancer: pooled analysis of two large prospective studies. Proc Am Soc Clin Oncol 2010 [Abstract 1007].

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

[23] Locatelli MA, Curigliano G, Fumagalli L, et al. Should liver metastases of breast cancer be biopsied to improve treatment choice? Proc Am Soc Clin Oncol 2010 [Abstract 1008].
[24] Schroth W, Goetz MP, Hamann U, et al. Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA 2009;302(13):1429–36.
[25] Goetz MP, Berry DA, Klein TE. Adjuvant tamoxifen treatment outcome according to cytochrome P450 2D6 (CYP2D6) phenotype in early stage breast cancer: findings from the International Tamoxifen Pharmacogenomics Consortium. In: Proceedings of 32nd SABCS December 2009, San Antonio, TX [Abstract 33].
[26] Jin Y, Desta Z, Stearns V, et al. CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 2005;97(1):30–9.
[27] Buzdar AU, Hortobagyi GN. Tamoxifen and toremifene in breast cancer: comparison of safety and efficacy. J Clin Oncol 1998;16(1 (January)):348–53.
[28] Morris KT, Toth-Fejel S, Schmidt J, Fletcher WS, Pommier RF. High dehydroepiandrosterone-sulfate predicts breast cancer progression during new aromatase inhibitor therapy and stimulates breast cancer cell growth in tissue culture: a renewed role for adrenalectomy. Surgery 2001;30(6 (December)):947–53.
[29] Bonneterre J, Thürlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000;18(22 (November)):3748–57.
[30] Nabholtz JM, Bonneterre J, Buzdar A, Robertson JF, Thürlimann B. Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. Eur J Cancer 2003;39(12 (August)):1684–9.
[31] Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 2003;21(11 (June)):2101–9.
[32] Kvinnsland S, Anker G, Dirix LY, et al. High activity and tolerability demonstrated for exemestane in postmenopausal women with metastatic breast cancer who had previously failed on tamoxifen treatment. Eur J Cancer 2000;36(8 (May)):976–82.
[33] Lønning PE, Bajetta E, Murray R, et al. Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: a phase II trial. J Clin Oncol 2000;8(11 (June)):2234–44.
[34] Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 2008;26(10 (April)):1664–70.
[35] Kaufmann M, Bajetta E, Dirix LY, et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. The Exemestane Study Group. J Clin Oncol 2000;8(7 (April)):1399–411.
[36] Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol 1998;16(2 (February)):453–61.
[37] Buzdar A, Douma J, Davidson N, et al. Phase III multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol 2001;19(14 (July)):3357–66.
[38] Miller WR. Biology of aromatase inhibitors: pharmacology/endocrinology within the breast. Endocr Relat Cancer 1999;6(2 (June)):187–95.
[39] Goss PE, Ingle JN, Chapman J-AW, et al. Final analysis of NCIC CTG MA.27: a randomized phase III trial of exemestane versus anastrozole in postmenopausal women with hormone receptor positive primary breast cancer. In: Proceedings of 33rd SABCS, December 8–12, 2010, San Antonio, TX [Abstract S1-1].
[40] Robertson JFR, Nicholson RI, Bundred NJ, et al. Comparison of the short-term biological effects of 7alpha-[9-(4 4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5,(10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. Cancer Res 2001;61:6739–46.
[41] Robertson JFR, Lindemann JPO, Llombart-Cussac A, et al. A comparison of fulvestrant 500 mg with anastrozole as first-line treatment for advanced breast cancer: follow-up analysis from the '*FIRST*' study. In: Proceedings of 33rd SABCS, December 8–12, 2010, San Antonio, TX [Abstract S1–3].
[42] Mauriac L, Romieu G, Bines J. Activity of fulvestrant versus exemestane in advanced breast cancer patients with or without visceral metastases: data from the EFECT trial. Breast Cancer Res Treat 2009;117(1):69–75.
[43] Bergh J, Jönsson PE, Lidbrink E, et al. First results from FACT – an open-label, randomized phase III study investigating loading dose of fulvestrant combined with anastrozole versus anastrozole at first relapse in hormone receptor positive breast cancer. In: Proceedings of 32nd SABCS December 2009, San Antonio, TX [Abstract 23].
[44] ATAC Trialists' Group. Results of the ATAC (arimidex, tamoxifen alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–2.
[45] Stuart NS, Warwick J, Blackledge GR, et al. Study of tamoxifen vs. megestrol acetate in advanced and recurrent breast cancer. Eur J Cancer 1996;32A:1888–92.
[46] Lønning PE, Taylor PD, Anker G, et al. High-dose estrogen treatment in postmenopausal breast cancer patients heavily exposed to endocrine therapy. Breast Cancer Res Treat 2001;67:111–6.
[47] Klijn JG, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 2001;19(2 (January)):343–53.
[48] El-Saghir NS, El-Hajj II, Makarem JA, Otrock ZK. Combined ovarian ablation and aromatase inhibition as first-line therapy for hormone receptor-positive metastatic breast cancer in premenopausal women: report of three cases. Anticancer Drugs 2006;17(8 (September)):999–1002.
[49] Carlson RW, Theriault R, Shurman CM, Rivera E, et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor-positive, metastatic carcinoma of the breast in premenopausal women. J Clin Oncol 2010;28(25):3917–21. Epub 2010 Aug 2.
[50] Hudis C. Dose-dense chemotherapy for breast cancer: the story so far. Br J Cancer 2000;82(12):1897–9.
[51] De Castro Junior G, Puglisi F, de Azambuja E, El Saghir NS, Awada A. Angiogenesis and cancer: a cross-talk between basic science and clinical trials (the "do ut des" paradigm). Crit Rev Oncol Hematol 2006;59(1 (July)):40–50.
[52] Hortobagyi GN. Treatment of breast cancer. N Engl J Med 1998;339(14 (October)):974–84.
[53] Carlson RW, Anderson BO, Burstein HJ, et al. Invasive breast cancer. J Natl Compr Canc Netw 2007;5(3 (March)):246–312.
[54] Valero V, Holmes FA, Walters RS, et al. Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. J Clin Oncol 1995;13(12 (December)):2886–94.
[55] Seidman AD, Berry D, Cirrincione C, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008;26(10 (April)):1642–9.

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

[56] Gonzalez-Angulo AM, Hortobagyi GN. Optimal schedule of paclitaxel: weekly is better. J Clin Oncol 2008;26(10 (April)):1585–7.
[57] Gradishar WJ, Tjulandin S, Davidson N, et al. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. J Clin Oncol 2005;23(31 (November)):7794–803 [Epub 2005 September 19].
[58] Thomas ES, Gomez HL, Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol 2007;25(33):5210–7.
[59] Lechleider RJ, Kaminskas E, Jiang X, et al. Ixabepilone in combination with capecitabine and as monotherapy for treatment of advanced breast cancer refractory to previous chemotherapies. Clin Cancer Res 2008;14(14):4378–84.
[60] http://www.cancer.gov/cancertopics/druginfo/fda-ixabepilone.
[61] http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/01/WC500062428.pdf.
[62] Vahdat LT, Pruitt B, Fabian CJ, et al. Phase II study of eribulin mesylate, a halichondrin B analog, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2009;27(18):2954–61.
[63] Twelves C, Loesch D, Blum J, et al. Updated survival analysis of a phase III study (EMBRACE) of eribulin mesylate versus treatment of physician's choice in subjects with locally recurrent or metastatic breast cancer previously treated with an anthracycline and a taxane. In: Proceedings of 33rd SABCS, December 8–12, 2010, San Antonio, TX [Abstract P6-14-18].
[64] Awada A, Bondarenko IN, Tarasova O, et al. Results of the first randomized phase II study of cationin loposomal paclitaxel (EndoTAG TM-1) targeting tumor endothelial cells in advanced triple-negative breast cancer (TNBC). In: Proceedings of the 2010 ESMO meeting, October 8–12, Milan, Italy [LBA 12].
[65] Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. J Clin Oncol 2002;20(14 (July)):3114–21.
[66] Nabholtz JM, Falkson C, Campos D, et al. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol 2003;21(6 (March)):968–75.
[67] Bontenbal M, Creemers GJ, Braun HJ, et al. Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre. J Clin Oncol 2005;23(28 (October)):7081–8.
[68] O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002;20(12 (June)):2812–23.
[69] Albain KS, Nag S, Calderillo-Ruiz G, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol 2008;26(24 (Aug)):3950–7.
[70] Martín M, Ruiz A, Muñoz M, et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol 2007;8(3 (March)):219–25.
[71] Seidman AD, Brufsky A, Ansari RH, et al. Phase III trial of gemcitabine plus docetaxel (GD) compared to capecitabine plus docetaxel (CD) with planned crossover to the alternate single agent in metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2009 [Abstract 1000].
[72] Shamseddine AI, Taher A, Dabaja B, Dandashi A, Salem Z, El Saghir NS. Combination cisplatin-vinorelbine for relapsed and chemotherapy-pretreated metastatic breast cancer. Am J Clin Oncol 1999;22(3 (June)):298–302.
[73] Sirohi B, Arnedos M, Popat S, et al. Platinum-based chemotherapy in triple-negative breast cancer. Ann Oncol 2008;19(11):1847–52.
[74] Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26(8):1275–81.
[75] Sparano J, Zhuang S, Londhe A, Lantz K, Lowery C. Relationship of anthracycline-free interval to outcomes in a phase 3 trial of pegylated liposomal doxorubicin plus docetaxel compared with docetaxel monotherapy in patients with advanced breast cancer treated with adjuvant anthracycline. In: Proceedings of 32nd SABCS, San Antonio, TX [Abstract 2095].
[76] Swain SM, Whaley FS, Gerber MC, et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 1997;15(4 (April)):1318–32.
[77] O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004;15(3 (March)):440–9.
[78] Slamon DJ, Leyland-Jones B, Shak S, et al. Concurrent administration of anti-HER2 monoclonal antibody and first line chemotherapy for HER2 overexpressing metastatic breast cancer A phase III, multinational, randomized controlled trial. N Engl J Med 2001;344:783–92.
[79] Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20(5 (March)):1215–21.
[80] Speyer J. Cardiac dysfunction in the trastuzumab clinical experience. J Clin Oncol 2002;20(5 (March)):1156–7.
[81] Burstein HJ, Kuter I, Campos SM, et al. Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol 2001;19(10 (May)):2722–30.
[82] Pegram M, Forbes J, Pienkovski T, et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. J Clin Oncol 2011;29(2 (Jan)):149–56.
[83] Blackwell KL, Burstein H, O'Shaughnessy J, et al. Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 2010;28(7):1124–30. Epub 2010 Feb 1.
[84] Scheuer W, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. Cancer Res 2009;69(24):9330–6.
[85] Hiroji I. Perspective of trastuzumab treatment initial treatment. Breast Cancer 2007;14:150–5.
[86] von Minckwitz G, du Bois A, Schmidt M, Maass N, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27(12):1999–2006.
[87] Swaby R, Blackwell K, Jiang Z, Sun Y, Dieras V, Zaman K. Neratinib in combination with trastuzumab for the treatment of advanced breast cancer: a phase I/II study. Proc Am Soc Clin Oncol 2009 [Abstract 1004].
[88] Wood ER, Truesdale AT, Mc Donald OB, et al. A unique structure for epidermal growth factor receptor bound to GW572016 (lapatinib): relationships among protein conformation, inhibitor off-rate, and receptor activity in tumor cells. Cancer Res 2004;64:6652–9.
[89] Molina M, Saez R, Ramsey E, et al. NH_2-terminal truncated HER-2 protein but not full-length receptor is associated with nodal metastasis in human breast cancer. Clin Cancer Res 2002;8:347–53.
[90] Saez R, Molina M, Ramsey E, et al. p95HER-2 predicts worse outcome in patients with HER-2-positive breast cancer. Clin Cancer Res 2006;12:424–31.

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

[91] Scaltriti M, Rojo F, Ocaña A, et al. Expression of p95HER2, a truncated form of the HER2 receptor, and response to anti-HER2 therapies in breast cancer. J Natl Cancer Inst 2007;99:628–38.
[92] Xia W, Liu LH, Ho P, et al. Truncated ErbB2 receptor (p95ErbB2) is regulated by heregulin through heterodimer formation with ErbB3 yet remains sensitive to the dual EGFR/ErbB2 kinase inhibitor GW572016. Oncogene 2004;23:646–53.
[93] Fujita T, Doihara H, Kawasaki K, et al. PTEN activity could be a predictive marker of trastuzumab efficacy in the treatment of ErbB2-overexpressing breast cancer. Br J Cancer 2006;94:247–52.
[94] Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355(26 (December)):2733–43.
[95] Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancer. J Clin Oncol 2008;209120(April):1993–9.
[96] Fumoleau P, Wardley A, Miles D, et al. Safety of pertuzumab plus trastuzumab in a phase II trial of patients with HER2-overexpressing metastatic breast cancer which had progressed during trastuzumab therapy. In: Proceedings of 30th SABCS 2006, December 13–16, San Antonio, TX [Abstract 73].
[97] Rabindran SK, Discafani CM, Rosfjord EC, Baxter M, Floyd MB, Golas J. Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. Cancer Res 2004;64:3958–65.
[98] Krop IE, Beeram m, Modi S, et al. Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. J Clin Oncol 2010;28(16):2698–704. Epub 2010 Apr 26.
[99] Burris 3rd HA, Rugo HS, O'Shaughnessy JA, et al. Phase II Study of the Antibody Drug Conjugate Trastuzumab-DM1 for the Treatment of Human Epidermal Growth Factor Receptor 2 (HER2) -Positive Breast Cancer After Prior HER2-Directed Therapy. J Clin Oncol 2011;29(4):398–405. Epub 2010 Dec 20.
[100] Miller K, Gianni L, Andre F, et al. A phase Ib/II trial of trastuzumab-DM1 (T-DM1) with pertuzumab (P) for women with HER2-positive, locally advanced or metastatic breast cancer (BC) who were previously treated with trastuzumab (T). Proc Am Soc Clin Oncol 2010 [Abstract 1012].
[101] Modi S, Stopeck AT, Gordon MS, et al. Combination of trastuzumab and tanespimycin (17-AAG KOS-953) is safe and active in trastuzumab-refractory HER-2 overexpressing breast cancer: a phase I dose-escalation study. J Clin Oncol 2007;25(34 (December)): 5410–7.
[102] Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J Clin Oncol 2009;27(33):5529–37.
[103] Johnston S, Pippen Jr J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol 2009;27(33):5538–46.
[104] Ro J, Pippen J, Pivot X, et al. Safety of first-line letrozole compared with lapatinib plus letrozole in patients with postmenopausal hormone receptor positive metastatic breast cancer: EGF30008 study. In: Proceedings of 32nd SABCS, San Antonio, TX [Abstract 5094].
[105] Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666–76.
[106] Miller KD. E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. Clin Breast Cancer 2003;3(6 (February)):421–2.
[107] Miles DW, Chan A, Romieu G, et al. Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC). In: Proceedings of 32nd SABCS 2009, San Antonio, TX [Abstract 41].
[108] Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2009 [Abstract 1005].
[109] O'Shaughnessy J, Miles D, Gray RJ, et al. A meta-analysis of overall survival data from three randomized trials of bevacizumab (BV) and first-line chemotherapy as treatment for patients with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2010 [Abstract 1005].
[110] Brufsky A, Bondarenko IN, Smirnov V, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer. In: Proceedings of 32nd SABCS, San Antonio, TX [Abstract 42].
[111] http://www.cancer.org/Cancer/news/News/fda-advisory-panel-votes-against-avastin-for-advanced-breast-cancer.
[112] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm237172.htm.
[113] Smerdel MP, Steffenson KD, Waldstrom M, Brandslund I, Jakodsen A. The predictive value of serum VEGF in multiresistant ovarian cancer patients treated with bevacizumab. Gynecol Oncol 2010;118(2 (August)):167–71.
[114] Choueiri TK. Axitinib a novel anti-angiogenic drug with promising activity in various solid tumors. Curr Opin Investig Drugs 2008;9(6 (June)):658–71.
[115] Burstein HJ, Elias AD, Rugo HS, et al. Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol 2008;26(11 (April)):1810–6.
[116] Barrios C, Liu M-C, Lee SC, et al. Phase III randomized trial of sunitinib (SU) vs. capecitabine (C) in patients (Pts) with previously treated HER2-negative advanced breast cancer (ABC). Proceedings of 32nd SABCS 2009, San Antonio, TX [Abstract 46].
[117] Bergh J, Greil R, Voytko N, et al. Sunitinib (SU) in combination with docetaxel (D) versus D alone for the first-line treatment of advanced breast cancer (ABC). Proc Am Soc Clin Oncol 2010 [Abstract LBA 1010].
[118] Crown J, Dieras V, Staroslawska E, et al. Phase III trial of sunitinib (SU) in combination with capecitabine (C) versus C in previously treated advanced breast cancer (ABC). Proc Am Soc Clin Oncol 2010 [Abstract LBA 1011].
[119] Baselga J, Grupo Español de Estudio Tratamiento y Otras Estrategias Experimentales en Tumores Sólidos, Roché H, et al. SOLTI-0701: a multinational double-blind, randomized phase 2b study evaluating the efficacy and safety of sorafenib compared to placebo when administered in combination with capecitabine in patients with locally advanced or metastatic breast cancer (BC). In: Proceedings of 32nd SABCS 2009, San Antonio, TX [Abstract 45].
[120] Tutt A, Robson M, Carmicheal J, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010;376(9737):235–44. Epub 2010 Jul 6.
[121] O'Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. New Engl J Med 2011;364(3):205–14.
[122] Baselga J, Gomez P, Awada A, et al. The addition of cetuximab to cisplatin increases overall response rate (ORR) and progression free survival (PFS) in metastatic triple-negative breast cancer (TNBC): results of a randomized phase II study (BALI-1). In: Proceedings of the 2010 ESMO meeting, October 8–12, Milan, Italy [Abstract 2740].
[123] Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. N Engl J Med 1996;335:1785–91.

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010

[124] Coleman R, Burkinshaw R, Brown J, et al. Zoledronic acid. Expert Opin Drug Saf 2011;10(1):133–45. Epub 2010 Nov 29.
[125] Hillner BE, Ingle JN, Chlebowski RT, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003;21:4042–57.
[126] Lipton A, Steger GG, Figueroa J, et al. Extended efficacy and safety of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy. Clin Cancer Res 2008;14(20 (October)):6690–6.
[127] Stopeck AT, Lipton A, Braun A, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010;28(35):5132–9. Epub 2010 Nov 8.
[128] Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004;22(17 (September)):3608–17.
[129] Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 2002;132(4 (October)):620–6 [discussion 626–7].
[130] Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 2006;24(18 (June)):2743–9.
[131] Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 2006;13(6):776–82.
[132] Korkaya H, Wicha MS. Selective targeting of cancer stem cells: a new concept in cancer therapeutics. BioDrugs 2007;21(5):299–310.
[133] El Saghir NS, Eniu A, Carlson RW, Aziz Z, Vorobiof D, Hortobagyi GN. Locally advanced breast cancer: treatment guideline implementation with particular attention to low- and middle-income countries. Cancer 2008;113(8 Suppl. (October)):2315–24.

Biographies

Nagi S. El Saghir, M.D., FACP is Professor of Clinical Medicine and Director of Breast Center of Excellence of the Naef K. Basile Cancer Institute at the American University of Beirut Medical Center. In addition to his publications in peer-reviewed journals, he is the author of the book *ABC of Breast Diseases from Prevention to Treatment, in Arabic.* He is specialty editor of *The Breast* and international editor of *Journal of Clinical Oncology* (Middle East and North Africa editions). He is member of the Breast Health Global Initiative (BHGI), EORTC Breast Cancer Group, ESMO developing Countries Task Force. He is Founding President of Lebanese Society of Medical Oncology. He served as member of ASCO International Committee, International Development and Education Award working group, and ESMO National and Regional Representative Committees, Dr. El Saghir received his M.D. from the Free University of Brussels, Belgium (1978), completed his residency in Internal Medicine at the Brooklyn Hospital-Downstate, SUNY in New York (1981), and completed his fellowship in Hematology-Oncology at St. Luke's-Roosevelt Hospital Center – Columbia University in New York (1983). He has served on the Faculty of King Saud University, Riyadh, Saudi Arabia as well as Oakwood Hospital and Wayne State University in Detroit, Michigan. He is certified by the American Boards of Internal Medicine and Medical Oncology.

Arafat Tfayli, M.D., is Associate Professor of Clinical Medicine at the NK Basile Cancer Institute American University of Beirut Medical Center, Beirut, Lebanon.

Hassan A. Hatoum, M.D., is Medical Resident, Staten Island, Hospital, Staten Island, New York, and Research Fellow, American University of Beirut Medical Center, Beirut, Lebanon.

Zahi Nachef, M.D., is Research Fellow at the NK Basile Cancer Institute, American University of Beirut Medical Center, Beirut, Lebanon.

Phuong Dinh, Ph.D., is a Research Oncologist at Institut Jules Bordet and Scientific Director of Breast International Group (BIG).

Ahmad Awada, M.D., Ph.D. is Head of the Medical Oncology Clinic at Institut Jules Bordet, Brussels, Belgium, where he also served as Head of New Drug Development Unit. He graduated from the Universite Libre de Bruxelles and trained in Brussels, Belgium as well as Amsterdam, Netherlands, and San Antonio, Texas. He is member of EORTC, ESMO, ASCO and Belgium Society of Medical Oncology. Professor Awada is widely published in numerous peer-reviewed journals.

Please cite this article in press as: El Saghir NS, et al. Treatment of metastatic breast cancer: State-of-the-art, subtypes and perspectives. Crit Rev Oncol/Hematol (2011), doi:10.1016/j.critrevonc.2011.01.010