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REVIEW ARTICLE

Systemic chemotherapy for metastatic breast cancer

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Abstract

Breast cancer is the leading cause of cancer among women worldwide and the most common cancer in China. Many factors influence the treatment strategy for metastatic breast cancer (MBC). Chemotherapy should be administered to patients with hormone receptor-negative tumors, symptomatic visceral metastasis, and a short disease-free interval. Sequential single-agent chemotherapy has similar efficacy as combination agents in terms of overall survival and quality of life. Anthracyclines are the cornerstone of first-line treatment for MBC, and taxanes represent the second treatment option after resistance. When progression or intolerable toxicity occurs after optimal treatment, the alternative treatments include capecitabine, vinorelbine, and gemcitabine. Ixabepilone and eribulin are relatively new effective single agents. A combination of cytotoxic agents for patients with rapid clinical progression can further improve the overall response rate and time to progression compared to single-agent treatment. For patients with MBC who were pretreated with anthracyclines in the neoadjuvant/adjuvant setting, a taxane-containing regimen such as docetaxel plus capecitabine or gemcitabine plus paclitaxel should be administered. Platinum-based therapies such as cisplatin or carboplatin have a role in the treatment of triple-negative breast cancer. Meanwhile, the efficacy of the addition of targeted drugs such as iniparib, bevacizumab, and cetuximab to chemotherapy remains unproven. Maintenance chemotherapy is routinely recommended in clinical practice at present. Patients who were previously treated with paclitaxel and gemcitabine have better progression-free and overall survival with maintenance chemotherapy according to a Korean phase III clinical trial. Sequential maintenance treatment with capecitabine monotherapy after capecitabine-based combination chemotherapy (X-based X) appears favorable based on a series of domestic studies.

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Breast cancer is the most common cancer among women worldwide [1–2] and among those in China [3]. Approximately 20%–30% of patients with breast cancer who were previously treated with radical surgery experience recurrence and metastasis. Moreover, 5% of all breast cancers are initially diagnosed at stage IV, with no opportunity for surgery [4]. Metastatic breast cancer (MBC), a commonly recognized incurable disease, is a clinical challenge. The aims of MBC treatment are to relieve and control symptoms, maintain quality of life, and extend the survival time [5].

Many factors influence the choice of treatment for MBC, including the expression of hormone receptors (HRs) and human epidermal growth factor receptor 2 (*HER2*), treatment history, the disease-free interval, visceral metastasis, performance status, and relevant symptoms, and these factors may also affect prognosis. Chemotherapy is a widely used treatment for patients with HR-negative cancer and those with HR-positive cancer who experience relapse after endocrine therapy. This paper reviewed the present application and development of chemotherapy for MBC.

Present application of MBC treatment strategies

HR and *HER2* expression and treatment history are the most important factors directing the initial treatment of MBC. For patients with HR-positive MBC, slow disease progression, and bone metastasis without visceral metastasis or visceral metastasis without symptoms, the optimal initial treatment is endocrine therapy. If a favorable disease profile is observed and the criteria for sub-sequential endocrine therapy after disease progression are met, then

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endocrine therapy can also be selected as a second-line treatment. Otherwise, when there is resistance to endocrine therapy, failure after several lines of endocrine therapy, and symptomatic visceral metastasis, systemic chemotherapy should be administered.

Treatment for MBC with *HER2* overexpression should include a trastuzumab-based regimen. In some situations, such as an initial indolent disease stage or for stable disease, trastuzumab can be given as a single agent or combined with endocrine therapy. In other situations, trastuzumab should be administered in combination with chemotherapy. New drugs targeting the *HER2* gene, such as lapatinib, pertuzumab, and trastuzumab emtansine (also known as T-DM1), are promising.

For patients with HR-negative MBC, symptomatic visceral metastasis, and a short disease-free interval, the optimal treatment is cytotoxic chemotherapy. We reviewed the application of chemotherapy in this paper.

Systemic chemotherapy for MBC

Effective cytotoxic agents for breast cancer include anthracyclines [doxorubicin, epirubicin, pegylated liposomal doxorubicin (PLD)], taxanes (paclitaxel, docetaxel, albumin-bound paclitaxel), non-taxane microtubule inhibitors (ixabepilone, vinorelbine, eribulin), and antimetabolite drugs (capecitabine, gemcitabine). Platinum-based drugs (cisplatin, carboplatin) are effective for treating triple-negative breast cancer (TNBC).

Combination chemotherapy vs. sequential monotherapy

In clinical practice, the choice of using a combination of cytotoxic chemotherapies or sequential monotherapy is one of the most controversial issues in the field of MBC chemotherapy. It is generally accepted that compared with sequential single-agent chemotherapy, combination chemotherapy provides a better overall response rate (ORR) and longer progression-free survival (PFS) but has little benefit concerning overall survival (OS) [6].

Recently, a meta-analysis illustrated that a combination of cytotoxic agents resulted in better OS than single-agent chemotherapy for patients with MBC. A greater number of adverse effects are observed with combination therapy, often resulting in lower dose administration and treatment interruption. Patient- and disease-related factors should be considered when choosing between combination and sequential single-agent chemotherapy for MBC. A combination of cytotoxic agents is more likely to be chosen for patients with rapid clinical progression, life-threatening visceral metastases, or a need for rapid symptom or disease control. Sequential single-agent chemotherapy is often administered to patients with poor performance status or internal complications because of its moderate adverse effects.

Single-agent chemotherapy

Anthracyclines have been considered the cornerstone of first-line treatment for MBC. As anthracyclines have been increasingly used as neoadjuvant/adjuvant therapy before or after radical surgery, these drugs are not optimal following disease relapse. Cardiac toxicity caused by dose accumulation limits the further use of anthracyclines in the metastatic setting. Previously, most researchers agreed that the maximum cumulative dose for doxorubicin is 550 mg/m^2, with a lower dose (450 mg/m^2) recommended for patients with hypertension and a history of thoracic radiotherapy. Many studies have found that for patients who have received a cumulative dose of > 300 mg/m^2 for doxorubicin or > 550 mg/m^2 for epirubicin, cardiac protection and regular heart function monitoring can be applied to minimize the risk of cardiac toxicity. Once the upper limit of anthracyclines is reached, a substitute treatment should be considered.

The antitumor effects of taxanes rely on maintaining the stability of microtubules. These therapies are preferred for patients with anthracycline resistance. As their use in the neoadjuvant and adjuvant therapy becomes more common, taxanes should be avoided in patients with rapid progression, especially within 12 months. Research has not revealed any evidence of complete cross-resistance between paclitaxel and docetaxel, and thus, a different taxane can be utilized after disease progression. The main dose-limiting toxicity of taxanes is peripheral neurotoxicity. The development of peripheral neuropathy depends on the cumulative dose, and it tends to appear after three to six treatment cycles. Early neuropathic manifestations should be supervised, including dysesthesia, numbness, tingling, and shooting pain. Generally, if ≥ grade 2 neuropathy is observed, treatment should be stopped until the neuropathy declines to ≤ grade 1.

When progression or intolerable toxicity after treatment with anthracyclines and taxanes occurs in patients with MBC, alternative treatments including capecitabine, vinorelbine, and gemcitabine can be used. According to phase II and III studies, the ORR of capecitabine and vinorelbine is 25%–29% after resistance to anthracyclines and taxanes arises. Studies of single-agent gemcitabine identified an ORR of 14%–42%.

Ixabepilone interacts with tubulin and maintains the stability of microtubules in a different manner than paclitaxel [7]. Ixabepilone is the first epothilone to be approved for clinical use. Current data suggest that epothilones have a role in treating taxane-resistant cancers, and ixabepilone is unaffected by some of the underlying mechanisms of chemoresistance. The efficacy of single-agent

ixabepilone was confirmed in a phase II clinical trial, in which patients who received ixabepilone (40 mg/m^2) every 3 weeks had an ORR of 11.5% and a disease stability rate of 50% (n = 126). Based on this study, single-agent ixabepilone was approved by the US Food and Drug Administration (FDA) for the treatment of MBC in patients who previously received anthracyclines, taxanes, and capecitabine.

Eribulin is a non-taxane microtubule dynamics inhibitor with a novel mechanism of action. Eribulin was evaluated in patients with advanced breast cancer or MBC who were previously treated with an anthracycline, taxane, and capecitabine. This treatment was associated with ORRs of 11.5 and 9.3% in patients with advanced breast cancer or MBC, respectively [8]. In the follow-up phase III clinical trial (EMBRACE) [9], among patients who had received two or more previous chemotherapy regimens for advanced disease, including an anthracycline and a taxane, eribulin mesylate (1.4 mg/m^2) on days 1 and 8 of a 21-day cycle was linked to a significant and clinically meaningful improvement in OS (13.1 months vs. 10.7 months, P = 0.04) and a higher ORR (12% vs. 5%, P = 0.005) compared with treatment of physician's choice, which mainly included single-agent vinorelbine, gemcitabine, and capecitabine.

When progression is observed after first-line chemotherapy, more lines of salvage therapy are needed to prevent further metastases or recurrences. However, when patients have not responded to three sequential single-agent therapies or they have a performance status of ≥ 3, supportive therapy should be considered.

Combination chemotherapy

Nine combination regimens for cytotoxic chemotherapies are recommended for MBC in the 2013 National Comprehensive Cancer Network (NCCN) guideline. The first four regimens are based on anthracyclines (5-FU, ADM, CTX; 5-FU, EPI, CTX; ADM, CTX; and EPI, CTX, whereas the combination of anthracyclines and paclitaxel in the previous edition is no longer recommended because of its enhanced toxicity. The fifth regimen is CTX, MTX, and 5-FU. Patients who were originally diagnosed with stage IV breast cancer or those who have not been treated with anthracyclines as a neoadjuvant or adjuvant therapy at the time of radical surgery could be given these regimens as a first-line treatment for MBC.

Patients who have been treated with anthracyclines in the neoadjuvant or adjuvant setting can be given a taxane-containing regimen such as docetaxel plus capecitabine or gemcitabine plus paclitaxel, as recommended by the NCCN, to avoid the cardiac toxicity associated with a high cumulative dose of anthracyclines. These two regimens are widely used in clinical practice, with significantly superior efficacy, time to progression (TTP), and OS, compared to single-agent taxanes, and they are among the few combination regimens that can improve OS. The clinical trials on which the registration was based were published in 2002 [10] and 2008 [11–12].

Several studies of combination therapies that can be used when patients become insensitive to the aforementioned taxane regimens have been published. The following phase III clinical trials compared the efficacy of combination therapy and single agents among women with MBC, confirming that combination therapy can improve efficacy and TTP while having little benefit regarding OS.

A phase III clinical trial compared the additional benefit of gemcitabine combined with vinorelbine compared with standard vinorelbine monotherapy in patients with MBC who were previously treated with anthracyclines and taxanes. Patients who were administered gemcitabine and vinorelbine had better PFS than those treated with vinorelbine alone (6 months vs. 4 months, P = 0.003). However, this trial did not identify a difference in OS (15.9 months vs. 16.4 months, P = 0.8). Although the frequencies of grade 3 and 4 non-hematological toxicities were similar, patients in the combination therapy group more commonly experienced neutropenia [13].

A second clinical trial compared the efficacy and toxicities of vinorelbine plus cisplatin (NP) with that of vinorelbine plus capecitabine (NX) in MBC. Patients with anthracycline- and taxane-resistant MBC were equally randomized into the NP or NX group. Response rates and toxicities were evaluated after two cycles of chemotherapy. The ORR was 48.0% in both groups. There were no significant differences disease control (78.0% vs. 83%) or 1-year survival rates (54.6% vs. 55.9%) between the groups. In addition, no significant difference was found in the incidence of toxicities between the groups. The NP and NX regimens displayed similar effects with acceptable toxicity [14].

A third clinical trial enrolled patients with anthracycline- and taxane-resistant MBC. Ixabepilone plus capecitabine prolonged PFS (6.2 months vs. 4.2 months, P < 0.001) and increased the ORR (43% vs. 29%, P < 0.001) relative to single-agent capecitabine, but this combination did not significantly improve OS compared with capecitabine alone (16.4 months vs. 15.6 months, P = 0.12) [15–16].

Treatment of TNBC

TNBC is an aggressive clinical phenotype associated with poor survival and characterized by the lack of expression (or minimal expression) of the estrogen and progesterone receptors, as well as the absence of *HER2* overexpression. TNBC displayed substantial overlap

with basal-type and breast cancer susceptibility gene 1 (BRCA1)- or BRCA2-related breast cancers, which are associated with a deficiency of aberrant DNA repair, suggesting that DNA-damaging agents may have an effect on TNBC [17].

This theory supports the use of DNA-damaging agents such as platinum-based therapies, and several studies have focused on their use in TNBC. In a retrospective analysis, the combination of platinum drugs and gemcitabine exhibited significant activity, particularly in patients with TNBC. These data suggest that platinum-based regimens may be a suitable choice for metastatic TNBC (mTNBC).

The Chinese Breast Cancer Study Group in the Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China, is conducting a nationwide multicenter phase III trial (CBCSG 006) aiming to evaluate the efficacy and tolerability of cisplatin and gemcitabine as a first-line therapy for mTNBC compared with standard treatment with paclitaxel plus gemcitabine. In a previous single-arm, phase II study, 64 patients were enrolled and treated for a median of six cycles. The median PFS was 7.2 months [95% confidence interval (CI) = 5.6–8.9 months], and OS was 19.1 months (95% CI = 12.4–25.8 months), with a median follow-up of 42 months. The ORR was 62.5% with a favorable safety profile. The efficacy of responses and the basal-like subtype were independent favorable factors for PFS and OS, respectively. It is likely that these findings illustrate a role of platinum drugs in the first-line treatment of mTNBC. The promising role of this combination as the front-line treatment for mTNBC is being evaluated in this ongoing phase III trial [18].

Poly-adenosine diphosphate ribose polymerase (PARP-1) is a key enzyme for detecting and repairing DNA single-strand breaks in the base excision and recombination pathway. PARP-1 also plays an important role in repairing DNA double-strand breaks and defects of homologous recombination. This protein may have the same effect in patients with BRCA1 mutation and TNBC. Iniparib, a PARP inhibitor, improved the survival of patients with mTNBC without significantly increasing toxic effects when added to chemotherapy [19–20]. However, a phase III study comparing the efficacy and safety of gemcitabine and carboplatin with or without iniparib found no significant difference in survival in patients with TNBC. A later study revealed that iniparib is unlikely to inhibit the function of PARP [21–22]. Although this study did not prove the efficacy of PARP inhibition, it resulted in the combination of gemcitabine and carboplatin being recommended by the NCCN because of its large sample analysis. In addition, the PARP inhibitors olaparib [23] and veliparib are currently being investigated in clinical trials.

Bevacizumab was approved as a first-line treatment for advanced breast cancer by the FDA through the agency's Fast Track Development Program. The Eastern Cooperative Oncology Group 2100 trial revealed that bevacizumab added to paclitaxel nearly doubled the PFS and tumor response rate compared to that observed with paclitaxel alone (11.8 months vs. 5.9 months, hazard ratio = 0.6, $P < 0.001$) [24]. However, trials of combination therapy with other drugs have not uncovered such a remarkable difference [25]. A meta-analysis illustrated that compared with single-agent chemotherapy, bevacizumab added to chemotherapy significantly improved PFS, but no difference in OS was noted. In several large-population studies and meta-analyses, bevacizumab improved response rates in patients with TNBC in subgroup analysis. It is unfortunate that because of the lack of improvement in OS and underlying serious adverse events, the FDA canceled the application for bevacizumab in breast cancer after re-evaluation. However, bevacizumab in combination with weekly paclitaxel remains in the NCCN guideline, and it can be administered to patients who responded poorly to standard chemotherapy.

Epidermal growth factor receptor (EGFR) is overexpressed in 30%–60% of breast cancers, including mTNBC, and it can be a target for treatment. Cetuximab, an EGFR inhibitor, has limited activity as a single agent, but it is active in combination with other chemotherapies. In a phase II trial, 173 patients with mTNBC were randomly assigned in a 2:1 ratio to receive cisplatin plus cetuximab or cisplatin alone. The primary endpoint was ORR, and secondary endpoints included PFS and OS. Cetuximab plus cisplatin doubled the ORR over that observed with cisplatin alone (20% vs. 10%), although the difference was not significant, and it appeared to prolong PFS and OS [26]. Another trial revealed that cetuximab plus carboplatin in mTNBC produced responses in fewer than 20% of patients, suggesting that alternate mechanisms for pathway activation might exist.

Apatinib is an oral, highly potent tyrosine-kinase inhibitor targeting vascular endothelial growth factor receptor 2. In a phase IIb study, the efficacy and safety of apatinib monotherapy were evaluated in heavily pretreated patients with mTNBC. The recommended initial dose of apatinib, 500 mg/day p.o. in a 4-week cycle, was administered to 56 patients. The ORR and clinical benefit rate were 10.7 and 25.0%, respectively. The median PFS and OS were 3.3 months (95% CI = 1.7–5.0 months) and 10.6 months (95% CI = 5.6–15.7 months), respectively. Regarding its safety profile, grade 3/4 hematologic toxicities including thrombocytopenia (13.6%), leukopenia (6.8%), neutropenia (3.4%), and anemia (1.7%) were noted. These data indicated that an apatinib dose of 500 mg is the recommended starting dose for patients with heavily pretreated mTNBC with a measurable partial response rate and PFS [27].

Maintenance treatment

It is challenging, even for experts in the field of breast cancer, to know when to interrupt or stop treatment in patients who exhibit a response or stable disease after first-line treatment. The concept regarding breast cancer as a 'chronic disease' is widely recognized and accepted in clinical practice. In line with this concept, the maintenance of treatment emphasizes the role of full-time management for advanced breast cancer.

Reasonable maintenance therapy encompasses the following options: endocrine therapy for hormone-sensitive patients with no previous resistance to endocrine therapy; trastuzumab for patients with *HER2*-positive cancers; and chemotherapy maintenance for patients with TNBC or those resistant to endocrine therapy. Chemotherapy maintenance will depend on the previous regimens as follows: continuation of single-agent chemotherapy until progression if the first-line treatment was a single agent; if the first-line treatment featured combination chemotherapy and it was interrupted because of its adverse effects, maintenance therapy tends to include a single agent from the previous combination regimen to prolong the PFS. Generally, maintenance therapy involves an alternative to or the continuation of a former effective regimen for as long as possible.

The Maintenance Paclitaxel 1 study evaluated the efficacy of paclitaxel as a candidate maintenance therapy. A total of 459 patients with MBC received six to eight cycles of first-line combination chemotherapy with epirubicin or doxorubicin plus paclitaxel (AT/ET). Among these patients, 215 who had a response or stable disease were randomly assigned to maintenance 3-week paclitaxel or control (no additional chemotherapy administration). Compared with the control, the administration of additional courses of paclitaxel did not improve PFS and OS in these patients [28].

The Spanish Breast Cancer Research Group (Grupo Español de Investigación del Cáncer de Mama; GEICAM) 2001-01 study evaluated the role of maintenance therapy with PLD in 288 patients who received first-line induction chemotherapy consisting of six cycles of doxorubicin and sequential docetaxel. A total of 155 patients free of disease progression were randomized to PLD (40 mg/m^2) every 28 days for six cycles or observation alone. This trial demonstrated that maintenance chemotherapy with PLD offers improved TTP (8.4 months vs. 5.1 months) in patients with MBC receiving first-line chemotherapy. However, considering the adverse effects, inconvenient administration, and high cost of PLD, it is difficult to promote its use in clinical practice [29].

A meta-analysis analyzed 11 randomized clinical trials and indicated that a longer first-line chemotherapy duration is associated with marginally longer OS and substantially longer PFS. However, first-line chemotherapy was administered for varying numbers of cycles in different studies, the increased toxicity was not well evaluated, and the assessment of quality of life varied, rendering the results of this study controversial [30]. The duration of first-line chemotherapy, whether maintenance therapy is beneficial, and who requires maintenance therapy remain unclear.

A prospective, randomized, multicenter, phase III Korean study published in 2013 found strong evidence supporting the utility of maintenance therapy. Of 324 patients with MBC who achieved disease control after six cycles of paclitaxel and gemcitabine (PG) chemotherapy, 231 were randomly assigned to maintenance chemotherapy with PG or observation until progression. The researchers concluded that, in patients with MBC who achieved disease control after an initial six cycles of PG chemotherapy, maintenance PG chemotherapy resulted in better PFS and OS than observation. In subgroup analysis, young age, premenopause, visceral metastases, HR negativity, and a greater number of metastatic sites were associated with an increased benefit from maintenance therapy. Although the rate of ≥ grade 3 toxicity was higher in the maintenance therapy group than in the observation group, this did not influence patients' quality of life [31].

The criteria for an ideal maintenance therapy drug are that it is an effective single agent, it has relatively low toxicity, and it can be easily administered for a long duration. Capecitabine is the preferred choice of maintenance therapy for patients with MBC. A series of studies from China revealed that single-agent capecitabine is a consistently effective maintenance treatment after responses to capecitabine-based combination chemotherapy [capecitabine plus docetaxel (XT) or capecitabine plus vinorelbine (XN)] with a favorable safety profile. Sequential maintenance with capecitabine monotherapy after capecitabine-based combination chemotherapy (X-based X) is an optimal choice of therapy for the full-time management for advanced breast cancer.

A phase II trial was conducted by the Affiliated Hospital of Academy of Military Medical Sciences in Beijing, China to analyze the efficacy of capecitabine monotherapy as a maintenance treatment for MBC after a response to capecitabine-based chemotherapy (XT or XN) in the first- or second-line setting. The median TTP of the 64 enrolled patients was 4.4 months, with an ORR of 5.1%. The incidence of hematologic toxicity was significantly lower for capecitabine monotherapy than for the combination therapy, indicating that capecitabine monotherapy is an effective maintenance treatment with a favorable safety profile [32].

The Cancer Institute and Hospital of the Chinese Academy of Medical Sciences in Beijing, China compared the

efficacy of maintenance capecitabine monotherapy after first-line treatment with XT or XN. An improvement in PFS was observed for XT-X compared with XN-X. Although a higher incidence of neurotoxicity and hand-foot syndrome was observed with XT-X, the overall tolerance was favorable. These findings illustrated that XT-X can be a first-line treatment option for MBC, whereas XN-X is suitable for patients with advanced breast cancer with no response or tolerance to taxanes [33].

The Chinese Society of Clinical Oncology launched a large, prospective, multicenter clinical trial to evaluate the efficacy and safety of X-based X, which is scheduled to end in December 2015. According to the data released thus far, 90.6% of the patients have experienced a clinical benefit from the X-based regimen, and 83.9% have begun maintenance capecitabine. Compared with the observation group, patients assigned to receive capecitabine maintenance therapy have exhibited significantly prolonged PFS (14.1 months vs. 11.4 months, $P = 0.0004$).

Conclusions

Many factors influence the choice of treatment for MBC, mainly including the status of biomarkers and treatment history. In recent years, targeted therapy has been flourishing, whereas chemotherapy appears to have had only minor development. However, chemotherapy retains a vital role in the treatment of MBC.

Anthracyclines and taxanes are the most widely used cytotoxic chemotherapeutics for breast cancer. Their application in neoadjuvant and adjuvant therapy may influence their use in subsequent treatment courses, and toxicity and resistance may force the use of more varied therapies. Capecitabine, vinorelbine, and gemcitabine have been adopted in clinical practice, and ixabepilone and eribulin are effective monotherapies. Combinations of effective drugs can further improve their efficacy. Platinum-based drugs have a role in the treatment of TNBC. Maintenance treatment is recommended in clinical practice according to the studies by Chinese and Korean researchers.

Although MBC remains incurable, the individual use of antitumor therapies based on the tumor molecular type and appropriate treatment strategies make MBC a chronic disease that can be treated long-term.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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