Review Article

Advances in chemotherapy for HER2-negative metastatic breast cancer

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Contributions: (I) Conception and design: H Mukai; (II) Administrative support: H Mukai; (III) Provision of study materials or patients: H Mukai; (IV) Collection and assembly of data: H Mukai; (V) Data analysis and interpretation: H Mukai; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Metastatic breast cancer cannot be curable, but significant improvement in overall survival has been observed with the appearance of new agents. The purpose of treatment is to prolong survival and to improve quality of life by reducing cancer-related symptoms. To achieve these goals, individualized approach is required. Chemotherapy is used for patients with hormone receptor negative breast cancer or hormone receptor positive patients who have cancer-related symptoms. The choice of regimen (single-agent or a combination), selection of a specific therapy and the duration of treatment depend on multiple factors, including the tumor burden, general health status, prior treatments and toxicities, and patient preferences.

Keywords: Breast cancer; chemotherapy; quality of life (QOL); survival

Submitted Apr 02, 2018. Accepted for publication May 31, 2018.
doi: 10.21037/cco.2018.06.01
View this article at: http://dx.doi.org/10.21037/cco.2018.06.01

Breast cancer is the world's most common disease in women, and is also a major factor that leads to death. It is reported that 5% of patients with breast cancer have distant metastasis at a diagnosis, and 30% of patients with early cancer subsequently experience the distant metastasis. Metastatic breast cancer cannot be completely cured; however, significant improvement in the survival period was observed consistent with the emergence of novel therapy (1,2).

The purpose of the treatment for metastatic breast cancer is to prolong the survival period and improve the cancer patients' quality of life (QOL) by managing cancer-related symptoms. To that end, not the same strategy for all patients but individual approach for each patient should be used (3).

In principle, chemotherapy is used for the following two indications. One is for hormone receptor-negative breast cancer. The endocrine therapy is not indicated for hormone receptor-negative breast cancer. Another is for the cases where the patients with hormone receptor-positive cancer present clinical symptoms caused by cancer, and the clinical effect of the endocrine therapy is deemed insufficient. For instance, cases with rapid tumor enlargement and cases with large tumor including the organ metastasis threatening the major organ function are included.

In general, chemotherapy is not combined with endocrine therapy for the hormone receptor-positive patients. This is because to minimize adverse events including an increase of thromboembolism (4). In addition, a meta-analysis showed that there were no differences in therapeutic effects between concomitant use of endocrine therapy with chemotherapy and chemotherapy alone (5).

Factors to consider in selecting chemotherapeutic regimens

For the therapeutic options for patients who undergo the chemotherapy, several factors that affect the individual treatment should be taken into account. Since many drugs are available for breast cancer, there is no optimum

treatment order applicable to all patients. The patients with metastatic breast cancer often receive numerous treatments during the course of treatment. Since metastatic breast cancer is generally considered incurable disease, participation in clinical trials is also recommended.

Tumor size

When a tumor is small and there are few symptoms, a single-agent chemotherapy is recommended. Cases that a combination therapy is recommended are as follows:

Large tumor
The patients with clinical symptoms caused by metastasis, such as stomachache due to liver metastasis and respiratory failure due to lung metastasis.

Rapid progression
The systemic therapy for brain metastasis is not recommended. If brain metastasis and systemic metastasis coexist, a treatment for the central nervous system and systemic treatment are done individually.

General health status

The performance status (PS) and Comprehensive Geriatric Assessment (CGA) are evaluated. Meanwhile, complications and the symptoms caused by cancer also influence the choice of drugs.

For example, anthracyclines is not used for patients who have a history of heart disorder or a high risk of the cardiac disturbance. In addition, in the case of the peritoneal dissemination with symptoms, oral anticancer drugs are not chosen because it is hard to take oral drugs for such patients. For patients who have risk of hyperglycemia and patients who seem to be not tolerant to the adverse events caused by steroids, premedication-free drugs, such as nanoparticle albumin-bound paclitaxel, capecitabine, and gemcitabine, are chosen.

Cancer therapy may not be indicated for the cases with a poor PS and sever comorbidities, because those patients are high risk of death due to other than breast cancer.

Anthracyclines are suitable for patients with stage IV breast cancer who did not receive adjuvant chemotherapy. Moreover, re-administration of anthracyclines may be possible for some patients when the patient who has a history or anthracycline administration and the disease-free survival (DFS) period is 1 year and more, and the cumulative dose of this drug is below the upper limit.

History of prior treatment and toxicity

Since drug(s) from different class without cross resistance is expected to have a high therapeutic efficacy, the different class drug(s) is recommended, in particular, in the case where disease progression occurs within 6 months after prior treatment (6). In addition, the use of the microtubule inhibitor, such as taxanes, eribulin, and vinorelbine, should be avoided for patients with severe peripheral neuropathy.

A head-to-head comparative study of eribulin and capecitabine showed that there was a difference in the toxicity profile between them although no significant difference in survival outcome was observed. Major toxicities of eribulin were neutropenia and alopecia, and those of capecitabine were hand-and-foot syndrome and diarrhea (7).

BRCA1/2 mutation

A platinum-based anticancer drug is often effective in metastatic breast cancer with BRCA1/2 mutation. Byrski *et al.* showed the response rates of platinum monotherapy was 80% in 20 patients with BRCA1-positive metastatic breast cancer (8). A phase III randomized trial (TNT study) comparing carboplatin and docetaxel showed that the response rate and progression-free survival (PFS) for BRCA-related breast cancer were significantly higher in carboplatin than those in docetaxel (9). Regarding non-BRCA-related TNBC, there is no clear evidence indicating that the platinum-based anticancer drugs result in higher benefits. However, TNT study showed that docetaxel and carboplatin had an approximately equivalent effect in patients without the BRCA mutation. Since the toxicity of carboplatin was mild as compared with docetaxel, carboplatin may be chosen as a treatment option.

Patients' preference

A treatment plan should be established in consideration of the patients' preferences. Some patients cannot tolerate the increasing risk of toxicity associated with the chemotherapy. Meanwhile, there are certain patients who choose the chemotherapeutic regimen even if the toxic risks increase. In the case where the patients want to reduce the hospital visits, every 3 weeks taxanes or anthracyclines as monotherapy, and CMF (cyclophosphamide,

methotrexate, and fluorouracil) and AC (doxorubicin and cyclophosphamide) regimens are available. To avoid alopecia, gemcitabine, vinorelbine S-1 or capecitabine can be used.

Orally administered drugs are generally more convenient than intravenous drugs. S-1 and capecitabine are both oral fluorouracil derivatives widely used in Japan. S-1 is a combination drug, based on a biochemical modification of fluorouracil, containing tegafur, gimeracil, and oteracil in a molar ratio of 1:0.4:1 (10). This combination enables the fluorouracil concentration to be increased while avoiding gastrointestinal toxic effects. S-1 is non-inferior to taxane with respect to overall survival and better than taxane with regard to health-related quality of life as a first-line treatment for patients with metastatic breast cancer (11,12). There were no significant differences in time to treatment failure or progression-free survival between the treatment groups.

Combination therapy

In the case where the disease rapidly progresses, combination therapy is chosen if a significant advantage in the response rate is expected.

The ECOG1193 study (13) comparing combination therapy of doxorubicin plus paclitaxel, doxorubicin monotherapy, and paclitaxel monotherapy showed that the overall response (ORR) was increased (47%, 36%, and 34%, respectively); and the time to progress (TPP) was also prolonged (8, 6, and 6 months, respectively). However, the OS was almost equivalent (22, 19, and 22 months, respectively). In addition, although a meta-analysis using 43 trials showed that the combination therapy extended OS (14), this result had not been compared with each treatment sequentially.

The patients may have an option to receive the treatment using bevacizumab concomitantly with the single chemotherapy; however, the fact that the concomitant use of bevacizumab with chemotherapy extended PFS, but not OS, should be considered.

The combination therapy had a slight effect in prolongation of OS as compared with a single use, while it had a higher toxic risk. Therefore, in principle, it is recommended to use the single use for metastatic breast cancer in consideration of QOL of the patient. Gemcitabine, carboplatin, and docetaxel every 3 weeks, which known to show strong bone marrow toxicity, are not suitable for combination therapy

High-dose chemotherapy

The high-dose chemotherapy with peripheral blood stem cell transplantation is not recommended for metastatic breast cancer. A systematic review published in 2011, which included six randomized trails, indicated that the high-dose chemotherapy did not improve OS (15).

Metronomic chemotherapy

Since metronomic chemotherapy is used at low-dose and short intervals, and having attractive effect and mild toxicity, the metronomic chemotherapy has been received recognition in treatment for advanced cancer (16).

One of the most tested regimens is a treatment with oral methotrexate + cyclophosphamide (17); and also vinorelbine and capecitabine are being examined (18).

Treatment period

The optimal treatment period for metastatic breast cancer has not been clear. The treatment period should be determined according to the treatment goal of each patient and observed toxicity. The continuous treatment after the maximum response is recommended for the younger patients; however, the treatment should be quit in the case where severe adverse events are seen; and the patients do not want a continuous treatment. In the case of chemotherapy as a first-line treatment for patients with hormone-positive, the treatment might be switched to endocrine therapy.

Some studies indicated the benefits of continuous treatment even after achieving the maximum response in patients with good response. Among 2,300 patients who underwent a first-line therapy, a meta-analysis in 2011 compared the responses between maintenance therapies and treatment termination. Both PFS (HR, 0.64) and OS (HR, 0.91) were prolonged when the treatment period of chemotherapy was long (19). The treatment with paclitaxel plus gemcitabine was performed for 324 patients in the randomized trial in 2013. Two-hundred thirty-one patients were divided into two groups: follow-up group and continuous chemotherapy treatment group, indicating that the improvement of 6 months PFS (60% and 36%) and the prolongation of OS (32 and 24 months) were confirmed in continuous group. However, more than grade 3 neutropenia and neuropathy were more increased in continuous group.

After a second-line therapy

For the second-line therapy, the drug(s), which was not used in the first-line therapy, should be used.

According to the European Society for Medical Oncology (ESMO) guideline, capecitabine, vinorelbine, and eribulin are recommended as a preferred regimen in terms of the efficacy and toxic profile for patients with a medical history of anthracyclines and taxanes (3).

The drugs which can be used after the third treatment includes: capecitabine, S-1, vinorelbine, gemcitabine, and irinotecan. The response rate of all drugs was 15–36%; and no effect on the OS prolongation has not been shown. According to the National Comprehensive Cancer Network (NCCN), benefit of chemotherapy is slight after the third regimen or PS 3; and therefore the best supportive care is recommended.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Mukai H, Ito M. Advances in chemotherapy for HER2-negative metastatic breast cancer. Chin Clin Oncol 2018;7(3):26. doi: 10.21037/cco.2018.06.01