TREATMENT OF METASTATIC BREAST CANCER PATIENTS: WHAT IS THE STANDARD CARE OF THE PATIENTS?

The clinical course for breast cancer patients varies considerably. Some patients can be cured with minimal operation, while others quickly develop systemic dissemination and die over a few months. Some patients, even with metastatic disease, live long after systemic treatment, while no benefit from chemotherapy is observed in other subsets of patients. The most important goal of treating breast cancer patients is to stop metastasis at source, i.e. eradicate all cancer cells before they metastasize to distant organs. The principal strategy to achieve this goal has been ‘detect and surgically excise the tumor as early as possible’. Based on this strategy, screening of breast cancer was successfully introduced for women aged 50 to 69 (1). Surgical operation has long been valued for its role in controlling primary breast cancer since the radical mastectomy was first reported (2). Extent of primary breast surgery has been reduced from radical mastectomy to breast-conserving treatment without any disadvantage in controlling this disease. The shift in the operational mode occurred when it became recognized that treatment failure after breast cancer surgery usually is due to the systemic dissemination of cancer cells before surgery, rather than an inadequate operative procedure.

The rationale for adding systemic therapy as a component of the initial treatment is that the prognosis of operable breast cancer patients is mostly governed by micrometastatic disease already existing at the time of initial diagnosis, even though no direct clinical evidence in diagnostic tests can be detected (3). Currently, systemic chemotherapy or endocrine therapy, combined with surgery and radiation therapy as the initial treatment of breast cancer, significantly reduce the recurrence and death rate in certain subsets of breast cancer patients. The highly diverse clinical outcome of breast cancer depends on a large number of factors, some are known, while without any doubt, many of them remain unclarified (4). Tremendous effort has been made to elucidate which patients are most likely to benefit from which treatments to prolong disease free survival and overall survival following the initial treatment for early breast cancer patients (5). However, a significant proportion of patients eventually still develop clinically overt metastatic disease, following the initial treatment complex. Metastatic breast cancer is generally recognized to be an incurable disease despite the recent advance in the treatment with endocrine and chemotherapy. The use of conventional chemotherapy or endocrine therapy in metastatic breast cancer is mainly for palliation. More than half the patients with metastatic breast cancer experience tumor shrinkage in response to chemo- or endocrine therapy resulting in substantial symptom relief and improvement in quality of life. However, the benefit from such systemic treatments generally lasts for only 8 to 12 months, and their disease eventually progresses.

Various attempts have been made to improve the treatment in metastatic breast cancer patients. Among them, aggressive approaches using high dose chemotherapy (HDCT) with autologous hematopoietic stem cell support have been accepted as promising new methods of treatment (6). It has been recently criticized however that favorable results reported by the early clinical phase II trials that used HDCT may reflect the result of patient selection bias for these trials (7).

The report by Yamamoto et al. in this issue of the Japanese Journal of Clinical Oncology demonstrates that a small percentage of metastatic breast cancer patients remain alive and progression-free for prolonged periods after initiation of systemic treatments (8). Long-term survivors are among patients with good performance status, a low number of metastatic sites, no disease connection with the liver and who have achieved complete remission after the first or second line systemic treatments. A series of tests of a larger number of metastatic breast cancer patients, with a longer follow-up period, demonstrated that approximately 3% of the patients remained alive and in complete remission for more than five years, and more than half of these patients were alive and disease-free with a minimum of 10 year’s follow-up (9). The fraction of long term survivors in these reports is indeed very small, but the meaning of the observed fact that a certain subset of metastatic breast cancer patients after systemic treatment can be alive and disease-free for a significant duration is great. All medical oncologists who are in charge of treating metastatic breast cancer patients should first recognize this fact. Upon diagnosis of recurrence in distant organs, surgeons who have followed the patients after the surgery for their primary breast cancer feel defeated. The connotation that cure of metastatic breast cancer is impossible often misleads surgeons, giving the idea that diagnosis of metastasis as early as possible has little meaning because all patients with metastasis seem to die of the disease. Is early detection of distant metastasis beneficial in breast cancer patients? The answer to this question is yes. The observation by Yamamoto et al. that long-term survivors are among patients with good performance status, a low number of metastatic sites and no disease connection with the liver does not necessarily support the value of early detection (8). Rather, metastases can be more effectively treated if detected earlier than if found at a more advanced stage.

More effective treatment of patients with recurrent disease implies that these patients can be cured, that their survival can be prolonged, or that their quality of life is improved. Early detection may be of emotional value to the patients, to the treating physicians and to the relationship between them. Furthermore, clinical trials testing innovative therapies might be well performed in patients with asymptomatic recurrence because effective palliative measures are not immediately required. This in turn indicates the need for an appropriate follow-up schedule of post-operative breast cancer patients and immediate confirma-
tion of the diagnosis when any abnormal findings which suggests recurrence are noted.

There seems to be no consensus among Japanese surgeons regarding an effective follow-up schedule in post-operative breast cancer patients. The American Society of Clinical Oncology (ASCO) presented a breast cancer surveillance guideline to determine an effective, evidence-based postoperative surveillance strategy for the detection and treatment of recurrent breast cancer (10). This guideline may be useful in assisting access to better care and in decreasing the cost of medical care.

Some surgeons are reluctant to treat metastatic breast cancer patients with intravenous chemotherapeutic agents because of their toxicity and alternative methods of treatment such as oral fluoropyrimidines are preferred. Many breast cancer patients seem to receive sub-optimal or inappropriate treatment after diagnosis of recurrence (11). What is currently the standard chemotherapeutic regimen for metastatic breast cancer patients? Although taxoids are promising against breast cancer, combination chemotherapy including anthracyclines such as CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) or AC (doxorubicin, cyclophosphamide) are still playing the key role in the treatment of metastatic breast cancer. A meta-analysis of randomized clinical trials in the metastatic setting comparing methotrexate- and doxorubicin-based regimens showed superiority for the latter in terms of overall survival (12). In Yamamoto’s series, 60% of the patients were treated with anthracycline-based regimens (8). However, because an increasing number of patients with breast cancer will have been treated with anthracycline-based regimen as an adjuvant treatment, selection of the first line chemotherapeutic regimen including anthracycline in the metastatic setting will be limited. A consistent policy for selecting chemotherapeutic in adjuvant and metastatic settings has become important.

The report also indicates the need for patient selection in order to apply the most appropriate systemic therapy. Based on the present observation, the authors proposed in another publication a prognostic index which incorporated several clinically relevant prognostic factors (13). It can be stated that metastatic breast cancer patients so far have been treated with ‘the greatest common divisor-like therapy’ which can be applied to all patients based on a policy of the greatest good for the greatest number. As the knowledge on biology of breast cancer expands and newer therapeutic agents such as anti-HER2 antibody, taxoids and several aromatase inhibitors become clinically available, selection of treatment for breast cancer patients is more individually tailored for each patient, based on prognostic and predictive factors. Even though we will have various treatment choices, it is still unlikely that a cure in all metastatic breast cancer patients will be achieved in the near future. Instead, we will be able to avoid toxic and expensive therapy for patients whose cancer is intrinsically resistant to the projected treatment.

The treatment strategy for this disease is becoming more and more complicated and higher standards of medical care are needed. In order to provide the best available treatment for the majority of breast cancer patients with maximum benefit, it is vitally important to understand the disease, the patients and the treatments.

References

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