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Adjuvant Chemotherapy with S-1 in Breast Cancer Patients after Primary Systemic Chemotherapy

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Abstract

Additional therapy following definitive breast surgery after primary systemic chemotherapy (PSC) has not been correctly evaluated. Two unsolved problems regarding additional chemotherapy following PSC in advanced breast cancer are the subjects of this article. First is the prognostic impact of additional chemotherapy after surgery in patients with residual disease after completion of standard PSC, and second is the use of oral anticancer drugs such as S-1, which are known as metronomic chemotherapy, in this setting. Although there are many ongoing trials for breast cancer patients with residual disease after PSC in various subtypes, survival benefit has not been validated in clinical trials. Orally effective anticancer drugs such as S-1 and capecitabine can be further candidates for additional postoperative chemotherapy after PSC. Further studies are needed to evaluate the usefulness of these metronomic chemotherapies in this setting.

Introduction

Additional therapy following definitive breast surgery after primary systemic chemotherapy (PSC) has not been correctly evaluated. There is no evidence as to whether additional postoperative chemotherapy improves recurrence-free or overall survival1 [1-3]. The presence of residual cancer cells, which could not be controlled by PSC, has the ability to cause the recurrence of disease and is associated with worse outcomes. Therefore, a new therapeutic challenge that can improve clinical outcomes is needed in advanced breast cancer patients. Shigekawa et al. [4] recently described the use of S-1 in advanced breast cancer in this context. Two unsolved problems regarding additional chemotherapy after PSC in advanced breast cancer are the subjects of this article. First is the prognostic impact of additional chemotherapy after surgery in patients with residual disease after PSC, and second is the use of oral anticancer drugs such as uracil-tegafur (UFT), S-1, and other 5-fluorouracil (5-FU) derivatives in this setting.

Postoperative Adjuvant Chemotherapy after Primary Systemic Chemotherapy

In general, breast cancer patients who have completed their planned course of PSC are not given postoperative chemotherapy because additional chemotherapy following surgical treatment after PSC has not been adequately evaluated in clinical trials. However, we often have patients with several axillary lymph node involvements after completing PSC in advanced breast cancer, and they have a high potential for disease recurrence. It is believed that postoperative recurrence of advanced breast cancer is caused by the growth of residual cancer cells that have not been controlled by PSC or by the regrowth of dormant cells. Therefore, the presence of residual disease after the completion of PSC can be a therapeutic challenge. The role of additional therapies in this setting is an area of active research and several clinical trials that are currently underway. NCT00877500 is a Phase II randomized study of ixabepilone, which is a microtubule inhibitor belonging to a class of antineoplastic agents, versus no additional chemotherapy in patients with residual disease after PSC for HER2-negative breast cancer [5]. NCT01401959 is a Phase II study that evaluates the effect of eribulin mesylate in patients who do not achieve complete pathologic response following PSC [6]. NCT02445391 is a randomized Phase III study of platinum-based chemotherapy versus observation in patients with residual triple-negative breast cancer following PSC [7]. NCT00925652 is a unique Phase II randomized study to determine the efficacy of adjuvant bevacizumab and metronomic chemotherapy in HER2-negative disease with residual disease following PSC. Bevacizumab is given once every three weeks for six months and then every six weeks for additional one and a half years. Then metronomic chemotherapy is used, i.e. cyclophosphamide and methotrexate are orally taken for six months [8]. NCT01772472 is a randomized Phase III study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive disease who have residual tumors present following PSC [9]. Thus, there are many ongoing trials for various subtypes of breast cancer in this setting. Sikov et al. [10] lined up the candidates as follows: patients with triple negative disease who were not given both an anthracycline and a taxane as PSC, patients treated with preoperative endocrine therapy who have a preoperative prognostic index (PEPI) score >0, and patients who did not complete their planned course of PSC.

Oral Anticancer Drugs as Postoperative Adjuvant Chemotherapy

Oral fluoropyrimidines such as UFT, doxifluridine, and other 5-FU derivatives have been widely used in Japan as postoperative or salvage chemotherapy for breast, gastric and colorectal cancers because of their ease of administration and compliance. The Adjuvant Chemo-endocrine Therapy for Breast Cancer (ACETBC) trial group in Japan has established the role of oral anticancer drugs in the adjuvant setting, particularly the efficacy of adjuvant UFT, for breast cancer since 1982. Noguchi et al. [11] reported the results of a pooled analysis of six randomized trials conducted to study the efficacy of UFT in the

adjuvant treatment of node-negative breast cancer. They concluded that adjuvant UFT improved the overall survival of node-negative breast cancer patients and reported that UFT was more effective in tumors measuring more than 2 cm and aneuploid tumors and more useful in patients older than 65 years. Furthermore, in pooled analysis of two randomized clinical studies comparing the efficacy of oral UFT (two years) with a cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) regime (six course), relapse-free survival was better with UFT than with CMF in ER-positive patients who were 50 years or older (HR, 0.59; 95% CI, 034–1.01). UFT was also shown to be non-inferior to CMF in terms of inhibiting recurrence of ER-positive early breast cancer [12,13]. UFT is defined as dihydropyrimidine dehydrogenase inhibitory-fluoropyrimidine (DIF) because excess uracil competes with 5-FU for dihydropyrimidine dehydrogenase, resulting in the enhancement of 5-FU antitumor activity. S-1 also belongs to DIF, and is combined with tegafur, gimeracil, and oteracil potassium at a molar ratio of 1:0.4:1. S-1 can be expected to have higher antitumor activity than UFT [14]. Regarding the usefulness of S-1 in the adjuvant setting for breast cancer, the Post-Operative Therapy with Endocrine and TS-1 (POTENT) trial, a randomized controlled Phase III study of postoperative chemotherapy in patients with ER-positive HER2-negative breast cancer, is ongoing in Japan [15]. The safety and feasibility of adjuvant therapy with S-1, which is administered for two weeks with a one-week withdrawal after standard PSC, was evaluated, and the percentage of eligible patients completing the 18-course treatment was 51.2%. The authors mentioned that a four week continuous medication schedule without rest may be too toxic for patients treated with standard PSC4). Toi et al. [16] remarked that capecitabine, one of the oral fluoropyrimidines, increased disease-free survival in HER2-negative breast cancer patients with residual disease after neoadjuvant chemotherapy (CREATE-X trial) at the 2015 San Antonio Breast Cancer Symposium.

Conclusion

Adjuvant chemotherapy following definitive breast surgery after PSC has not been correctly evaluated. There are many ongoing clinical trials attempting to solve this clinical question. Orally effective anticancer drugs such as S-1 and capecitabine have been widely used as salvage chemotherapy for breast cancer, and are further candidates for additional postoperative chemotherapy after PSC. Further studies are needed to evaluate the usefulness of these metronomic chemotherapies in this setting.

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