Chemotherapy and other drug therapies for older patients with cancer: JSMO-JSCO clinical practice guidelines

Breast cancer

CQ 10

Should anthracycline anticancer drugs be administered in postoperative chemotherapy for HER2-negative breast cancer in hormone receptor-positive older patients?

Recommendation

It is proposed that anthracycline anticancer drugs be administered if the baseline risk of the patient requires chemotherapy. [Strength of recommendation: 2 (rate of agreement: 86%); strength of evidence: B]

Background

1. Standard postoperative treatment for hormone receptor-positive, HER2-negative breast cancer

Standard postoperative treatment for breast cancer is administered by combining endocrine therapy, chemotherapy, and HER2 monoclonal antibodies, depending on the subtype.

In principle, standard postoperative treatment for hormone receptor-positive, HER2-negative breast cancer is endocrine therapy. Chemotherapy may also be administered in accordance with the risk of relapse. Key drugs in chemotherapy are anthracycline anticancer drugs. Regimens including doxorubicin or epirubicin are frequently selected.

2. Approach to postoperative treatment for hormone receptor-positive older patients with HER2-negative breast cancer

Chemotherapy is not recognized as a standard therapy in postoperative treatment for hormone receptor-positive older patients with HER2-negative breast cancer. Furthermore, sufficient data on tolerability for chemotherapy are not available. Therefore, in actual clinical settings, the following options are considered for each patient: adding chemotherapy to endocrine therapy, single therapy with endocrine therapy, or observation of the course of disease. Particularly, the cardiac toxicity of anthracyclines is irreversible, and age is one of the risks for it. Moreover, an older patient tends to have reduced cardiac function prior to the commencement of treatment. It is also important to consider the

balance between therapeutic effects and adverse events in determining the following aspects: whether or not chemotherapy should be added to the underlying endocrine therapy and, if chemotherapy is to be added, whether or not anthracycline anticancer drugs should be used. In other words, a key question to be answered in the clinic is whether or not chemotherapy with an anthracycline anticancer drug should be added to endocrine therapy in postoperative treatment for HER2-negative breast cancer in hormone receptor-positive older patients.

Given the above, the key clinical issue was identified: “What kind of drug therapy is appropriate for breast cancer in older patients?” To address this issue, the following clinical question (CQ) was set: “Should anthracycline anticancer drugs be administered in postoperative chemotherapy for HER2-negative breast cancer in hormone receptor-positive older patients?”

Literature review and clinical interpretation

Standard postoperative treatment for hormone receptor-positive, HER2-negative breast cancer is endocrine therapy. Chemotherapy is added in line with the risk of relapse. The key drugs in chemotherapy are anthracycline anticancer drugs. Regimens including doxorubicin or epirubicin are frequently selected. However, anthracycline anticancer drugs have irreversible cardiac toxicity. It is anticipated that administering these drugs to an older patient may increase the risk of heart failure as they tend to have various complications. Therefore, at present, the following aspects are determined on an individual basis particularly for older patients: whether or not to administer chemotherapy and whether or not to include an anthracycline anticancer drug in chemotherapy. Given the above, we examined whether or not chemotherapy with anthracycline anticancer drugs can be recommended in cases in which it is necessary to administer chemotherapy due to a high risk of relapse.

The following outcomes were considered as benefits for the present CQ: prolongation of survival, prolongation of relapse-free survival, and the maintenance of quality of life (QOL). Meanwhile, the following outcomes were considered as harms: the incidence of treatment-related death and the incidence of cardiac toxicity. It is true that hospitalization due to adverse events and the incidence of grade 3 or more adverse events are important. However, it was determined that they are less important than the incidence of treatment-related death and cardiac toxicity.

In our literature search, we systematically searched for the following kinds of studies: clinical studies on postoperative chemotherapy in older patients, clinical studies on postoperative chemotherapy that includes or does not include an anthracycline anticancer drug, and studies on anthracycline-induced cardiac toxicity. The initial screening extracted nineteen papers. Following the second screening, ten papers were adopted, including those extracted through hand-searching. No papers were found that studied only hormone receptor-positive (luminal type) older patients. Few papers mentioned HER2, let alone a subgroup analysis by subtype. This may be because the concept of subtype is relatively new and because older patients account for a small proportion in clinical studies. As the present CQ examines the significance of anthracycline anticancer drugs for hormone receptor-positive (luminal type) older patients, control groups need to consist of subjects for whom observation of the course of disease without treatment or endocrine monotherapy is administered. Thus, the CQ has the following three levels: first, whether or not postoperative endocrine therapy is required; second, whether or not chemotherapy should be added to endocrine therapy; and third, if chemotherapy is added, whether or not an anthracycline should be included. We conducted a literature search with keywords in a way such that we could find answers to all of the above questions. However, we were only able to find RCTs that looked into the details of chemotherapy. No papers were found that could be referenced in examining the significance of adding chemotherapy to a no-treatment regimen or endocrine monotherapy. Meanwhile, the 2005 version of the Early Breast Cancer Trialists' Collaborative Group's meta-analysis[1] reported an analysis of the comparison of a no-treatment regimen and tamoxifen. It also reported an analysis of tamoxifen monotherapy and that of adding chemotherapy. Although details overlap between the 2012 version and the 2005 version, the latter was also adopted. Additionally, the current standard drug for postoperative endocrine therapy for postmenopausal hormone receptor-positive breast cancer is aromatase inhibitors. The BIG1-98 study compared these drugs with tamoxifen. Thus, we referenced the study in the International Society of Older Oncology recommendations and added it to our references through hand-searching. The following therapies were compared and examined for the body of evidence: chemotherapy involving an anthracycline anticancer drug and chemotherapy not involving an anthracycline anticancer drug. Four randomized comparative trials (RCTs) and two observational studies for the present CQ were also referenced for CQ 11, which examines the necessity of anthracycline anticancer drugs in postoperative therapy

for triple-negative breast cancer in older patients.

It should be noted that an overall similar tendency was observed in terms of overall survival and relapse-free survival (or disease-free survival). The majority of results support the efficacy of chemotherapy that includes an anthracycline anticancer drug. The U.S. Oncology 9735 study[2] does not support the use of anthracycline anticancer drugs. That study found that overall survival and disease-free survival were significantly prolonged with a treatment that does not involve anthracycline anticancer drugs (docetaxel-cyclophosphamide combination therapy) compared with doxorubicin-cyclophosphamide combination therapy (AC). The same tendency was observed in a subgroup analysis of 160 older patients aged 65 years or older (16%) who were selected from a total of 1,016 subjects. This study also conducted subgroup analyses of disease-free survival in relation to ER and HER2. Although similar tendencies were observed in both ER and HER2, there was no significant difference. Therefore, it is not possible to determine whether the same results can be achieved in hormone receptor-positive (luminal type) older patients. Three studies were identified that support the use of anthracycline anticancer drugs (CALGB49907[3], ICEII-GBG52[4], and CALGB40101[5]). The ICEII-GBG52[4] study is a phase II study that investigated older patients aged 65 years or older who were in good condition (not frail). The study compared combination therapy with albumin-bound paclitaxel and capecitabine and the following standard, postoperative adjuvant chemotherapies: epirubicin-cyclophosphamide combination therapy (EC) and cyclophosphamide-methotrexate-fluorouracil combination therapy (CMF). Although the number of subjects was small at 391, the study was focused on older patients, of whom 65% had hormone receptor-positive (luminal type) disease. Primary endpoints were treatment discontinuation and adverse events. No significant difference was observed between the two groups in terms of survival period and disease-free survival period. The CALGB49907[3] study is a comparative study that examined the non-inferiority of capecitabine monotherapy compared with CMF or AC standard therapy in patients aged 65 years or older. The study was discontinued prior to completion when it was found that capecitabine is inferior to standard therapy during the relapse-free survival period, which was the primary endpoint. This occurred when the 600th subject was enrolled. An analysis of all subjects showed more favorable results in the standard therapy group both in terms of relapse-free survival and overall survival. Since CMF was included in the standard therapy group of this study, it was not a genuine comparison with

anthracycline anticancer drugs. Nevertheless, the study is important in examining the present CQ because, first, the study was focused on older patients and, second, two-thirds of subjects were hormone receptor-positive. The CALGB40101[5] study is a large-scale comparative study that directly compared anthracycline anticancer drugs and non-anthracycline anticancer drugs. From among a total of 3,871 subjects, 61% were aged 50 years or older, and 68% were hormone receptor-positive. This study did not indicate the non-inferiority of paclitaxel monotherapy compared with AC in terms of relapse-free survival and overall survival. Similar results were observed in hormone receptor-positive cancer. Given the above, no data were found that directly evaluated hormone receptor-positive (luminal type) older patients. It is considered that results from clinical studies that involve a large number of such cases would support the significance of anthracycline anticancer drugs in terms of the survival period and the relapse-free survival period.

Extremely few incidents of treatment-related death were observed in all studies. In all of the four above-mentioned RCTs, a total of 19 cases of treatment-related death were observed. Of these, 13 were in standard treatment groups in which anthracycline anticancer drugs were used, whereas six were in groups in which non-anthracycline drugs were used. The CALGB40101[5] study included seven cases of myelogenous leukemia or myelodysplastic syndrome in treatment-related death. These cases were observed at 11-34 months following enrollment. It is difficult to determine the degree of importance of death due to late toxicity in older cases, particularly in patients with a blood disease or heart disease.

An observational study was found that evaluated the QOL of 350 subjects during the period from pre-treatment to post-treatment month 24[6]. It is an association study of the CALGB49907 study. The 350 subjects in the observational study were selected from 633 subjects enrolled in the CALGB49907 study, which validated the non-inferiority of capecitabine monotherapy compared with standard therapies, namely CMF and AC. According to the study, QOL during treatment and at the time of treatment completion is significantly more favorable in patients to whom capecitabine was administered. However, the difference between those to whom capecitabine was administered and those to whom it was not administered decreased by 12 months following the completion of treatment. Thereafter, no difference was observed until post-treatment month 24.

Finally, in terms of cardiac toxicity, reports on heart-related adverse events in all the RCTs were examined. In addition to these, an observational study on cardiac toxicity in

older patients[7] was included through hand-searching. Extremely few cases of heart-related treatment-related death have been reported in patients to whom anthracycline anticancer drugs were administered. Only three such cases were identified in the CALGB40101 study and the U.S. Oncology 9735 study[2,5]. Heart-related adverse events were observed in both groups in the ICEII-GBG52 study. However, none of them was a treatment-related death from cardiac toxicity. Rather, the number of heart-related adverse events was smaller in standard therapy groups with EC or CMF than in the study treatment group in which anthracycline anticancer drugs were not included[4]. From among patients to whom AC was administered in the CALGB49907 study, none experienced heart failure[3]. It should be noted that this finding is from patient data registered for a clinical study and that the incidence rate of cardiac toxicity in actual clinical settings may be higher. An observational study of approximately 40,000 patients has been conducted using the U.S. SEER-Medicare-linked database. The study examined factors related to congestive heart failure caused by anthracycline anticancer drugs in patients aged 66-80 years[7]. Of all the examined patients, anthracycline anticancer drugs were postoperatively administered to 4,712 patients, chemotherapy with drugs other than anthracycline anticancer drugs was administered in 3,912 patients, and 34,705 patients did not receive chemotherapy. Fifty-six percent of patients who underwent chemotherapy with anthracycline anticancer drugs were hormone receptor-positive, and 55% of patients who underwent chemotherapy with drugs other than anthracycline anticancer drugs were hormone receptor-positive. Results indicated that the risk of congestive heart failure was significantly higher in patients aged 66-70 years to whom anthracycline anticancer drugs were administered (hazard ratio: 1.26; 95% confidence interval: 1.12-1.42). Meanwhile, the incidence rate of congestive heart failure in patients aged 71-80 years was overall higher than in those aged 66-70 years, although no significant difference was observed. It should be noted that the incidence rate of congestive heart failure in the study is based on diagnoses linked to Medicare claims; therefore, the actual incidence rate may be lower. Although multiple prospective clinical studies on older patients were identified, all of them were subgroup analyses. Thus, it was determined that the strength of evidence is "medium (B)."

In terms of the benefit-harm balance, it was considered that the prolongation of survival and relapse-free survival through chemotherapy with an anthracycline anticancer drug is a significant benefit. It was also considered that the alleviation of the psychological and

physical burden on the patient and their family through the prolongation of relapse-free survival is a particularly significant benefit. It was suggested that the degree of harm from the therapy is small from the following perspectives: first, the impact of treatment involving anthracycline anticancer drugs on the incidence of treatment-related death and cardiac toxicity is not clear. and second, QOL decreased only during treatment. Given the above, it was confirmed that a favorable benefit-harm balance can be maintained.

Voting results

From among fourteen panel members, twelve voted for "mild recommendation for administering anthracycline anticancer drugs" and two voted for "mild recommendation for not administering anthracycline anticancer drugs." It was determined that the level of recommendation would be "mild recommendation (proposal) for administering anthracycline anticancer drugs."

Future research questions

During the examination for the present CQ, no papers were identified that investigated the prognosis of postoperative chemotherapy by subtype in older patients with luminal-type cancer.

In the case of older patients, whether or not a significant difference in prognosis can be observed depends on their mean life expectancy. In this sense, it is not clear if results from overseas clinical studies can be directly applied to Japanese older patients. Further, determining factors of relapse may vary between older patients and non-older ones. Thus, clinical studies that directly examine Japanese subjects are required going forward.

References

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CQ 11

Can anthracycline anticancer drugs be omitted in postoperative chemotherapy for triple-negative breast cancer in older patients?

Recommendation

It is proposed that anthracycline anticancer drugs not be omitted. [Strength of recommendation: 2 (rate of agreement: 71%); strength of evidence: B]

Background

1. Approach to postoperative treatment for triple-negative breast cancer in older patients

Standard postoperative treatment for triple-negative breast cancer is chemotherapy. The key drugs in chemotherapy are anthracycline anticancer drugs. Regimens mainly including doxorubicin or epirubicin are frequently selected. Meanwhile, chemotherapy is not recognized as a standard therapy for older patients. Furthermore, sufficient data on tolerability for chemotherapy in older patients are not available. Therefore, in actual clinical settings, chemotherapy or observation of the course of disease is considered on an individual basis. Particularly, the cardiac toxicity of anthracyclines is irreversible, and age is one of the risks for it. Moreover, an older patient tends to have reduced cardiac function prior to the commencement of treatment. Therefore, the balance between therapeutic effect and adverse events is particularly important in older cases. It is expected that it is possible to alleviate chemotherapy-induced adverse events by avoiding anthracycline anticancer drugs. However, when the aim of treatment is to cure cancer, it is a great dilemma that not using highly efficacious anthracycline anticancer drugs may lead to reduced therapeutic effects. Whether or not it is possible to omit anthracycline anticancer drugs is a critical clinical question in selecting a postoperative chemotherapy for triple-negative breast cancer.

Given the above, the key clinical issue was identified: “What kind of drug therapy is appropriate for breast cancer in older patients?” To address this issue, the following clinical question (CQ) was set: “Can anthracycline anticancer drugs be omitted in postoperative chemotherapy for triple-negative breast cancer in older patients?”.

Literature review and clinical interpretation

Standard postoperative treatment for triple-negative breast cancer is chemotherapy. The key drugs in chemotherapy are anthracycline anticancer drugs. Regimens mainly

including doxorubicin or epirubicin are selected. Meanwhile, the cardiac toxicity of anthracyclines is irreversible. The balance between therapeutic effect and adverse events is particularly important in older cases. It is expected that it is possible to alleviate chemotherapy-induced adverse events by avoiding anthracycline anticancer drugs. However, a concern remains that not using such drugs may lead to reduced therapeutic effects. At present, whether or not anthracycline anticancer drugs be adopted as chemotherapeutic agents is considered on an individual basis particularly for older patients. Given the above, we examined whether it is possible to omit anthracycline anticancer drugs in postoperative chemotherapy for triple-negative breast cancer.

The prolongation of survival and relapse-free survival was described as a benefit in the scope of our examination. However, the reduction of the survival period and relapse-free survival as a result of omitting anthracycline anticancer drugs was considered as a harm and adopted as an important outcome for the present CQ. The incidence of treatment-related death and cardiac toxicity was described as a harm. However, a reduction in such incidence was considered as a benefit and adopted as an important outcome for the present CQ. The maintenance of quality of life (QOL) was considered as a benefit also for the present CQ. It is true that hospitalization due to adverse events and the incidence of grade 3 or more adverse events are important. However, it was determined that they are less important than the adopted outcomes.

In our literature search, we systematically searched for the following kinds of studies: clinical studies on postoperative chemotherapy in older patients, clinical studies on postoperative chemotherapy that includes or does not include an anthracycline anticancer drug, and studies on anthracycline-induced cardiac toxicity. A quantitative meta-analysis was also conducted for the present CQ.

The initial screening extracted nineteen papers. Following the second screening, twelve papers were adopted, including those added through hand-searching. However, no randomized comparative trials (RCTs) or observational studies were identified that solely looked into older patients with triple-negative breast cancer. Meanwhile, the 2012 version of Early Breast Cancer Trialists' Collaborative Group's meta-analysis[1] was adopted because it reported an analysis of the comparison between a no-treatment regimen and chemotherapy.

Evidence was evaluated with a focus on the following papers: two RCTs that compared chemotherapy with an anthracycline anticancer drug and chemotherapy that does not

include an anthracycline anticancer drug only in older patients aged 65 years or older[2,3] and two RCTs that compared chemotherapy with an anthracycline anticancer drug and that which does not include an anthracycline anticancer drug in subjects including a certain number of older patients (patients aged 65 years or older accounted for approximately 15% of the total subjects)[4,5]. These four trials were also evaluated for CQ 10, which considered the significance of anthracycline anticancer drugs in postoperative treatment for hormone receptor-positive (luminal type) cancer in older patients.

Therapies provided for intervention groups in the RCTs varied. However, standard therapies for control groups in these trials were combination therapies of anthracycline anticancer drugs and cyclophosphamides, such as doxorubicin-cyclophosphamide (AC) combination therapy and epirubicin-cyclophosphamide (EC) combination therapy. Two of the RCTs solely examined older patients aged 65 years or older. In these studies, cyclophosphamide-methotrexate-fluorouracil (CMF) combination therapy, which does not include an anthracycline anticancer drug, was also adopted for a standard therapy. Furthermore, capecitabine was used in both of the RCTs. Capecitabine monotherapy was administered in the CALGB 49907 study[2], and the combination therapy of capecitabine and albumin-bound paclitaxel was administered in the ICE II-GBG52 study[3]. From among a total of 633 subjects in a subgroup analysis of the CALGB 49907 study, 206 (33%) were hormone receptor-negative. Of these, the relapse-free survival of subjects who received capecitabine monotherapy was inferior to that of the standard treatment group that received AC or CMF (hazard ratio [HR]: 4.39; 95% confidence interval [CI]: 2.9-6.7; $p < 0.001$). The overall survival of these hormone receptor-negative subjects who received capecitabine monotherapy was also inferior to that of the standard treatment group that received AC or CMF (HR: 3.76; 95% CI: 2.23-6.34; $p < 0.001$)[2]. As HER2 expression was not analyzed in the study, these hormone receptor-negative cases may include HER2-positive patients. In the ICE II-GBG52 study, an analysis of 391 subjects including 69 (18%) with triple-negative breast cancer compared a capecitabine-albumin-bound paclitaxel combination therapy group and a standard treatment group with standard treatment with EC or CMF therapy. Although no significant difference in survival period nor disease-free survival was observed between the two groups, an increase in treatment discontinuation and non-hematological toxicity was observed in the capecitabine-albumin-bound paclitaxel combination therapy group[3]. The subjects of the CALGB40101 study, which is a large-scale RCT, were not limited to older patients. Findings from this

study did not indicate the non-inferiority of paclitaxel monotherapy compared to the standard AC therapy in terms of relapse-free survival and overall survival. Similar results were observed in a subgroup analysis of hormone receptor-negative cancer[4]. No subgroup analysis of older patients or patients with triple-negative breast cancer was conducted. The proportion of subjects aged 50 years or older in all studies was 61%, and that of hormone receptor-positive subjects was 68%. HER2 expression was analyzed in approximately half the subjects and was not observed in 84% of them. Therefore, it should be noted that the proportion of patients with triple-negative breast cancer relative to the total subjects may be 30% or less. Meanwhile, 1,016 subjects were enrolled in the U.S. Oncology 9735 study, which is another RCT. The subjects of this study were also not limited to older patients[5]. The study compared AC and a treatment in which an anthracycline anticancer drug was not used (docetaxel-cyclophosphamide combination therapy) in terms of disease-free survival and overall survival. A 7-year follow up survey of the study indicated that both disease-free survival and overall survival were prolonged in the docetaxel-cyclophosphamide combination therapy group. This tendency was also observed in subgroup analyses of the following populations: older patients aged 65 years or older (160 subjects, 16%), hormone receptor-negative patients (294 subjects, 30%), and HER2-negative patients (124 subjects, 12%). Results from the above studies are not necessarily consistent. However, it can be assumed that older patients who have triple-negative breast cancer or hormone receptor-negative breast cancer may require adjuvant chemotherapy with an anthracycline anticancer drug. Thus, it is necessary to consider the possibility that omitting anthracycline anticancer drugs in postoperative chemotherapy for triple-negative breast cancer may shorten the survival period and the relapse-free survival period.

We identified two observational studies that summarize cardiac toxicity as an adverse event only among older patients[6,7]. One of the observational studies used the U.S. SEER-Medicare-linked database and examined factors related to congestive heart failure in approximately 40,000 patients aged 66-80 years[7]. Of all the examined patients, anthracycline anticancer drugs were postoperatively administered to 4,712 patients, chemotherapy with drugs other than anthracycline anticancer drugs was administered to 3,912 patients, and the remaining 34,705 did not receive chemotherapy. Results indicated that the risk of congestive heart failure was higher in patients aged 66-70 years to whom an anthracycline anticancer drug was administered (HR: 1.26; 95% CI: 1.12-1.42). Age

was a significant predicting factor in a multivariate analysis. From among patients who underwent chemotherapy with an anthracycline anticancer drug, 28% were hormone receptor-negative, and 30% of patients who underwent chemotherapy with drugs other than anthracycline anticancer drugs were hormone receptor-negative. Thus, it is assumed that approximately 30% of those who underwent chemotherapy had triple-negative breast cancer. The other observational study also used the U.S. SEER-Medicare-linked database. It examined cardiac toxicity in approximately 30,000 patients aged 65 years or older. Of these, anthracycline anticancer drugs were administered to approximately 2,300 patients. An increased risk of cardiac toxicity including congestive heart failure was observed in them. Eleven percent were hormone receptor-negative. A subgroup analysis found an increased risk of cardiac toxicity in such patients as well. No clear difference or tendency in terms of the incidence rate of cardiac toxicity was observed in the above four RCTs[2-5]. Being in an advanced age per se is a risk for reduced cardiac function. In contrast to young patients, an anthracycline anticancer drug can be administered to a limited number of older patients who have cardiac function that allows them to tolerate this drug. However, the above intervention studies and observational studies suggest that the impact of anthracycline anticancer drugs on cardiac function is not so severe that the administration of such drugs does not have to be avoided. That said, data in these studies are all from European and North American subjects. Given the fact that the baseline risk of heart disease of Japanese patients is lower than that of Europeans and Americans, the impact of anthracycline anticancer drugs can be greater in Japanese than in Europeans and Americans. Moreover, it should be noted that a large-scale observational study based on real-world data found that anthracycline anticancer drugs increased the risk of cardiac toxicity.

The numbers of treatment-related death from chemotherapy with an anthracycline anticancer drug were small in all four RCTs. An observational association study of the CALGB49907 study evaluated the maintenance of QOL[8] and found that QOL during treatment and at the time of treatment completion was significantly more favorable in patients to whom capecitabine was administered. However, the difference between the capecitabine group and the other group decreased by 12 months following the completion of treatment. It was considered that a decrease in QOL due to an anthracycline anticancer drug is reversible.

The above evaluations of the efficacy and adverse events of anthracycline anticancer

drugs suggest that omitting these drugs in postoperative chemotherapy for triple-negative breast cancer and hormone receptor-negative breast cancer in older patients may shorten the survival period and the relapse-free survival period. It is not clear if omitting these anthracycline anticancer drugs will reduce the incidence rate of cardiac toxicity or treatment-related death. Moreover, it was considered that a reduction in QOL due to an anthracycline anticancer drug is temporary. It was confirmed that a favorable benefit-harm balance can be maintained. Although multiple prospective clinical studies on older patients were identified, they were all subgroup analyses. Further, none of them examined triple-negative breast cancer. Thus, it was determined that the strength of evidence is "medium (B)."

We conducted a meta-analysis of the prospective CALGB49907 study[2] and the ICE II-GBG52 study[3]. The results suggested that omitting anthracycline anticancer drugs may shorten the survival period and the relapse-free survival period (Figure 1).

Voting results

Taking the above into account, fourteen panel members participated in voting. In the first round of voting, one voted for "strong recommendation for omitting anthracycline anticancer drugs," two for "mild recommendation for omitting anthracycline anticancer drugs," nine for "mild recommendation for not omitting anthracycline anticancer drugs," and two for "strong recommendation for not omitting anthracycline anticancer drugs." A recommendation could not be determined. Voting was again conducted following a post-voting meeting. In this round, one voted for "mild recommendation for omitting anthracycline anticancer drugs," ten voted for "mild recommendation for not omitting anthracycline anticancer drugs," and three voted for "strong recommendation for not omitting anthracycline anticancer drugs." It was determined that the recommendation would be "mild recommendation (proposal) for not omitting anthracycline anticancer drugs."

Future research questions

In examining this CQ and CQ 10, we could not find papers that examined postoperative chemotherapy by subtype in older patients. Thus, we investigated subgroup analyses and data that included different subtypes to examine evidence for older patients with triple-negative breast cancer. As there will be a larger number of treatment options for triple-

negative breast cancer going forward, clinical studies on older patients with a focus on this subtype are required.

References

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CQ 12

What kind of treatment is recommended for postoperative drug therapy for HER2-positive breast cancer in older patients?

Recommendation

Combination therapy with trastuzumab and chemotherapy is more recommended than chemotherapy on its own. [Strength of recommendation: 1 (rate of agreement: 92%); strength of evidence: B]

Background

1. Approach to postoperative treatment for HER2-positive breast cancer in older patients

The standard treatment for HER2-positive breast cancer is concomitant therapy of chemotherapy and trastuzumab, which is an anti-HER2 monoclonal antibody. Endocrine therapy is additionally administered in hormone receptor-positive cases. Meanwhile, postoperative chemotherapy per se is not necessarily recognized as a standard therapy for older patients. Furthermore, sufficient data on tolerability for chemotherapy and trastuzumab in older patients are not available. Therefore, the following options are adopted in actual clinical settings: combination therapy with trastuzumab and chemotherapy, chemotherapy on its own, or trastuzumab monotherapy. The following options are further considered for hormone receptor-positive cases: endocrine therapy or observation of the course of disease. These options are considered on an individual basis. Anthracycline anticancer drugs are key drugs in chemotherapy for breast cancer. Anthracycline-induced cardiac toxicity is irreversible, and age is one of the risk factors of cardiac toxicity. Additionally, trastuzumab monotherapy without chemotherapy has not been proven to be efficacious. Therefore, treatment guidelines recommend not avoiding chemotherapy without due consideration. Further, studies have found trastuzumab-induced reversible cardiac toxicity. Therefore, how postoperative treatment for older patients with HER2-positive breast cancer should be administered is an important issue in the clinic.

Given the above, the key clinical issue was identified: “What kind of drug therapy is appropriate for breast cancer in older patients?” To address this issue, the following clinical question (CQ) was set: “What kind of postoperative drug therapy is recommended for older patients with HER2-positive breast cancer?”

Literature review and clinical interpretation

A standard treatment for HER2-positive breast cancer is the concomitant therapy of chemotherapy and trastuzumab, which is an anti-HER2 monoclonal antibody. Endocrine therapy is additionally administered in hormone receptor-positive cases. Meanwhile, chemotherapy per se is not recognized as a standard treatment for older patients. Furthermore, sufficient data on tolerability for chemotherapy and trastuzumab are not available. Therefore, the following options are adopted for older patients who have undergone surgery for HER2-positive breast cancer in actual clinical settings: combination therapy with trastuzumab and chemotherapy, chemotherapy alone, or trastuzumab monotherapy. The following options are further considered for hormone receptor-positive cases: endocrine therapy or observation of the course of disease. These options are considered on an individual basis. Further, trastuzumab monotherapy without chemotherapy has not been proven to be efficacious. Trastuzumab-induced cardiac toxicity is a concerning adverse event, although it is reversible. Given the above, we examined what kind of postoperative drug therapy can be recommended for older patients with HER2-positive breast cancer. The issue at hand for the present CQ was the overall HER2-positive cases because, first, tolerability is not an issue in endocrine therapy for older patients and, second, a concomitant therapy with chemotherapy and trastuzumab can be considered for HER2-positive cases irrespective of whether the patient is hormone receptor-positive or hormone receptor-negative.

The following aspects were adopted as key outcomes for the present CQ: prolongation of survival, prolongation of relapse-free survival, maintenance of QOL, incidence of treatment-related death, and incidence of cardiac toxicity. The prolongation of survival, prolongation of relapse-free survival, and maintenance of QOL were considered as benefits, and the incidence of treatment-related death and incidence of cardiac toxicity were considered as harms. It is true that hospitalization due to adverse events, the incidence of grade 3 or more adverse events, and the completion of scheduled treatment are important. However, it was determined that they are not serious.

The initial screening was conducted through a systematic literature search, which extracted 18 papers. Following the detailed examination of the extracted papers, a second screening was conducted. One paper of an integrated analysis, four randomized comparative trials (RCTs), and one single-arm study were adopted. Two papers on large-scale RCTs were referenced in the integrated analysis and were added through hand-

searching. No RCTs or observational studies on older patients with HER2-positive breast cancer were found. We conducted a qualitative systematic review of the seven papers. During our literature search, we found no evidence of trastuzumab monotherapy as a postoperative treatment. Therefore, we examined the significance of adding trastuzumab to chemotherapy in postoperative chemotherapy for older patients.

The following four RCTs were adopted: the HERA study[1], the BCIRG006 study[2], the NSABP B-31 study[3], and the N9831 study[3]. Adults of any age including older subjects were enrolled in these studies. Doxorubicin-cyclophosphamide (AC) combination therapy or the sequential administration of a taxane anticancer drug (docetaxel or paclitaxel) was administered in the control groups of these studies. Results from the RCTs suggest that adding trastuzumab prolongs overall survival and disease-free survival. Furthermore, in a single-arm clinical study, trastuzumab was added to paclitaxel monotherapy for 406 cases of lymph node metastasis-negative, HER2-positive breast cancer with a tumor size of up to 3 cm. The study reported favorable outcomes, indicating that 3-year disease-free survival was 98.7% (95% confidence interval [CI]: 97.6-99.8)[4]. From 406 cases in the study, 41 were aged 70 years or older (10.1%) and 96 were aged 60-69 years (23.6%).

Non-older subjects were also enrolled in the clinical studies. The proportion of subjects aged 60 years or older was approximately 16% in the HERA, NSABP B-31, and N9831 studies[1,3]. In the BCIRG006 study, 52% were younger than 50 years of age[2]. The proportions of older subjects were low in these studies. Moreover, they were not consistent across the studies. However, a subgroup analysis of the NSABP B-31 and N9831 studies, which included subjects aged 60 years or older, found that compared with chemotherapy on its own, adding trastuzumab to chemotherapy improved overall survival (hazard ratio [HR]: 0.51; 95% CI: 0.37-0.69) and disease-free survival (HR: 0.63; 95% CI: 0.49-0.82)[3]. A subgroup analysis of the HERA study on subjects aged 60 years or older indicated a tendency of a more favorable disease-free survival in the trastuzumab combination therapy group than in the control group (HR: 0.70; 95% CI: 0.40-1.23)[5]. The above findings suggest that combination therapy with trastuzumab and chemotherapy is also effective in older patients. Compared with chemotherapy alone, the benefits of trastuzumab therapy are largely consistent across studies in terms of the prolongation of survival and relapse-free survival. Thus, we determined that the strength of evidence is "medium (B)."

In examining the incidence of treatment-related death, we analyzed the rate of cardiac death as well as the rate of treatment-related death. From 1,677 subjects to whom trastuzumab was administered in the HERA study, lethal adverse events were observed in six (0.4%). From 1,719 subjects in the control group of the study, lethal adverse events were observed in three (0.2%). However, no significant difference was observed between the two groups ($p = 0.34$). The causal relationship between adverse events and the therapeutic agent is not clear[5]. Furthermore, one case of cardiac death was observed in the control group.

In the BCIRG006 study, treatment-related death due to secondary leukemia, which was assumed to be associated with doxorubicin, was observed, whereas no cases of cardiac death were observed[2]. The ages of the patients in these cases are unknown. In the NSABP B-31 and N9831 studies, three cases of treatment-related death were observed in the trastuzumab combination therapy group. Of these, two were due to interstitial pneumonia that was suspected to be associated with trastuzumab and one was cardiomyopathy[6]. The ages of the patients in these cases are unknown. Meanwhile, in the HERA and BCIRG006 studies[2] and the N9831[7] study, the incidence rate of cardiac toxicity was higher in the trastuzumab combination therapy groups than in the control groups. In the HERA study, from among 1,595 subjects in the trastuzumab combination therapy group, heart failure with symptoms was observed in 29 (1.73%), and from among 1,540 subjects in the control group, heart failure with symptoms was observed in one (0.06%) ($p < 0.001$). In the same study, a reduced left ventricular ejection fraction (LVEF) (reduced by 10% or greater compared to pre-treatment or reduced to 50% or lower) was observed in 113 subjects (7.1%) in the trastuzumab combination therapy group and 34 (2.2%) in the control group[5]. An analysis by age group was not conducted. In the BCIRG 006 study, the incidence rate of NYHA III or IV heart failure increased from 0.7% (seven subjects out of 1,073) to 2.0% (21 subjects out of 1,074) after trastuzumab was added to AC and the sequential administration of docetaxel. In the same study, the incidence rate of reduced LVEF increased from 11.2% (114 subjects) to 18.6% (194 subjects) after trastuzumab was added to AC and the sequential administration of docetaxel. An analysis by age group was not conducted. However, it should be noted that although the efficacy of docetaxel-carboplatin-trastuzumab therapy (TCH) was equivalent to that of AC-docetaxel-trastuzumab therapy, the incidence rate of congestive heart failure was low at 0.4% (four subjects) in the TCH group. TCH may be an effective option when trastuzumab is

administered to a patient with a baseline risk, such as an older patient. Furthermore, because trastuzumab has cardiac toxicity, great care is required when the drug is administered to a patient with cardiac dysfunction. In the NSABP B-31 and N9831 studies, NYHA III and IV heart failure was observed in 4.1% and 2.9% of subjects, respectively, over the course of 3 years[6]. From among 31 subjects who developed heart failure in the NSABP B-31 study, the progress of 27 was observed over the course of 6 months or longer. It has been reported that of these 27 subjects, heart failure symptoms persisted in one. Age is a risk factor of heart failure. The risk of heart failure has been found to be approximately 2.7 times higher in patients aged 60 years or older than in those aged younger than 50 years[8]. A similar analysis was reported from the N9831 study. The risk of heart-related events was approximately 3.2 times higher in patients aged 60 years or older than in those aged younger than 50 years[7]. Finally, QOL maintenance was analyzed as a secondary endpoint in the BCIRG 006 study[9]. In this analysis, changes in QOL scores were not affected by whether or not trastuzumab was included in combination therapy. Scores related to adverse events and physical function temporarily decreased following the commencement of treatment in all groups, but they recovered within 1 year thereafter. However, an analysis by age group was not conducted.

The above studies suggest that concomitant therapy with chemotherapy and trastuzumab in older patients with HER2-positive breast cancer can prolong overall survival and relapse-free survival. This provides significant benefits. Meanwhile, the incidence rate of trastuzumab-induced, treatment-related death is low. Although heart failure and reduced cardiac function that are induced by trastuzumab have been observed, symptoms are reversible in most cases. As QOL can be maintained, it is considered that the disadvantage of trastuzumab is not significant. Thus, it was confirmed that a favorable benefit-harm balance can be maintained when trastuzumab is added to an existing treatment. Furthermore, it was assumed that the cardiac toxicity of trastuzumab can be tolerated by the patient and their family because heart failure and reduced LVEF due to the drug are reversible.

Voting results

One of the panel members withdrew from voting on the grounds of an academic conflict of interest. The remaining thirteen panel members participated in voting taking the above into account. Twelve panel members voted for “strong recommendation for administering

combination therapy with trastuzumab and chemotherapy," and one voted for "mild recommendation for administering the combination therapy." It was determined that the level of recommendation would be "strong recommendation (proposal) for administering combination therapy with trastuzumab and chemotherapy."

Future research questions

Adding trastuzumab to chemotherapy in postoperative adjuvant therapy for HER2-positive breast cancer has been proven to be efficacious. However, further studies are required on the effects of trastuzumab monotherapy without chemotherapy in patients at all ages. A randomized comparative study on Japanese patients aged 70 years or older who have HER2-positive breast cancer has suggested that trastuzumab monotherapy may be a possible treatment option if the patient cannot tolerate chemotherapy, from a perspective of balance between efficacy, safety, and QOL[10], although the study was not in the scope of the literature search for the present guidelines.

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