Chemotherapy and Hormone Therapy for Breast Cancer: Current Status and Perspective


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Abstract: Chemotherapy or hormone therapy should be properly employed depending on the stage of breast cancer. The aim of therapy differs according to the stage of the disease; for example, palliation of symptoms or prolongation of life in metastatic diseases, enhancing the curative rate in adjuvant therapy, or increasing the rate of breast conservation during neoadjuvant treatments. Compared to classical CMF (cyclophosphamide, methotrexate and fluorouracil), chemotherapy, regimens containing anthracyclines, such as doxorubicin or epirubicin, are standard for metastatic, adjuvant and neoadjuvant cases. Recently, the benefits of taxans (docetaxel and paclitaxel) have been established for metastatic breast cancer. In hormone-receptor positive patients, tamoxifen is absolutely standard for metastatic or adjuvant cases. Luteinizing hormone-releasing hormone agonists or aromatase inhibitors are also useful. Other promising agents include trastuzumab for HER2/neu-positive patients and bisphosphonate for patients with bone metastasis. The benefits of systemic therapy, however, are limited and relative compared to the risk of toxicity. The benefits of chemotherapy, in particular, are occasionally nearly equal to the risk. Therefore, correct information on the benefits and risks of treatment must be given to patients to enable them to make a fully informed decision as to which therapy they wish to pursue.

Key words: Breast cancer; Chemotherapy; Hormone therapy; Adverse reactions

Introduction

Breast cancer often involves the regional lymph nodes and is frequently associated with small distant metastases from a relatively early stage. When the cancer is confined to the site of origin, local treatment by surgery alone or surgery combined with radiotherapy may lead
to complete cure; at this early stage, breast cancer can be regarded as a local disease. However, as mentioned above, micrometastasis occurs relatively early in the course, followed by overt metastasis. When micrometastasis occurs, the disease is no longer curable by surgery alone, and recurrence is often noted. Anticancer drugs and hormones exert systemic effects, and act on cancer cells throughout the body, including those in micrometastatic foci. However, drug therapy alone is not sufficient to effect a complete cure of the disease — this is one of its important limitations. It is therefore desirable to supplement local treatment with drug therapy for systemic treatment of breast cancer, employing proper timing and methodology.

**Expected Benefits and Risks of Treatment**

The goal of drug therapy varies according to the stage of breast cancer. One of the following three situations generally exists.

1. Distant metastasis is present, so that definitive cure is not likely after drug therapy; only alleviation of symptoms and some prolongation of life may be expected.
2. No distant metastasis, and surgery is feasible; postoperative adjuvant chemotherapy may increase the cure rate.
3. The primary tumor mass is large, but there is no distant metastasis. In this case, preoperative chemotherapy may allow breast-conserving surgery.

Thus, the goal of drug therapy varies according to the stage of the disease, and it is very important to clearly recognize the goal. The final decision regarding the choice of treatment and continuation of treatment must be made by weighing the benefits and risks (adverse reactions) of the treatment. For example, many patients are ready to receive treatment that has been shown to yield a higher cure rate, but may cause hair loss and nausea. On the other hand, some patients may find it difficult to tolerate the severe adverse effects of anticancer drug therapy for prolonged periods if it becomes apparent that complete cure is not likely. The physician-in-charge should be fully aware of the expected benefits and risks of the treatment and explain these in clear terms to the patient. This may not be difficult if the expected benefits of treatment outweigh the risks. However, when this is not the case, since there is little difference between benefit and risk regarding anticancer drug therapy, the judgment should depend on the decision of the individual. Each patient reserves the right to decide whether or not to receive the treatment, and to choose any of the therapeutic options available; the final decision should therefore be left to the judgment of the patient. To facilitate such judgment on the part of the patients, medical care providers should provide accurate information as clearly as possible to the patients.

**Outline of Drug Therapy**

In general, hormone therapy exerts its effects gradually, and elicits only mild adverse reactions. During hormone therapy, improvement may be preceded by a temporary aggravation, the so-called flare phenomenon. On the other hand, chemotherapy exerts its effects more promptly, and often elicits severe adverse reactions. Currently, the therapeutic usefulness of both hormone therapy and anticancer drug therapy remains established. Combined chemotherapy and hormone therapy has been attempted, but its superiority has not yet been clearly demonstrated. In general, either chemotherapy or hormone therapy is administered first, and the other alternative is used thereafter, if required.

When the patient is estrogen-receptor-positive (ER-positive) and/or progesterone-receptor-positive (PgR-positive), hormone therapy is expected to be effective. When a patient with metastatic breast cancer is classified as hormone-sensitive based on the receptor expression, hormone therapy, as a rule, should be administered first, to be replaced by chemotherapy if resis-
For postoperative adjuvant therapy, chemotherapy should be given first for a period of 3–6 months, and hormone therapy thereafter. In the case of therapy with tamoxifen, a representative hormonal drug, it has been recommended that the drug be continued for 5 years. For preoperative chemotherapy, anticancer drugs that are expected to have prompt effects are often used, aimed at tumor mass reduction. Such chemotherapy is usually indicated in patients with localized advanced cancer, as in stage IIIA or IIIB. In recent years, however, it has also been given for earlier stages of breast cancer. Usually, 4–6 courses are used for preoperative chemotherapy. When indicated for patients in high risk, postoperative chemotherapy may also be administered, followed by hormone therapy.

Since patient survival has been reported to be similar, regardless of whether chemotherapy is administered preoperatively or postoperatively, the aim of preoperative chemotherapy is to facilitate breast conservation. In general, if preoperative chemotherapy reduces the tumor diameter to less than 3 cm, the lesion becomes amenable to breast-conserving surgery. Another advantage of preoperative chemotherapy is that it becomes evident sooner than later whether or not the tumor is responsive to anticancer chemotherapy. With this information, the subsequent course of anticancer chemotherapy can be altered as necessary. Table 1 shows representative anticancer chemotherapies for breast cancer.

Table 1 Representative Chemotherapeutic Regimens for Breast Cancer
Product names are shown in parentheses.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Chemotherapeutic Regimen</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical CMF</td>
<td>Cyclophosphamide (Endoxan®)</td>
<td>100mg/body, p.o., d1–15</td>
<td>every 4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate (Methotrexate®)</td>
<td>40mg/m², i.v., d1, d8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil (5-FU®)</td>
<td>500mg/m², i.v., d1, d8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous CMF</td>
<td>Cyclophosphamide (Endoxan®)</td>
<td>600mg/m², i.v., d1</td>
<td>every 3 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate (Methotrexate®)</td>
<td>40mg/m², i.v., d1</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5-Fluorouracil (5-FU®)</td>
<td>600mg/m², i.v., d1</td>
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<tr>
<td>Modified intravenous CMF</td>
<td>Cyclophosphamide (Endoxan®)</td>
<td>500mg/m², i.v., d1, d15</td>
<td>every 4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate (Methotrexate®)</td>
<td>40mg/m², i.v., d1, d15</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil (5-FU®)</td>
<td>500mg/m², i.v., d1, d15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAF (FAC)</td>
<td>Cyclophosphamide (Endoxan®)</td>
<td>500mg/m², i.v., d1</td>
<td>every 3 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adriamycin (Adriacin®)</td>
<td>50mg/m², i.v., d1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil (5-FU®)</td>
<td>500mg/m², i.v., d1, d8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAF</td>
<td>Cyclophosphamide (Endoxan®)</td>
<td>100mg/m², p.o., d1–15</td>
<td>every 4 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adriamycin (Adriacin®)</td>
<td>30mg/m², i.v., d1, d8</td>
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<tr>
<td></td>
<td>5-Fluorouracil (5-FU®)</td>
<td>500mg/m², i.v., d1, d8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel (Taxotere®)</td>
<td>60–70mg/m², i.v., 1h</td>
<td>every 3 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (Taxol®)</td>
<td>175–210mg/m², i.v., infusion over 3h</td>
<td>every 3 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* a) The total dose of adriamycin should be limited to 450mg/m², because of the cumulative cardiotoxicity of the drug.
* b) To prevent allergy and edema, dexamethasone (Decadron) 8 mg/day (in two divided doses) should be administered orally for 3 days, starting before chemotherapy.
* c) To prevent allergy, intravenous dexamethasone (Decadron), 20mg, should be administered twice, i.e., 12–14h, and 6–7h before the start of therapy, and oral diphenhydramine (Restamin), 50mg, and intravenous ranitidine (Zantac), 50mg, should be administered 30min. before the start of therapy.
Hormone Therapy for Metastatic Breast Cancer

Many breast cancers show estrogen-dependent proliferation. Administration of antiestrogens can, therefore, be expected to cause tumor mass reduction. The most well established drug for hormone therapy is tamoxifen (Nolvadex®). This is a first-line drug for the treatment of breast cancer in postmenopausal patients. If the patient is ER- and/or PgR-positive, hormone therapy is indicated. Tamoxifen is administered orally at the dose of 20 mg/body every morning. In both ER- and PgR-positive cases, the response rate to tamoxifen therapy is 50–70%. The time to progression is about 6 months, and the duration of response is 12–18 months. Tamoxifen does not elicit such severe adverse reactions as anticancer chemotherapeutic drugs. Cautious watchfulness is necessary for rare adverse reactions, including endometrial cancer, cerebrovascular disease, pulmonary embolism, venous thrombosis, and cataract. These disorders occur in about 5–6 of 1,000 patients. Periodic gynecological examination is recommended for early detection of endometrial cancer. Toremifene (Fareston®), whose actions on the endometrium are weaker than those of tamoxifen, is known to be as effective as tamoxifen, but whether or not it’s administration is actually associated with reduced incidence of endometrial cancer has not yet been clearly established. When the patient has a history of embolism or thrombosis, other hormone therapy (aromatase inhibitors, as described below) would be desirable.

Second-line hormone therapy consists of treatment with the recently developed aromatase inhibitors. Aromatase is an estrogen-converting enzyme present in fat, liver and muscle tissue. Aromatase inhibitors suppress the production of estrogen in these peripheral tissues. In Japan, fadrozole (Afema®), an aromatase inhibitor, is commercially available. Afema is administered orally at the dose of 2 mg/body every morning. Adverse reactions such as nausea, vomiting, and hot flushes may occur, but these are mild. This class of drugs has been established for second-line therapy in postmenopausal patients with metastatic breast cancer. The therapy has been reported to be effective in 20–30% of patients who do not show the expected response to tamoxifen. Another drug of this class, anastrozole (Arimidex®), has become commercially available in Japan since February 2001.

Progestosterone therapy is considered as third-line therapy. The mechanisms of actions of progestosterone preparations have not been fully elucidated. In Japan, medroxyprogesterone acetate (Hyson H®, Provera®, a representative drug of this class, is used. This agent is administered orally at the dose of 600–1,200 mg/body daily. Weight gain may occur in 20–50% of patients, and obesity may interfere with the continuation of this drug. The drug may also be used as an appetite stimulant in patients with advanced disease who are cachectic. This therapy has been designated as third-line, because of the more severe adverse effects associated with its administration in comparison with those associated with tamoxifen or fadrozole therapy.

The estrogen balance in the body changes dramatically after menopause. Specifically, before menopause, the ovaries function actively to secrete abundant amounts of estrogen. After menopause, the ovarian activity decreases, with resultant fall in the estrogen levels. In premenopausal patients with breast cancer, secretion of estrogen from the ovaries must be inhibited. Ovariectomy has long been known to be effective in the treatment of breast cancer. At present, it is possible to competitively block follicle-stimulating hormone released from the pituitary, and thereby to inhibit the production of estrogen by the ovaries. Goserelin (Zoladex®) or leuprolide (Leuplin®), which are luteinizing hormone-releasing hormone analogues (LH-RH analogues), represent established drugs for the treatment of breast cancer in premenopausal women. Zoladex®, 3.6 mg, or Leuplin®,
3.75 mg, is injected subcutaneously once every 4 weeks. There are scarcely any adverse reactions, besides hot flushes. In premenopausal patients, therefore, direct antitumor effect by lowering the estrogen levels is aimed at by using combined LH-RH-analogue and tamoxifen therapy. Recently, the usefulness of this therapeutic strategy has been demonstrated, and it is now being established as the first-line hormone therapy for premenopausal patients.

Chemotherapy (Anticancer Drug Therapy) for Metastatic Breast Cancer

Following the development of alkylating agents and antimetabolites, the usefulness of therapy with CMF, a combination chemotherapeutic regimen, was first established. This drug combination consists of cyclophosphamide (Endoxan®), methotrexate (Methotrexate®), and 5-fluorouracil (5-FU®). The response rate, in terms of complete response or partial response, was 40–50%. Subsequently, anthracyclines were developed. Representative anthracyclines include adriamycin (Adriacin®) and epirubicin (Farmorubicin®). CAF, a drug combination containing adriamycin, and FEC, a drug combination containing epirubicin, are now standard chemotherapeutic drug regimens. The response rate to these regimens is 50–60%, which is significantly higher than that to CMF therapy. The duration of response is 6–12 months, and the mean length of survival following either CAF or FEC therapy is 2 years. The 5-year survival rate may be 10–20%, but the 10-year survival rate is only around 3–4%. Therefore, complete cure is difficult in most cases.

In a breakthrough study, high-dose chemotherapy in combination with hematopoietic stem cell transplantation was attempted. Standard-dose chemotherapy is associated with a complete response rate of only 10–20%, whereas high-dose chemotherapy yields a corresponding percentage on the order of 40%. However, the disease often recurs, and complete cure is rarely achieved. Until now, distinct superiority of this treatment over the conventional chemotherapeutic regimens has not been clearly established; high-dose chemotherapy still remains in the investigational stage, requiring further designing and study. Cancer Institute Hospital is currently conducting studies of high-dose chemotherapy combined with gene therapy.

In recent years, the efficacy of the tubulin inhibitors, taxanes, has been established. Taxanes include paclitaxel (Taxol®) and docetaxel (Taxotere®). Docetaxel is given at the dose of 60–70 mg/m² once every three weeks; the response rate is about 30–50%. Paclitaxel is given by intravenous infusion over 3 h at the dose of 175–210 mg/m²; the response rate is on the order of 30%. The greatest advantage of taxanes is that they are effective in anthracycline-resistant cases. To reduce the incidence and severity of neutropenia and to provide a higher dose density, weekly administration has been tried. The dose is 30–35 mg/m² for docetaxel, and 80 mg/m² (drip infusion over 1 h) for paclitaxel. Although taxanes are effective as monotherapy, combination regimens with anthracycline are now being extensively studied. A large-scale randomized trial to compare with adriamycin + Taxotere® (AT) and adriamycin + cyclophosphamide (AC) revealed that the former was superior to the latter in terms of the response rate and time to progression. AT was also superior to CAF in terms of the response rate and time to progression. Combinations of anthracyclines and taxanes may become one of the standard chemotherapeutic regimens for cancer of the breast in the future.

What is the appropriate duration of chemotherapy? Should chemotherapy be continued for prolonged periods? Therapeutic results were compared between patients in whom the treatment was continued and those in whom the treatment was not continued after obtaining a complete response, partial response or no response to the initial therapy. The results revealed that the time to progression was longer in patients in whom the therapy was...
continued, however, there was no overall difference in the length of survival between the two groups. Thus, while prolongation of chemotherapy may not necessarily result in complete cure, it is able to delay disease progression. Therefore, decisions in the clinical setting may be made as follows. If there are scarcely any adverse reactions and the patient can visit the hospital periodically without much difficulty or suffering, prolonged chemotherapy may be considered. If, on the other hand, there are severe adverse reactions, therapy may be discontinued temporarily, and then resumed when the disease shows progression. A possible strategy is to administer chemotherapy at longer intervals. Any decision should be arrived at only after discussing in detail the advantages and disadvantages of the available treatment options with the patient.

Adverse Reactions of Anticancer Drugs and the Choice of Regimen

The major adverse reactions of anticancer drugs are nausea/vomiting and hair loss. Although adriamycin (or epirubicin) and taxanes are extremely useful drugs, therapy with which is associated with the highest response rates, both cause severe hair loss. There is no effective prophylaxis available against this side effect. In general, hair loss begins about 2 weeks after the start of medication, and becomes substantial by 3–4 weeks. Short hair reappears about 3 months after withdrawal of the medication, and hair growth to the pretherapeutic level occurs after about 6 months after the drug withdrawal. Hair loss, once it sets in, continues throughout the duration of the chemotherapy, necessitating the use of a wig. On the other hand, although there are variations in severity among individuals, nausea/vomiting usually last only for about 2–5 days after an intravenous dose, and the patient’s condition usually improves thereafter. CMF therapy or oral fluorouracil derivatives are usually associated with very slight hair loss and mild nausea. The CAF and FEC regimens may cause severe hair loss and severe nausea/vomiting. With taxanes, while the hair loss may be severe, nausea/vomiting is usually mild. In cases of metastatic breast cancer, chemotherapy does not greatly influence the survival, although the response rates to different regimens may vary. Therefore, in patients who do not want to risk hair loss, chemotherapy beginning with the CMF or oral fluorouracil regimen may be considered. However, if hair loss is acceptable to the patient, CAF, FEC or taxanes should be administered as first-line therapy. In such cases, who are susceptible to nausea/vomiting, taxane therapy should be preferred over the other two regimens as first-line therapy.

Administration of CAF, FEC and taxane regimens is often associated with leukopenia. Taxane + adriamycin therapy is especially likely to cause leukopenia. Treatment-related death due to sepsis should be avoided in these cases. If a patient with a neutrophil count of less than 1,000/mm$^3$ develops fever, intravenous infusion of a broad-spectrum antibiotic should be initiated promptly, along with administration of granulocyte colony-stimulating factor (Neutrogin®, Gran®, Neu-up®). Patients should be instructed to take an oral antibiotic promptly if they develop a fever of 38°C at home. Adriamycin also exerts cardiotoxicity, and its total dose should be limited to 450 mg/m$^2$. To prevent docetaxel-induced allergy and edema, oral dexamethasone (Decadron®), 8 mg/day (in two equally divided doses), should be administered for 3 days beginning from the day before the initiation of docetaxel therapy. To prevent allergic reaction to paclitaxel, dexamethasone (Decadron®), 20 mg, should be administered intravenously twice, i.e., 12–14 h, and 6–7 h, before the start of paclitaxel therapy, and oral diphenhydramine (Restamin®), 50 mg, and intravenous ranitidine (Zantac®), 50 mg, should be administered 30 min before the start of therapy.

Postoperative Adjuvant Therapy

For hormone therapy and chemotherapy as
postoperative adjuvant therapy in breast cancer, the recommendations made by the Consensus Panel at St. Gallen in 2001 have generally been accepted (Tables 2 and 3). In addition, the consensus statement by the US National Institute of Health (NIH) has been available on the Internet since November 2000 (http://odp.od.nih.gov/consensus/cons/114/114_intro.htm).

The most important prognostic factor in patients with breast cancer is the lymph node status. Chemotherapy is basically indicated for patients with positive axillary lymph node metastasis, and hormone therapy should be added if such patients are ER- and/or PgR-positive. Even if no axillary lymph node metastasis is detected, aggressive chemotherapy should be considered if the risk of metastasis is deemed to be high. In patients with positive lymph nodes, surgery followed by chemotherapy reportedly yields a 15.4% improvement in 10-year disease-free survival rate in patients younger than 50 years old, and a 5.4% improvement in absolute survival rate in patients between 50 and 69 years of age. In cases where lymph node metastasis is not detected, chemotherapy should be considered in an average/high risk group. Chemotherapy is not indicated in the minimal/low-risk group.

Table 2 Adjuvant Systemic Treatment for Patients with Operable Breast Cancer
(Cited from the Consensus Panel of St. Gallen, 2001)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Treatment According to Responsiveness to Endocrine Therapies*1</th>
<th>Endocrine-Responsive</th>
<th>Endocrine-Nonresponsive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk Group</td>
<td>Premenopausal</td>
<td>Postmenopausal</td>
</tr>
<tr>
<td>Node-negative,</td>
<td>Tamoxifen or none</td>
<td>Tamoxifen or none</td>
<td>Not applicable</td>
</tr>
<tr>
<td>minimal/low risk</td>
<td>Ovarian ablation (or LH-RH analogue) + tamoxifen ± chemotherapy<em>2, or chemotherapy + tamoxifen</em>2, or Ovarian ablation (or GnRH analog)</td>
<td>Tamoxifen, or</td>
<td>Chemotherapy*3</td>
</tr>
<tr>
<td>Node-negative,</td>
<td>Chemotherapy + tamoxifen*2 [± ovarian ablation (or GnRH analog)] or tamoxifen, or Ovarian ablation (or GnRH analog)</td>
<td>Chemotherapy + tamoxifen,*2</td>
<td>Chemotherapy*3</td>
</tr>
<tr>
<td>average/high risk</td>
<td>Node-positive</td>
<td>Chemotherapy</td>
<td>Chemotherapy*3</td>
</tr>
<tr>
<td></td>
<td>Ovarian ablation (or GnRH analog) + tamoxifen [± chemotherapy*2]</td>
<td>Chemotherapy</td>
<td>Chemotherapy*3</td>
</tr>
</tbody>
</table>

NOTE. Brackets [ ] indicate questions pending answers from ongoing clinical trials. Regarding GnRH, research was conducted using goserelin.

*1 See footnote in Table 3 regarding responsiveness to endocrine therapies.

*2 The addition of chemotherapy is considered an acceptable option based on evidence from clinical trials. Considerations about a low relative risk, age, toxic effects, socioeconomic implications, and information on the patient’s preference might justify the use of tamoxifen alone. For patients with endocrine-responsive disease, whether tamoxifen should be started concurrently with chemotherapy of delayed until the completion of chemotherapy must await the result of ongoing trials.

*3 For patients with endocrine-nonresponsive disease, questions of timing, duration, agent, dose, and schedules of chemotherapy are subjects for research studies.

Chemotherapy As Postoperative Adjuvant Therapy*7

An Italian group reported the long-term (20 years) results of CMF therapy. CMF is considered to be one of the standard chemotherapeutic regimens, because it yields definite improvement in the disease-free survival rate as compared with the results in untreated patients. A meta-analysis revealed that a regimen containing an anthracycline was better than CMF. How-
Hormone Therapy As Postoperative Adjuvant Therapy

The usefulness of tamoxifen for postoperative adjuvant therapy has been widely recognized. A meta-analysis showed that its benefits were apparent across all age groups, and an approximately 50% decrease (odds ratio) in the risk of recurrence and 25% decrease (odds ratio) in the death rate, on the average, were reported. Tamoxifen therapy should be continued for at least 5 years. The risks and benefits of more prolonged therapy are now under investigation. Tamoxifen has been reported to be beneficial in patients who are ER- and/or PgR-positive; the higher the ER expression level, the greater the benefit. Conversely, the treat-

Table 3 New Definition of Risk Categories for Patients with Node-Negative Breast Cancer
(Cited from the Consensus Panel of St. Gallen, 2001)

| Risk Category         | Endocrine-Responsive* | Endocrine-Nonresponsive*
|-----------------------|-----------------------|------------------------
| Minimal/low risk*2     | ER- and/or PgR-positive, and all of the following features: | Not applicable         |
|                       | pT* ≤2 cm, and        |                        |
|                       | Grade 1*, and         |                        |
|                       | Age* ≥35 years        |                        |
| Average/high risk     | ER- and/or PgR-positive, and at least one of the following features: | ER- and PgR-negative   |
|                       | pT* >2 cm, and        |                        |
|                       | Grade 2–3*, and       |                        |
|                       | Age* <35 years        |                        |

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.

*1 Responsiveness to endocrine therapies is related to expression of ER and PgR in the tumor cells. The exact threshold of ER and/or PgR staining (with currently available immunohistochemical methods), which should be used to distinguish between endocrine-responsive and endocrine-nonresponsive tumor, is unknown. Even a low number of cells stained positive (as low as 1% of tumor cells) identify a cohort of tumors having some responsiveness to endocrine therapies. Probably, as it typical for biologic systems, a precise threshold does not exist. However empirically chosen, approximately 10% positive staining of cells for either receptor might be considered as a reasonable threshold, accepted by most. Furthermore, it is clear that the lack of staining for both receptors confers endocrine nonresponsiveness status.

*2 Some Panel members recognize lymphatic and/or vascular invasion as a factor indicating greater risk than minimal or low. On the other hand, mucinous histologic type is associated with low risk of relapse.

*3 Pathologic tumor size (i.e., size of the invasive component).

*4 Histologic and/or nuclear grade.

*5 Patients with breast cancer at young age have been shown to be at high risk of relapse.

However, the absolute differences between the two were small, with an overall improvement of 3.2% in the 5-year recurrence-free survival rate and 2.7% in the 5-year overall survival rate.

Recently, it has been shown that 4 courses of adriamycin + cyclophosphamide therapy followed by 4 courses of paclitaxel therapy given as postoperative adjuvant therapy, prolong the recurrence-free survival and overall survival rates in patients with lymph node metastasis. The absolute benefit was slight, with a 4% improvement in the recurrence-free survival rate and 2% improvement in the overall survival rate. However, this study was a large-scale study covering more than 3,000 patients, and the differences were evidently statistically significant. In USA, the use of paclitaxel for postoperative adjuvant therapy was approved in October 1999. It is expected that postoperative adjuvant therapy consisting of an anthracycline and a taxane will become established as a standard regimen in the near future.
ment is of no benefit in patients who are both ER- and PgR-negative. Moreover, there tend to be adverse effects, so that tamoxifen should not be used in patients who are both ER- and PgR-negative.

Since estrogen secretion from the ovary is decreased in premenopausal patients, ovariectomy or LH-RH analogue therapy is considered as the basic policy. LH-RH analogue therapy combined with tamoxifen therapy have recently been shown to be equal to or superior in efficacy to CMF therapy. LH-RH analogue + tamoxifen therapy has also become a standard regimen for postoperative adjuvant therapy in premenopausal patients.

**Future Drug Therapy**

Trastuzumab (Herceptin®), a monoclonal antibody directed against HER2, and bisphosphonates, useful drugs for bone metastasis, are recently established treatments. Trastuzumab is effective in patients with metastatic breast cancer who are positive for HER2. A randomized trial has demonstrated that combined paclitaxel and trastuzumab therapy is superior to paclitaxel monotherapy, in terms of the response rate and length of survival. Comparative studies have begun to investigate the usefulness of trastuzumab in postoperative adjuvant therapy, as the drug appears to show promise. Like the relationship between ER expression and the beneficial effects of tamoxifen therapy, determination of HER2 expression is expected to be utilized widely for predicting the sensitivity to trastuzumab treatment, and incorporated into the treatment system of breast cancer.

Bisphosphonates (Aredia®, Onclast®, Biphon®) interfere with invasion of the bone by osteoclasts. This kind of agents is useful for patients with hypercalcemia. In recent years, the beneficial effects of these agents on bone metastasis have been studied, and clinical improvement of bone pain, improved QOL, and delay in the development of osseous complica-

tions, including bone fracture, have been demonstrated. Unfortunately, the National Health Insurance in Japan covers bisphosphonates used only for the treatment of hypercalcemia. Currently, studies on bisphosphonates as therapeutic drugs, or prophylactic agents to delay the development of bone metastasis, are underway, and these agents may soon be used clinically for such purposes.

Aromatase inhibitors, hormone agents which are equal or superior to tamoxifen, have also been developed, and their propriety as first-line therapy is now under investigation.

**Conclusion**

In choosing a drug treatment for breast cancer, it is important to clearly recognize the purpose of the treatment, namely whether it is used for metastatic breast cancer aimed at prolongation of life or amelioration of symptoms, as postoperative adjuvant therapy aimed at cure of the disease, or as preoperative therapy aimed at breast conservation, and to weigh the benefits and risks, bearing in mind the adverse reactions to the treatment, particularly hair loss, nausea/vomiting, and leukopenia. Implementation of drug therapy for breast cancer requires sufficient knowledge, appropriate judgment, and preparedness for management of adverse reactions. Drug therapy of breast cancer is advancing rapidly. As of January 2001, 432 hospitals are accredited in parallel with the accreditation of physicians and the specialist system. Consultation or referral of the patients to these experts could be encouraged.

**REFERENCES**


