Adjuvant Chemotherapy for Breast Cancer

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HER2-negative breast cancer

Introduction

- Adjuvant chemotherapy refers to the use of cytotoxic chemotherapy after breast cancer surgery, administered with the goal of eradicating microscopic foci of cancer cells.
- In general, similar chemotherapy regimens are used as adjuvant chemotherapy regardless as to whether tumors are ER or PR receptor positive or negative.

INDICATIONS FOR TREATMENT

- The decision to use adjuvant chemotherapy takes into account tumor histology, expression of ER and/or PR receptors, tumor stage and grade, patient age, as well as high-risk features such as lymphovascular invasion.

- Adjuvant or neoadjuvant chemotherapy is standard for patients with triple-negative breast cancer (TNBC) and either a tumor size >0.5 cm or pathologically involved lymph nodes.
- Genomic analysis and benefit-risk calculators are also employed to help determine appropriate candidates for adjuvant chemotherapy in with ER-positive tumors.

Benefit of adjuvant chemotherapy

- The data to support adjuvant chemotherapy (versus no treatment) and specifically, the administration of anthracycline and taxane therapy in the adjuvant setting come from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).
- In the 2012 EBCTCG meta-analysis, the use of an anthracycline-containing regimen compared with no treatment resulted in the decreased risk of recurrence , decreased breast cancer mortality and overall mortality.

- Compared with no treatment, the use of CMF was also associated with comparable improvement in these outcomes at 10 years.

REGIMEN SELECTION AND ADMINISTRATION

- There is no single worldwide standard adjuvant chemotherapy regimen in the treatment of breast cancer.
- The AC-T regimen delivered on a dose-dense schedule is the preferred regimen for most patients .

- The rationale for utilizing this regimen is based on evidence demonstrating that an anthracycline-containing regimen is at least equivalent to the historical standard regimen CMF and that the addition of taxane to an anthracycline-based regimen further improves outcomes.
- The benefits of taxane incorporation seen were independent of age, nodal status, tumor size, tumor grade, and estrogen receptor (ER) status.

- Although no regimen has proven to be superior to AC-T, non-anthracycline-based regimens may be an appropriate strategy for certain groups patients:
- Patients with lower-risk disease (eg, those with node-negative, hormone receptor-positive breast cancer or node-negative, hormone receptor-negative breast cancer <1 cm) for whom chemotherapy is indicated.
- Patients with a history of cardiac disease.
- Patients unwilling to accept the risks of anthracycline-based therapy.

- In such patients for whom anthracyclines are not an appropriate choice, TC given every three weeks for four cycles may be an appropriate alternative .
- For patients in whom steroid treatment or risk of peripheral neuropathy is a particular concern, and where there are concerns about anthracycline exposure, CMF is occasionally recommended.

- Although an anthracycline plus taxane-based regimen may be superior to TC in high-risk disease, data suggest comparable outcomes in lower-risk disease.
- Previous data demonstrate that TC is more effective than AC alone.
- Considering these data together, in higher-risk, ER-positive cancers and in TNBC, there may be a benefit with anthracyclines, whereas in lower- risk disease, **four** cycles of TC is an appropriate option.

Importance of chemotherapy schedule

- "Dose-dense" adjuvant treatment, in which treatment is given more frequently than the historical every- three-week schedule, is associated with better DFS outcomes and similar tolerability compared with standard dosing.

- It is not known which of the common dose-dense strategies of every-two-week AC x 4 followed by every-two-week paclitaxel x 4 or every-two- week AC x 4 followed by weekly paclitaxel x 12 is superior.
- Sequential versus concurrent anthracycline plus taxane chemotherapy (eg, AC then T) was associated improvement in disease recurrence rates compared with concurrent regimens (eg, TAC).

Schedule of taxanes

- A RCT conducted by the ECOG in the adjuvant setting demonstrated that paclitaxel is more effective when used in a lower, but dose-dense fashion compared with a higher dosage on a three-week schedule (80 mg/m^2 every week x 12 versus 175 mg/m^2 every three weeks x4).

- Docetaxel, by contrast, appeared to be more effective when given at higher doses every three weeks (100 mg/m^2 every three weeks x 4 versus 35 mg/m^2 weekly x 12) .
- The comparison of paclitaxel every week versus docetaxel every three weeks did not suggest a difference in DFS or OS.

TIMING OF CHEMOTHERAPY AND RADIATION

- Adjuvant chemotherapy is typically started within four to six weeks after surgery.
- Earlier treatment is not necessarily better, but observational data suggest a delay of more than three months is detrimental.
- For patients who are also going to receive adjuvant radiation therapy, standard clinical practice is to proceed with chemotherapy before radiation therapy.

Patients who received neoadjuvant treatment

- The survival benefit for use of capecitabine in women with residual disease after standard neoadjuvant chemotherapy, particularly in those with triple-negative breast cancer (TNBC), suggests that such patients may be appropriate candidates for adjuvant capecitabine.

- Nearly all women with estrogen receptor-positive, HER2-negative cancers will have residual disease after neoadjuvant chemotherapy; these patients should receive adjuvant endocrine therapy alone.

Adjuvant systemic therapy for HER2-positive breast cancer

- All of the trials establishing the benefit of trastuzumab limited eligibility to women with either node-positive or node-negative high-risk breast cancer (usually defined as tumor size >1 cm).
- UpToDate recommend chemotherapy plus trastuzumab for all women with HER2-positive, node-positive breast cancer and for women with HER2-positive, node-negative tumors >5 mm and sometimes offer chemotherapy and trastuzumab for even smaller tumors (3 to 4 mm), especially if they are HR negative.

- Trastuzumab should be administered concomitantly with the non-anthracycline components of chemotherapy, rather than sequentially after chemotherapy.

- Trastuzumab is administered with a loading dose (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) prior to the usual dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg).

- The standard course of adjuvant trastuzumab is one year.
- The greatest amount of benefit is achieved within the first 6 months.

- Moreover, for stage II or III patients in the United States, adding adjuvant pertuzumab for one year is common, and pertuzumab requires concurrent trastuzumab administration.

Option of adjuvant dual anti-HER2 therapy

- The option for using a second anti-HER2 agent exists if the initial disease was considered to be high risk (typically node-positive or >2 cm).
- The approach for such patients is to offer the concurrent adjuvant pertuzumab with trastuzumab as evidence exists for improvements in DFS.

CHOICE OF CHEMOTHERAPY

- Tumors >2 cm and/or node positive — sequential regimen of anthracyclines followed by taxanes with trastuzumab (and pertuzumab) or the non-anthracycline regimen, docetaxel plus carboplatin plus trastuzumab, with or without pertuzumab (TCH[P]).
- Node-negative tumors <2 cm — paclitaxel-trastuzumab (TH) regimen .

Patients who were treated with neoadjuvant therapy

- Residual disease — switch to ado-trastuzumab emtansine (T-DM1) in the adjuvant setting and continue for 14 cycles.
- No residual disease-- continue adjuvant trastuzumab, with or without pertuzumab, to complete a year of HER2-directed therapy.

Summary

- Chemotherapy is offered to patients with early-stage HR-positive cancers that have high-risk characteristics, such as high-grade tumor, large tumor size (≥2 cm), pathologically involved lymph nodes, and/or high 21-gene recurrence score.

- For patients with triple-negative breast cancer, adjuvant chemotherapy is administered if the tumor size is ≥0.5 cm.
- Patients with HER2-positive breast cancer with a tumor size >1 cm typically receive a combination of chemotherapy plus HER2-directed therapy.
- The management of small (≤1 cm) HER2-positive breast cancers is controversial.

- For patients who received the full course of planned neoadjuvant chemotherapy:

- Patients with HR-positive breast cancer should receive endocrine therapy.

- Patients with triple negative breast cancer who have a complete response to neoadjuvant therapy would typically not receive further chemotherapy in the adjuvant setting.

- In cases where the tumor has not had a complete response to neoadjuvant therapy, adjuvant capecitabine may be administered.

- Patients with HER2-positive breast cancer who have a pathologic complete response at the time of surgical resection should receive trastuzumab, with or without pertuzumab, following completion of surgery to complete a year of treatment.
- In cases where the tumor has not had a complete response to neoadjuvant therapy, adjuvant ado-trastuzumab emtansine for 14 cycles, rather than trastuzumab, is recommended.


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