Title. "Concurrent versus sequential administration of adjuvant chemotherapy and tamoxifen in early breast cancer patients."

Original protocol information: eligibility criteria, treatment schema and statistical section

Note. The protocol of the study object of the present manuscript (TRIAL B, according with the original protocol) was in parallel with the protocol of another study (TRIAL A, according with the original protocol).

Aims of the study

TRIAL A
(Peri-operative adjuvant chemotherapy in breast cancer patients)

Primary aim

To compare the overall survival (primary endpoint) of patients assigned to peri-operative chemotherapy with that of control group.

Secondary aims

Evaluation of Disease-free survival and toxicity (secondary end-points).

TRIAL B
(Concurrent versus sequential administration of adjuvant chemotherapy and tamoxifen in breast cancer patients)

Primary aim

To compare the overall survival (primary end-point) of patients who received concurrent chemo-hormonotherapy administration (tamoxifen given concurrently with chemotherapy) with patients who received sequential chemo-hormonotherapy administration (tamoxifen given after chemotherapy).

Secondary aims

Evaluation of Disease-free survival and toxicity (secondary end-points).

Study design

TRIAL A
(Peri-operative adjuvant chemotherapy in breast cancer patients)

Randomization

Patients will be randomly assigned by telephone to receive a) one cycle of chemotherapy 48 to 72 hours after surgical removal of the tumor (peri-operative treatment) or b) no peri-operative treatment.

Pre-randomization stratification

The only pre-randomization stratification is the stratification by center.

Post-randomization stratification

- Age.
- Menopausal status.
- Nodal status.
- Hormonal receptor status (positive, negative ore unknown).
- Clinical tumor classification (T).

Inclusion criteria

- Patients affected by primary breast carcinoma with diagnosis confirmed by extemporaneous histological examination during breast surgery.
- Age ≤ 65 years.
- Performance Status ≤ 1 according to ECOG (Eastern Cooperative Oncology Group) criteria.
- Clinical stages T_1-T_{3a}, N_{0-1}, M_0.
- Normal cardiac function evaluated by electrocardiography and clinical examination.
- Normal hepatic function (serum aspartate aminotransferase in the normal range, serum bilirubin ≤ 1·2 mg/dL).
- Normal renal function (serum creatinine ≤ 1·2 mg/dL).
- Adequate bone marrow function (hemoglobin ≥ 10g/dl white blood cells count ≥ 3.500/µl and platelets ≥ 120.000/µl).

Exclusion criteria

- Previous or concomitant malignancy, except curatively treated basocellular carcinoma or curatively treated in situ cervix carcinoma.
- Tumor classified, during the clinical examination, as T_{3b-4} and/or N_{2-3}.
- Mastitis carcinomatosa.
- Difficult geographic availability.
- Serious medical illness or psychiatric illness that would prevent the administration of adjuvant treatment and/or the long term follow-up.

Peri-operative adjuvant treatment

CEF:
Cyclophosphamide 600 mg/m^2
Epidoxorubicin 60 mg/m^2
Fluorouracil 600 mg/m^2, administered the same day after 42 or 72 hours the surgical removal of the tumor

Adjuvant treatment

Following histological examination of axillary nodes, patients will be treated according to nodal status:

- Node negative patients will not receive any further treatment.
- Node positive patients will be enrolled in TRIAL B.

Radiation therapy limited to the breast is planned only for patients treated with conservative surgery.

TRIAL B
(Concurrent versus sequential administration of adjuvant chemotherapy and tamoxifen in breast cancer patients)

Randomization
The patients are randomly assigned, by telephone, to receive chemotherapy and tamoxifen concurrently or sequentially.

Post-randomization stratification

- Age.
- Menopausal status.
- Nodal status.
- Hormonal receptor status (positive, negative ore unknown).
- Clinical tumor classification (T).

Inclusion criteria

- Patients affected by histologically confirmed breast cancer who had undergone radical mastectomy or breast-conserving surgery, in addition to full ipsilateral axillary lymph node dissection, with at least one involved node.
- Age ≤ 65 years.
- Performance Status ≤ 1 according to ECOG (Eastern Cooperative Oncology Group) criteria.
- Normal cardiac function evaluated by electrocardiography and clinical examination.
- Normal hepatic function (serum aspartate aminotransferase in the normal range, serum bilirubin ≤ 1·2 mg/dL).
- Normal renal function (serum creatinine ≤ 1·2 mg/dL) .
- Adequate bone marrow function (hemoglobin ≥ 10g/dl white blood cells count ≥ 3.500/µl and platelets ≥ 120.000/µl).

Note
The following loco-regional treatment are considered radical:

T_{1a-2a} N_{0-1a} (T < 4cm)

- Halsted's radical mastectomy.
- Patey's modified radical mastectomy.
- Madden's modified radical mastectomy.
- Sectorial mastectomy or tumorectomy, axillary lymph nodes dissection (breast radiotherapy must be administered).

T_{2a-3a} N_{0-1a} (T > 4cm)

- Halsted's radical mastectomy
- Patey's modified radical mastectomy
- Madden's modified radical mastectomy

T_{1a-3a} N_{1b-2}

- Halsted's radical mastectomy

Exclusion criteria

- Previous or concomitant malignancy, except curatively treated basocellular carcinoma or curatively treated in situ cervix carcinoma.
- Difficult geographic availability.
- Serious medical illness or psychiatric illness that would prevent the administration of adjuvant treatment and/or the long term follow-up.

Adjuvant treatmen

The first chemotherapy cycle will be administered within 30 days after surgery.
All patients will receive the same adjuvant chemotherapy consisting of alternating regimens of CEF and CMF every 21 days for a total of 12 cycles. Therefore, patients enrolled from TRIAL A and already treated with peri-operative chemotherapy (i.e., one cycle of CEF) will receive CMF at the first cycle, and other further 10 cycles of CEF alternated with CMF.

CEF:
Cyclophosphamide 600 mg/m^2
Epirubicin 60 mg/m^2
5-Fluorouracil 600 mg/m^2, administered the same day

CMF:
Cyclophosphamide 600 mg/sqm,
Methotrexate 40 mg/sqm,
5-Fluorouracil 600 mg/sqm, administered the same day

Tamoxifen at 20 mg/day orally for 5 years will be administered concurrently with the first chemotherapy cycle in the patients randomized to receive the concurrent treatment or 30 days after the last chemotherapy cycle in patients randomized to receive the sequential treatment.
Radiation therapy limited to the breast is planned only for patients treated with conservative surgery

Dose modifications

Day 21 after chemotherapy → In case of lack of bone marrow recovery (defined as white blood cell count < 3500 cell/μL and platelet count < 100 000 cell/μL) the treatment will be delay by 7 days
Day 28 after chemotherapy →In case of persistent lack of bone marrow recovery the treatment will be delay by other 7 days
Day 35 after chemotherapy → In case of white blood cells count < 3500cell/μL but > 2500/μL and platelets count < 100 000 cell/μL but > 70 000 cell/μL only the 75% of the dose of each drugs will be administered.

The same reduction of dose will be applied in case of symptoms related to leukopenia and thrombocytopenia. The patients who do not receive the treatment within the 35th day after chemotherapy will be withdrawn from the study.

Treatment discontinuation

The treatment will be discontinued in case of:

- Patient refusal
- Severe toxicity or allergy
- Progression of disease

Statistical consideration of the study

Statistical consideration

The significant level assumed for the study is $p < 0.05$ (alpha error = 0.05). We consider a power of 70% appropriate for the aim of our research. Data from the literature show a 3-year overall survival of approximately 70-75% and a 5-year overall survival of 65% in breast cancer patients who underwent radical treatment.

Sample size

Assuming that the new treatment is able to reduce the risk of death of 1/3, a 3-year overall survival of approximately 83% and a 5-year overall survival of approximately 76% is expected. Therefore, the number of events (=death) required for our purpose is 150. The enrolment of 200 patients/years for the first three years with the 2 additional years of follow-up appears adequate for our purpose and should guarantee to detect 150 events. The follow-up will be prolonged until the observation of the needed number of events.
The power of the study for disease-free survival will be, obviously, greater than that we will obtain for overall survival.

Post-randomization stratification and subgroup analysis

A stratification analysis for prognostic factors (age, menopausal status, nodal status, tumor size and hormonal receptor status -positive, negative or unknown) and the study of the interaction between each prognostic factor and the treatment is also planned.
This analysis will only have a descriptive significance because we must consider the problems of relative multiple confronts and the small sample of subgroups with lack of statistical power.