PROMISE

(Prevention Of Menopause Induced by chemotherapy.
A Study in Early breast cancer patients)

Prevention of chemotherapy-induced menopause by
temporary ovarian suppression with triptorelin vs. control
in young breast cancer patients.
A randomised phase III multicenter study
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1 PROMISE STUDY PROTOCOL SUMMARY

Title of the study: Prevention of chemotherapy-induced menopause by temporary ovarian suppression with Triptorelin versus control in young breast cancer patients. A randomized phase III multicenter study

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Statistical coordinator: P. Bruzzi. (Genoa, Italy)

Data center: Centro Trials Istituto Nazionale per la Ricerca sul Cancro L.go R. Benzi 10 16132 Genova (Italy)

Background: Early menopause is a frequent side effect induced by chemotherapy in premenopausal patients. The percentage of patients developing amenorrhea differs depending on the type of chemotherapy regimen administered. However, the most commonly used chemotherapy regimens, such as CMF or CEF induce amenorrhea in more than 60% of patients. Alkylating agents, such as cyclophosphamide, are considered the main cause of amenorrhea induced by chemotherapy. However, new chemotherapy regimens not containing alkylating agents, such as the combination of anthracyclines and taxanes, also seems to induce a high percentage of amenorrhea.

Early menopause induced by chemotherapy has been shown to be associated with a better prognosis in premenopausal breast cancer patients with hormone responsive tumors. This finding may be explained by the therapeutic effect of suppressing the ovarian estrogen production. However, early menopause also carries important consequences such as: menopausal symptoms, effects on bone density and cardiovascular effects. Moreover, early menopause and lack of fertility is not easily accepted by young patients.

Treatment with a gonadotropin-releasing hormone analog (Gn-RHa) may decrease the gonadotoxicity associated with cancer chemotherapy. In rats it has been shown that the use of LH-RH analog is active in the prevention of chemotherapy-induced ovarian follicular loss. An increasing number of phase II clinical studies suggest the possibility to preserve fertility by the use of prior and concomitant Gn RH analogs with chemotherapy. However the evaluation of the role of GnRH in a phase III study is still lacking.

Objectives:

Primary: to evaluate the ability of LH-RHa (Triptorelin) to prevent chemotherapy induced menopause in premenopausal patients undergoing chemotherapy compared to patients treated with chemotherapy without Triptorelin.

Study design: multicenter phase III study. Patients will be randomized to receive or not Triptorelin during the administration of chemotherapy.

Study parameters. FSH, LH and E2 will be used as biochemical markers of menopausal status. They will be evaluated before treatment and 3, 6, 9 and 12 months after the last cycle of chemotherapy. FSH, LH and E2 assessments will be stopped before the 12th month in patients who have resumption of menstrual activity and values of FSH, LH and E2 indicating ovarian function preservation. The absence of menstrual activity resumption associated with a high value of FSH (e.g. > 40 IU/l or > the lower limit indicating post-menopausal status for the reference laboratory) 12 months after the last chemotherapy cycle will indicate a post-menopausal status.
Main eligibility criteria:
- Stage I-II-III premenopausal breast cancer patients who are candidates for chemotherapy
- Written informed consent

Treatment
Triptorelin will be administered at least 1 week before chemotherapy and then every 4 weeks for the duration of chemotherapy. The last administration of LH-RH will be given before the last cycle of chemotherapy.
Patients with hormone sensitive tumors who resume their ovarian function after LH-RH stop will restart treatment with LH-RH analog until obtaining a suppression of ovarian function for a total time of 2 years.

Start date: 6/2003
Participating centers: 20
Number of Patients: N. 140 for arm (Total n. 280).
2 BACKGROUND

Breast cancer is the most common malignancy among women. Although the mean age of patients developing breast cancer is 45-50 years, nearly 25% of women diagnosed with breast cancer are premenopausal. Date from our previous study on adjuvant chemotherapy carried out in 1214 breast cancer patients showed that 43% of patients were premenopausal. Moreover 277 pts (23%) were younger than 45; in particular 85 pts (7%) were 36-40; 45 (4%) 31-35 and 16 (1%) pts were less than 31. Adjuvant chemotherapy has become the standard treatment for node-positive and high-risk node-negative premenopausal women with breast cancer. Early menopause is a frequent side effect induced by chemotherapy in premenopausal patients. The percentage of patients developing early menopause differs depending on the type of chemotherapy regimen administered and on patient age.

The most commonly used chemotherapy regimens, such as CMF or CEF induce menopause in more than 60% of patients. Alkylating agents, such as cyclophosphamide, are considered the main cause of drug induced amenorrhea (DIA). However, new chemotherapy regimens such as the combination of anthracyclines and taxanes, also seem to induce a high percentage of amenorrhea (personal data).

Early menopause induced by chemotherapy is associated with a better prognosis in premenopausal breast cancer patients. This finding may be explained by the therapeutic effect of suppressing the ovarian estrogen production. However, premature menopause also carries significant consequences such as the following: hot flashes and night sweats, psychosocial problems, atrophic vaginitis, dyspareunia, dysuria, skeletal osteoporosis with consequent fractures, and cardiovascular effects. Moreover, early menopause and loss of fertility is not easily accepted by young patients who wish to bear children after cancer treatment. More women may decide to attempt pregnancy after cancer treatment if they can be reassured that it will not have an adverse affect on their survival.
Until now a standard system to prevent chemotherapy-related loss of fertility in female patients has not been identified. Chemotherapy regimens without alkylating agents may reduce the percentage of patients developing amenorrhea, however the efficacy of these regimens is reduced. Fisher and al performed a randomized clinical trial comparing sequential methotrexate and fluorouracil (MF) versus cyclophosphamide, methotrexate and fluorouracil (CMF) for the treatment of node negative breast cancer patients with estrogen receptor negative tumors. The benefit from both therapies was evident in all patients, but the advantage of CMF compared to MF was greater in those \( \leq 49 \) years. The percentage of chemotherapy induced amenorrhea in women treated with MF was only 9%.

Current attempts to preserve ovarian function are mainly based on invasive procedures, such as cryopreservation and reimplantation of ovarian tissue not easily available in all centers.

Treatment with a gonadotropin-releasing hormone analog (LH-RHa) may decrease the gonadal toxicity associated with cancer chemotherapy. Ataya et al demonstrated that the use of LHRH analog in rats is active in the prevention of chemotherapy-induced ovarian follicular loss. Four groups of female rats were randomized to receive no treatment or cyclophosphamide (CTX) (5mg/kg/day for 21 days) or cyclophosphamide plus LHRHa, or LHRHa alone. One ovary from each animal was serially sectioned and examined for number and size of follicles. CTX caused a significant reduction in total number of growing follicles (medium-to large follicles). LHRHa resulted in a reduction of medium-to-large follicles and an increase in the number of small follicles, the same effects had CTX plus LHRHa, resulting in an increase in the total number of follicles. LHRHa treatment deprived follicles from gonadotropins, so the recruitment from the pool of primordial follicles into the CTX sensitive pool was altered, preserving the functional potential of the ovary.

Another study performed by the same author in rhesus monkeys led to the same conclusions. Six adult female rhesus monkeys underwent unilateral ovariotomy and were divided into two groups; one group received CTX plus LHRHa and the other CTX plus placebo. FSH, estradiol
and progesterone were weekly determined. FSH level significantly increased in the CTX group, while it significantly decreased in the CTX + LHRHa group. At the end of the treatment the remaining ovary was removed and the size and number of follicle were analyzed. CTX caused a significant reduction of nonprimordial follicles compared to the CTX + LHRHa group10.

Data on the protective effect of Gn-Rh in human beings come from a small phase III negative study and from phase II studies.

The first study performed by Waxman et al in patients with Hodgkin’s disease undergoing chemotherapy with MVPP or CHVPP failed to demonstrate the ability of LHRH to prevent fertility. Thirty men and eighteen women were randomly allocated to receive either buserelin or no buserelin prior to and for the duration of chemotherapy. At follow-up assessment three years from the end of treatment, all men treated with buserelin were oligospermic and four of the eight women receiving buserelin were amenorrhoeic11.

An other study was a prospective clinical trial in patients who underwent chemotherapy for lymphoma, leukemia and nonmalignant disease such as systemic lupus erythematosus or other autoimmune disease. An injection of depot D-TRP6-GnRHa was administered prior to the start of chemotherapy and monthly until its conclusion. This group was compared with a control group of 55 women who had been treated with the same chemotherapy. All but one (98%) of the patients receiving GnRHa co-treatment resumed spontaneous ovulation within 6 months while in the control group only 40% of patients resumed ovarian function12.

Recchia et al performed a phase II pilot study to investigate the protective effects on ovarian function and the efficacy and tolerability of Goserelin added to adjuvant chemotherapy for early breast cancer in 64 premenopausal patients. After a median follow-up of 55 months, 86% of patients had resumed normal menses. No unexpected adverse events were reported13.

Fox et al reported a study in which thirteen early breast cancer patients were treated with leuprolide during the course of adjuvant chemotherapy in an effort of protect the ovary from the cytotoxic effects of chemotherapy. In 11 patients leuprolide was given in a dose of 3,75 mg im
one week prior to chemotherapy and repeated every 3-4 weeks until completion of chemotherapy; two patients received leuprolide 7,5 mg on a similar schedule. Menstrual periods resumed in all patients within 12 months of the completion of chemotherapy\textsuperscript{14}.

A summary of these studies is reported in table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Phase</th>
<th>Gonal function preservation</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waxman JH Can Ch Phar 1997</td>
<td>30 men 18 women with HD MVPP or CHVPP</td>
<td>III Random</td>
<td>No statistically significant</td>
<td>difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Buserelin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-No Buserelin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blumenfeld Z J Soc Gyn Inv 2001</td>
<td>44 women lymphoma leukemia nonmal. diseases</td>
<td>Depot D-TRP6-GnRH vs a control group</td>
<td>98% pts resumed ovulation vs 40% in the control group</td>
<td></td>
</tr>
<tr>
<td>Fox KR ASCO 2001</td>
<td>13 breast cancer</td>
<td>Leuprolide</td>
<td>Menstrual periods resumed in all pts</td>
<td></td>
</tr>
<tr>
<td>Recchia F Anti-Canc. Dr 2002</td>
<td>64 breast cancer</td>
<td>Goserelin</td>
<td>86% pts resumed normal menses</td>
<td></td>
</tr>
</tbody>
</table>

In our institution we are performing a phase II study to evaluate if Goserelin 3,6 mg given subcutaneously during chemotherapy is able to prevent chemotherapy induced amenorrhea in pre-menopausal breast cancer patients. Twenty out of 29 planned patients have been enrolled.

Aim of the present study is to confirm in a phase III study the ability of LH-RH analogs to prevent chemotherapy induced early menopause in early breast cancer patients.

**3 STUDY OBJECTIVE**

**3.1 Primary objective**

To evaluate the incidence of chemotherapy induced early menopause in breast cancer young patients treated with Triptorelin prior and during adjuvant chemotherapy as compared to women receiving chemotherapy without Triptorelin.
3.2 **Secondary objective**

To compare the toxicity of chemotherapy plus Triptorelin versus chemotherapy alone, according to NCI Common Toxicity Criteria (Appendix 2).

3.3 **End - Point**

Menopausal status will be assessed by:

- FSH, LH, E2 assessment 3, 6, 9, 12 months after the last cycle of chemotherapy

- Menstrual activity assessment 3, 6, 9, 12 months after the last cycle of chemotherapy

Patients who will not resume any menstrual and with high FSH values (e.g. ≥40) 12 months after the last cycle of chemotherapy will be considered as post-menopausal patients.

4 **ETHICS**

The current revision of the Declaration of Helsinki (See Appendix 1) is the accepted basis for clinical study ethics, and must be fully followed and respected by all engaged in research on human beings.

4.1 **Good Clinical Practice**

Good clinical practice is a standard for clinical studies which encompass the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies.

It is the responsibility of the investigator(s) to ensure that the study is performed in accordance with the international Good Clinical Practice standards and according to all local laws and regulations concerning clinical studies.(DM July 15, 1997)

4.2 **Informed Consent**

It is the responsibility of the investigator(s) to ensure that informed consent is obtained from each subject participating in the study, after explanation of the aims, methods, benefits and potential hazards of the study. An information sheet giving details of the trial will be provided
for the patient to read and retain. The consent must be obtained before any study-specific procedures are performed. All consent forms must be signed and dated by the investigator.

### 4.3 Ethics Committee

It is responsibility of the investigator(s) to submit a copy of the protocol and detailed patient information sheet and consent form to an ethics committee in order to obtain approval to conduct the study. Ethics committee approval must be obtained before the study is started.

### 5 STUDY DURATION

Start of the recruitment: 6/2003

End of the recruitment: 6/2005

Follow-up: information about menopausal status will be taken 3, 6, 9, and 12 months after the last cycle of chemotherapy or until relapse of menstrual activity in patients who have a resumption of menstrual activity before the 12th month from the end chemotherapy.

### 6 STUDY DESIGN

This is a prospective, multicentric, open label, randomized, phase III study.

N° of participating centers: 20

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Patients with stage I-II-II breast cancer candidate to chemotherapy

RANDOM

Chemotherapy alone

Chemotherapy + Triptorelin
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7 PATIENT POPULATION

7.1 Inclusion criteria

- Written informed consent
- Histologically or cytologically confirmed breast carcinoma resected at time of original diagnosis.
- Stage I-II-III breast cancer patients who are candidates for chemotherapy. The type of adjuvant chemotherapy schedules allowed are the following:
  - FE$_{60-75-100}$C (5-fluorouracil 600 mg/mq day 1, epirubicin 60-75-100 mg/mq day 1 or fractionated on day 1 and 8, cyclophosphamide 600 mg/mq day 1) every 21 or 28 days
  - CMF (cyclophosphamide 100 mg/mq per os days 1-14, methotrexate 40 mg/mq days 1 and 8, 5-fluorouracil 600 mg/mq days 1 and 8) every 28 days
  - A$\rightarrow$CMF the minimum allowable starting dose for A (doxorubicin) given as a single agent (followed by CMF described below) is 60 mg/mq
  - EC$\rightarrow$Paclitaxel (epirubicin 90 mg/mq day 1 in combination with cyclophosphamide 600 mg/mq day 1 every 21 days followed by paclitaxel 175 mg/mq day 1 every 21 days)
  - FEC$\rightarrow$paclitaxel (5-fluorouracil 600 mg/mq in combination with epirubicin 90 mg/mq and cyclophosphamide 600 mg/mq day 1 every 21 days followed by paclitaxel 175 mg/mq day 1 every 21 days)
  - EC$\rightarrow$docetaxel (epirubicin 90 mg/mq day 1 in combination with cyclophosphamide 600 mg/mq day 1 every 21 days followed by docetaxel 100 mg/mq day 1 every 21 days)

- Premenopausal status defined as the presence of active menstrual cycles or normal menses within six weeks before initiation of chemotherapy.
- No evidence of metastases or localized or distant breast cancer recurrence
• Age ≥ 18 and ≤ 40

7.2 **Exclusion criteria**

• Prior chemotherapy and/or radiotherapy for cancer or non neoplastic disease

• Evidence of distant metastases. Any suspicious manifestation requires appropriate investigation to exclude metastases.

• Previous or concomitant other malignancy within the past 5 years except basal or squamous cell carcinoma of the skin or adequately treated in situ carcinoma of the cervix.

• History of noncompliance to medical regimens and patients who are considered potentially unreliable.

• Pregnancy or nursing
8 STUDY MEDICATION

Triptorelin is a synthetic decapeptide (D-Trp6 GnRH) agonist analogue of natural GnRH. The principal modification consists of substitution of natural glycine in position 6 by a D-amino acid (D-tryptophan).

Studies in animals and man have shown that continued administration of triptorelin exerts, after a short initial stimulation, an inhibitory effect on the gonadotrophin secretion with consequent suppression of testicular and ovarian function.

In male patients with prostate cancer, the administration of triptorelin 3.75mg resulted in a rise in plasma concentrations of testosterone for the first few days (flare-up phenomenon) then a decrease to castration levels. Castration was maintained for 28 days till the next injection. The peak circulating levels were achieved after 2.94 days.

In women administered triptorelin 3.75mg, the castration response was achieved after 8 or 9 days respectively, and lasted 41 and 38 days respectively for the two castration thresholds. A similar profile was observed for FSH and LH levels.

Amenorrhea was maintained during 79 days post dosing.

8.1 Expected Toxicity

Triptorelin’s side effects are similar to the symptoms of menopause: hot flashes, vaginal dryness, vaginal bleeding, reduction in libido. Moreover Triptorelin can decrease the bone mineral density. Rare adverse effects are: headache, nausea, vomiting, constipation, diarrhea, anorexia, fever, sweating, mood swings, depression, palpitation, cutaneous rash, loss of hair, vertigo, insomnia or somnolence, visual disturbance and paresthesia, peripheral edema, allergic reaction. It is also possible injection site reaction.
8.2 Dose and administration

In patients randomized to receive Triptorelin 3.75 mg it will be administered intramuscularly at least one week before chemotherapy and then every 4 weeks for the duration of chemotherapy. The last administration of Triptorelin will be given before the last cycle of chemotherapy. Patients with hormone sensitive tumors who resume their ovarian function after stopping chemotherapy and Triptorelin will restart treatment with LH-RH analog until obtaining a suppression of ovarian function for a total time of 2 years.

9 CONCOMITANT TREATMENTS

All concomitant treatments are allowed except for hormonal treatments other than Tamoxifen.
10 STUDY PARAMETERS

The primary study end-point is the percentage of Triptorelin treated patients who are protected from chemotherapy-induced menopause compared to patients who don’t receive Triptorelin during chemotherapy.

FSH will be used as a biochemical marker of menopausal status. It will be evaluated before treatment and 3, 6, 9, and 12 months after the last cycle of chemotherapy. A high value of FSH (e.g. \( \geq 40 \text{ IU/l} \) or \( \geq \) the lower limit indicating post-menopausal status for the reference laboratory) will indicate a post-menopausal status.

Patients who do not resume any menstrual activity and have a high FSH value as defined above, 12 months after the last cycle of chemotherapy, will be considered patients with chemotherapy induced early menopause.

The long-term maintenance of ovarian function will be evaluated by assessment of FSH, LH, E2 and menstrual activity 30 months after the last cycle of chemotherapy.

Secondary end-point of the study is to compare the toxicity of chemotherapy plus Triptorelin versus chemotherapy alone according to NCI Common toxicity criteria (Appendix2).
11 STUDY PROCEDURES

At baseline:

– Informed consent
– Complete medical history, ECOG performance status, physical examination, height, weight, menstrual activity.
– Check of inclusion and exclusion criteria
– Hematology, blood chemistry
– Evaluation of baseline serum FSH, LH, E2 (within four weeks before the start of chemotherapy)
– Pregnancy test by assessment of beta HCG (within four weeks before the start of chemotherapy)
– Bone computerized mineralometry
– Dispense trial medication

During treatment (before each chemotherapy cycle)

– Toxicity evaluation
– ECOG performance status
– Hematology, blood chemistry

3, 6, 9, and 12 months after the last cycle of chemotherapy

– Evaluation of serum FSH, LH, E2
– ECOG performance status
– Physical examination
– Menstrual activity
– Hematology, Blood chemistry
6 and 12 months after the last cycle of chemotherapy

- Bone computerized mineralometry

12 Flow chart of examination

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>BASELINE</th>
<th>EACH CT CYCLE</th>
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<th>6</th>
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<tr>
<td>Menstrual activity</td>
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<td>Hematology, blood chemistry</td>
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<td>Serum FSH, LH, E2</td>
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<td>Beta HCG</td>
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<td>Toxicity</td>
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<tr>
<td>Bone computerized mineralometry</td>
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<td>X</td>
<td>X</td>
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</tbody>
</table>

12.1 Adverse events

An adverse event is any undesirable event associated with the use of a drug, whether or not considered drug related, and includes any side effect, injury, toxicity, or sensitivity reactions.

It also includes any undesirable clinical or laboratory change which does not commonly occur in the patient.
12.2 Serious events

A serious adverse event includes any event that is fatal or life-threatening, requires patient hospitalization, prolongs hospitalization or is disabling. Death, congenital anomaly, cancer or overdose are always considered serious.

“Life-threatening” means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

“Requires patient hospitalization” should be defined as hospital admission required for treatment of the adverse event. Hospital admission for scheduled elective surgery would not be serious adverse event.

If the adverse event is serious, it must be reported within 24 hours working days by fax to the Sponsor and to the Ethic Committee and to Direzione Sanitaria of every participating center (See Appendix 4). The sponsor address to send SAE form is: Lucia Del Mastro (Divisione di Oncologia Medica I – Istituto Nazionale per la Ricerca sul Cancro – Lrgo R. Benzi, 10 – Genova 16132 Tel. +39 10 5600665 Fax +39 10 5600850 E-mail: lucia.delmastro@istge.it)

Withdrawal from the study and therapeutic measures shall be at the discretion of the investigator. A full explanation for the discontinuation from the study will be made on the appropriate case report form. All adverse events will be followed up by the investigator until satisfactory resolution; local authorities will be informed by the investigator according to local regulations.

The sponsor has a legal responsibility to notify both the local and international regulatory authorities about the safety of a new drug. Prompt notification of major adverse events by the investigator is essential so that legal obligations are met.
13 ADMINISTRATIVE ASPECTS

All the information about patients and treatment will be registered in Case Report Forms. The copy will be sent to Centro Trials e Sperimentazioni Cliniche Controllate, Istituto Nazionale per la Ricerca sul Cancro, Largo Rosanna Benzi 10, 16132 Genova.

The investigator will retain copies of all pertinent information for a period of at least 15 years from study completion.
14 STATISTICAL CONSIDERATIONS

Assuming an incidence of permanent menopause following chemotherapy of 60% (defined as the proportion of patients not menstruating within 1 year of termination of chemotherapy), for alpha=0.05 (2-sided) and beta=0.1 (90% power), 140 patients per arm will be needed in order to detect a 20% absolute reduction (from 60% to 40%) in the incidence of menopause in the experimental arm.

15 PUBLICATION POLICY

The final publication(s) of the trial results will be written in the name of the study coordinator and the steering committee. One representative of scientific secretary will be included among the authors.

16 PATIENT RANDOMIZATION AND DATA MANAGEMENT

Patients will be randomized by phone call at Centro Trials e Sperimentazioni Cliniche Controllate, telephone number 010-354103 from Monday to Friday from 8:30am to 16:00 pm from Monday to Friday.

Patient data recorded on CRF will be collected and analyzed by Centro Trials e Sperimentazioni Cliniche Controllate.

17 TRIAL SPONSORSHIP FINANCING AND INSURANCE

- Sponsor: Istituto Nazionale per la Ricerca sul Cancro - Genova

- Requested Grant: Associazione Italiana per la Ricerca sul Cancro. The grant will cover cost of: insurance, drug supply, monitoring study, CRF, data collection and management

- Insurance will be supplied by Istituto Nazionale per la Ricerca sul Cancro - Genova

- The drug Triptorelin for the use prior and during chemotherapy will be supplied by IPSEN
18 APPENDIX 1 (Helsinki Declaration)

WORLD MEDICAL ASSOCIATION
DECLARATION OF HELSINKI

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; and the 41st World Medical Assembly, Hong Kong, September 1989.

Introduction
It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Assembly binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care, which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures, and the understanding of the aetiology and pathogenesis of disease.

In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research, a fundamental distinction must be recognized between medical research, in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that, the standards, as drafted, are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles, and should be based on adequately performed laboratory and animal experimentation, and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol, which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country, in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons, and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person, and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out, unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks, in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, and to minimize the impact of the study on the subject's physical and mental integrity, and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects, unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation, if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation, not in accordance with the principles laid down in this Declaration, should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study, and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study, and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious, if the subject is in a dependent relationship to him or her, or may consent under duress. In that case, the informed consent should be obtained by a physician, who is not engaged in the investigation, and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject, in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved, and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Clinical Care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if, in his or her judgment, it offers hope of saving life, reestablishing health, or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient --including those of a control group, if any should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1.2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person, on whom biomedical research is being carried out.

2. The subjects should be volunteers either healthy persons, or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research, if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.
19 APPENDIX 2 (NCI-C)

NCI COMMON TOXICITY CRITERIA

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<tr>
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<td>WBC $ \times 10^9$/L</td>
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<tr>
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<td>WNL</td>
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<tr>
<td>Hgb g/dL</td>
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<td>Granulocytes/Bands X $10^9$/L</td>
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<td>TOXICITY</td>
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<tr>
<td>Partial thromboplastin time WNL</td>
<td>1.01 - 1.66 x N</td>
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CONSENSO INFORMATO

Io sottoscritta __________________________________________________________
sono stata informata dal Dott. ____________________________________________
di essere stata operata per un tumore della mammella e del fatto che attualmente non presento
alcun segno di malattia.
Sono stata anche informata del fatto che è possibile diminuire il rischio che la malattia si
ripresenti ricorrendo a una chemioterapia a cui ho accettato di sottopormi.
Mi è stato spiegato che la terapia che mi verrà somministrata può comportare la comparsa di
menopausa precoce nelle pazienti in premenopausa in una percentuale elevata di casi.
Sono stata informata del fatto che nell’uomo ad oggi non esiste un metodo standard per prevenire
la menopausa precoce indotta dalla chemioterapia e che il trattamento con un farmaco analogo al
fattore di rilascio dell’ormone luteinizzante (LHRH) può ridurre la tossicità della chemioterapia
sull’ovaio.
Gli studi che sono stati condotti fino ad oggi con gli analoghi dell’LHRH hanno portato a dati
discordanti sulla loro efficacia nel preservare la funzione ovarica durante la chemioterapia.
Mi è stato spiegato che in questo centro è in corso una sperimentazione volta a stabilire se la
somministrazione di Triptorelin (un analogo dell’LHRH) 3,75 mg sottocute ogni 28 giorni
durante la chemioterapia è in grado di preservare la funzionalità ovarica e se esiste una
differenza in tossicità nelle somministrazione di Triptorelin in contemporanea alla chemioterapia
rispetto alla somministrazione della chemioterapia da sola.
Ho compreso che decidendo di partecipare a questo studio, in base ad un sistema chiamato
“randomizzazione”, che significa secondo un ordine casuale, potrò ricevere o meno la
somministrazione di Triptorelin durante la chemioterapia.
Il possibile vantaggio del mantenimento della funzionalità ovarica consiste nell’evitare le
conseguenze della menopausa prematura e principalmente vampate di calore, sudorazioni
notturne, problemi psicosociali, vaginite atrofica, dispareunia, disuria, osteoporosi con rischio di
fratture.
Questo trattamento prevede la somministrazione di un farmaco chiamato Triptorelin per via
intramuscolare alla dose di 3,75 mg ogni 28 giorni, partendo da una settimana prima della
chemioterapia sino alla fine della chemioterapia. Le pazienti con recettori ormonali positivi che
riprendersanno una regolare attività mestruale dopo la chemioterapia riprenderanno la
somministrazione di Triptorelin sino ad ottenere un blocco della funzionalità ovarica per un periodo di tempo totale di 2 anni.
Sono stata informata del fatto che se accetterò di effettuare questo trattamento mi sarà chiesto di sottopormi a periodici esami del sangue per la determinazione dei dosaggi ormonali che serviranno a definire il mio stato menopausale.
Sono stata edotta sui principali possibili effetti collaterali del Triptorelin:
- Reazioni allergiche, rush cutanei
- Vampate di calore, sudorazioni
- Sbalzi d’umore
- Secchezza o sanguinamento vaginale
- Riduzione della densità minerale ossea
Nel caso io decida di partecipare allo studio, sarò coperta da una polizza assicurativa che è stata stipulata con la Compagnia di Assicurazioni …………. a garanzia di eventuali danni derivanti dallo studio stesso.
Sono stata informata del fatto che la decisione di partecipare deve essere presa liberamente e senza alcuna pressione e che se decido di partecipare i dati della mia malattia potrebbero essere richiesti dalle autorità sanitarie ed essere oggetto di pubblicazioni scientifiche, ma in ogni caso la mia identità sarà protetta da riservatezza.
In considerazione delle informazioni ricevute, che ho compreso per intero, decido di sottopormi al trattamento proposto.
Potrò comunque in qualsiasi momento liberamente decidere di ritirarmi dallo studio senza conseguenze per le mie ulteriori terapie.
Per qualsiasi problema o bisogno di chiarimento potrà fare riferimento al Dott/Dott.ssa__________________________
Data________________________
La paziente______________________ Il medico______________________
LETTERA PER IL MEDICO CURANTE

Alla cortese attenzione
Dr........................................

Egregio/a Collega,

ccon la presente, La informiamo che la Sua paziente
Sig.ra........................................................................
operata per carcinoma della mammella, sta partecipando ad uno studio clinico nazionale
multicentrico dal titolo: “A randomized phase III study of prevention of chemotherapy-induced
menopause by temporary ovarian suppression with Triptorelin versus no prevention of
chemotherapy-induced menopause in premenopausal breast cancer patients – Studio
randomizzato di fase III sulla prevenzione della menopausa indotta dalla chemioterapia
attraverso la soppressione ovarica temporanea con Triptorelin verso nessuna prevenzione della
menopausa indotta da chemioterapia in pazienti premenopausa operate per carcinoma
mammario”
Lo studio suddetto ha come obiettivi:
– valutare l’efficacia del Triptorelin nella prevenzione della menopausa precoce indotta da
chemioterapia
– confrontare l’efficacia in termini di tossicità della chemioterapia con contemporanea
somministrazione di Triptorelin verso la chemioterapia senza concomitante
somministrazione di Triptorelin
La somministrazione del Triptorelin avverrà per via intramuscolare alla dose di 3,75 mg ogni 28
giorni, a partire da 1 settimana dall’inizio della chemioterapia e per tutta la durata della
chemioterapia; l’ultima somministrazione di Triptorelin sarà effettuata prima della fine della
chemioterapia.

Mi auguro di avere con lei una stretta collaborazione per quanto riguarda lo stato di salute della
paziente durante e dopo la chemioterapia.

Rimango a Sua disposizione per ogni chiarimento.

Cordiali saluti.
Dr.................................................................
Tel.................................................................
21 APPENDIX 4  (SAE form)
**SCHEDA DI SEGNALAZIONE DI SOSPETTA REAZIONE AVVERSA**

*(Confidenziale)*

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<th>N.</th>
<th>INIZIALI DEL PACIENTE</th>
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<th>SESSO</th>
<th>DATA D’INSORGENZA DELLA REAZIONE</th>
<th>ORIGINE E’NICA</th>
<th>CODICE MINISTERO SANITA’</th>
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**DESCRIZIONE DELLE REAZIONI ED EVENTUALE DIAGNOSI**

* NEL CASO INCUADREZZI BIOLOGICI E/ O MEDICINALI:

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<tr>
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<td>DIPARTIMENTO</td>
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<tr>
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**GRAVITÀ DELLA REAZIONE**

- MORTI
- HA PROVOCATO CAVI PROLUNGATI
- L’OSTETRALIZZAZIONE
- HA PROVOCATO INVALIDITÀ GRAVE O PERMANENTE
- HA MESSO IN PERICOLO LA VITA DEL PACIENTE

**ENTI**

- OSSIA
- RISPETTO CON PUBBLICI O PRIVATI

**ESAMI STRUMENTALI E/O DI LABORATORIO RELEVANTI**

**SPECIFICARE SE LA REAZIONE È PREVISTA NEL FOGGIO ILLUSTRATIVO**

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**COMUNITÀ FARMACO/E REAZIONE**

**INFORMAZIONI SUL FARMACO**

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<tr>
<td>A)</td>
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<tr>
<td>B)</td>
</tr>
<tr>
<td>C)</td>
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**LA REAZIONE SI E’ MIGLIORATA Dopo LA SOSPENSIONE DEL FARMACO**

| SI | NO |

**INDICAZIONI PER CUI IL FARMACO E’ STATO USATO**

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<th>FARMACO (I) CONCOMITANTE (I) E DATA (I) DI SOMMINISTRAZIONE</th>
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**CONFEZIONI CONCOMITANTI E PREDISPOSIZIONI**

**LA SCHEDA E’ STA INVIA ALLA**

| AZIENDA FARMACEUTICA | ULIS | DIPARTIMENTO SANITARIO | MINISTERO DELLA SANITÀ |

**INFORMAZIONI SUL SEGNALATORE**

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**DATA DI COMPILAZIONE**

| CODICE USL |

**FIRMA**

| FIRMA RESPONSABILE |

---

*Nota: il segnalatore è un farmacista, riporta sulla descrizione della reazione avversa, se è possibile anche l’eventuale diagnosi.*
22 REFERENCES


