

CEBO: (Center for Evidence Based Oncology)



incidence of skeletal related events (SRE)
in patients with breast carcinoma

IKARUS PROJECT

Non-interventional epidemiologic study

PROJECT PROTOCOL

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PROJECT PROTOCOL

- design and statistical data processing -

<p>Project title:</p> <p>Project abbreviation:</p> <p>Project authors:</p> <p>Coordinating investigator:</p> <p>Coordinating and statistical centre:</p>	<p>Analysis of incidence of skeletal related events (SRE) in patients with breast carcinoma</p> <p>IKARUS</p> <p>Finek, J., Svobodnik, A., Dusek L.</p> <p>Finek, J.</p> <p>CEBO, IBA MU in Brno, Czech Republic</p>
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<p>Study type:</p> <p>Population of patients:</p> <p>Study hypothesis:</p> <p>Number of patients:</p>	<p>Multicentre, non-interventional, epidemiologic and explorative. Prospective and retrospective part.</p> <p>Patients with an advanced breast carcinoma and metastases affecting the skeleton diagnosed in 2000 (retrospective part of the trial) and after the start of the project (prospective part of the trial).</p> <p><u>Retrospective part:</u> Explorative study aiming to assess the incidence of skeletal related events in a predefined group of patients, description of prevention and treatment practice in skeletal related events in 2000-2005, analysis of survival and progression free survival.</p> <p><u>Prospective part:</u> Analysis of temporal changes in prevention and treatment practice in skeletal related events, relation between treatment type and pain.</p> <p>At least 650 patients in the retrospective part. At least 650 patients in the prospective part. At least 1300 patients overall (900 in the Czech Republic, 400 in Slovakia).</p>
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A INTRODUCTION

Skeletal related events present a serious health problem for patients with breast carcinoma, both in terms of occurrence frequency and in terms of overall influence on patient's quality of life. In a number of clinical trials, a positive effect of bisphosphonates has been proved on the decrease of risk of incidence of skeletal related events (SRE). The bisphosphonates have been shown to be effective in the prevention of incidence of SRE.

The following situations are described as skeletal related event:

- pathologic fracture,
- vertebral compression fracture,
- radiotherapy for bone metastasis,
- surgical therapy for bone metastasis,
- tumour-induced hypercalcaemia.

B PROJECT OBJECTIVES

The **primary objective** of the project is the assessment of skeletal related events in patients with a metastatic breast carcinoma treated in the Czech Republic and in Slovakia.

The **secondary objectives** of the study include:

- analysis of treatment practice in skeletal related events,
- analysis of bisphosphonate usage practice in the prevention of skeletal related events in metastases affecting the skeleton in a common clinical practice,
- analysis of patient compliance in bisphosphonate treatment,
- analysis of time interval between the occurrence of a bone metastasis and the incidence of a skeletal related event,
- analysis of patients' survival related to skeletal related events.

C PROTOCOL DESIGN

The retrospective and the prospective part of the project will start simultaneously.

Retrospective part

In each project site, relevant data concerning SRE incidence and treatment will be gathered retrospectively for 25 consecutive patients with metastatic breast carcinoma diagnosed since the beginning of 2000. The data will undergo a central statistical processing.

Prospective part

In each project site, 25 consecutive patients with breast carcinoma – diagnosed with metastases affecting the skeleton after the start of this project – will be included prospectively into monitoring. Relevant data concerning the incidence and treatment of skeletal related events will be recorded in a six-month interval. The data will undergo a central statistical processing.

C.1 Population of the patients

Retrospective part

All patients with metastatic breast carcinoma and with a minimum 5-year follow-up who have been diagnosed with metastases affecting the skeleton in 2000.

Prospective part

All patients with advanced breast carcinoma who will be diagnosed with metastases affecting the skeleton after the start of this project.

C.2 Involved centres

All Complex Cancer Centres (CCCs) in the Czech Republic and selected centres in Slovakia will be invited to participate in the project.

C.3 Collected data

The set of examined parameters is listed in Table 1.

Table 1: Parameters examined in patients involved in the IKARUS project.

Group of parameters	Parameters
Basic identification data	Centre ID Patient ID Patient initials
Demographic data	Date of birth Date of diagnose Menopause status TNM classification ER, PgR, HER
Treatment data	Adjuvant chemotherapy Adjuvant hormone therapy
Survival data	Date of death or last contact Date of relapse
Bone metastases and skeletal related events (SRE)	Date of diagnosis of bone metastasis Date of diagnosis of SRE Incidence of hypercalcaemia Treatment of SRE
Bisphosphonates	Medicinal product title Start date of therapy Reason for ending the therapy Concomitant analgesic therapy

C.4 Medicinal products being tested

The IKARUS project is not intended to test any specific product. The project aims to analyse data from a population of patients with advanced breast carcinoma with bone metastases. Various products can be used to prevent skeletal related events (SRE). In case of incidence of a SRE, various therapy methods can be used. All patients treated with any method will be included into the IKARUS project.

C.5 Data management

The data can be collected in two ways:

Electronic

A parametric electronic questionnaire will be used with a central data repository in the statistical centre. The individual centres will access this questionnaire through a web form. The electronic CRF will use the system TrialDB, developed at Yale University, Connecticut, USA. The data digitization will be performed by the means of web forms

and a secured communication, using a 128-bit key for encryption. Only authorized persons will have access to the CRF, using their login and access code.

Classic

A printed CRF will be used, a central digitization will be performed by trained personnel directly in the statistical centre.

C.6 Reporting of adverse events

As demanded by the company Novartis, all serious adverse events (SAE) must be reported in all patients with a completed CRF who have been treated with Novartis products.

The electronic CRF includes several items concerning the safety of the overall therapy. For the patients using Novartis products, an automatic checkup for potential serious adverse events (SAE) is set in the system, as well as an automatic dispatch of these SAE to Novartis. The automatic checkup and dispatch of potential SAE is performed once a day.

For all other patients with a completed CRF who have been treated with products from other companies, the doctors participating in the project must report the SAE in compliance with rules and legislation in force.

C.7 Ethics committee approval

Does not apply (a strictly non-interventional project).

C.8 Competent authority approval

The competent authority will be informed about the project.

C.9 Personal data protection

All patients involved in this project will be identified by an unique ID. It will be impossible to reveal the patient's identity from this ID. The source data will be checked by the monitor. Only the examining physician or accredited healthcare professionals will be acquainted with the unique ID of a given patient.

The personal identification data collected in this project are the following: date of birth, gender and initials. The character of identifiers of personal data follows all relevant legal requirements, as confirmed by an assignee (with regard to the size of

population and to the access to other data, these identification data can be considered as non-specific and the individual patients as unidentifiable).

C.10 Data storage and management

The data will be stored in the Oracle 9i database, on a server of the Masaryk University (Brno, Czech Republic).

C.11 Quality assurance and quality control

An independent monitoring will be performed in all centres involved in the project, with the objective to check data consistency in the CRF of the project and in the source documentation. The monitor will also oversee an undesired selection of patients included in the project.

C.12 Statistical data processing

With regard to the explorative character of the project, methods of descriptive statistics will be employed, commonly used in epidemiologic studies. The primary objective of the project is the assessment of frequency of incidence of skeletal related events in a target patient population; the estimate will be accompanied by an appropriate confidence interval. The Kaplan-Meier method will be employed for the survival analysis. The statistical data processing will involve a correlation analysis of possible relations between collected data.

The final report will involve a descriptive evaluation of all monitored parameters in individual patients. A descriptive statistical analysis will respect the type of data (continuous, ordinal and binary) and the distribution of values (normal, log-normal etc.). Basic statistical parameters will be calculated (average, median, relative rate) and confidence measures in the assessment of parameters in groups of patients (SD, SE, confidence interval, percentiles).

Within the statistical processing, data from all patients included in the study will be used; no targeted selection will be performed.