SYNOPSIS

Title
NMSG 20#13

A phase II study of carfilzomib-cyclophosphamide-dexamethasone and high-dose melphalan followed by randomization between observation or maintenance with carfil-zomib and dexamethasone in patients with relapsed multiple myeloma after high-dose melphalan with autologous stem cell support

Design
Prospective non-randomised phase II study followed by randomized open-label study

Objectives

- **Primary end-points:** Comparison of time to progression (TTP) after first high-dose melphalan with stem cell support (HDT) and TTP after a sec-ond HDT combined with carfilzomib-cyclophosphamide-dexamethasone (CAR-CY-DEX). Comparison of TTP between carfilzomib-dexamethasone maintenance and observation in patients treated with a second HDT.
- **Secondary end-points:** Toxicity of CAR-CY-DEX as induction regime and carfil-zomib as part of the high-dose melphalan conditioning Response rates of induction therapy and HDT Time to marrow regeneration (neutrophil- and platelet recov-ery) after the HDT Toxicity of maintenance treatment with carfilzomib-dexamethasone Comparison of overall survival between carfilzomib-dexamethasone maintenance and observation in patients treated with a second HDT Quality of life

Patient population
Multiple myeloma patients with first relapse more than one year after single or dou-ble high-dose melphalan with stem cell support and who have at least 2.0 x 106 CD34+ stem cells/kg body weight saved in the freezer and are eligible for a second HDT

Number of patients
200

Inclusion criteria
Myeloma diagnosis according to IMWG criteria First treatment demanding relapse after HDT according to IMWG criteria More than 2.0 x 106 CD34+ stem cells / kg body weight in the freezer for stem cell support Signed informed consent given prior to any study related activities have been performed Age > 18 years

Exclusion criteria
Demographic
Allogeneic transplantation scheduled as a part of the treatment
Treatment demanding relapse less than one year after HDT Myeloma treatment after the first HDT, except radiotherapy, bisphosphonates, denosumab and corticosteroids less than 6 days for symptom control Patients not having received HDT as first line treatment Previous treatment with carfilzomib Expected survival of less than six months Performance status (WHO) ≥ 3

Laboratory

Serum M-component < 5 g/l and urine M-component < 200 mg/l Any of the following laboratory abnormalities:

o Absolute neutrophil count (ANC) < 1.0 × 109/L

o Hemoglobin < 5 mmol/L (<80 g/L) (prior RBC transfusion or recom-binant human erythropoietin use is permitted)

o Platelet count < 50 × 109/L (< 30 × 109/L if myeloma involvement in the bone marrow is > 50%)

o Serum ALT or AST > 3.5 times the upper limit of normal and serum direct bilirubin > 34 µmol/L (2 mg/dL)

o Creatinine clearance (CrCl) < 15 mL/minute, either measured or cal-culated using a standard formula

Concurrent conditions Concurrent disease making treatment with carfilzomib, cyclophosphamide or dexamethasone unsuitable Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to enrolment Major surgery within 21 days prior to enrolment Acute active infection requiring treatment Known or suspected hypersensitivity or intolerance to melphalan, dexa-methasone or Captisol® (a cyclodextrin derivative) Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrolment, NYHA Class III or IV heart failure, uncon-trolled angina, clinically significant pericardial disease, uncontrolled severe arrhytmias, or cardiac amyloidosis LVEF <40%, determined by 2-D transthoracic echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA) Pleural effusions requiring thoracentesis or ascites requiring paracentesis within 14 days prior to enrolment Serious hepatic disorder, including active hepatitis B or C infection Other serious medical or psychiatric illness likely to interfere with participa-tion in this clinical study Use of any investigational agents or experimental medical device within 28 days prior to enrolment into the study

Ethical/other

Carfilzomib-cyclophosphamide-dexamethasone, high-dose melphalan with autologous stem cell

support and carfilzomib/dexamethasone maintenance versus observation in relapsed

multiple myeloma

Version 1.3 8/52 30-12-2013

Pregnant or lactating females Females of childbearing potential must agree to ongoing pregnancy testing and to practice contraception Male subjects must agree to practice contraception

Treatment schedule

Induction regime:

Four cycles of CAR-CY-DEX (Cycle 1 with iv carfilzomib 20 mg/sqm on days 1 and 2, and iv carfilzomib 36 mg/sqm on days 8, 9, 15 and 16. Cycle 2 - 4 with iv carfilzomib 36 mg/sqm on days 1, 2, 8, 9, 15 and 16. P.o.

cyclophosphamide 300 mg/sqm on days 1, 8 and 15 and p.o. dexamethasone 20 mg on days 1, 2, 8, 9, 15 and 16 in each 28-days cycle).

Conditioning regimen:

Iv carfilzomib 27 mg/sqm on day –2 and –1

Iv melphalan 200 mg/sqm on day –2

> 2.0 x 106 CD34+ stem cells/kg body weight on day 0

Granulocyte colony stimulating factor, prophylactic antibiotics, antiviral medication and antifungal therapy according to local routine. The use of herpes zoster prophy-laxis is mandatory.

Maintenance treatment: Two months after HDT patients are randomized (1:1) to either observation or maintenance therapy with iv carfilzomib 27 mg/sqm every sec-ond week and p.o. dexamethasone 20 mg every second week. The maintenance dose of carfilzomib will be escalated to 56 mg/sqm after 4 weeks provided acceptable side effects.

The randomization procedure will be stratified according to relapse 1 – 2 year or > 2 years after HDT, ISS stage and standard versus high-risk cytogenetics.

Participating centres

Centres within the Nordic Myeloma Study Group (NMSG)