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2nd Nordic Mantle-Cell Lymphoma protocol

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Registration date 05/02/2008	**Overall study status** Completed	
Last Edited 13/12/2016	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
Primary treatment with high-dose therapy and purged/unpurged autologous stem cell transplantation (ASCT), including rituximab for induction and in-vivo purging and maintenance

Acronym

Nordic MCL2 Trial

Study objectives
The 2nd Nordic Mantle Cell Lymphoma protocol plans to test:
1. The effect on failure-free, progression-free and overall survival of intensified induction chemotherapy, by maxi-cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), high-dose cytarabine and rituximab followed by carmustine, etoposide, cytarabine, and melphalan (BEAM)/carmustine, etoposide, cytarabine, and cyclophosphamide (BEAC) and autologous stem cell transplant
2. The effect on the stem-cell products of in-vivo purging with rituximab 375 mg/m^2, two doses subsequent to mobilisation with high-dose cytarabine
3. The effect of further rituximab treatment post-transplant in patients with an increasing polymerase chain reaction (PCR) signal in a quantitative PCR

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scientific Ethics Committee of Copenhagen and Frederiksberg, 25/04/2001, ref: 02-008/01

Study design
Unrandomised phase-II study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mantle cell lymphoma

Interventions
INDUCTION:
Three series of maxi-CHOP and Ara-C and two series of rituximab:
1. Maxi-CHOP:
1.1. Cyclophosphamide (CTX) 1200 mg/m^2 day one
1.2. Doxorubicin 75 mg/m^2 day one
1.3. Vincristine 2 mg total day one
1.4. Prednisolone 100 mg total days one to five
The maxi CHOP infusions are given as bolus according to local routine. Forced diuresis and Mesna is optional.

2. High-dose Ara-C:
2.1. Patients 60 years of age or younger: Ara-C 3 g/m^2 every 12 hours for two days as 3-hour infusions (total of 4 infusions)
2.2. Patients greater than 60 years: Ara-C 2 g/m^2 every 12 hours for two days as 3-hour infusions

Supportive care including ultracortenol eyedrops should be given according to local routine. The interval between each series of maxi-CHOP and high-dose Ara-C is three weeks. Following each

treatment it is recommended that, from day eight, the haematological values should be monitored regularly until the white blood cells (WBC) and platelets start to rise. Supportive treatment with haemopoietic growth factor, e.g. filgrastim 5 microgram/kg subcutaneous (s.c.) daily, during the period of neutropenia can be given according to local routine. Also prophylactic antibiotics may be given according to local routine. Dose reductions of marrow-toxic drugs may be done according to local routine, or according to the following guidelines:
2.2.1. If the leucocyte count is not at least 3 x 10^9/l or the platelet count not at least 150 x 10^9 /l 21 days after the preceding course of chemotherapy, the dosages of CTX and doxorubicin or of Ara-C is reduced to 2/3 of initial dosage
2.2.2. If the leucocyte count is not at least 2 x 10^9/l or the platelet count not at least 100 x 10^9 /l 21 days after the preceding course of chemotherapy, the dosages of CTX and doxorubicin or of Ara-C are reduced to 1/3 of initial dosage
2.2.3. If the leucocyte count is not at least 1.5 x 10^9/l or the platelet count not at least 75 x 10^9 /l 21 days after the preceding course of chemotherapy, bone-marrow toxic therapy (CTX, doxorubicin, Ara-C is withheld until the counts rise again

3. Rituximab:
375 mg/m^2 given from cycle 2 at day one; rituximab will be given with standard infusion rates and following standard pre-treatment with paracetamol and antihistamine treatment.

STEM CELL MOBILISATION:
The third dose of HD-Ara-C is used as stem-cell mobilisation, followed from day five by filgrastim 10 microg/kg s.c. once daily.

IN-VIVO PURGING:
Rituximab 375 mg/m^2 is given at days one and nine after the start of mobilising HD-Ara-C.

STEM CELL HARVEST:
To be done according to local routine.

IN-VITRO PURGING:
Following stem-cell harvest, the fresh product may be subject to in-vitro purging according to local routine. Alternatively, the product may be frozen, while being assessed for tumour-cell contamination. If found contaminated, the product may be in-vitro purged upon thawing prior to re-infusion.

CONSOLIDATION (optional):
A fourth course of maxi-CHOP and HD-Ara-C may be given following the stem-cell harvest, depending on local circumstances (queue in transplant unit etc). If a sufficient number of stem cell is not reached after one mobilisation, the stem cell harvest may be repeated following this course of HD-ara-C. In that case, the rituximab in-vivo purging should be repeated also.

HIGH-DOSE THERAPY: BEAM OR BEAC*:
1. BEAM:
1.1. Carmustine (BCNU) 300 mg/m^2 (1-hour intravenous [i.v.] infusion) day one
1.2. Etoposide 100 mg/m^2 (1-hour i.v. infusion) every 12 hours days two to five
1.3. Ara-C 400 mg/m^2 (24-hour i.v. infusion) days two to five
1.4. Melphalan 140 mg/m^2 (1-hour i.v. infusion) day six

2. BEAC:
As BEAM, with cyclophosphamide 3000 - 6000 mg/m^2 replacing melphalan according to local routine.

*Small variations of the BEAM and BEAC regimens do occur at various centres, and the high-dose therapy should always be given according to local routine.

Filgrastim support post-transplant: Filgrastim 5 microg/kg s.c. once daily, starting day five or according to local routine.

Infection prophylaxis: Pneumocystis carinii and herpes prophylaxis is obligatory, given according to local routine. Other prophylaxis is given according to local routine.

RITUXIMAB PRE-EMPTIVE TREATMENT POST-TRANSPLANT:
Responding patients, in whom qualitative polymerase chain reaction (PCR)-negative status converts to a PCR-positive status, or in whom two serial quantitative PCR assays show increasing minimal residual disease without clinical, radiological or morphological signs of progression, should receive rituximab 375 mg/m^2 weekly for four weeks, and the PCR of blood and bone marrow repeated one month later.

The treatment lasted six months, and the duration of follow-up is to death or relapse.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), rituximab, BEAM (carmustine, etoposide, cytarabine, melphalan), BEAC (carmustine, etoposide, cytarabine, cyclophosphamide), autologous stem cell transplant

Primary outcome(s)
Event-free survival, assessed every four months the first two years, subsequently every six months until death or relapse

Key secondary outcome(s))
1. Progression free and overall survival
2. Molecular remission duration
3. Tumour-cell free stem-cell products

Assessed every four months the first two years, subsequently every six months until death or relapse.

Completion date
31/12/2006

Eligibility

Key inclusion criteria

1. Newly diagnosed patients fulfilling the diagnostic criteria of mantle cell lymphoma
2. Ann Arbor stage II - IV
3. 18 - 65 years of age, either sex
4. Have given informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Any organ dysfunction or failure that may present a risk to the patient during any phase of protocol treatment:
1. Renal function decreased corresponding to P-creatinine and/or blood urea nitrogen (BUN) increased to 2 x upper normal limit, unless clearly explained by the lymphoma
2. Liver biochemistry abnormal (P-Bilirubin, alanine aminotransferase [ALAT] or alkaline phosphatase increased to 2 x upper normal limit) unless clearly explained by the lymphoma
3. Chronic infections including human immunodeficiency virus (HIV) and hepatitis B
4. Pregnancy or lactation: for women of the childbearing age at inclusion adequate anti-conception must be secured (P-pills, depot injection gestagen or intra-uterine device)
5. Other malignancy except skin (non-melanoma) or cervix carcinoma stage 1

Date of first enrolment
25/04/2001

Date of final enrolment
31/12/2006

Locations

Countries of recruitment
Denmark

Finland

Norway

Sweden

Study participating centre
Rigshospitalet
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Sponsor information

Organisation
Individual sponsor (Denmark)

Funder(s)

Funder type
Research organisation

Funder Name
Nordic Cancer Union (Norway) (grant refs: 0504-D, 5-03-D, 7-05-D)

Funder Name
Kræftens Bekæmpelse (grant ref: DP 4-072)

Funder Name
Novo Nordisk Foundation (Novo Nordisk fonden) (Norway)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/10/2008		Yes	No

Results article	results	25/02/2010		Yes	No
Results article	results	01/08/2012		Yes	No
Results article	results	02/12/2016		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes