**Nordic Lymphoma Group**

**NLG-MCL5 (MARiT)**

**Rituximab, High Dose Ara-C and Dexamethasone or Betamethasone Followed by BEAM in High-risk Mantle Cell Lymphoma Patients 18-65 years**

**A Nordic Lymphoma Group Phase-II Trial**

**EudraCT number:** 2011-001557-85

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The Nordic MCL5 study is paralleled by a identical British study headed by Simon Rule, Plymouth and Stephen Robinson, Bristol. The studies are conducted separately, with different EudraCT numbers and sponsors, but built similarly to enable pooling of the results.

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Revised history

<table>
<thead>
<tr>
<th>Version</th>
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<tr>
<td>5.0</td>
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<td>The changes involves the following parts of the protocol (changes highlighted in bold type):</td>
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<td>Title: Rituximab, High Dose Ara-C and Dexamethasone or Betamethasone Followed by BEAM in High-risk Mantle Cell Lymphoma Patients 18-65 years</td>
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<td>Page 2</td>
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<td>The British PI and sponsor are omitted from the Nordic protocol. The Nordic MCL5 study is paralleled by a identical British study headed by Simon Rule, Plymouth and Stephen Robinson, Bristol. The studies are conducted separately, with different EudraCT numbers and sponsors, but built similarly to enable pooling of the results.</td>
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<td>Page 7</td>
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<td>Only MIPI-B high risk patients are included (Appendix 7). The results in all patients will be compared to a historic control of corresponding patients in the Nordic MCL2 Trial.</td>
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<td>Inclusion criteria:</td>
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<td></td>
<td>1. Age 18-65 years</td>
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<td>2. 3. Nordic countries: high risk patients defined by Mantle Cell Lymphoma International Prognostic Index Biological (MIPI-B, Appendix 7), or, in patients without assessable Ki67 expression, by the MIPI. In UK all patients in need of treatment.</td>
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</table>
Prognostic Indices

Validation of the MIPI in the NLG-MCL2 population showed that the MIPI, the simplified MIPI (sMIPI) and the MIPI-biological (MIPI-B), (Details of MIPI and MIPI-B calculation : Appendix 7)

Objectives of the study

... If Ki67 is not available, MIPI high risk patients can be included.

Rituximab - ... Rare, sporadic cases of progressive multifocal leucoencephalopathy (PML) have been reported following rituximab treatment. Regular monitoring of neurological events is part of the protocol.

Stem cell harvest:
The 6th cycle of Ara-C is normally used for mobilization of stem cells. Cycle 5 may also be used at the discretion of the treating physician.

Radiotherapy: This is rarely indicated in MCL which is a systematic disease. In situation where radiotherapy is deemed to the benefit of the patient, it can be ordinated at the discretion of the treating physician, and should not lead to exclusion of the study.

Other treatments/Medications: should only be given when approved by the study investigator.

Response criteria: Cheson et al 1999 used because PET scan is not yet sufficiently validated in MCL.

Table 2

UK-Unk

The Nordic MCL5 protocol will therefore be a phase-II trial aiming at including enough patients to be able to analyse 60 MIPI-B high risk patients for response, and all patients for time to treatment failure and overall survival.
| Page 36 | Appendix 7  
|---------|---------------------------------------------------|
|        | addition of  
|         | Mantle Cell Lymphoma International Prognostic Index MIPI  
|         | 0.03535 x age (years) +  
|         | 0.6978 (if ECOG/WHO > 1) +  
|         | 1.367 x log_{10}(LDH/ULN) +  
|         | 0.9393 x log_{10}(WBC count)  
|         | MIPI-B Low risk: < 5.70  
|         | MIPI-B Intermediate risk: 5.70 – less than 6.20  
|         | MIPI-B High risk: >6.20  
| Page 36 | MIPI and MIPI-B is easily calculated via the web (Example: Calculate by QxMD)  
| Page 38 | Addition of study centre 14  
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1. Study Synopsis

Rituximab, High Dose Ara-C and Dexamethasone or Betamethasone Followed by BEAM in High-risk Mantle Cell Lymphoma Patients 18-65 years

Trial Design

MCL5 Protocol

**Total number of patients:** 60

**Expected accrual time:** May 2011 – June 2013

**Study design:** Phase II multicenter trial in Nordic countries.

**Objectives of study:**

Primary: To increase the rate of complete response and complete response unconfirmed in mantle cell lymphoma by intensified immunochemotherapy with rituximab, high-dose Ara-C and dexamethasone. The results will be compared to a historic control of corresponding patients in the Nordic MCL2 Trial.

Secondary:
- To improve the secondary end points (below).
- To establish a biobank aiming at further studies of biomarkers

Tertiary: To increase the proportion of patients without detectable minimal residual disease, and to treat recurrence of minimal residual disease without clinical disease with rituximab (preemptive treatment).
Safety and efficacy is evaluated at an interim analysis after the first ten patients and compared to a historical control of the previous Nordic MCL2 study. Early response is additionally evaluated with molecular (MRD) and metabolic (PET) staging after 3 (CT and MRD) and 5 (CT, FDG-PET, MRD) cycles and 3 months posttransplant.

Primary endpoint:

- Rate of complete response (CR) and complete response unconfirmed (CRu) pretransplant

Secondary endpoints:

- Time to treatment failure
- Progression free survival
- Overall survival
- Toxicity
- Evaluation of response with FDG-PET
- Evaluation of response with MRD
- Stem cell harvest yield
- Evaluation of biomarkers for biology and prediction of response and response duration

Criteria for patient selection:

**Inclusion criteria:**
1. Age 18-65 years.
2. Histologically confirmed (according to the WHO classification) mantle cell lymphoma stage II-IV at time of diagnosis. The diagnosis has to be confirmed by phenotypic expression of CD5, CD20 and cyclin D1 or the t(11;14) translocation.
3. Nordic countries: high-risk patients defined by Mantle Cell Lymphoma International Prognostic Index Biological (MIPI-B, Appendix 7), or, in patients without assessable Ki-67 expression, by the MIPI.
4. No previous treatment for lymphoma except one cycle of any chemotherapy regimen.
5. WHO performance status of 0 – 2.
6. Life expectancy of more than 3 months.
7. Written informed consent.

**Exclusion criteria:**
1. Severe cardiac disease: NYHA grade 3-4.
2. Impaired liver, renal (GFR<50ml/min) or other organ function not caused by lymphoma, which will interfere with the treatment.
3. Pregnancy/lactation
4. Men or women of reproductive potential not agreeing to use acceptable method of birth control during treatment and for six moths after completion of treatment.
5. Any other prior malignancy than non-melanoma skin cancer or stage 0 (in situ) cervical carcinoma.
6. Known seropositivity for HIV, HCV, HBsAg or other active infection uncontrolled by treatment.
7. Psychiatric illness or condition which could interfere with their ability to understand the requirements of the study.
8. Treatment with any experimental compound within 30 days of start of MCL5 protocol treatment.
9. Patients with known allergy towards murine proteins.
10. Recent vaccination with live virus vaccine.

Treatment plan:

Six cycles of rituximab, high dose Ara-C and dexamethasone, cycle duration 21 days, followed by high dose chemotherapy (HDCHT) with BEAM and autologous peripheral stem cell rescue for a total treatment duration of 6 months. Preemptive therapy with rituximab at isolated molecular relapse post-transplant (increasing MRD signal without clinically detectable disease). Follow up regularly for five years, then annually until relapse.

- **Rituximab**: 375 mg/m$^2$ i.v.d 1. In cycle 1 the rituximab dose is split 1/3 on day 1 and 2/3 on day 2 to avoid reaction.
- **Ara-C**: <60 years: 3g/m$^2$/1 hour infusion every 12 hour d 1-2, ≥60 but <66 years: 2g/m$^2$/1-hour i.v. infusion every 12 hour d 1-2. GCS-F support mandatory from day 3
- **Dexamethasone** 40mg p.o. d 1-4 or equivalent dose of betamethasone: 32 mg p.o. d 1-4.

2. Study background and rationale

Mantle cell lymphoma (MCL) is incurable and has a short median survival with standard chemotherapy (1). It often presents with disseminated disease including bone marrow and gastro-intestinal tract involvement and a huge tumour burden. A characteristic cytogenetic aberration is detectable in >90% patients, the t(11;14)(q13;q32) by which the cyclin D1 gene on chromosome 11 is translocated to the enhancer of the IgH gene on chromosome 14, leading to cyclin D1 protein over expression. The genetic changes underlying MCL are complex including concomitant disturbances in the control of proliferation, apoptosis and DNA repair contribute to the resistance to treatment (2).

Treatment

**CHOP and Ara-C**

MCL has for long been considered one of the lymphoma subtypes with the poorest prognoses with only about 3 years median survival from the time of diagnosis. However, a recent update of two cohorts of MCL patients of prospective European MCL protocols showed prolongation of median survival to almost 5 years, mainly due to treatment with CHOP and R-CHOP) (3). The still high relapse rate and mortality, leads to a continuing active search of more effective compounds and regimens in MCL. Ara-C, given as DHAP (dexamethasone, Ara-C and cisplatinum) or as high-dose Ara-C alone plus rituximab is highly active as salvage therapy in MCL not responding to CHOP or R-CHOP (4, 5).
Following the disappointing results of the Nordic MCL1-study based on escalated CHOP + ASCT with only 25% CR before transplant and a continuous pattern of relapse, the Nordic MCL Group conducted the MCL2 Trial with a regimen of R-maxi-CHOP alternating with R-high dose (HD) Ara-C followed by ASCT (6). Much higher response rates and long-term progression-free and overall survival were achieved compared to the MCL1 trial (7): The regimen of maxi CHOP alternating with HD-Ara-C (2-3g/m²/1 hour twice daily for two days) for 3 cycles of each block and with the addition of rituximab from cycle 4 followed by consolidating BEAC/BEAM more than doubled the complete response (CR + CRu) rate before transplantation to 55% and increased the median response duration from the 3 years of the MCL1 to not reached of the MCL2. In a recent update, the 10-year response duration rate was 54% and the 10-year survival 57% (Geisler et al ASBMT 2011).

The European Mantle Cell Network has recently completed a study comparing R-CHOP versus R-CHOP alternating with R-DHAP in first line induction therapy before the myeloablative consolidation and found R-CHOP alternating with R-DHAP more effective in terms of response and response duration (8). They conclude that the standard of care of MCL patients up to 65 years should be induction therapy including Ara-C and rituximab followed by ASCT. The French LyMa Trial took the next step by leaving out the CHOP components and giving induction with 4 cycles of R-DHAP only, followed by high-dose therapy with BEAM and the stem-cell transplant (9). They achieved 82.5% and 92% complete and overall response, respectively, before the ASCT, demonstrating that the CHOP components may have minor importance in MCL.

More intense Ara-C containing regimens like hyperCVAD + methotrexate and Ara-C (M/A) in combination with rituximab have induced similar high complete remission rates of >80% in single institution trials (10), but this could not be reproduced in a multi-institution trial (11). In both studies, the combination was associated with quite high toxicity, possibly due to the use of high-dose methotrexate, which may have a limited importance in MCL (12).

High-dose Ara-C has not been tested first-line as single chemotherapy but based on the encouraging results of the Nordic MCL2 study with alternating R-CHOP and R-Ara-C, the European MCL younger study of alternating R-CHOP and R-DHAP, and the LyMA results (7-9) it is now warranted to explore whether the outcome can be even better by leaving out the CHOP components altogether and the cisplatinum. If high-dose Ara-C monochemotherapy is shown to be effective and tolerable, this regimen may then become the backbone chemotherapy of new studies comparing other agents, e.g. new CD20 antibodies.

**Ara-C pharmacology**

Ara-C (cytarabine) is an antimetabolite analogue of cytidine with arabinose as sugar moiety instead of ribose. Cytarabine is converted to the triphosphate form within the cell and then competes with cytidine for incorporation into DNA, mainly DNA polymerase, leading to cessation of DNA replication, prolongation and repair, specifically during the S-phase of the cell cycle.
Pharmacokinetics:
Ara-C is rapidly and widely distributed into tissues and also crosses the blood-brain barrier to a limited extent. During a continuous i.v. or s.c. infusion, cytarabine concentrations in the cerebrospinal fluid (CSF) are higher than those attained after rapid i.v. injection and are about 40 to 60% of plasma concentrations. Ara-C is converted intracellularly into its active form (cytosine arabinoside triphosphate), which inhibits DNA polymerase by competition with its physiological substrate, deoxycytidine triphosphate. It is metabolized rapidly by cytidine deaminases. Ninety percent of a given dose is excreted in the kidney as the inactive metabolite uracil arabinoside (Ara-U) (13). High dose Ara-C follows similar kinetics in plasma, although a slow terminal phase may appear, which may contribute to toxicity. In patients with decreased renal function Ara-U half-life was about 75 hours and the Ara-U serum levels became about 12-fold higher than in normal circumstances.

Side effects:
Neurotoxicity: High dose (HD) Ara-C has caused severe CNS toxicities as paraplegia, disseminated necrotizing leukoencephalopathy, blindness, cerebral and cerebellar dysfunction including personality changes, somnolence and coma, all which are usually reversible. Ara-C neurotoxicity is correlated to decreased renal function probably linked to the accumulation of Ara-U and is rarely seen in patients with normal renal function (14, 15). It is therefore important to treat only patients with adequate renal function and to prevent renal damage due to tumour lysis by adequate hydration and allopurinol.

Other side effects: Ara-C is myelotoxic, necessitating regular control of white blood counts and platelet counts. After HD Ara-C treatment GCS-F support is mandatory to keep treatment intervals and shorten the nadir period. Reversible corneal toxicity and hemorrhagic conjunctivitis may be prevented or diminished by prophylaxis with a local corticosteroid eye drop or high dose systemic steroids. HD Ara-C regularly leads to reversible gastrointestinal mucositis. Reversible hepatic-, lung- and skin toxicity are not rare.

In the light of the complete absence of severe Ara-C toxicity so far in the Nordic MCL2-and 3 protocols we consider a trial of HD Ara-C monochemotherapy feasible in younger patients with normal renal function (8,16).

Rituximab
The anti-CD20 antibody rituximab combined with CHOP chemotherapy increases response rates and prolongs PFS but not survival (17). Immunochemotherapy with anti-CD20 antibodies and chemotherapy is now considered standard of care in MCL.
High dose therapy with autologous stem cell rescue
Following CHOP induction, high dose radiochemotherapy with autologous stem cell rescue significantly prolonged the progression-free survival compared to Interferon-α in a randomized trial to interferon maintenance by The European MCL Network, and is since considered to be standard in Europe for younger mantle cell patients (18). In the European MCL younger trial (R-CHOP compared to R-CHOP alternating with R-DHAP), the MRD measured by quantitative PCR was highly significantly reduced by the subsequent high-dose radiochemo-therapy and MRD-negativity led to prolongation of survival (19).

Prognostic indices
A Mantle Cell Lymphoma International Prognostic Index, the MIPI, was proposed by Hoster et al in 2008 (20). Validation of the MIPI in the NLG-MCL2 population showed that the MIPI and the MIPI-biological (MIPI-B), incorporating the Ki-67 expression as marker of proliferation, all segregate the risk groups better than the International Prognostic Index (IPI) for aggressive lymphomas (21). The MIPI-B identified almost half of the patients (46%) as having high-risk disease, with a significantly poorer response rate (Table 2) and a median survival less than 5 years, findings now confirmed by our recent MCL2 update (Fig. 2). Also the patients of the intermediate risk group, however, had a continuous mortality many years after end of treatment. (Details of MIPI and MIPI-B calculation: Appendix 7).

In conclusion, although the present Nordic MCL regimen may be considered as one the most effective to date, improvement of treatment is still clearly warranted in the majority of MCL patients. Based on the present NLG and European MCL Network experience we consider HD Ara-C the most active drug in MCL. We aim to study the efficacy of HD Ara-C with rituximab and dexamethasone in patients younger than 66 years in MIPI-B high-risk.

Fig. 2

Early predictors for response

a. MRD.
Molecular remission is a strong predictor of remission (19). By repeat estimates of MRD we will have an early indicator of the rapidity of tumour clearance by treatment.

b. PET.
Fluorodeoxy-glucose (FDG)-PET is proposed by Cheson et al to separate CRu from PR in lymphoma patients with residual mass (22, 23). There is still limited knowledge of the benefit of PET scans in MCL, and it is important to investigate the native pattern of uptake in this lymphoma. The proliferation rate is reflected by the FDG uptake and varies widely in lymphoma. PET evaluation early in treatment is subject to pitfalls due to inflammatory response also enhanced by rituximab (24, 25). Nevertheless in the NLG-MCL3 study we found an excellent correlation with molecular remission and PET negativity at cycle 5 (16). In this study we will study the value of PET and MRD to predict CR and time to progression.

c. Rituximab concentration.
Despite widespread use of rituximab in lymphoma treatment very little is known about optimal dosing and schedule. Rituximab concentration in the blood has been proposed to correlate to residual tumour load. A low concentration is hypothetically a mirror of consumption due to binding capacity in CD20 expression populations ie lymphoma.

3. Objectives of the study

**Primary**: To increase the rate of complete response and complete response unconfirmed in mantle cell lymphoma by intensified immunochemotherapy with rituximab, HD Ara-C and dexamethasone. Only MIPI-B high risk patients are included. The results of the MIPI-B patients will be compared to a historical control (the Nordic MCL2). If Ki-67 is not available, MIPI high-risk patients can be included.

**Secondary**: To improve the secondary end points (below), including achievement of molecular remission.

**Tertiary**: To maintain molecular remission by intervention with rituximab in patients with recurrence of minimal residual disease without clinical signs of disease (pre-emptive treatment).

Safety and efficacy is evaluated at an interim analysis after the first ten patients and compared to a historical control of the previous Nordic MCL2 study.

Early response is additionally evaluated with molecular (MRD) and metabolic (PET) staging after 3 (CT, MRD) and 5 (CT, PET, MRD) cycles and 3 months posttransplant.

**Primary endpoint:**

- The rates of complete response (CR) and complete response unconfirmed (CRu) after induction cycle 5.
Secondary endpoints:

- Time to treatment failure
- Progression free survival
- Overall survival
- Toxicity
- Evaluation of response with PET
- Evaluation of response with MRD
- Stem cell harvest yield
- Evaluation of biomarkers for biology and prediction of response

4. Diagnosis and tissue collection

A surgical biopsy should be preferred to needle biopsy to secure enough tumour material for further studies (TMA is not possible in needle biopsies!). Frozen material should be secured if possible in addition.

A histological diagnosis of mantle cell lymphoma is established by the local pathologist at each centre. The diagnosis has to be confirmed by expression of CD5, CD20 and cyclin D1 or demonstration of a t (11;14).

In all cases, a paraffin block will be sent to a member of the central pathology board in each country for establishment of a tissue microarray (TMA) biobank and for confirmation of diagnosis. New stainings for cyclin D1, CD20, CD5, CD23, Ki67 and SOX11 and Ki67 will be performed centrally. In the Nordic countries, the percentage of Ki67 expression will also be assessed by the local pathologist at the time of diagnosis. A tissue microarray (TMA) biobank will later be established for future revision and studies of biomarkers. Ten – fifteen additional slices are also stored for future research analyses of gene structures and functions in the central biobank.

Additionally 10ml bone marrow aspirate should be taken to be separated, frozen in DMSO and stored (optional, appendix 4).

5. Methodology

Treatment

This is a prospective, multicenter, phase II clinical trial to determine the efficacy and safety of induction therapy with rituximab and HD Ara-C every three week for 6 cycles followed by BEAM and autologous stem cell rescue as primary treatment in patients <66 years with mantle cell lymphoma.

Four doses of weekly rituximab will be given when molecular monitoring detects a rising level of disease specific molecular marker.

Investigational techniques

FDG-PET is performed pre-treatment (optional), after cycle 5 and 3 months post-transplant if positive pre-transplant.

PCR of t(11;14) or idiotypic Ig heavy chain gene rearrangement are used for estimate of molecular remission and performed after cycle 3, cycle 5 and 3 months post –transplant and
subsequently every 6 months until 5 years (Appendix 3). MRD will also be quantitated in the stem cell harvest.

Samples for rituximab concentration after cycle 5 will be stored.

Ki-67 will be done prospectively assessed by the pathologist of the referring clinic, and the result used for inclusion in the trial. Later, at the central pathology review, the Ki-67 assessment will be done according to the current guidelines, by counting 200 lymphoma cells, i.e. the positive cells among 100 lymphoma cells in two high power fields (26).

6. Evaluation of efficacy and safety

Efficacy

CT-scan of the neck, chest and abdomen will be performed before start of therapy, after induction cycle 3 and 5, and again 3, 6 and 12 months post transplant, and subsequently on clinical indication.

Bone marrow biopsy and aspiration is done for morphology and flow cytometry and MRD detection before start of therapy and then at the same time points as above, but continued every 6 months until 5 years of follow-up (Appendix 3). The bone marrow biopsy is only repeated if there was morphological lymphoma involvement in the previous biopsy. Appropriate investigations of other involved sites should be performed when clinically indicated, eg endoscopy and ENT examination.

If progressive disease based on standard Cheson criteria develops at any time after the third cycle of R-Ara-C during induction, the patient will go off study.

Safety

The safety and tolerability will be assessed by way of clinical examination and relevant laboratory parameters at regular visits. To ensure safety and stem cell harvest outcome an interim analysis will be performed of the first 10 patients pre transplant before inclusion of further patients. More than two patients with life-threatening toxicities, harvest failure or progressive disease should lead to temporary cessation of the trial, and reanalysis.

7. Patient registration and selection

Registration and CRFs

Registration is done by submitting an inclusion/exclusion form by fax to the secretariat in Uppsala, Sweden (address details, see page 1).

The secretariat will issue a unique registration number for each patient. After registration of the patient, a confirmatory receipt will be sent by e-mail.

How and when to send CRFs

CRFs should be submitted as soon as they are completed. This is especially important in the phase I part of the study. If the CRFs are not received by the secretariat in due time, a reminder will be sent.
Inclusion criteria:
1. Age 18-65 years.
2. Histologically confirmed (according to the WHO classification) mantle cell lymphoma stage II-IV at time of diagnosis. The diagnosis has to be confirmed by phenotypic expression of CD5, CD20 and cyclin D1 or the t(11;14) translocation.
3. High-risk patients defined by Mantle Cell Lymphoma International Prognostic Index Biological (MIPI-B, Appendix 7), or, in patients without assessable Ki-67 expression, by the MIPI.
4. No previous treatment for lymphoma except one cycle of any chemotherapy regimen.
5. WHO performance status of 0 – 2.
6. Life expectancy of more than 3 months.
7. Written informed consent.

Exclusion criteria:
1. Severe cardiac disease: NYHA grade 3-4.
2. Impaired liver, renal (GFR<50ml/min) or other organ function not caused by lymphoma, which will interfere with the treatment.
3. Pregnancy/lactation
4. Men or woman of reproductive potential not agreeing to use acceptable method of birth control during treatment and for six months after completion of treatment.
5. Any other prior malignancy than non-melanoma skin cancer or stage 0 (in situ) cervical carcinoma.
6. Known seropositivity for HIV, HCV, HBsAg or other active infection uncontrolled by treatment.
7. Psychiatric illness or condition that could interfere with the capability of the patient to understand the requirements of the study.
8. Treatment with any experimental compound within 30 days of start of MCL5 protocol treatment.
9. Patients with known allergy towards murine proteins.
10. Recent vaccination with live virus vaccine.

Inclusion criteria for high-dose therapy
1. Patients in CR, CRu or PR according to International workshop of standardized response criteria in non-Hodgkin’s lymphomas after induction therapy with HD Ara-C and rituximab.
2. Stem cell harvest of $ \geq 2 \times 10^6 \text{CD34+ cells/kg}$

Exclusion criteria for high-dose therapy
1. Failure to harvest $\geq 2\times 10^6 \text{CD34+ cells/kg}$. Bone marrow can be allowed as stem cell support in such cases.
2. Patients who have not reached CR, CRu or PR after induction treatment.
3. More than 25% tumour cells in the bone marrow by bone marrow biopsy
4. Patients who have not recovered from toxicity of induction therapy.
8. Treatment

**Induction treatment:**
Six cycles of rituximab, HD Ara-C and dexamethasone, cycle duration 21 days, followed by high dose chemotherapy (HDCHT) with BEAM and autologous peripheral stem cell rescue for a total duration of 6 months.
Preemptive therapy with rituximab at isolated molecular relapse post-transplant. Follow up for five years.
In patients with a huge tumour burden and/or a poor performance status pretreatment with steroids or one cycle of any chemotherapy regimen is allowed.

- **Rituximab:** 375 mg/m² i.v. d 1. In cycle 1 the rituximab dose is split 1/3 on day 1 and 2/3 on day 2 (to decrease reaction).
- **Ara-C:** <60 years: 3g/m²/1-hour i.v. infusion every 12 hour d 1-2; >60 but <66 years: 2g/m² 1-hour i.v. infusion every 12 hour d 1-2.
  - G-CSF support mandatory, given according to local routine
- **Dexamethasone** 40mg p.o. d 1-4 or equivalent dose of betamethasone p.o. 32 mg d 1-4. To ensure compliance exact daily doses are dispensed at discharge accompanied by clear information.

**Stem cell harvest:**
The 6th cycle of Ara-C is normally used for mobilization of stem cells. Cycle 5 may also be used at the discretion of the treating physician. Filgrastim (10 µg/kg/day sc) should be given from day 3/4 until stem cell harvest is completed. A minimum of 2x10⁶ CD34+ cells/kg is necessary to proceed to high-dose therapy. For patients who do not mobilize the proper amount of stem cells, a regular bone marrow harvest can be performed or plerixafor used according to local routine.

**In vivo purging:**
Rituximab 375 mg/m² is given as an extra dose for in vivo purging at day 8(9) of the mobilization cycle before stem cell harvest.

**High-dose chemotherapy:**
Patients in CR, CRu or PR as defined by standard methods (according to Cheson 1999 (22), not taking in account molecular response or FDG-PET) after induction treatment will go on to high-dose therapy with BEAM regimen followed by reinfusion with peripheral autologous stem cells at a amount of at least 2 x 10⁶/kg CD34+ cells.

**BEAM:**
- BCNU 300 mg/m² (day 1)
- Etoposide 200 mg/m² (days 1-4 or 2-5)
- Ara-C 400 mg/m² (days 1-4 or 2-5)
- Mephalan 140 mg/m² (day 5 or 6)

Filgrastim (5 µg/kg/day) sc may be given from day 4 after reinfusion of stem cells and until neutrophil recovery.
**Radiotherapy**: This is rarely indicated in MCL which is a systemic disease. In situation where radiotherapy is deemed to the benefit of the patient, it can be ordinated at the discretion of the treating physician, and should not lead to exclusion of the study.

**Other treatments/Medications**: should only be given when approved by the study investigator

### 9. Toxicity and dose reductions

**Rituximab – dose adjustment and reporting serious adverse events**

There will be no reductions or escalations of the rituximab dose. If an infusion related or hypersensitivity reaction to rituximab is seen, the infusion rate of drug administration is altered as described in Appendix 5. The total dose administered remains the same in such cases. In case of a serious or life threatening reaction, the infusion should be terminated and such adverse event reported. Rare, sporadic cases of progressive multifocal leucoencephalopathy (PML) have been reported following rituximab treatment. Regular monitoring of neurological events is part of the protocol.

**Ara-C**

Haematological and non-haematological toxicity will be graded according to the WHO Common Toxicity Criteria. Chemotherapy will be postponed in patients experiencing grade > grade 2 non-haematological toxicity until the patient has recovered from the toxicity. In case of nausea/vomiting, drug therapy may be continued with concomitant administration of appropriate anti-emetics.

**The Ara-C dose** is reduced to 50% if alkaline phosphatase (ALP) increase > 3 times UNL it and transaminase levels increase > 3 times ULN at start of the next cycle.

When neutrophils (ANC) < 1.0 x 10⁹/L and/or platelets < 100 x 10⁹/L at start of the cycle, the next Ara-C cycle should be postponed until these values have been reached and then given at full dose. When dose reductions otherwise are considered, one of the members of the writing committee should be contacted.

**Criteria for discontinuation of study treatment**

In absence of unacceptable toxicity or other cause for discontinuation (see below), patients will receive study treatment as outlined above. The following events are deemed sufficient cause to terminate study treatment:

- Severe (grade 4) non-haematological toxicity except alopecia
- Progressive disease after 3 cycles or later
- The patients own wish to terminate study treatment
- The responsible physician considers a change of therapy would be in the best interest of the patient
10. Tests performed at diagnosis
- Clinical examination and complete medical history.
- Full blood count, biochemistry (creatinine, GFR according to Cockroft-Gault) bilirubin, ALAT, ALP, albumin, LDH, Ig levels.
- Plasma, whole blood and serum for storage.
- Surgical biopsy (avoid needle biopsies if possible to secure enough material) of tumour tissue for morphology and immunochemistry, frozen tissue if possible.
- Bone marrow biopsy/aspiration for morphology, immunochemistry and flow cytometry.
- Bone marrow (10ml) and blood (50ml) to Copenhagen for PCR for t(11;14)/ idiotypic IgH rearrangement (appendix 4).
- Bone marrow aspirate (10-15ml) or blood (in case of leukemic disease) for separation and DMSO freezing of MNC on liquid nitrogen for later phosphoflow signalling analysis is recommended but not mandatory (appendix 4).
- CT-scan of neck, thorax and abdomen/pelvis.
- FDG-PET pre-treatment (optional).
- ENT-examination, gastroscopy/colonoscopy and other examinations if clinically indicated.
- Percentage of Ki-67 expressing cells in diagnostic specimen, by semi-quantitative assessment (“eyeballing”).

11. Tests performed at response evaluation after cycle 3 and 5.
- Clinical examination and complete medical history Full blood count, biochemistry (creatinine, bilirubin, ALAT, ALP, albumin, LDH), Ig levels.
- Bone marrow aspiration for morphology, flow cytometry and PCR.
- (Bone marrow biopsy only if previously morphologically involved).
- CT-scan of neck, thorax and abdomen/pelvis.
- FDG-PET scan only after cycle 5 (not after cycle 3).

12. Tests performed post transplant in follow up (starting 3 months posttransplant)
- Clinical examination and complete medical history every 3 months for 2 years, then every 6 months.
- Full blood count, biochemistry (creatinine, bilirubin, ALAT, ALP, albumin, LDH), levels every 3 months for 2 years, then every 6 months.
- Ig levels at 3, 12, and 24 months.
- Bone marrow aspiration for morphology, flow cytometry and PCR at 3 and 6 months posttransplant and then every 6 month until 5 years.
- (Bone marrow biopsy only if involved in previous sample).
- CT-scan of neck, thorax and abdomen/pelvis at 3, 6 and 12 months posttransplant and then on clinical indication or if MRD positive.
- FDG-PET scan at 3 months posttransplant - only if positive after cycle 5.

Stem-cell harvest:
Samples must be secured in the blood bank for later MRD analysis in Copenhagen (appendix 3). Samples from each harvest day or pooled samples will be shipped to Copenhagen at a later time point agreed upon by the investigator and the Molecular Lab. in Copenhagen.
Haematological and non-haematological toxicity will be graded according to the WHO Common Toxicity Criteria.

Criteria for discontinuation of study treatment
In absence of unacceptable toxicity or other cause for discontinuation (see below), patients will receive study treatment as outlined above. The following events are deemed sufficient cause to terminate study treatment.

- Progressive disease
- Severe (grade 4) non-haematologic toxicity except alopecia
- The patient’s own wish to terminate study treatment
- If the responsible physician believes a change of therapy would be in the best interest of the patient

13. Criteria for evaluation and endpoints

Response criteria: Cheson et al. 1999 used because PET scan is not yet sufficiently validated in MCL.

Complete remission (CR)
Disappearance of all disease-related symptoms and measurable lesions, including normalisation of other abnormal initial parameters (if any) such as biochemical abnormalities definitely assignable to lymphoma (e.g. S-LDH), X-rays and bone marrow. All lymph nodes must have regressed to < 1.5 cm in their largest transverse diameter and to ≤ 1.0 cm for those nodes which were 1.1 to 1.5 cm before treatment.

Complete remission unconfirmed (CRu)
The criteria of a CR are fulfilled, except that residual lymph node(s) mass greater than 1.5 cm have regressed by more than 75% in the sum of the products of the two largest perpendicular diameter(s). A CRu should when possible be assigned to a CR or PR by histological examination (biopsy).

Partial remission (PR)
Decrease of at least 50% in the sum of the product of the two largest perpendicular diameters in all measurable and evaluable lesions and disappearance of disease-related symptoms with no lesion increasing 25% or more in size and without any new lesions appearing.

No change/stable disease (NC)
The patient does not qualify for complete or partial remission or progressive disease.

Progressive disease (PD)
Increase in size of 25% or more of the product of the two largest perpendicular diameters of one or more measurable and evaluable lesions during treatment or the occurrence of new lesions.
Relapse
During follow-up the occurrence of relapse in patients previously registered as being in CR will be registered. The following data will be registered:

1. Relapse yes/no
   if yes:
2. Date of relapse
3. Site of relapse

At relapse, every centre is free to initiate further treatment according to local guidelines. At this point the patient will exit the study, although centres are encouraged to keep sending in follow-up forms to allow establishing the overall survival time.

Endpoint definitions

Time to treatment failure
Time to treatment failure is the interval between the registration date and the date of documented progression or lack of response, first relapse, death for any reason or discontinuation of therapy because of toxicity, whichever occurs first. Otherwise, patients will be censored at the last date they were known to be alive. For patients not responding at any time point on study treatment, TTF is defined as 1 day.

Progression free survival
Progression-free survival is the interval between the first assessment within 3 months of completion of therapy that documents response to the date of disease progression or relapse. Otherwise, the patients are censored at the last date of follow up. Patients still alive in a CR or lost to follow-up are censored at the last date they were known to be alive. Patients who die due to causes other than NHL are censored at the date of death.

Overall survival
Overall survival is the interval between the registration date to the date of death of any cause. Patients still alive or lost to follow-up are censored at the last date they were known to be alive.

Cause of death
During the study and after its completion the cause of death will be recorded according to the following criteria:

1. Lymphoma
2. Treatment toxicity
3. Secondary malignancy
4. Other disease not related to 1, 2 or 3
5. Other cause

14. Reporting adverse events

All adverse events (AE) higher than grade 2 (severe AE’s – SAE’s) occurring during the treatment period and until the end of the last treatment administration will be reported in the treatment
evaluation form. During the follow-up period of at least 5 years, all events suggesting severe organ or immune dysfunction, or secondary cancer must be reported.

**Reporting serious adverse events**

Serious adverse (SAE) are defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment. Unexpected serious adverse events are those SAE’s of which the nature or severity is not consistent with information in the relevant source documents. Adverse events which are considered as serious are those which result in

- Death (including those due to progressive disease)
- A life threatening event
- Unplanned hospitalisation or prolongation of hospitalisation*
- Severe/permanent disability
- A congenital anomaly

* Except for hospitalisation caused by neutropenia, thrombocytopenia and fever, which is considered an expected haematological toxicity.

During the protocol treatment all deaths and all SAE’s that are unexpected must be reported to the national coordinator by e-mail or by fax without delay and within 7 days after being informed of the event. The national coordinator will be responsible for reporting the event to the National Agency and to the data centre at the Uppsala University Hospital Centre. All details should be documented on the Serious Adverse Event and Death Report Forms.

In circumstances where it is not possible to submit a complete report, an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 14 calendar days and sent to the national coordinator. All SAE reports must be dated and signed by the responsible investigator or one of his/her authorised staff members.

At any time after the completion of protocol treatment, unexpected Serious Adverse Events that are considered to be possibly related to protocol treatment and ANY death (regardless the cause) must also be reported using the same procedure, within 7 days after the SAE or death was known to the investigator.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The investigator, using the following definitions, makes the assessment of causality:

<table>
<thead>
<tr>
<th>RELATIONSHIP</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNRELATED</td>
<td>There is no evidence of any causal relationship</td>
</tr>
<tr>
<td>UNLIKELY</td>
<td>There is little evidence to suggest a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medicati</td>
</tr>
<tr>
<td></td>
<td>on). There is another reasonable explanation for the event (e.g. the patients’ clinical condition, other concomitant treatments).</td>
</tr>
<tr>
<td>POSSIBLE</td>
<td>There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial</td>
</tr>
</tbody>
</table>
medication). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROBABLE</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
</tr>
<tr>
<td>DEFINITELY</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
</tr>
<tr>
<td>NOT ASSESSABLE</td>
<td>There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.</td>
</tr>
</tbody>
</table>

The data centre will forward all SAE reports within 24 hours of receipt to the study co-ordinator and the study central data manager.

15. **Study duration:**

16. **Criteria for study discontinuation**
In absence of unacceptable toxicity or other cause for discontinuation (see below), patients will receive study treatment as outlined above. The following events are deemed sufficient cause to terminate study treatment:

- Progressive disease or no response as determined after 3 cycles
- Severe (grade 4) non-haematologic toxicity except alopecia
- The patient’s own wish to terminate study treatment
- The responsible physician considers other therapy the best interest of the patient

17. **Statistical considerations**
Table 2 shows the response rates in the MCL2 protocol:

<table>
<thead>
<tr>
<th>MIPI-B</th>
<th>CR (%)</th>
<th>CRu (%)</th>
<th>CR+ CRu</th>
<th>PR (%)</th>
<th>NR (%)</th>
<th>Unkn (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low: 23 (19%)</td>
<td>13 (57)</td>
<td>3 (13)</td>
<td>16 (70)</td>
<td>7 (30)</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Interm.: 41 (34%)</td>
<td>21 (51)</td>
<td>4 (10)</td>
<td>25 (61)</td>
<td>16 (39)</td>
<td>0</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>High: 55 (46%)</td>
<td>18 (33)</td>
<td>5 (9)</td>
<td>23 (42)</td>
<td>26 (47)</td>
<td>6 (11)</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>52 (44)</td>
<td>12 (10)</td>
<td>64 (54)</td>
<td>49 (41)</td>
<td>6 (5)</td>
<td>Unkn (%)</td>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

| CR + CRu Low + Interm. vs. High: 41/64 (64%) vs 23/55 (42%): P<0.03 |

In a randomised trial aiming to demonstrate an increase of the rate of complete response and complete response unconfirmed (CR/CRu) in the MIPI-B high risk patients from 42 to 60% with a type I error risk of 5% and a type II error risk of 20%, would require 130 patients in each arm. To achieve in a phase-II study a CR/CRu rate >60% that would be significantly better than the 23 of 55 (42%) MIBI-B high-risk patients in the MCL2 used as historic control (P=0.033) 60 patients would have to be recruited.
The MCL5 protocol will therefore be a phase-II trial aiming at including enough patients to be able to analyse 60 MIPI-B high-risk patients for response, and all patients for time–to-treatment failure and overall survival.

18. Publication rules

Manuscripts based on this protocol will be made according to the "Vancouver System": Uniform Requirements for Manuscripts Submitted to Medical Journals (latest updated version 2000: www.icmj.org). Authorship is based on important contributions to:

- Idea, planning or modifying the protocol, collection, analysis or interpretation of data
- Writing or critically revising the manuscript
- Acceptance of the final manuscript.

All three aspects must be covered.

The chairman of the writing committee is the main responsible for accomplishing the goals of the protocol, and will also be responsible for writing the manuscript. In that case he will be 1st author. If important contributions from members of the study group warrant separate publications, the contributor in question will be first author on that article. Members of the writing committee are expected to fulfil the above criteria and to be co-authors.

All manuscripts will be distributed to the contributors prior to submission for publication. Preliminary results from the study may be subject to presentation at international and national meetings.

19. Ethical aspects

Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the declaration of Helsinki (Tokyo, Venice and Hong Kong amendments), or the laws and the regulations of the country, whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the guidelines for Good Clinical Practice issued by the European Union. As a pre-requisite for implementation, the protocol will have to be approved by the local, regional or national Ethical Review Boards according to the existing national and local regulatory requirements.

Informed consent

All patients will be informed of the aims of the study, including the possible adverse events, the procedures involved and the possible hazards to which he/she will be exposed. They will be informed as to the strict confidentiality of their data, but that their medical records will be reviewed for trial purposes by authorised individuals other than their treating physician. It will be emphasised that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered. In accordance with the guidelines of Good Clinical Practice the “consent must be documented either by the subject’s dated signature or by the signature of an independent witness who records the subject’s assent”.

24
20. References


8. Hermine O et al. Alternate courses of 3 x CHOP and 3 x DHAP plus rituximab followed by high dose Ara-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to six courses of CHOP plus rituximab in mantle cell lymphoma: Results of the MCL Younger Trial of the European Mantle Cell Network. ASH Annual Meeting Abstracts) 2010; #110.


### WHO/ECOG Performance Status Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair</td>
</tr>
</tbody>
</table>
## Appendix 2

### WHO recommendations for grading of acute and subacute toxic effects

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Hematological (adults)

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 110 g/l</td>
<td>95-109 g/l</td>
<td>80-94 g/l</td>
<td>65-94 g/l</td>
<td>&lt;65 g/l</td>
<td>&lt;4.0 g/l</td>
</tr>
<tr>
<td>≥ 6.8 mmol/l</td>
<td>5.8-6.7 mmol/l</td>
<td>4.95-5.8 mmol/l</td>
<td>4.0-4.9 mmol/l</td>
<td>&lt;4.0 mmol/l</td>
<td>&lt;1.0 mmol/l</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leuko (1000 mm³)</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 4.0</td>
<td>4.0</td>
<td>3.0-3.9</td>
<td>2.0-2.9</td>
<td>1.0-1.9</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Granulo (1000 mm³)</td>
<td>≥ 2.0</td>
<td>1.5-1.9</td>
<td>1.0-1.4</td>
<td>0.5-0.9</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Platelets (1000 mm³)</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100</td>
<td>100</td>
<td>75-99</td>
<td>50-74</td>
<td>25-49</td>
<td>&lt;25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haemorrhage</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>petechiae</td>
<td>mild blood loss</td>
<td>gross blood loss</td>
<td>debilitating blood loss</td>
<td></td>
</tr>
</tbody>
</table>

#### Gastrointestinal

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.25 x N¹</td>
<td>1.25-2.5 x N¹</td>
<td>2.6-5 x N¹</td>
<td>5.1-10 x N¹</td>
<td>&gt; 10 x N¹</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aminotransferases (ASAT, ALAT)</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.25 x N¹</td>
<td>1.25-2.5 x N¹</td>
<td>2.6-5 x N¹</td>
<td>5.1-10 x N¹</td>
<td>&gt; 10 x N¹</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alkaline phosphatase</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.25 x N¹</td>
<td>1.25-2.5 x N¹</td>
<td>2.6-5 x N¹</td>
<td>5.1-10 x N¹</td>
<td>&gt; 10 x N¹</td>
<td></td>
</tr>
</tbody>
</table>

| Oral possible | no change | soreness/erythema | erythema, ulcers; can eat solids | ulcers; requires liquid diet only | > 10 x N¹ alimentation not |
| Nausea/vomiting | none | nausea | transient vomiting | vomiting requiring intractable extra therapy | vomiting requiring intractable extra therapy |
| Nausea/vomiting with Prophylactic antiemetics | none | nausea | transient vomiting | vomiting requiring intractable extra therapy | vomiting |
| Diarrhoea | none | haemorrhagic dehydration | transient | tolerable | intolerable |
| Renal

<table>
<thead>
<tr>
<th>Blood creatinine</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.25 x N¹</td>
<td>1.25-2.5 x N¹</td>
<td>2.6-5 x N¹</td>
<td>5.1-10 x N¹</td>
<td>&gt; 10 x N¹</td>
<td></td>
</tr>
</tbody>
</table>

| Proteinuria | no change | < 0.3 g% | 0.3-1.0 g% | > 1.0 g% | nephrotic syndrome |
| Haematuria | no change | microscopic | < 3 | < 3-10 g/l | > 10 g/l uropathy |

| Pulmonary | no change | mild symptoms | exertional dyspnoe | dyspnoea at rest | complete bed rest required |

| Fever with drug | none | fever < 38 °C | fever 38°C-40°C | fever > 40°C | fever with hypotensi |

| Allergic | no change | oedema | bronchospasm; no parenteral therapy | bronchospasm parenteral therapy required | anaphylaxis |
## Who recommendations for grading of acute and subacute toxic effects

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no change</td>
<td>erythema</td>
<td>dry desquamation</td>
<td>moist desquamation, ulceration</td>
<td>exfoliative dermatitis; necrosis requiring surgical intervention.</td>
</tr>
<tr>
<td></td>
<td>vesiculation, pruritus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair loss</td>
<td>minimal hair alopecia</td>
<td>moderate, patchy but reversible</td>
<td>complete alopecia</td>
<td>non-reversible alopecia</td>
</tr>
<tr>
<td><strong>Infection</strong> (specify site)</td>
<td>none</td>
<td>minor infection</td>
<td>moderate infection</td>
<td>major infection with hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhythm</td>
<td>no change</td>
<td>sinus tachycardia, &gt;110 at rest</td>
<td>unifocal PVC, atrial arrhythmia</td>
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<td>somnolence &gt;50% of waking hours</td>
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</table>

*a: Upper limit of normal value of population under study.

b: This does not include constipation resulting from narcotics.

c: Only treatment-related pain is considered, *not* disease-related pain. The use of narcotics in grading pain, depending upon the tolerance level of the patient.
Appendix 3

Molecular study Form
(to be used whenever molecular samples are submitted to Copenhagen.

To:
The Leukemia Laboratory 4041
Department of Haematology
Rigshospitalet
9 Blegdamsvej
DK 2100 Copenhagen
Denmark

Attention: Lone Bredo Pedersen
Phone + 45 3545 3826, Fax +45 3545 4780
email: lone.bredo.pedersen@rh.regionh.dk

Please find enclosed samples from our patient:

Patient initials and 3-digit number:......................

Who is being treated according to the MCL5 Protocol

Samples are taken date:......................... and consist of:

☐ 10 ml bone-marrow aspirate, anticoagulated  ☐ Frozen tumor tissue
☐ 50 ml blood, anticoagulated
☐ Stem cell product

Sincerely,

Signature:........................................Hospital:...............................Country.............Date..............................

Handling of biological material

50 ml of peripheral venous blood and 10 ml of bone marrow aspirate should be collected in a sterile tube containing EDTA as an anticoagulant. The sample should be sent by mail to Copenhagen for arrival in less than 72 hours. Please label the tubes, and avoid shipment that will arrive at week-ends.

Peripheral stem cell product should be frozen in DMSO and kept frozen until shipment. At least 10^7 cells from each harvest day or pooled throughout the harvest should be shipped and tubes marked with accurate numbers of cells in each tube. Shipment on dry ice at request, avoid arrival at week-end.

Frozen tumor tissue for micro-array analysis should be kept frozen at -70 C and shipped on dry ice at request.

Important: Please fax a copy of this form at the day of shipment.
Appendix 4

Preparation of mononuclear cells (MNC) from bone marrow or blood for phosphoflow signalling analysis performed later in Oslo, Norway

Peripheral blood can be applied from patients with leukemic disease, otherwise use bone marrow suspension.

Reagents: Ficoll Pague Plus (density 1.077g/mL) from GE Healthcare or similar product
- bring to room temperature before use
RPMI
Fetal calf serum (FCS)
RPMI with 2% FCS, 2 IE heparine

1. Dilute 10 – 15 mL bone marrow or blood 1:1 in RPMI containing 2% FCS and heparine. Mix the bone marrow/blood and media by inverting the tube several times or by drawing the mixture in and out of a pipette.

2. Ficoll separation of mononuclear cells (MNC), wash two times in RPMI, resuspend the MNC in 1 ml FCS and count the cells.

3. Freeze at 10-20 million cells/mL in 1 mL per vial (note: not fewer than 10 million cells/vial to maintain good viability of the cells): Dilute the cells in FCS until the cell suspension constitutes half of the final volume. Resuspend well by pipetting.

4. Then, add ice cold FCS w/ 20% DMSO slowly to the cells by adding drop by drop (this should take 2 minutes (If the 20% DMSO solution is added to quickly, the plasma cell membrane will burst). Minimize pipetting at this stage, only pipette up and down 1-2 times to mix when all the DMSO has been added, using a pipette that can take most of the cell solution. Then, transfer 0.5 - 1 mL cell solution / freezing vial.

5. Transfer the vials to -70°C for at least 30 minutes (or overnight), then transfer to liquid N2-tank for long term storage.

Alternative methods for separation and freezing of MNC on liquid N2-tank according to local practice may be applied
Appendix 5

Rituximab administration

Caution: Do not administer Rituximab as an intravenous push or bolus injection.

Hypersensitivity reactions may occur whenever protein solutions such as Rituximab are administered. Premedication, consisting of paracetamol (acetaminophen) and diphenhydramine should be administered before each infusion of Rituximab. Rituximab should be administered intravenously through a dedicated line at an initial rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be continued at one-half the previous rate after symptoms have abated (see table below). Subsequent Rituximab infusion can be administered at an initial rate of 100 mg/hr, and increased at 30 minute intervals by 100 mg/hr increments to a maximum of 400 mg/hr.

<table>
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<tr>
<th>Rituximab Infusion Rate Adjustments</th>
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<tr>
<td>Infusion Rate</td>
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<tr>
<td>Decrease 1/2</td>
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<tr>
<td>Interrupt* Treatment</td>
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</table>

*Interrupt antibody infusion until adverse clinical events have resolved; resume the antibody infusion at a rate not to exceed the initial rate of infusion and escalate as tolerated.
Appendix 6

**Protocol: MCL-5 (MARiT)**

Rituximab, high dose Ara-C and dexamethasone followed by BEAM in Mantle Cell Lymphoma

**Flow sheet-1 - TREATMENT**

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</table>

1. Females of childbearing potential
2. CT of areas involved with lymphoma prior to therapy
3. Bone marrow biopsy only if involved in previous biopsy
4. Rituximab should be split on days 1 (1/3) and 2 (2/3) in cycle 1
5. One dose of Rituximab at day 8
6. 2 ml bone marrow (not more than routinely required)
7. 10 ml blood
8. 5 ml bone marrow aspirate
9. 50 ml blood and 5 ml bone marrow aspirate
Appendix 6 continued

Protocol: MCL-5 (MARiT).

Rituximab, high dose Ara-C and dexamethasone followed by BEAM in Mantle Cell Lymphoma

Flow sheet-2 – FOLLOW-UP

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<td>Bone marrow biopsy</td>
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<td>Bone marrow and blood flow cytometry</td>
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<td>Bone marrow and blood for MRD analyses, CPH</td>
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1 PET-scan only if positive pretransplant (week 15)
2 Bone marrow biopsy only if involved in previous sample
6 2 ml bone marrow 10 ml blood(not more than routinely required)
9 50ml blood and 5 ml bone marrow aspirate
Appendix 7

Mantle Cell Lymphoma International Prognostic Index-Biological MIPI-B:

0.03535 x age (years) +
0.6978 (if ECOG/WHO > 1) +
1.367 x log_{10}(LDH/ULN) +
0.9393 x log_{10}(WBC count) +
0.02142 x Ki-67 (5)

MIPI-B Low risk: < 5.70
MIPI-B Intermediate risk: 5.70 – less than 6.50
MIPI-B High risk: > 6.50

Mantle Cell Lymphoma International Prognostic Index MIPI

0.03535 x age (years) +
0.6978 (if ECOG/WHO > 1) +
1.367 x log_{10}(LDH/ULN) +
0.9393 x log_{10}(WBC count)

MIPI-B Low risk: < 5.70
MIPI-B Intermediate risk: 5.70 – less than 6.20
MIPI-B High risk: > 6.20

MIPI and MIPI-B is easily calculated via the web (Example: Calculate by QxMD)
Appendix 8

Participating centres (NLG study centre numbers)

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