Randomized phase III study of Rituximab with intensified CHOP chemotherapy (R-iCHOP-14) versus Rituximab with High-Dose Sequential Therapy and Autologous Stem Cell Transplantation (R-HDT+ASCT) in Adult Patients (18-65 yrs) with Stage II-IV High-intermediate or High Risk Diffuse Large B-Cell Lymphoma

PROTOCOL

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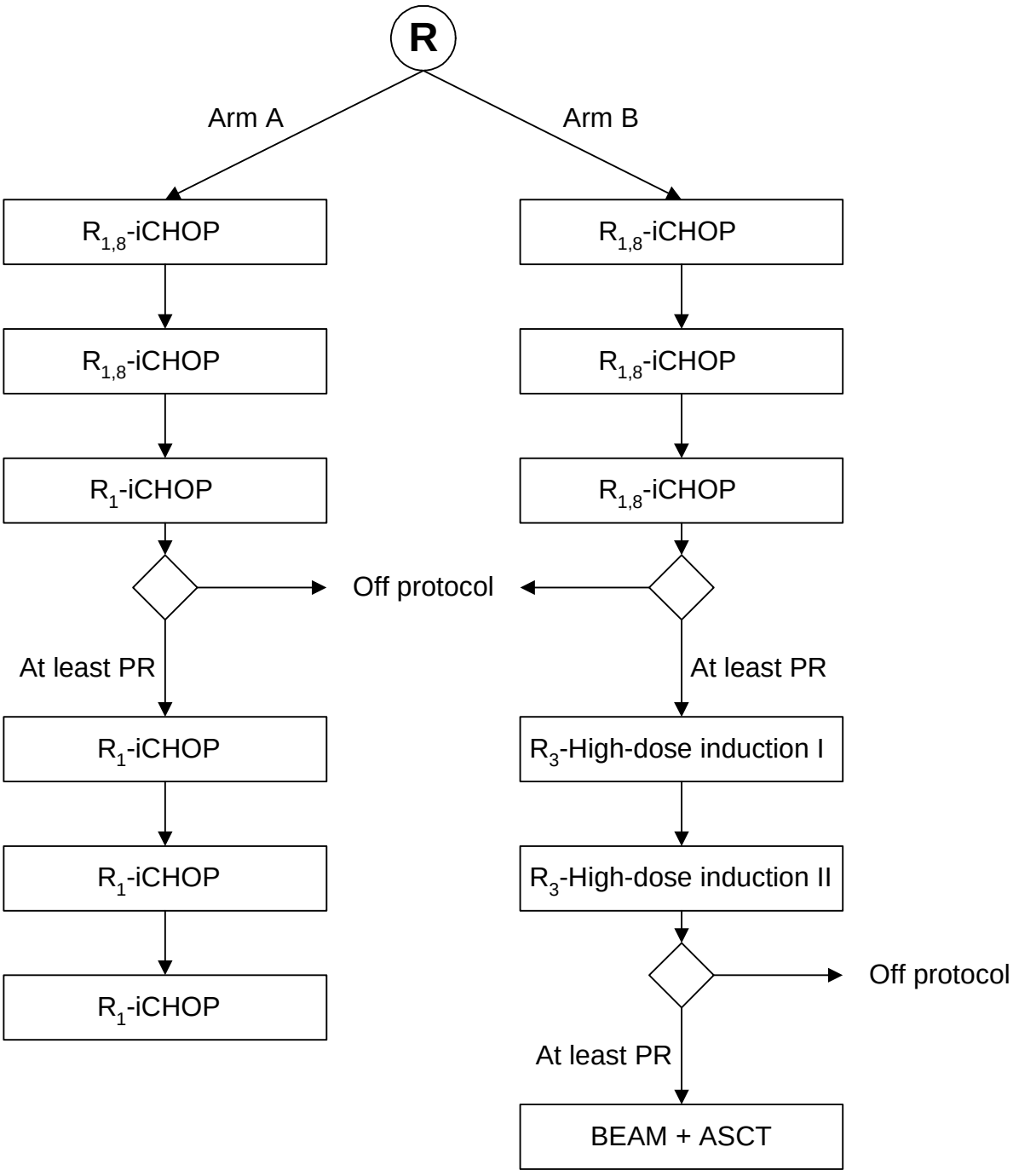
1. Scheme of study

High-intermediate or high risk DLBCL,
Ann Arbor stage II-IV, age 18-65 yrs inclusive



R=rituximab

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3. Synopsis

Study phase	Phase III
Study objectives	Evaluation of the effect of 6 x intensified CHOP + 8 x rituximab (R-iCHOP-14) v. 3 x intensified CHOP + 8 x rituximab + High-dose sequential therapy with up-front Autologous Stem Cell Transplantation (R-HDT+ASCT)
Patient population	Patients with stage II-IV high-intermediate or high risk (age-adjusted IPI:2-3) diffuse large B-cell lymphoma (DLBCL), CD20 positive, previously untreated, age 18-65 years inclusive and WHO performance status 0-2
Study design	Prospective, multicenter, randomized
Duration of treatment	Expected duration of treatment is 12 weeks (Arm A) v. 16 weeks (Arm B)
Number of patients	250 patients registered and randomized
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported
Planned start and end of recruitment	Start of recruitment: III 2005 End of recruitment: IV 2008

4. Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
Study Coordinators	G.W. van Imhoff	UMCG, Groningen, The Netherlands
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4.1. Pathology review

A central review of the diagnosis is performed for each case by Prof. dr. Ph.M. Kluin (e-mail: p.m.kluin@path.umcg.nl) and Dr. K. Hebeda (e-mail: k.hebeda@pathol.umcn.nl) to confirm the diagnosis of DLBCL according to the WHO lymphoma classification and the CD20 positivity. A review by more hemato-pathologists will be performed when judged appropriate.
The review analysis will be done without the knowledge of patient outcome. It will comprise:

- confirmation of the diagnosis of Diffuse Large B-cell Lymphoma as defined in the WHO classification
- confirmation of the B-cell nature and the presence of the CD20 antigen with the L26 anti-CD20 antibody and if necessary an additional anti-CD79a antibody.
- an analysis of biological markers of proven prognostic significance in DLBCL, i.e. BCL2 and germinal center B-cell protein versus non-germinal B-cell protein expression (CD10, BCL6 and MUM1/IRF4).

Once a patient is randomized, the local pathologist as well as the central pathologist will be notified by e-mail. The local pathologist will be asked to send the report with one representative Hematoxylin & Eosin stained slide as well as 10 unstained slides (APES coated glass slides) or if desired a paraffin tissue block. The tissue blocks will be returned within 6 months after receipt, the slides will remain in the central review laboratory. A copy of the results of the review will be sent to the local pathologist and to the HOVON Data Center.

All histological materials are to be sent to:
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Secretariaat Afdeling Pathologie en Laboratoriumgeneeskunde
Kamer Z1.17, Universitair Medisch Centrum Groningen
Hanzeplein 1
9713 GZ Groningen
Nederland

Possible side studies on tumor materials might be initiated during the course of the trial. For these studies a separate addendum to the study protocol will be written, which will be approved by the members of the HOVON lymphoma working party and the central medical ethics board of the study (see paragraph 18.4).

5. Introduction

5.1. High-intermediate- and high-risk DLBCL

The majority (80%) of aggressive lymphomas are classified as diffuse large B-cell lymphoma (DLBCL).[1] Although CHOP (-like) chemotherapy has been considered standard treatment for patients with aggressive non-Hodgkin's lymphoma (NHL) in the past decades,[2] the prognosis of patients with a high risk score according to the International Prognostic Index (IPI)[3], is dismal. The probability of reaching a complete remission is only 44%, and 60% of these patients will relapse. Ultimately only 26% of these high risk patients will be alive at 5 years from diagnosis.[3]

5.2. Anti-CD20 (rituximab)

Anti-CD20 (rituximab) is a chimeric humanized mouse monoclonal antibody directed to the CD20 antigen which is present on B-lymphocytes. CD20 is also expressed by most B-cell NHL, including DLBCL.[1] Treatment of relapsed DLBCL with rituximab alone results in a response duration of 3 months. Phase I/II studies in patients with aggressive NHL using anti-CD20 combined with CHOP demonstrated 72% CR and 94% overall response.[4-6] The French GELA group has completed a

randomized study of rituximab combined with full-dose CHOP (8 cycles given at 3 weekly interval) in DLBCL. This study of 400 elderly patients demonstrated that CHOP combined with rituximab (R-CHOP) as compared with CHOP alone (CHOP) resulted in a significantly better CR/CRu rate (76% v. 60%), a better event-free survival (69% v. 49%) and a better survival (83% v. 68%). The improved outcome of the R-CHOP combination was observed in all IPI risk groups.[7] These superior results of R-CHOP have recently been confirmed in young patients. In a large randomized international study (MiNT) of 824 patients with age-adjusted IPI 0-1 risk it was demonstrated that 6 courses of R-CHOP-like as compared to 6 courses of CHOP-like therapy resulted in a significantly better estimated 2 year time to treatment failure (76% v. 60%) and overall survival (94% v. 87%).[8] In both the GELA and MiNT study the addition of rituximab resulted in a significant reduction of patients with primary treatment failure, i.e. patients not responding to therapy or with early disease progression on protocol (8% v. 21% and 4% v. 15%, respectively).

5.3. CHOP-21, CHOP-14, iCHOP-14

By adding granulocyte colony-forming stimulating factor (G-CSF), the interval between CHOP schedules can be reduced from 3 to 2 weeks without a concomitant increase of toxicity. A large randomized trial of the German High Grade Lymphoma Study Group has demonstrated an increased CR rate (76% v. 60%) and 5 year overall survival (53% v. 41%) in elderly patients with aggressive NHL treated with a total of 6 courses of CHOP scheduled every 2 weeks combined with G-CSF (CHOP-14) as compared with 6 courses of CHOP scheduled every 3 weeks (CHOP-21).[9] HOVON has recently conducted a randomized study in young patients with intermediate-risk aggressive NHL (HOVON 26) comparing 8 courses of standard CHOP-21 with 6 courses of intensified-CHOP-14 (iCHOP-14) combined with G-CSF. This study was designed to test the effect of dose-density on outcome. The duration of therapy was shortened from 24 weeks in the standard CHOP-21 arm to 12 weeks in the iCHOP-14 arm and the dose of cyclophosphamide and doxorubicin was increased from 750 mg/m^2 to 1000 mg/m^2 and 50 mg/m^2 to 70 mg/m^2 respectively in each cycle of the iCHOP-14 arm, thus keeping the cumulative dose of CHOP in both arms of the study the same. Although follow-up is still short and more mature data will have to be awaited, preliminary results of the first 400 patients entered in this randomized study (interim analysis May 2004), indicated a significant improvement in 2 year disease-free survival of 75% in the iCHOP-14 v. 60% in the CHOP-21 arm (p= 0.006). Differences in event-free survival and overall survival were (not yet) significant: event-free survival shows an improvement of 54% in the iCHOP-14 arm over 48% in the CHOP-21 arm (p =0.068), and overall survival shows an improvement of 77% in the iCHOP-14 arm over 72% in the CHOP-21 arm (p = 0.173). Taken together these data indicate that a dose dense schedule, i.e. CHOP-14 or iCHOP-14 combined with G-CSF may be considered superior to CHOP-21 in both elderly and young patients with aggressive NHL.

5.4. High-dose treatment and autologous stem cell transplantation

Approximately 40% of young patients who relapse more than 1 year after first-line treatment with CHOP can still be rescued by high-dose treatment with autologous stem cell transplantation (ASCT), provided the disease is chemo-sensitive, i.e. responding to second-line chemotherapy.[10,11] Consequently, high-dose chemotherapy followed by ASCT has been explored as first-line treatment in young patients with poor-risk aggressive lymphoma. A prospective randomized Italian study subsequently showed that short high-dose sequential chemotherapy followed by ASCT was better than standard therapy in poor-risk patients without bone marrow involvement.[12] Yet, the efficacy as well as the optimal treatment schedule and timing of ASCT remain to be elucidated [13,14].

Full-dose CHOP-like standard therapy followed by ASCT was not superior to standard CHOP-like therapy for unselected patients with aggressive NHL in randomized trials conducted by GELA,[15] the Italian Non-Hodgkin Lymphoma Group,[16] and EORTC.[17] Retrospective subgroup analysis of GELA's LNH87-2 trial as well as the Italian study, however, indicated a benefit of ASCT for patients with aa IPI 2-3 risk who completed standard induction therapy,[16,18] although this was not confirmed in the EORTC study.[17] Abbreviated standard chemotherapy followed by ASCT yielded no difference [19-21] compared to standard therapy, and abbreviated high-dose chemotherapy showed even inferior results compared to standard therapy in patients with aa IPI 2-3 risk aggressive lymphoma[22]. In contrast to these data, a recently published randomized trial in patients with aa IPI 0-2 by GOELAMS reported an improved EFS for high-dose therapy with ASCT compared to standard CHOP that was restricted to aa IPI 2 patients only.[23]

The efficacy of up-front high-dose sequential therapy followed by ASCT has also been investigated by HOVON in two consecutive phase II studies (HOVON 27 and 40)[24]. Between 1994 and 2001, 147 newly diagnosed poor-risk aggressive NHL patients, aged ≤ 65 years with Ann Arbor stage III-IV and LDH >1.5 x upper limit of normal (ULN), entered the HOVON 27 and HOVON 40 trials. Based on the treatment outcome of patients with this combination of risk factors enrolled in a previous HOVON study,[19] they were expected to have survival of only 23% at 5 years when treated with CHOP. Treatment in HOVON 27 consisted of two up-front high-dose induction courses followed by BEAM plus ASCT in responding patients. In HOVON 40 the same treatment was preceded by three iCHOP-14 courses. Patients characteristics in both trials were comparable, 80% had DLBCL, 77% had stage IV, median LDH levels were 3.1 x ULN. Complete remission (CR) in both trials was 45%-51%. Before ASCT, CR was 14% in HOVON 27 v. 28% in HOVON 40 (p=0.03). Treatment failure was similar (27%). Four year survival estimates in HOVON 27, compared to HOVON 40 were overall survival (OS) 21% v. 50% (p= 0.007); event-free survival (EFS) 15% v. 49% (p=0.0001); disease-free survival (DFS) 34% v. 74% (p=0.008). This different outcome favoring HOVON 40 remained highly significant when corrected for competing risk factors in multivariate analysis.

Although the outcome of HOVON 40 showed a significant improvement compared to the outcome of patients with similar risk factors treated with CHOP, or HDT+ASCT according to HOVON 27 protocol, this still does not answer the question whether up-front ASCT is necessary in high-risk patients. However, these results strongly support the notion that up-front ASCT is probably more successful in patients having reached a CR(u) after an adequate amount of induction therapy. One in every fourth patient had primary refractory disease, and primary treatment failure in HOVON 40 (26%) was not different from HOVON 27 (27%), which is probably inherent to patients with poor-risk aggressive NHL. As this apparently could not be overcome by increasing the dose or shortening the time interval of chemotherapy, other treatment modalities are needed. Anti-CD20 monoclonal antibodies (rituximab) given in combination with chemotherapy may significantly reduce the risk of treatment failure in patients with diffuse large B-cell lymphoma [7,8], without clinically significant increased toxicity. This makes rituximab an obvious candidate for combination with high-dose treatment for poor-risk diffuse large B-cell lymphoma patients.

In the current study, designed for adult, Ann Arbor stage II-IV, poor-risk DLBCL patients, we will compare the current best CHOP schedule (i.e. iCHOP-14) combined with rituximab (R-iCHOP-14) to high-dose therapy and ASCT according to the HOVON 40 protocol combined with rituximab (R-HDT+ASCT). The cumulative rituximab dose in both study arms will not be different and equal to that published by the GELA,[7] in order to avoid possible confouding effects due to differences in rituximab dose.
Two different formulations of G-CSF with proven efficacy can be used to support (i)CHOP chemotherapy: i. filgrastim given daily s.c. for 11 days or, ii. pegfilgrastim given once s.c. on day 2. Nowadays the latter formulation is used most frequently because of its ease of administration. Pegfilgrastim will therefore be applied during iCHOP in this study. Daily G-CSF (filgrastim) administration has proven to be safe and efficacious to mobilise stem cells and to support HDT in the HOVON 40 protocol [24]. Pending more mature published data on the efficacy and safety of pegfilgrastim for stem cell mobilization and HDT support , daily filgrastim administration will be used for stem cell mobilization and HDT support .

6. Study objectives

- The primary objective of this two arm randomized phase III trial is to identify the arm that results in the better event-free survival for patients with Ann Arbor stage II-IV high-intermediate or high risk (age-adjusted IPI: 2-3) diffuse large B-cell lymphoma (DLBCL), CD20-positive, previously untreated, age 18-65 years inclusive and WHO performance status 0-2. The arms to be compared are:

- o A: 8 x rituximab combined with 6 x intensified CHOP every 2 weeks (iCHOP) (standard-arm), and
- o B: 6 x rituximab combined with 3 x iCHOP followed by 2 x rituximab plus high-dose sequential therapy and up-front autologous stem cell transplantation (experimental arm).

♦ The secondary objectives of this trial are to evaluate the overall survival, the disease-free survival, the complete remission rate and the progression on protocol.

7. Study design

Details of all treatments (dose and schedule) are given in chapter 9.

7.1. Remission induction

Patients with CD20-positive high-intermediate or high risk DLBCL meeting all eligibility criteria (see 8.1) will be randomized on entry between:

Arm A: 6 cycles of rituximab-iCHOP q 2 weeks plus G-CSF: pegfilgrastim (Neulasta®)

and

Arm B: 3 cycles of rituximab-iCHOP q 2 weeks plus G-CSF: pegfilgrastim (Neulasta®), followed by rituximab-HDT Induction I, rituximab-HDT Induction II plus ***daily*** G-CSF: filgrastim (Neupogen®, SingleJect®), followed by BEAM with ASCT. ***Daily*** G-CSF: filgrastim (Neupogen® SingleJect®) will replace pegfilgrastim in the iCHOP chemotherapy cycle during which stem cells will be harvested

All patients will be evaluated for response after 3 cycles of R-iCHOP. In arm A after 6 cycles of R-iCHOP; in arm B after Induction course II and after ASCT (if applicable, otherwise after last cycle administered). All patients who progress on protocol or have not attained at least a PR after 3 cycles of R-iCHOP (Arm A and B), will go off protocol treatment.

8. Study population

8.1. Eligibility for registration

All eligible patients have to be registered and randomized before start of treatment (see paragraph 16).

8.1.1. Inclusion criteria

- Patients with a confirmed histologic diagnosis of DLBCL according to the WHO classification (Appendix A)
- Ann Arbor stage II-IV
- High-intermediate or high risk NHL according to age-adjusted IPI score (aa IPI=2-3) (Appendix G)
- DLBCL must be CD20 positive
- Age 18-65 years inclusive
- WHO performance status ≤ 2 (Appendix E)
- Negative preganacy test (if applicable)
- Written informed consent

8.1.2. Exclusion criteria

- Intolerance of exogenous protein administration
- Severe cardiac dysfunction (NYHA classification II-IV, Appendix F) or LVEF < 45 %
- Significant renal dysfunction (serum creatinine ≥ 150 μmol/l), unless related to NHL
- Significant hepatic dysfunction (total bilirubin ≥ 30 μmol/l or transaminases ≥ 2.5 times normal level), unless related to NHL
- Suspected or documented Central Nervous System involvement by NHL
- Testicular DLBCL
- Primary mediastinal B cell lymphoma
- Patients known to be HIV-positive
- Patients with active, uncontrolled infections
- Patients with uncontrolled asthma or allergy, requiring steroid treatment
- Patient is a lactating woman
- Unwillingness or not capable to use effective means of anticonception (all men and pre-menopausal women)
- Prior treatment with chemotherapy, radiotherapy or immunotherapy for this lymphoma, except a short course of prednisone (< 1 wk) and/or cyclophosphamide (< 1 wk and not in excess of 900 mg/m^2 cumulative) or local radiotherapy in order to control life threatening tumor related symptoms
- History of active cancer during the past 5 years, except basal carcinoma of the skin or stage 0 cervical carcinoma

9. Treatments

9.1. Arm A: R-iCHOP x 6

R-iCHOP chemotherapy + G-CSF

Agent	Dose/day	Route	Days
Cyclophosphamide	1000 mg/m^2	i.v.	1
Doxorubicin	70 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2 (max. 2 mg)	i.v.	1
Prednisone	100 mg	p.o.	1, 2, 3, 4, 5
G-CSF (pegfilgrastim, Neulasta®)	6 mg	s.c.	2
Rituximab (Mabthera®)	375 mg/m^2 (max. 750 mg)	i.v.	day 1, 8 cycles 1-2 day 1 cycles 3-6

Patients in arm A will be treated with 6 cycles of R-iCHOP, every 2 weeks. In addition, they will receive G-CSF (pegfilgrastim) on day 2 of each cycle of iCHOP. Rituximab will be given on day 1 and 8 in cycles 1-2, on day 1 in cycles 3-6 (total 8 x rituximab).
Because the 1st rituximab infusion (during iCHOP course no. 1) will usually take a few hours time, this 1st infusion may also be scheduled on day 2 for logistic reasons (see also 9.4).

Assessment of response after 3 cycles is described in 11.2. Patients who have not achieved at least PR will go off protocol treatment. Patients in PR or CR after cycle 3 will receive another 3 cycles of R-iCHOP + G-CSF every 2 weeks.

9.2. Arm B: 3 x R-iCHOP + R-High-dose sequential therapy and ASCT

9.2.1. R-iCHOP x 3

R-iCHOP chemotherapy + G-CSF

Agent	Dose/day	Route	Days
Cyclophosphamide	1000 mg/m^2	i.v.	1
Doxorubicin	70 mg/m^2	i.v.	1
Vincristine	1.4 mg/m^2 (max. 2 mg)	i.v.	1
Prednisone	100 mg	p.o.	1, 2, 3, 4, 5
G-CSF (pegfilgrastim, Neulasta®)	6 mg	s.c.	2
Rituximab (Mabthera®)	375 mg/m^2 (max. 750 mg)	i.v.	day 1, 8

Patients in arm B will be treated with 3 cycles of R-iCHOP, every 2 weeks. In addition, they will receive G-CSF (pegfilgrastim) on day 2 of each cycle of iCHOP. However, G-CSF (filgrastim) daily from day 2 through harvesting will replace pegfilgrastim at the cycle of iCHOP in which stem cells are mobilized for harvesting. Rituximab will be given on day 1 and 8 in cycles 1-3, (total 6 x rituximab). Because the 1st rituximab infusion (during iCHOP course no. 1) will take a few hours time, this 1st infusion may also be scheduled on day 2 for logistic reasons (see 9.4). Assessment of response after 3 cycles is described in 11.2. Patients who have not achieved at least PR will go off protocol treatment. Patients in PR or CR after cycle 3 will go on with R-High-dose induction I.

9.2.2. R-High-dose Induction I

R-High-dose Induction I + G-CSF (*starts on day 15 of 3rd iCHOP cycle*)

Agent	Dose/day	Route	Days
Cyclophosphamide	1000 mg/m^2 / 12 hourly (cumulative dose 4000 mg/m^2)	i.v.	1, 2
MESNA (Uromithexan)	200 mg/m^2 / 4 hourly (cumulative dose 2400 mg/m^2)	i.v.	1, 2 (-10 min to +8 hr inclusive after last cyclophosphamide infusion)
Doxorubicin	35 mg/m^2 (cumulative dose 70 mg/m^2)	i.v.	1, 2
Prednisone	100 mg	p.o.	1, 2, 3, 4, 5
G-CSF (Neupogen® SingleJect®)	5 µg/kg	s.c.	5-recovery ANC
Rituximab (Mabthera®)	375 mg/m^2 (max. 750 mg)	i.v.	day 3

Induction I starts 2 weeks after the 3rd cycle of iCHOP-14 provided hematological recovery has occurred. Induction I consists of: 1000 mg/m^2 cyclophosphamide in 250 ml 0.9% NaCl twice daily in 30-60 min., with an interval of 12 hours, days 1, 2 (total dose: 4000 mg/m^2); 35 mg/m^2 doxorubicin in 100 ml NaCL 0.9% i.v in 30 min., days 1, 2 (total dose 70 mg/m^2); rituximab 375 mg/m^2 i.v. day 3; 100 mg prednisone days 1-5. MESNA (Uromithexan) 200 mg/m^2 in 50-100 ml NaCL 0.9% 6 times daily, starting 10 minutes before and ending 8 hours after the last cyclophosphamide infusion (total dose: 12 x 200 = 2400 mg/m^2). After each induction course, patients will receive 5 µg/kg G-CSF (filgrastim) s.c. daily from day 5 until neutrophils reach at least 0.5 x 10^9/l for two consecutive days.
As soon as hematological recovery is observed, Induction II will be given. Hematological recovery is defined as a platelet and neutrophil count >100x10^9/l and >1.0x10^9/l without transfusion support, respectively.

9.2.3. R-High-dose Induction II

R-High-dose Induction II + G-CSF (starts immediately after hematological recovery of Induction I, within 42 days).

Agent	Dose/day	Route	Days
Etoposide	250 mg/m^2 / 12 hourly (total dose 2000 mg/m^2)	i.v.	1,2,3,4
Mitoxantrone	30 mg/m^2	i.v.	1
Prednisone	100 mg	p.o.	1, 2, 3, 4, 5
G-CSF (Neupogen® SingleJect®)	5 µg/kg	s.c.	5-recovery ANC
Rituximab (Mabthera®)	375 mg/m^2	i.v.	day 5

Induction II consists of: 250 mg/m^2 etoposide in 500 ml NaCl 0.9% i.v. in 120 min., 12 hourly days 1-4 (total dose 2000 mg/m^2); 30 mg/m^2 mitoxantrone in100 ml NaCl 0.9% in 30 min., day 1; Rituximab 375 mg/m^2 i.v. day 3; and 100 mg prednisone days 1-5. Hematological recovery is defined as a rising platelet and neutrophil count >100x10^9/l and >1.0x10^9/l respectively. After each induction course, patients will receive 5 µg/kg G-CSF (filgrastim) s.c. daily from day 5 until neutrophils reach at least 0.5 x 10^9/l for two consecutive days.

9.2.4. Stem cell harvest

Peripheral blood stem cells will be harvested and cryo-preserved as soon as possible, preferably during iCHOP or otherwise after Induction I or Induction II according to standard institutional procedures, provided the bone marrow does not contain (anymore) lymphoma on histology. No CD34$^+$ selection will be performed. At least 2.5x10^6 viable CD34$^+$ cells/kg, as checked by standard institutional procedures should be harvested to be eligible for BEAM.

9.2.5. BEAM followed by ASCT

Patients attaining at least a partial response (PR) after Induction II, with a harvest of at least 2.5x10^6 CD34$^+$ cells/kg, will subsequently receive high-dose therapy and ASCT as soon as possible after hematological recovery from Induction II, but no longer than 42 days from start Induction II.

BEAM + ASCT (starts after hematological recovery of Induction II).

Agent	Dose/day	Route	Days
BCNU (carmustine)	300 mg/m^2	i.v.	-6
Etoposide	100 mg/m^2 / 12 hourly	i.v	-5,-4,-3,-2
Ara-C	100 mg/m^2 /12 hourly	i.v	-5,-4,-3,-2
Melphalan	140 mg/m^2	i.v.	-1
Stem cell reinfusion	≥ 2.5 x 10^6 / kg	i.v.	0

High-dose chemotherapy consists of BEAM: 300 mg/m^2 carmustine, day -6; 100 mg/m^2 etoposide and 100 mg/m^2 Ara-C, every 12 hours, day -5 through -2; 140 mg/m^2 melphalan, day -1. Stem cells will be re-infused on day 0.

9.3. Dose modifications R-iCHOP

Dose modifications will not be made in the first R-iCHOP course. During the next courses modifications of the treatment schedule will only be made in case of:

a) Myelosuppression

If leucocytes are < 3.0 x 10^9/l and/or platelets < 100 x 10^9/l: delay course for one week.
If leucocytes or platelets remain below these values, then the doses of doxorubicin and cyclophosphamide have to be reduced according to the following the scheme:

Leucocytes x 10^9/l		Platelets x 10^9/l	Cyclophosphamide	Doxorubicin	Vincristine	Prednisone
≥ 3.0	and	≥ 100	100%	100%	100%	100%
2.0-2.9	and	≥ 100	75%	75%	100%	100%
1.0-1.9	or	50 - 99	50%	50%	100%	100%
<1.0	or	< 50	0%	0%	100%	100%

During the next course the full dose should be resumed.

b) Neurotoxicity

Dose modifications of vincristine are made at the discretion of the medical attendant.

9.4. Special management rituximab administration

Antibody infusions may be given to patients in an outpatient clinic setting or following hospital admission as an inpatient. A peripheral or central intravenous (IV) line will be established. Vital signs (blood pressure, pulse, respiration, and temperature) should be monitored every 15 minutes

during the first hour or until stable and then hourly until the infusion is discontinued and vital signs are stable. Pre-medication with paracetamol (1000 mg) and/or anti-histaminics (e.g. clemastine 2 mg) is advised. The initial dose should be 50 mg/hr for the first 30 minutes. If no adverse event is seen, the dose may be escalated in 30 minutes intervals with increment steps of 50 mg/hr, to a maximum of 400 mg/hr. Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 antibody. When any of the following events is noted, antibody infusion should be temporarily discontinued, the patient should be observed and the severity of the adverse events should be evaluated:

- fever > 38.5° C;
- mild/moderate rigors;
- mild/moderate mucosal congestion or edema;
- drop in systolic blood pressure > 30 mm Hg.

The patient should be treated according to the best available local practices and procedures. Following observation, if the patients systems improve, the infusion should be continued at ½ the previous rate. Following the antibody infusion, the IV line should be kept open for medications. If there are no complications, the IV line may be discontinued after one hour of observation. If complications occur during infusion, the patient should be observed for two hours after the completion of the infusion.

If no adverse event is seen with the previous infusion, the infusion rate at the start of following infusions can be increased to 100 mg/hr and if no further adverse event is observed the infusion rate can be increased with 30 minutes intervals with increment steps of 50 mg/hr to a maximum of 400 mg/hr. Because the 1st rituximab infusion (during iCHOP course no. 1) will take a few hours time, this 1st infusion may also be scheduled on day 2, solely for logistic reasons.

9.5. Patients with detectable circulating tumor cells and rituximab treatment

In patients with WBC > 10 x 10^6/l, the initial rate of infusion should be reduced to 25 mg/hr. Patients with detectable circulating lymphoma cells may experience transient fever and rigors, shortness of breath, and hypotension with infusion of chimeric anti-CD20 antibody. When these adverse events are noted, antibody infusion should be temporarily discontinued, the patient should be observed and severity of the adverse events should be evaluated. The patient should be treated according to the best available local practices and procedures. Following observation, if the patients symptoms improve, the infusion should be continued, initially, at ½ the previous rate. Upon resolution of all adverse events and in the judgement of the investigator, the patient may be gradually escalated to a maximum infusion rate of 400 mg/hr, and the remainder of the treatment can be carried out. Following the antibody infusion, the IV line should be kept open for medications. If there are no complications, the IV line may be discontinued after one hour of

observation. If complications occur during infusion, the patient should be observed for two hours after the completion of the infusion.

9.6. Special management orders during high-dose sequential therapy and ASCT (Arm B)

High-dose treatment (Induction I, II, BEAM+ASCT) will only be administered by an experienced team in a nursing ward with appropriate skills in hematological intensive care. Patients will receive hematological supportive care, including vigorous hydration, anti-emetics, allopurinol, irradiated platelet and red blood cell transfusions, prophylactic oral antibacterial and anti-fungal treatment as well as immediate treatment with intravenous broad spectrum antibiotics and/or intravenous anti-fungal treatment in case of fever and/or documented or suspected infection, according to guidelines of the participating institution. This usually will imply hospital admittance untill recovery depending on the practice of the participating center.

9.7. Concomitant medication and treatment

9.7.1. Drugs

Concomitant medication introduced in the patient since the beginning of the treatment, with the exception of medication which is an integral part of standard prophylactic institutional medication used in conjunction with chemotherapy (anti-emetics, allopurinol); rituximab (antihistaminica, paracetamol); HDT (anti-emetics, oral antibacterial and anti-fungal medication (SDD); stem cell reinfusion (steroid, antihistaminics), will be recorded on the Case Report Form (CRF) in case of any adverse event of CTCAE grade ≥ 2. Patients should receive full hematological supportive care including irradiated blood transfusions and blood products, antibiotics, anti-emetics etc., where applicable. It is advised to administer ondansetron (Zofran) 8 mg twice or trice daily or granisetron (Kytril) 1 mg orally once or twice daily with each chemotherapy cycle.

9.7.2. Radiotherapy

Radiotherapy **before start or during protocol treatment** is only permitted for major localized problems, i.e. in case of potential or actual life threatening symptoms due to localized lymphoma mass or infiltration. No radiotherapy after end of treatment is allowed. Therefore, testicular DLBCL and primary mediastinal B-cell lymphoma are not eligible for this study.

10. End of protocol treatment

Reasons for going off protocol treatment are:

1. Less than PR after 3 R-iCHOP cycles (arm A and arm B)
2. Progression on protocol including relapse/progression after initial PR or CR(u) (i.e. before completion of treatment)
3. Failure of hematological recovery at day 42 from start Induction I
4. Failure of hematological recovery at day 42 from start Induction II
5. Failure to harvest sufficient stem cells for ASCT
6. Excessive toxicity requiring stopping of protocol treatment (including toxic death)
7. No compliance of the patient (especially refusal to continue treatment)
8. Intercurrent death
9. Lost to follow-up
10. Normal completion of protocol treatment

11. Required clinical evaluation

Also see Appendix B for a specification of staging and restaging evaluations.

11.1. Observations prior to start of treatment

- History (including B symptoms)
- Physical examination (including WHO performance)
- Laboratory tests (including Hb, WBC and differential, platelet count, sodium, potassium, calcium, creatinine, uric acid, bilirubin, glucose, alkaline phosphatase, γ-GT, ALAT, ASAT, LDH, protein, albumin, immuno-electrophoresis)
- Routine urine analysis
- Imaging + measurements (including chest X-ray, CT or MRI neck, thorax and abdomen)
- Lymph node biopsy for morphology and immunopathology of involved site
- Immunophenotyping of lymph node for CD20, CD3, (CD19 or CD79a optional)
- Cryo-preservation of lymph node tissue for external PA review and ancillary biological studies
- Bone marrow aspirate and biopsy (including CD20/CD79a stain)
- Peripheral blood microscopical smear examination
- ABO and RhD blood group, irregular antibody screening, anti Hepatitis B and C, HIV

11.2. Observations after 3 and 6 cycles of R-iCHOP, Induction I, Induction II and ASCT

- History (including B symptoms)
- Physical examination (including WHO performance)
- Laboratory tests (including Hb, WBC and differential, platelet count, sodium, potassium, creatinine, uric acid, bilirubin, glucose, alkaline phosphatase, γ-GT, ALAT, ASAT, LDH, protein, albumin, immuno-electrophoresis)
- Routine urine analysis
- Imaging + measurements of involved and/or new areas (including chest X-ray, CT or MRI neck, thorax and abdomen) (omit after Induction I)
- Bone marrow aspirate and biopsy (if positive at previous evaluation, including CD20/CD79a stain)
- PET scanning at end of protocol treatment (ASCT) in case of PR to asses final response

11.2.1. Response assessment after cycle 3 and 6 of R-iCHOP, Induction II and ASCT

Response will be formally evaluated according to the criteria of response in Appendix B (Cheson criteria). In addition to these criteria, PR by CT will be reclassified to CRu in case of a negative PET scan at originally involved nodal sites as defined by CT. If possible, a biopsy should be performed in case of PR on CT after treatment with a positive PET scan to confirm the presence of viable tumor. Patients with a positive biopsy, or (if biopsy is not feasible) unequivocal PET accumulation (if necessary confirmed by repeat PET scanning) in sites identified as PR sites at CT scanning after protocol treatment will be considered treatment failures. In case of inconsistency or absence of PET results and absence of histological confirmation, final response at end of protocol treatment will be classified according to the classical Cheson criteria. All relevant information on drug dose, measurable lesions, tumor response and treatment-related toxicity will be collected.

11.3. Observations during follow up

Follow up for patients in CR or CRu will be every 3 months during the first two years, every 6 months the next two years and annually thereafter. After relapse, patients will be followed until death.

- Physical examination (including WHO performance)
- Blood count, LDH
- Any clinically indicated examinations (thoracic and abdominal scan annually)
- Any documentation of abnormal events (e.g. secondary malignancies)
- Any treatment off protocol

12. Toxicities

12.1. iCHOP-14

CHOP is a commonly used chemotherapeutic regimen with well-known side effects. The most frequent side-effect is myelosuppression which may hamper patient adherence to the projected schedule of CHOP (see table 2).

12.2. Rituximab

Side effects of rituximab may include fever, rigors, mucosal congestion or edema, and drop in systolic blood pressure. These side effects are only observed during rapid infusion of rituximab. Special management is provided in paragraph 9.4. In patients who experience side effects the infusion time has to be restricted to 100 mg/hr.

12.3. High-dose sequential therapy and ASCT

Substantial hematological and non-hematological toxicities may be expected after Induction I, II and BEAM. Substantial mucositis sometimes necessitating parenteral nutrition is the most frequent non-hematological toxicity during intensive treatment. Pooled results for all reported non-hematological toxicities grade 3-4 and hematological toxicity and transfusions from protocols HOVON 27 and 40 are presented in Table 1 and 2.

Table 1: Non-hematological toxicity grade 3-4 according to treatment course pooled results from protocols HOVON 27 and HOVON 40

	Percentage of patients experiencing toxicity*							
	iCHOP* *(n=81)*		**Induction I** *(n=133)*		**Induction II** *(n=123)*		**ASCT** *(n=98)*	
Toxicity CTCAE-grade****	***3***	***4***	***3***	***4***	***3***	***4***	***3***	***4***
Oral (mucositis)	1	0	8	2	22	8	25	11
Cutaneous/Allergy	1	0	0	0	1	0	1	0
Liver	2	0	1	2	2	2	3	2
Hemorrhage	1	0	0	0	2	0	1	0
Diarrhea	0	1	3	0	4	0	10	1
Renal	0	0	2	1	1	0	1	1
Cardial	1	2	1	1	2	0	5	2
Neurotoxicity	1	0	2	0	1	0	2	1
Other	14	1	6	2	6	2	10	5
Infections (WHO grade)	25	6	18	1	29	3	29	4

* iCHOP in HOVON 40 only, total number of cycles 235;

**Nausea, vomiting and hair loss excluded;

Table 2: Hematological toxicity and transfusions, pooled results from protocols HOVON 27 and HOVON 40

	iCHOP* *(n=81)*	**Induction I** *(n=133)*	**Induction II** *(n=123)*	**ASCT** *(n=98)*
Transfusions median (range)				
Platelet transfusions**	0 (0-21)	1 (0-15)	2 (0-72)	3 (0-51)
RBC transfusions***	2 (0-24)	4 (0-29)	4 (0-39)	4 (0-63)
Days to recovery median (range)				
Neutrophils > 0.5 x 10^9/l	0 (0-27)	14 (11-27)	17 (0-47)	15 (6-58)
Platelets > 20 x 10^9/l	0 (0-32)	15 (0-48)	17 (0-139)	14 (6-160)
Platelets > 100 x 10^9/l	0 (0-36)	20 (0-85)	26 (14-363)	41 (9-679)

* iCHOP in HOVON 40 only, total number of cycles 235
** x 5 donor units

*** x 1 donor unit

Hematological toxicity, including time to recovery of platelets, neutrophils, number of platelet and red blood cell transfusions will be documented.

All non-hematological toxicities will be scored according to the NCI Common Terminology Criteria of Adverse Events, version 3.0 (Appendix D).

13. Reporting serious adverse events

An Adverse Event (AE) is any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs during or following treatment regardless of the causal relationship. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the treatment.

Serious Adverse Events (SAE) are defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment. Adverse events which are considered as serious are those which result in:

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- severe/permanent disability
- a congenital anomaly

Note that any death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

Unexpected Serious Adverse Events are those SAE's of which the nature or severity is not consistent with information in the relevant source documents. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as a source document in that country.

Reporting Serious Adverse Events

During protocol treatment all deaths, all SAE's that are life-threatening and any *unexpected* SAE must be reported to the HOVON Data Center by fax **within 48 hours of the initial observation of the event**. All details should be documented on the **Serious Adverse Event and Death Report**. 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 HOVON Data Center. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized 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 to the HOVON Data Center using the same procedure, **within 48 hours 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 assessment of causality is made by the investigator using the following:

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patients clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patients clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

The HOVON Data Center will forward all reports within 24 hours of receipt to the study coordinator and the study central datamanager. The report of an SAE will be the signal for the central data-manager to ask the investigator or the responsible local datamanager to complete and send as soon as possible all relevant CRF's for the involved patient with details of treatment and outcome. It is of utmost importance that all SAE's (including all deaths due to any cause) are reported in a timely fashion. Patients without a report of an SAE are implicity considered alive without SAE. This

information will be used in monitoring the incidence of SAE's, the estimation of overall survival and monitoring of safety of experimental treatments.

14. Endpoints

14.1. Primary endpoint

- Event-free survival (i.e. time from registration to induction failure (i.e. less than PR after 3 x R-iCHOP, no CR (CRu) after 6 R-iCHOP (arm A) or ASCT (arm B), death, progression or relapse whichever occurs first); the time to failure of patients with induction failure (less than PR after 3 x R-iCHOP) is set at one day.

14.2. Secondary endpoints

- Complete response (including CRu)
- Progression on protocol (progression or relapse after initial PR or CR during protocol treatment)
- Overall survival measured form the time of registration
- Disease-free interval (duration of the first CR) measured from the time of achievement of CR (including CRu) after protocol treatment to day of relapse or death from any cause (whichever occurs first).

15. Data collection

Data will be collected on Case Report Forms (CRF) to document eligibility, safety and efficacy parameters, compliance to treatment schedules and parameters necessary to evaluate the study endpoints. Data collected on the CRF are derived from the protocol and will include at least:

- inclusion and exclusion criteria
- baseline status of patient including medical history and stage of disease
- timing and dosage of protocol treatment
- adverse events
- parameters for response evaluation
- any other parameters necessary to evaluate the study endpoints
- survival status of patient
- reason for end of protocol treatment

Each CRF page will be identified by a pre-printed trial number, and a unique combination of patient study number (assigned at registration), hospital and patient name code (as documented at registration) to be filled out before completing the form.
The CRF will be completed on site by the local investigator or an authorized staff member. Each page must be dated and signed by the local investigator upon completion. All CRF entries must be based on source documents. The CRF and written instructions for completing the CRF will be provided by the HOVON Data Center.
Copies of the CRF will be kept on site. The original CRF pages must be sent to the HOVON Data Center at the requested time points. How and when to send in forms is described in detail in the CRF header and the CRF instructions.
All data from the CRF will be entered into the study database by the HOVON Data Center.

16. Registration and randomization

The patient should be registered immediately after satisfactory completion of screening tests and obtaining written informed consent, and before the start of chemotherapy. Patients need to be registered at the HOVON Data Center of the Erasmus MC - Daniel den Hoed, Rotterdam by phone call: +31.10.4391568 or fax +31.10.4391028 Monday through Friday, from 09:00 to 17:00 or via the Internet via TOP (Trial Online Process; https://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.

The following information will be requested at registration:

1. Protocol number
2. Institution name
3. Name of caller/responsible investigator
4. Patient’s initials or code
5. Patient’s hospital record number
6. Sex
7. Date of birth
8. Date of diagnosis of DLBCL (including CD20 positivity)
9. Age-adjusted IPI risk score
10. Ann Arbor stage
11. LDH and ULN LDH
12. PA number, location of tissue blocks (pathologist and institution)
13. Eligibility criteria

All eligibility criteria will be checked with a checklist.

Each patient will be given a unique patient study number. Patients will be randomized, stratified by center, HOVON risk score (Ann Arbor stage III/IV *and* LDH > 1.5 x ULN v. others) and age-adjusted IPI-score (2 v. 3) with a minimization procedure, ensuring balance within each stratum and overall balance. Patient study number and result of randomization will be given immediately by TOP or phone and confirmed by fax or email.

17. Statistical considerations

This phase III trial follows a two-armed randomized design, with one interim analysis being planned. The objective of this randomized phase III trial is to identify the treatment (6 × R-iCHOP or 3 × R-iCHOP R-High-dose sequential therapy and ASCT) that yields the better event-free survival. In addition, the design shields patients from an ineffective treatment by requiring early termination of the trial if the results are (clearly) in favor of one treatment over the other.

17.1. Patient number and power considerations

The sample size calculation of the design is based on the 3 year event-free survival endpoint. Event-free survival is defined as in paragraph 14. If no induction failure has been observed, patients will be censored at last follow-up.

With respect to the sample calculations the following assumptions are made:

- The 3 year event-free survival in arm A (6 × R-iCHOP) is assumed to be 35%. This is motivated as follows. The 3 year event-free survival in patients with stage III/IV and LDH > 1.5 x ULN, i.e. IPI 2-3, in the HOVON 3 and HOVON 27 study equals 15 %. The GELA (elderly patients) and the Mint study (young patients) both showed a 16-20% improvement of the CHOP + rituximab arm over the CHOP arm. Adding these effects a 3 year event-free survival in arm A of 35% is expected.
- It is assumed that the 3 year event-free survival in arm B (3 × R-iCHOP + R-High-dose sequential therapy and ASCT) equals 55%. This is motivated as follows. The 3 year event-free survival in patients with stage III/IV and LDH > 1.5 x ULN, i.e. IPI 2-3, in the HOVON 40 study equals 49%. A conservative (see the above mentioned result found in the GELA and Mint study) estimate of the effect of the addition of rituximab to the HOVON 40-scheme would be a 6% improvement of the 3 year event-free survival. Together this amounts to an expected 3 year event-free survival of 55%.
- The last two assumptions imply that the trial is to detect a hazard ratio of 0.569 between the two arms.

- The null hypothesis is formulated as the hazard ratio of arm A over B is equal to or smaller than one. The alternative hypothesis is formulated as the hazard ratio of arm A over B is greater than one.
- The probability of rejecting the null hypothesis, while in fact it is true, is limited to 5% (α = 0.05).
- The probability of failing to reject to the null hypothesis, while in fact it should be rejected, is limited to 20% (β = 0.20).
- The sample size calculation is based on a two-sided test.
- The accrual is assumed to take place over a period of 3 years.
- The follow-up will continue for 1 year after the last inclusion.
- Randomization between the two-arms will take place on a 1:1 base.

Using the Freedman-Peto approach to sample size calculation for a time-to-event endpoint, the above assumptions imply that at least 222 patients have to be included. In the sample of 222 patients 104 events are expected to occur. To account for an unexpected loss of 10%, the total number of patients to be included in the study is set at 250.

17.2. Statistical analysis

All main analyses will be done in accordance with the intention to treat principle.

17.2.1. Analysis of the primary endpoint

The formal comparison, with respect to the efficacy on event-free survival, between the treatments will be evaluated using a two-sided log-rank test with significance level 0.05. From this test we infer which of the two treatments yields the better event-free survival.

All other analyses (of primary and secondary endpoints) are of a non-inferential, i.e., of a hypotheses-generating nature: no conclusions will be drawn from them.

An analysis of the event-free survival will be performed and will consist of:

- An actuarial Kaplan-Meier curve per arm.
- A point estimate of the median event-free survival and its corresponding 95% confidence interval for each arms.

A Cox proportional hazard model for the event-free survival will be fitted. All stratification factors will be included as covariates. In addition the age-adjusted IPI (including serum LDH level at diagnosis as quotient of upper limit of normal value for the participating hospital) and the GCB v.

non-GCB phenotype, all considered having prognostic value, will also be included in the Cox proportional hazard model.

17.2.2. Analysis of the secondary endpoints

With respect to the secondary endpoints overall survival and disease-free interval:

- The overall survival is defined as the time between the date of randomization and the date of death (due to any cause). Patients who are still alive when last traced are censored at the date of last follow-up.
- The disease-free interval is defined as in paragraph 14, with patients being censored if no relapse or death has occurred at last follow-up.
- The analysis of the overall survival and the disease-free interval will consist of actuarial Kaplan-Meier curves per arm, and a point estimates of the median and corresponding 95% confidence interval for each arm. Moreover, Cox proportional hazard models for the overall survival and the disease-free interval will be fitted. All stratification factors will be included as covariates. In addition the age-adjusted IPI (including serum LDH level at diagnosis as quotient of upper limit of normal value for the participating hospital) and the GCB v. non-GCB phenotype, all considered having prognostic value, will also be included in the Cox proportional hazard model.

With respect to the secondary endpoints complete response and progression on protocol:
An analysis of complete response and progression on protocol will be performed and will consist of frequency tables of the endpoints versus arm, and point estimates and 95% confidence intervals of the proportions complete response and progression on protocol per arm. In addition, logistic regression models for the complete response and progression on protocol will be fitted. All stratification factors will be included as covariates. In addition the age-adjusted IPI (including serum LDH level at diagnosis as quotient of upper limit of normal value for the participating hospital) and the GCB v. non-GCB phenotype, all considered having prognostic value, will also be included in the logistic regression model.

17.3. Interim analyses and safety monitoring

A Data and Safety Monitoring Board (DSMB) will be installed before the start of the study. The DSMB is an independent committee of knowledgeable people with respect to, among others, clinical experience of the treatments being used, the statistical properties of the design, et cetera. The primary responsibility of the DSMB is to prevent patients from being put at risk unnecessarily, and to guarantee the integrity of the study. In this the DSMB is, at any time, free in its recommendations to the study coordinators and the study statistician.

One interim analysis has been planned. It will be performed, when half of the required number of patients has been included, on the evaluable patients. The results of the interim analysis are confidential and will only be presented to the DSMB. If and only if the DSMB recommends that the study should be stopped or modified, the results will be communicated to the principal investigators for further decisions.

The planned interim analysis comprises of, by treatment arm:

- The number of entered patients at the time of interim analysis.
- The number of evaluable patients at the time of interim analysis.
- An overview of the treatments given.
- The number and type of failures and incidence of SAE's and other side effects and infections (CTCAE grade).
- The failure rate on induction treatment.
- A test for the difference in failure rate between the arms. It is recommend to terminate the trial if the failure rate in arm B (experimental arm) is higher than in arm A (standard arm), and the null hypothesis of no difference in failure rate is rejected at the significance level of 0.10.
- The number and types of events on the endpoints event-free survival, overall survival and disease-free interval, as well as actuarial estimates for these endpoints.
- A two-sided log-rank test for the difference in event-free survival between the arms. A difference in the event-free survival in favor of arm B is in general no reason to recommend early stopping of the study. However, it is recommended to terminate the trial if the log-rank test rejects the null hypothesis with an extreme p-value, indicating an excessive advantage of arm B, and the number of evaluable patients in each arm is at least 50. The p-value is considered extreme if it exceeds the significance level of 0.001.

All results will be presented to the DSMB.

The study will be monitored closely before the interim analysis. Monitoring will be based on the reported SAE's, for these are not subject to data delay. In particular, the number of patients with an SAE and the number of deaths are monitored. Both numbers are, at regular time points, tested for difference between the arms. The significance level used for these tests is set at 0.10, and will be adjusted for the sequential multiple testing. If the SAE or death incidence is significantly higher in the experimental arm, an early report will be presented to the DSMB.

18. Ethics

18.1. Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

18.2. Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (Edinburgh, Scotland, 2000) and the ICH-GCP Guidelines of 17 January 1997. The local investigator is responsible for ensuring that the study will be conducted in accordance with the protocol, the ethical principles of the Declaration of Helsinki, current ICH Guidelines on Good Clinical Practice (GCP), and applicable regulatory requirements.

18.3. Patient information and consent

Written informed consent of patients is required before randomization. The procedure and the risks and the opinions for therapy in NHL will be explained to the patient.

18.4. Side studies on tumor material

Possible side studies on tumor materials might be initiated during the course of the trial. These studies will be limited to protein or RNA/DNA characteristics of the tumor cells, but to prevent studies on hereditary disorders, not of hereditary DNA characteristics of the normal cells of the patient. All side studies will be approved by the members of the HOVON lymphoma working party. For each future biological side study a separate addendum to this protocol will be written and submitted to the central medical ethics board of the principal study. The Code for Proper Secondary Use of Human Tissues in The Netherlands, version 2002 will be used, http://www.fmwv.nl/gedragscodes/goedgebruik/CodeProperSecondaryUseOfHumanTissue.pdf . To enable participation of all patients included in the study, patients are requested to give permission to use their tumor material for future biological side studies at entry.

19. Trial insurance

The HOVON insurance program covers all patients from participating centers in the Netherlands according to Dutch law (WMO). The WMO insurance statement can be viewed on the HOVON Web site www.hovon.nl.

Individual participating centers from outside the Netherlands have to inform the HOVON about the national laws regarding the risk insurance of patients participating in a study. If necessary HOVON will extend the insurance to cover these patients.

19.1. Intergroup studies

The HOVON insurance program does not cover the risk insurance of patients from centers participating within another cooperative group taking part in an intergroup study. The other participating groups will cover the insurance of patients registered/randomized through their offices.

20. Publication policy

The final publication of the trial results will be written by the Study Coordinator(s) on the basis of the statistical analysis performed at the HOVON Data Center. A draft manuscript will be submitted to the Data Center and all co-authors (and the sponsor, where applicable) for review. After revision by the Data Center, the other co-authors (and the sponsor), the manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the study coordinator(s), the lead investigators of the major groups (in case of intergroup studies), investigators who have included more than 5% of the evaluable patients in the trial (by order of inclusion), the statistician(s) and the HOVON data-manager in charge of the trial, the review pathologists and others who have made significant scientific contributions.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomized treatment arms may be made publicly available before the recruitment is discontinued.

Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This also includes studies based on biopsy material or any other biological material retrieved from the patients during the study. This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms nor an analysis of any of the study endpoints unless the final results of the trial have already been published.

21. Glossary of abbreviations

(in alphabetical order)

aa IPI	Age-adjusted IPI
ABO	ABO blood group
AE	Adverse Event
ALAT	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
ASCT	Autologous Stem Cell Transplantation
ASAT	Aspartate Amino Transferase
BCNU	Carmustine
BEAM	BCNU, Etoposide, Ara-C, Melphalan
BM	Bone Marrow
CGH	Comparative Genomic Hybridisation
CHOP	Cyclophosphamide, Doxorubicin, Vincristine (Oncovin), Prednisone
CKTO	`Commissie voor Klinisch Toegepast Onderzoek'
CR	Complete Remission/Response
CRF	Case Report Form
CRu	Complete Remission unconfirmed
CR1	First Complete Remission
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-Free Survival
DLBCL	Diffuse Large B-cell Lymphoma
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EFS	Event-Free Survival
ENT	Ear Nose Throat
EORTC	European Organization for Research and Treatment of Cancer
FISH	Fluorescent In Situ Hybridization
GCB	Germinal Center B-Cell
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GELA	Groupe d'Etudes des Lymphomes de l'Adulte
GOELAMS	Groupe Ouest–Est des Leucémies et des Autres Maladies du Sang
γGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
HDT	High Dose Treatment
HIV	Human Immunodeficiency Virus
HOVON	Dutch-Belgian Hematology-Oncology Cooperative Group
HR	High Risk
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
iCHOP	Intensified CHOP

IPI	International Prognostic Index
IV	Intravenous
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MiNT	MabThera international Trial
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NYHA	New York Heart Association
OS	Overall Survival
PA	Pathology
PB	Peripheral Blood
PD	Progressive Disease
PET	Positron emission tomography
PO	Per Os
PPD	Product of the two largest Perpendicular Diameters
PR	Partial Response
R	Rituximab
RhD	Rhesus factor
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SD	Stable Disease
SPD	Sum of the Products of the two largest perpendicular Diameters
SUV	Standardized Uptake Value
TMA	Tissue Micro Array
TOP	Trial Online Process
ULN	Upper Limit of Normal
US	Ultrasound
WBC	White Blood cell Count
WHO	World Health Organization
WMO	'Wet Medisch-Wetenschappelijk Onderzoek met mensen'

22. References

(1) Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organisation Classification of Tumours. Pathology and Genetics of Tumours of the Haematopoietic and Lymphoid Tissues. IARC WHO Classification of Tumours, ed. Lyon: IARC Press; 2001.

(2) Fisher RI, Gaynor ER, Dahlberg S et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med. 1993;328:1002-6.

(3) The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. N Engl J Med. 1993;329:987-994.

(4) Maloney DG, Grillo-Lopez AJ, Bodkin DJ et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-Hodgkin's lymphoma. J Clin Oncol. 1997;15:3266-3274.

(5) Coiffier B, Haioun C, Ketterer N et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood. 1998;92:1927-32.

(6) Vose JM, Link BK, Grossbard ML et al. Phase II Study of Rituximab in Combination With CHOP Chemotherapy in Patients With Previously Untreated, Aggressive Non-Hodgkin's Lymphoma. J Clin Oncol. 2001;19:389-397.

(7) Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus Rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235-42.

(8) Pfreundschuh MG, Trumper L, Gill D et al. First Analysis of the Completed Mabthera International (MInT) Trial in Young Patients with Low-Risk Diffuse Large B-Cell Lymphoma (DLBCL): Addition of Rituximab to a CHOP-Like Regimen Significantly Improves Outcome of All Patients with the Identification of a Very Favorable Subgroup with IPI=O and No Bulky Disease. [abstract]. Blood. 2004;104:(abstract 157).

(9) Pfreundschuh M, Trumper L, Kloess M et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. Blood. 2004;104:634-641.

(10) Philip T, Guglielmi C, Hagenbeek A et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333:1540-5.

(11) Guglielmi C, Gomez F, Philip T et al. Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the Parma trial. J Clin Oncol. 1998;16:3264-9.

(12) Gianni AM, Bregni M, Siena S et al. High-dose chemotherapy and autologous bone marrow transplantation compared with MACOP-B in aggressive B-cell lymphoma. N Engl J Med. 1997;336:1290-7.

(13) Shipp MA, Abeloff MD, Antman KH et al. International Consensus Conference on High-Dose Therapy With Hematopoietic Stem Cell Transplantation in Aggressive Non-Hodgkin's Lymphomas: Report of the Jury. J Clin Oncol. 1999;17:423.

(14) Strehl J, Mey U, Glasmacher A et al. High-dose chemotherapy followed by autologous stem cell transplantation as first-line therapy in aggressive non-Hodgkin's lymphoma: a meta-analysis. Haematologica. 2003;88:1304-1315.

(15) Haioun C, Lepage E, Gisselbrecht C et al. Comparison of autologous bone marrow transplantation with sequential chemotherapy for intermediate-grade and high-grade non-Hodgkin's lymphoma in first complete remission: a study of 464 patients. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 1994;12:2543-51.

(16) Santini G, Salvagno L, Leoni P et al. VACOP-B versus VACOP-B plus autologous bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the non-Hodgkin's Lymphoma Cooperative Study Group. J Clin Oncol. 1998;16:2796-2802.

(17) Kluin-Nelemans HC, Zagonel V, Anastasopoulou A et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst. 2001;93:22-30.

(18) Haioun C, Lepage E, Gisselbrecht C et al. Survival Benefit of High-Dose Therapy in Poor-Risk Aggressive Non-Hodgkin's Lymphoma: Final Analysis of the Prospective LNH87-2 Protocol--A Groupe d'Etude des Lymphomes de l'Adulte Study. J Clin Oncol. 2000;18:3025-3030.

(19) Verdonck LF, van Putten WLJ, Hagenbeek A et al. Comparison of CHOP Chemotherapy with Autologous Bone Marrow Transplantation for Slowly Responding Patients with Aggressive Non-Hodgkin's Lymphoma. N Engl J Med. 1995;332:1045-1051.

(20) Kaiser U, Uebelacker I, Abel U et al. Randomized Study to Evaluate the Use of High-Dose Therapy as Part of Primary Treatment for "Aggressive" Lymphoma. J Clin Oncol. 2002;20:4413-4419.

(21) Martelli M, Gherlinzoni F, De Renzo A et al. Early Autologous Stem-Cell Transplantation Versus Conventional Chemotherapy as Front-Line Therapy in High-Risk, Aggressive Non-Hodgkin's Lymphoma: An Italian Multicenter Randomized Trial. J Clin Oncol. 2003;21:1255.

(22) Gisselbrecht C, Lepage E, Molina T et al. Shortened First-Line High-Dose Chemotherapy for Patients With Poor-Prognosis Aggressive Lymphoma. J Clin Oncol. 2002;20:2472-2479.

(23) Milpied N, Deconinck E, Gaillard F et al. Initial Treatment of Aggressive Lymphoma with High-Dose Chemotherapy and Autologous Stem-Cell Support. N Engl J Med. 2004;350:1287-1295.

(24) van Imhoff G, van der Holt B, MacKenzie M, van 't Veer M, Wijermans P, Ossenkoppele G et al. Impact of 3 courses of intensified CHOP prior to high-dose sequential therapy followed by ASCT as first line treatment in poor risk aggressive non-Hodgkin lymphoma. Comparative analysis of HOVON studies 27 and 40. Journal of Clinical Oncology (in press). June 2005.

Appendices

A. NHL WHO classification

B-cell neoplasms

WHO		
1		Precursor B-cell lymphoblastic leukemia / lymphoma
2		B-cell chronic lymphocytic leukaemia / small lymphocytic lymphoma
3		B-cell prolymphocytic leukemia
4		Lymphoplasmocytic lymphoma
5		Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type
6		Nodal marginal zone lymphoma (+/- monocytoid B cells)
7		Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes)
8		Plasma cell myeloma / Plasmocytoma
9		Follicular lymphoma; grade I, grade II, grade III
10		Mantle-cell lymphoma
11	♦	Diffuse large B-cell lymphoma Subtypes: Primary mediastinal B cell lymphoma (not eligible in this study) Intravascular B cell lymphoma T cell rich B cell lymphoma Primary effusion lymphoma (not eligible in this study)
12		Burkitt's lymphoma
13		Unclassifiable

T-cell neoplasms

WHO		
21		Precursor T-cell lymphoblastic leukemia / lymphoma
22		T-cell prolymphocytic leukemia
23		T-cell granular lymphocytic leukemia
24		Aggressive NK-cell leukemia
25		Adult T-cell leukemia / lymphoma (HTLV1+)
26		Extranodal NK / T-cell lymphoma, nasal-type
27		Enteropathy type T-cell lymphoma
28		Hepatosplenic γ / δ T-cell lymphoma
29		Subcutaneous panniculitis-like T-cell lymphoma
30		Mycosis fungoides/Sézary syndrome
31		Anaplastic large cell lymphoma, primary cutaneous type
32		Peripheral T-cell lymphoma (not otherwise characterized)
33		Angioimmunoblastic T-cell lymphoma
34		Anaplastic large cell lymphoma (T- and null-cell types), primary systemic type
35		Unclassifiable

B. HOVON Staging and Response Criteria for Non Hodgkin's Lymphomas

This document describes the minimally required staging and evaluation procedures and response criteria that will be applied in all HOVON NHL studies. It is based on international working group recommendations (Cheson et al., JCO, Vol.17, 1999, pp1244-1253).

Response is currently assessed on the basis of clinical, radiologic, and pathologic (i.e., bone marrow) criteria. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL.

Immunophenotyping of blood or bone marrow has not been included as standard minimum requirement for the staging and restaging of lymphoma, even though it may be done standard in some centers (Hanson, Blood, Vol 94, 1999, pp 3889-3896). It may be a requirement in specific studies involving monoclonal antibodies.

Staging and restaging procedures
Only minimal requirements are specified.

A. Staging at on study before start of treatment
- History (including B symptoms)
- WHO Performance status
- Physical examination
- Laboratory tests
  - Hb, WBC, differential, platelet count, LDH
  - Calcium, creatinine, uric acid, glucose, albumin, bilirubin, ALT
  - paraprotein by immuno-electrophoresis
  - quantitative immunoglobulins only if immuno-electrophoresis abnormal
  - Hepatitis-B in case of abnormal liver function tests
  - HIV test
- Tumor biopsy for histology and immunohistology
- Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology
- Bone marrow aspirate for cytology
- Peripheral blood for cytology
- Imaging
  - CT thorax and abdomen including pelvis
  - US cervical region strongly recommended (Br J Hem. 88 (3) 626-8, 1994); alternative: CT cervical region
- Consultation of ear-nose-throat specialist if indicated (i.e. complaints or gastro-intestinal lymphoma)
- Gastroscopy if indicated (i.e. localization ENT, thyroid)
- Lumbal punction if indicated (i.e. localization testis, nasopharynx or brain)

B. Restaging for the evaluation of treatment
Restaging for the evaluation of treatment should be performed within 2 months after the end of treatment to assess response. Additional moments of restaging, e.g. after 3 cycles of CHOP, are specified in the study protocol.
- History (including B-symptoms)
- WHO Performance status
- Physical examination
- Laboratory tests
  - Hb, WBC, platelet count, LDH
  - Repeat previously abnormal tests
- Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology if involved previously
- Bone marrow aspirate for cytology if involved previously
- Peripheral blood for cytology if involved previously

- Imaging
  - CT thorax and abdomen including pelvis
  - US of cervical region; alternative: CT cervical region
  - Assessment of other localizations only if involved previously

C. Restaging during follow-up to determine remission status (until progression)
In case of CRu (see below) repeat CT 2-4 months after last CT for response evaluation.
- Physical examination
- WHO Performance status
- Laboratory tests
  - Hb, WBC, platelet count, LDH
- **Only if indicated**, i.e. LDH elevation or clinical signs of progression:
  - Bone marrow biopsy (≥ 20 mm biopsy core) for histopathology (if indicated)
  - Bone marrow aspirate for cytology (if indicated)
  - Peripheral blood for cytology (if indicated)
  - Imaging
    - CT thorax and abdomen including pelvis (if indicated)
    - US of cervical region; alternative CT of cervical region (if indicated)

Staging & Remission Status Evaluation

	On Study	***Evaluation of Treatment***	***Follow up***
• *History*	*x*	*X*	*x*
• *WHO performance status*	*x*	*X*	*x*
• *Physical examination*	*x*	*X*	*x*
• *Laboratory tests*			
▪ *Hb*	*x*	*X*	*x*
▪ *WBC*	*x*	*X*	*x*
▪ *Differential*	*x*	*o.i.*	
▪ *Platelet count*	*x*	*X*	*x*
▪ *LDH*	*x*	*X*	*x*
▪ *Calcium*	*x*	*o.i.*	
▪ *Creatinine*	*x*	*o.i.*	
▪ *Uric acid*	*x*	*o.i.*	
▪ *Glucose*	*x*	*o.i.*	
▪ *Bilirubin*	*x*	*o.i.*	
▪ *ALAT*	*x*	*o.i.*	
▪ *Albumin*	*x*	*o.i.*	
▪ *Immuno-electrophoresis*	*x*	*o.i.*	
▪ *Quantitative immunoglobulins*	*o.i.*	*o.i.*	
▪ *Hepatitis-B*	*x*		
▪ *HIV test*	*x*		
• *Tumor biopsy*	*x*	*o.i.*	*o.i.*
• *BM biopsy*	*x*	*o.i.*	*o.i.*
• *BM aspirate*	*x*	*o.i.*	*o.i.*
• *PB for cytology*	*x*	*o.i.*	*o.i.*
• *Imaging**			
▪ *CT thorax*	*x*	*X*	*o.i.*
▪ *CT abdomen including pelvis*	*x*	*X*	*o.i.*
▪ *US/CT cervical region*	*r.*	*r.*	*o.i.*
• *ENT consultation*	*o.i.*	*o.i.*	*o.i.*
• *Gastroscopy*	*o.i.*	*o.i.*	*o.i.*
• *Lumbal punction*	*o.i.*	*o.i.*	*o.i.*

o.i. *on indication*
r. *strongly recommended*
* *see also parargraph 11.2.1 for special PET criteria in this protocol*

Bone marrow evaluation
Bone marrow biopsy* must be adequate (≥ 20 mm biopsy core).
A bone marrow aspirate and biopsy should always be performed at diagnosis. If positive they should be repeated to determine response. They should also be performed in case of new abnormalities in the peripheral blood.

Bone marrow biopsies should be scored as
- positive unequivocal cytologic or architectural evidence of malignancy
- negative no aggregates or only a few well-circumscribed lymphoid aggregates
- indeterminate increased number or size of aggregates without cytologic or architectural atypia

The bone marrow report should be reported not only as positive or negative for lymphoma, but the percentage of invasion and the lymphoma subtype should be indicated, the latter to describe any discordance with the nodal disease.

* see also parargraph 11.1 for requirements of CD20/CD79a immunostain for this protocol.

Measurable disease and size of disease.
Response evaluation is primarily based on bi-dimensionally measurable nodes, nodal masses or nodules in liver or spleen.

Nodes with largest diameter ≤ 1 cm are considered normal and not pathologic. The size of a single node, nodal mass or nodule is defined as the product of the two largest perpendicular diameters (PPD). Nodes of which only one dimension is specified are considered as circular for the calculation of PPD size. If after treatment a nodal mass consisting of individual confluent nodes breaks up in separate nodes the sum of the PPD of the separate nodes must be compared with the size of the pretreatment nodal mass.
All nodules in liver and spleen are considered pathologic, irrespective of size.

The sum of the PPD (SPD) of a set of indicator lesions is used as a quantitative measure for response evaluation. The indicator lesions have to be chosen from the nodes and nodal masses in the following way. If the number of nodes or nodal masses before treatment is 6 or less, all these are considered as indicator lesions. If the number of nodes or nodal masses is more than 6, a minimum number of at least 6 indicator lesions have to be chosen. These nodes or nodal masses should be selected according to the following features:

a) they should be among the largest dominant sites
b) they should be clearly measurable in at least two perpendicular dimensions,
c) they should be from as disparate regions of the body as possible
d) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

The choice of the indicator lesions should be made before start of treatment. All indicator lesions must be numbered and measured bi-dimensionally before start of treatment and at the evaluation times specified in the protocol. The location and size must be documented and reported in the CRF.

Assessable disease
Assessable disease is considered all abnormalities that are not bi-dimensionally measurable, e.g. positive bone marrow or peripheral blood.

RESPONSE CRITERIA

Complete response (CR) requires the following:
1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy
2. Normal LDH (i.e. ≤ ULN). An elevated LDH detracts from a CR unless it is attributable to causes not related to NHL, e.g. hemolysis.
3. All nodes and nodal masses must have reduced in size to ≤ 1.0 cm in greatest transverse diameter, or
4. If some nodes have regressed to a size between 1.0 and 1.5 cm in greatest transverse diameter from a size over 1.5 cm, while none have a size over 1.5 cm, the SPD of the indicator lesions must have regressed by more than 75%.
5. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable and/or no longer considered enlarged on physical examination. However, no normal size can be specified, because of the difficulties in accurately evaluating splenic size. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
6. Any nodules in liver or spleen must have disappeared.
7. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site.

CR/unconfirmed (CRu) includes those patients who fulfill criteria 1, 2, 4 and 5 above, but with one or more of the following features/exceptions*:
1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the PPD size. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD size compared with the size of the original mass. The SPD size of the indicator lesions must have regressed with more than 75%.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

In case of apparent CRu it is recommended to perform, if possible, a cytological punction or biopsy of a residual lymph node mass to determine the cytopathological status. It is also recommended in case of CRu to repeat CT or US of the residual lesion after 2-4 months.

Partial response (PR) requires the following:
1. ≥ 50% decrease in SPD of the indicator lesions.
2. ≥ 50% decrease in SPD of splenic and hepatic nodules if present and bi-dimensionally measurable at start of treatment.
3. No increase in the size of any single node, nodule, liver, or spleen by more than 25%.
4. No new sites of disease.
5. All patients who meet the criteria for CR or CRu except for an LDH >ULN that is not attributable to other causes than NHL or with remaining but decreased nodules in liver or spleen, or with remaining assessable disease are classified as PR.

Stable disease (SD) is defined as less than a PR (see above) but is not progressive disease (see below).

Progressive disease (PD) requires the following
1. ≥50% increase in the PPD-size of any at baseline identified abnormal node, nodal mass or nodule.
2. Appearance of any new lesion during or at the end of therapy.

* see also paragraph 11.2.1 for special PET criteria in this protocol.

Endpoints during follow up

Progression of disease is defined for all patients, irrespective of response on treatment. The following criteria apply:
1. ≥ 50% increase from nadir in the PPD-size of any previously identified abnormal node.
2. Appearance of any new lesion.

Relapse requires the following:
1. Previous achievement of CR or CRu.
2. Progression of disease as defined above.

Note:
1. *Relapse is the same as progression of disease after CR or CRu.*
2. *An abnormal or increasing abnormal LDH, not attributable to other causes than NHL, is not sufficient evidence for the determination of progression. Imaging studies must be performed in such a case.*
3. *Note the difference between PD as response category and Progression of disease as event during or after treatment. All patients whose best response on treatment is PD, per definition also have reached the endpoint Progression of disease. But also other patients with a better response may eventually show progression of disease.*

Failure is defined as
1. either no complete response (i.e. no CR or CRu) on treatment or
2. relapse

Definitions of End Points for Clinical Trials

End Point	Response Category	Definition	Point of Measurement
Overall survival	All patients	Death from any cause	Entry onto trial
Event-free survival	All patients	Failure or death from any cause	Entry onto trial
Progression-free survival	All patients	Disease progression or death from NHL	Entry onto trial
Disease-free survival	CR, CRu	Time to relapse	First documentation of response
Response duration	CR, CRu, PR	Time to relapse or progression	First documentation of response
Time to next treatment	All patients	Time when new treatment is needed	Entry onto trial
Cause-specific death	All patients	Death related to NHL	Entry onto trial

C. Ann Arbor staging classification

Stage	Definition
I	Involvement of a single lymph node region (I) or of a single extra-lymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extra-lymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (III_S) or by localized involvement of an extra-lymphatic organ or site (III_E) or both (III_{SE})
IV	Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues, with or without associated lymph node involvement

B symptoms
The absence or presence of fever, night sweats, and/or unexplained loss of 10% or more of body weight in the six months preceding admission are to be denoted in all cases by the suffix letter A or B, respectively.

Extra-nodal involvement
Involvement of extra lymphatic tissue on one side of the diaphragm by limited direct extension from an adjacent nodal site is classified as extra-nodal extension and denoted by suffix letter E. The E category may also include an apparently discrete single extra-nodal deposit consistent with the extension from a regionally involved node. More extensive extra-nodal disease, e.g. multiple extra-nodal deposits, is classified as stage IV. A single extra-lymphatic site as the only site of disease should be classified as I_E.

Notes
1. For the purpose of defining the number of anatomical lymph node regions the following areas are considered as one region:
- All nodes at one side of the neck are considered as in one region, i.e. consisting of the sub-regions supra-clavicular, cervical, sub-mandibular, occipital, pre-auricular and post-auricular.
- The axillary region includes the infraclavicular nodes.
- The mediastinum is considered as one region, including the sub-carinal and pericardial nodes.

2. The lung-hilus is considered as a separate region. Thus involvement of both the mediastinum and a hilar localization implies stage II disease.
3. Hilar nodes should be considered lateralized and when involved on both sides constitute stage II disease.

D. Common Terminology Criteria for Adverse Events

The grading of toxicity and adverse events will be done using the NCI Common Terminology Criteria for Adverse Events, CTCAE version 3.0, published Dec 12, 2003. A complete document (72 pages) may be downloaded from the following sites:

http://ctep.info.nih.gov/reporting/ctc.html
http://www.hovon.nl (under Studies > Documents)

A hardcopy may be obtained from the HOVON Data Center on request.

E. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

F. NYHA* scoring list

Grade 1	No breathlessness
Grade 2	Breathlessness on severe exertion
Grade 3	Breathlessness on mild exertion
Grade 4	Breathlessness at rest

The *New York Heart Association functional and therapeutic classification applied to dyspnoea

G. Age-adjusted International Prognostic Index

The age-adjusted international prognostic index (IPI) distinguishes 4 risk groups of patients according to their Ann Arbor stage, WHO performance status and LDH.

Risk factors are:

- Ann Arbor stage III or IV
- WHO performance status 2-4
- LDH > 1x Upper limit of normal (ULN)

The age-adjusted IPI:

- Low risk : 0 risk factors
- Low-intermediate risk : 1 risk factor
- High-intermediate risk : 2 risk factors
- High risk : 3 risk factors

H. Patiënteninformatie

Patiënteninformatie behorende bij de studie:

Een vergelijkende studie tussen 6 R-iCHOP chemotherapie en 3 R-iCHOP gevolgd door hoge-dosis chemotherapie en autologe stamceltransplantatie (R-HDT+ASCT) bij volwassen patiënten (18-65 jaar) met een stadium II-IV hoog-intermediair en hoog risico diffuus grootcellig B-cel lymfoom.

Randomized phase III study of Rituximab with intensified CHOP chemotherapy (R-iCHOP-14) versus Rituximab with High-Dose Sequential Therapy and Autologous Stem Cell Transplantation (R-HDT+ASCT) in Adult Patients (18-65 yrs) with High-intermediate and High risk Diffuse Large B-Cell Lymphoma

Inleiding

Geachte mevrouw, mijnheer,

Uw behandelend arts heeft u voorgesteld aan het hierboven genoemde onderzoek deel te nemen en al het één en ander uitgelegd. Uw toestemming of weigering moet u kunnen baseren op goede voorlichting onzerzijds. Daarom ontvangt u deze schriftelijke informatie, die u rustig kunt (her) lezen en in eigen kring bespreken. Ook daarna kunt u altijd nog vragen voorleggen aan de artsen die aan het einde van deze informatie genoemd staan.

Uw medische situatie en de bestaande mogelijkheden tot behandeling

Bij u is de diagnose diffuus grootcellig B-cel lymfoom (DLBCL) gesteld, een vorm van het non-Hodgkin lymfoom (NHL). Dit is een kwaadaardige aandoening van de lymfeklieren. In uw geval is er sprake van een stadium II, III of IV, met de aanwezigheid van 2 of meer ongunstige risicofactoren volgens de zogenaamde ‘age-adjusted International Prognostic Index’. Dit houdt in dat de ziekte reeds in een gevorderd stadium is. Patiënten met een DLBCL worden in het algemeen behandeld met intensieve CHOP chemotherapie (celremmende medicijnen, ook wel cytostatica genoemd) gecombineerd met rituximab (R-iCHOP). Rituximab is een antilichaam gericht tegen een eiwit (het zgn. CD20 antigeen) dat aanwezig is op de oppervlakte van kwaadaardige lymfoom cellen. Hoewel met deze gecombineerde aanpak groei van het lymfoom kan worden teruggedrongen en bij een groot aantal van de patiënten het lymfoom tijdelijk verdwijnt, blijft de kans op definitieve genezing uiteindelijk kleiner dan 40%. De medische wetenschap blijft daarom zoeken naar betere methoden.

Doel en achtergrond van het onderzoek

Uw deelname wordt gevraagd voor een fase III studie (zie bijgesloten folder getiteld: wetenschappelijk onderzoek bij patiënten met kanker).
Het doel van een dergelijke studie is om te onderzoeken of een nieuwe behandelingsvorm een essentiële verbetering betekent vergeleken met de huidige behandeling. De nieuwe aanpak bestaat uit behandeling met intensieve chemotherapie aangevuld met een autologe stamceltransplantatie. In deze fase III studie wordt de helft van de patiënten behandeld met de gebruikelijke 6 kuren chemotherapie (R-iCHOP) (arm A) en de andere helft van de patiënten krijgt 3 kuren R-iCHOP gevolgd door een intensieve behandeling met autologe stamceltransplantatie (arm B). Door middel van loting wordt bepaald welke behandeling u zult krijgen. Uzelf en de behandelend arts hebben hierop geen invloed. Als u wilt deelnemen aan dit onderzoek is er dus 50% kans dat u op de gebruikelijke manier wordt behandeld.

Behandelingsplan in Arm A (6 x R-iCHOP):

Als u in deze arm behandeld wordt, zult u gedurende 12 weken 6 chemotherapiekuren R-iCHOP (Rituximab, Cyclofosfamide, Adriamycine, Vincristine en Prednison) ontvangen. Deze kuren worden 1 x per 2 weken gegeven, gedurende 5 dagen. Rituximab, Cyclofosfamide, Adriamycine en Vincristine worden in een ader ingespoten en Prednison wordt in tabletvorm dagelijks gedurende 5 dagen ingenomen. Daarnaast krijgt u G-CSF, een hormoon dat het herstel van de beenmerg- en bloedcellen stimuleert. G-CSF wordt toegediend door middel van een onderhuidse injectie met een langwerkend G-CSF (Neulasta) op dag 2 van elke iCHOP kuur. Rituximab zal bij de 1^e en 2^e iCHOP kuur zowel op de 1^e als de 8^e dag, worden toegediend, bij de 3^e t/m 6^e kuur telkens op de eerste dag van de iCHOP kuur. Na 3 kuren wordt geëvalueerd in hoeverre het lymfoom heeft gereageerd. Ditzelfde gebeurt opnieuw na 6 kuren.

Behandelingsplan in Arm B (3 x R-iCHOP + Inductie I, II en AutoSCT):

De behandeling in deze arm bestaat uit een drietal fasen, genoemd *pre-inductie, inductie en stamceltransplantatie.* De behandelingsduur is ongeveer 16 weken.

1. Fase I: Pre-inductie behandeling 3 x iCHOP

In deze fase ontvangt u eerst 3 R-iCHOP kuren chemotherapie zoals beschreven bij arm A. Rituximab wordt bij alle kuren zowel op de 1^e als 8^e dag gegeven. G-CSF wordt toegediend door middel van een onderhuidse injectie met een langwerkend G-CSF (Neulasta) op dag 2 van elke iCHOP kuur. Dit wordt vervangen door een kortwerkend G-CSF (Neupogen) dagelijks gegeven

van dag 2 t/m dag 11, tijdens de kuur waarbij stamcelmobilisatie plaats vindt (zie verder). Indien na drie kuren het lymfoom goed heeft gereageerd worden daarna twee intensieve chemotherapie kuren (Inductie I en Inductie II) gegeven als voorbereiding op een daarna volgende autologe stamceltransplantatie.

2. *Stamcel oogst*

Zodra dat mogelijk is, afhankelijk van eventueel in het beenmerg (nog) aanwezige tumorcellen, zullen bij u stamcellen d.m.v. een zgn. stamcelferese worden verzameld. Stamcellen zijn jonge cellen uit het beenmerg, die onder invloed van chemotherapie en G-CSF in het (perifere) bloed gaan circuleren (stamcelmobilisatie). Er is veel ervaring met het verzamelen van stamcellen waarbij kortwerkend G-CSF (Neupogen) dagelijks wordt toegediend na de chemotherapie. Daarom wordt van deze wijze van toediening gebruik gemaakt in arm B van de studie bij de kuur waarbij stamcellen worden verzameld. Het verzamelen van stamcellen gebeurt met behulp van een z.g.n. ferese apparaat. Hierbij wordt uw bloed via een speciale catheter (=infuusnaald) afgenomen en door het ferese apparaat geleid waarbij de stamcellen er uitgefilterd worden. Het overige bloed krijgt u dan weer terug via dezelfde catheter.
De aldus verzamelde stamcellen worden ingevroren en bewaard voor de afsluitende behandeling, de transplantatie (zie verder). Indien het niet lukt om bij u stamcellen uit het bloed te verzamelen, kunnen deze stamcellen soms ook uit het beenmerg worden gehaald. Stamcelafname uit het beenmerg vindt plaats onder verdoving door middel van beenmergpuncties, waarbij het merg wordt opgezogen door een holle naald. Over beide procedures, zowel stamcelferese als beenmergafname, is aanvullende patiënteninformatie aanwezig.
De stamcellen die worden verzameld zullen worden ingevroren en bewaard voor de derde fase van de behandeling de stamceltransplantatie. De stamcellen zullen, liefst zo vroeg mogelijk, al tijdens de eerste fase van de behandeling (R-iCHOP kuren), worden verzameld. Echter dit is ook mogelijk tijdens de tweede behandelingsfase (zie onder). Het moment waarop deze stamcelverzameling bij u het beste kan plaatsvinden wordt door uw behandelende arts in overleg met u beslist.

3. *Fase II: Inductie kuren*

Na de eerste behandelingsfase met 3 x R-iCHOP volgt de tweede behandelingsfase, de inductiekuren. Deze behandeling bestaat uit een tweetal hoog gedoseerde cytostatica kuren gecombineerd met rituximab en G-CSF, die met een tussenliggende periode van ongeveer 4 weken worden gegeven.

Deze twee hoge-dosis chemotherapie kuren (ook wel inductie kuren genoemd) zijn bedoeld om zoveel mogelijk nog resterende kwaadaardige cellen op te ruimen. Deze kuren worden in het ziekenhuis gegeven. Zij bestaan uit een combinatie van cytostatica welke een aantal dagen achter elkaar worden toegediend. Na elke kuur zit een rust pauze van 2 tot 3 weken. In deze weken moet het lichaam zich van de kuur herstellen. Na deze twee kuren wordt opnieuw een restadiëringsonderzoek verricht. Als de ziekte nog steeds gunstig reageert op de behandeling volgt dan de volgende derde behandelingsfase met de stamceltransplantatie.

4. Fase III: Autologe Stamceltransplantatie (ASCT)

Indien de ziekte goed reageert op de behandeling en er voldoende stamcellen uit bloed en/of beenmerg zijn verzameld, volgt de derde behandelingsfase, de autologe stamceltransplantatie.
Deze behandeling bestaat uit zeer intensieve chemotherapie met verschillende cytostatica gedurende een aantal dagen. Deze kuur is er op gericht de laatste eventueel nog aanwezige kwaadaardige cellen, op te ruimen. Omdat deze intensieve kuur ook het beenmerg zeer sterk aantast, krijgt u direct na de kuur uw eigen (= autologe) verzamelde stamcellen door middel van een infuus terug. Dit heet autologe stamceltransplantatie of autologe beenmergtransplantatie. De teruggegeven stamcellen kunnen via de bloedbaan het beenmerg bereiken en daar zorgen voor een herstel van de bloedaanmaak. De bijwerkingen van deze behandeling zijn te vergelijken met die bij de inductiekuren. Voor het herstel van het bloed zult u zo'n 3 tot 4 weken opgenomen zijn.

Bijwerkingen

Nadere informatie over algemene bijwerkingen van *chemotherapie* kunt u vinden in de folder over chemotherapie van het Koningin Wilhelmina Fonds (Nederlandse Kankerbestrijding).
Niet alle mogelijke bijwerkingen zijn hierbij vermeld. Het is ook niet zo dat alle genoemde bijwerkingen met zekerheid bij elke patiënt zullen optreden. Bij het optreden van onbegrepen klachten of verschijnselen is het aangewezen om te overleggen met Uw behandelend arts.

1 R-iCHOP bijwerkingen (arm A en arm B)

De belangrijkste bijwerking van de R-iCHOP chemotherapie is tijdelijke onderdrukking van de normale bloedcelaanmaak, waardoor een tijdelijk tekort aan rode bloedcellen, witte bloedcellen en bloedplaatjes kan ontstaan. De rode bloedcellen worden zo nodig aangevuld met transfusies. De tekorten aan witte bloedcellen worden behandeld met G-CSF injecties. Er blijft echter een klein risico dat u tijdens de CHOP kuren een verhoogde vatbaarheid voor infecties heeft. Wanneer er koorts optreedt in combinatie met een gebrek aan witte bloedcellen zult u, zonodig in het ziekenhuis, behandeld worden met antibiotica.

Een eventueel tijdelijk tekort aan bloedplaatjes wordt opgevangen door bloedplaatjestransfusies, zodat u zo min mogelijk risico loopt spontane bloedingen te krijgen. Voorts kunnen tintelingen in de vingers en soms een doof gevoel in de voeten optreden alsmede obstipatie. Dit zijn bijwerkingen van Vincristine, welke van tijdelijke aard zijn. CHOP behandeling leidt vrijwel altijd tot tijdelijke kaalheid. Ook de vruchtbaarheid wordt vaak aangetast. Bij mannen zal desgewenst en indien mogelijk voor het starten van de behandeling worden geprobeerd zaad in te vriezen (semen preservatie).
Rituximab kan tijdens de toediening milde en tijdelijke bijwerkingen hebben, welke bestaan uit koorts, koude rillingen, hoofdpijn, een gevoel van moeheid, soms jeuk, en tijdelijke roodheid van de huid. Daarnaast komt ook soms misselijkheid voor en een geringe bloeddrukdaling. Echter, vrijwel al deze bijwerkingen zijn te voorkomen door het infuus langzaam te laten lopen. Om deze reden wordt het infuus gedurende 4 uur toegediend, en wordt paracetamol en soms anti-allergische medicatie toegediend.

2 Hoge-dosis therapie (arm B)

De belangrijkste bijwerkingen van de hoge dosis therapie (Inductie I, II en AutoSCT) zijn dezelfde als bovengenoemd maar dan in sterkere mate. Ook bij deze kuren is een belangrijke bijwerking een tijdelijke onderdrukking van de aanmaak van rode- en witte bloedcellen, en bloedplaatjes in het beenmerg. Ook andere bijwerkingen zoals: haaruitval (tijdelijk), misselijkheid en mucositis (ontsteking van het slijmvlies van mondkeelholte en maagdarmkanaal) kunnen in versterkte mate optreden. In de herstelfase na elke kuur is het daarom belangrijk om u zoveel mogelijk te beschermen tegen infecties. Daartoe krijgt u antibiotica (tegen infectie gerichte medicijnen) die u moet slikken. Ook is het mogelijk dat u tussendoor transfusies met rode bloedcellen en bloedplaatjes nodig hebt. Om de periode van verminderde bloedaanmaak te verkorten krijgt u bovendien ook na deze kuren het medicijn G-CSF (Neupogen) toegediend. Gedurende deze intensieve behandeling zult U tijdelijk worden opgenomen in het ziekenhuis totdat uw behandelend specialist het verantwoord vindt u naar huis te laten gaan. Dit zal afhankelijk zijn van de mate en ernst van de bijwerkingen van de behandeling, het herstel van de bloedwaarden en de wenselijkheid en mogelijkheden om u verder poliklinisch, of in dagbehandeling te controleren en behandelen. Vanzelfsprekend zal uw behandelend specialist dit met u bespreken. Het is belangrijk de adviezen van uw specialist nauwkeurig op te volgen.

Extra onderzoek en controle

Het vaststellen van de resultaten van de behandeling gebeurt aan de hand van lichamelijk onderzoek, bloedonderzoek, beenmergonderzoek (indien noodzakelijk) en röntgenonderzoek

inclusief CT-scans en PET-scans. U blijft daarna onder regelmatige controle van de specialist. Voor de studie is geen extra onderzoek nodig, wel worden uw ziektegegevens bijgehouden.

Weefselonderzoek

Om de kwaliteit van de gehele klinische studie te bewaken is het gebruikelijk om de met behulp van microscopisch onderzoek gestelde diagnosen die door de verschillende pathologen in de ziekenhuizen werden gesteld te controleren. Dit geldt dus ook voor de patholoog van uw ziekenhuis en gebeurt door een centrale beoordeling van het oorspronkelijke weefselonderzoek door twee door HOVON aangewezen Nederlandse pathologen die zeer ervaren zijn in dit specifieke gebied van de pathologie (centrale pathologie review). Hiervoor vraagt het HOVON Data Centrum bij de patholoog die de diagnose bij u gesteld heeft, bewaard weefsel op. Dat is bewaard in de vorm van een zogenaamd paraffine blokje. De patholoog wordt gevraagd om dit blokje op te sturen of 11 hiervan gesneden ongekleurde weefselplakjes, zogenaamde coupes. De review patholoog gebruikt deze om de diagnose te bevestigen, de aanwezigheid van het CD20 antigeen op de lymfoomcellen te bevestigen en vier kleuringen te verrichten waarvan in de literatuur is aangetoond dat zij een voorspellende waarde kunnen hebben wat betreft de prognose. Deze vier kleuringen hebben betrekking op de eigenschappen/kenmerken van de tumorcellen. Een dergelijk onderzoek is voor uzelf niet direct van belang en geeft ook geen informatie over andere zaken zoals het erfelijk materiaal. Met het oog hierop zal indien u deelneemt aan de studie, u gevraagd worden in te stemmen met het versturen van bovengenoemd weefselblokje of de hiervan gesneden coupes naar de centrale review pathologen.

HOVON streeft hiernaast ernaar om wetenschappelijk onderzoek te stimuleren dat meer inzicht kan geven in de klinische betekenis van bepaalde tumoreigenschappen. Regelmatig worden in wetenschappelijke tijdschriften studies gepubliceerd waarin nieuwe tumoreigenschappen worden beschreven die mogelijk een voorspellende waarde hebben ten aanzien van de prognose, dat wil zeggen de reactie op de ingestelde behandeling en de overleving. Het betreft uitsluitend al goed wetenschappelijk beschreven eigenschappen van de tumor zelf en nooit de erfelijke eigenschappen zoals die in (het DNA van) uw normale cellen zijn vastgelegd. Dergelijke studies op tumor materiaal worden altijd pas tijdens de studie opgezet en na het beëindigen van de klinische studie uitgevoerd. Dit betekent dat de uitkomst ervan nooit belang kan hebben voor u zelf (pas na enkele jaren zijn er onderzoeksresultaten), maar de resultaten kunnen ons wel een beter inzicht geven in het gedrag van de ziekte en de reactie op de behandeling, en ons zo op weg helpen naar een verdere verfijning van de diagnostiek en hopelijk verbetering van de behandeling in de toekomst. De patholoog van uw ziekenhuis heeft in het archief “restmateriaal” van de tumor dat hiervoor gebruikt kan worden. Als een dergelijke eventuele “side-study” van start gaat vraagt het

HOVON Data Centrum een paraffineblokje of een in de diepvries bewaard weefselstukje op bij de patholoog die de diagnose bij u gesteld heeft en deze in het archief heeft bewaard. Deze worden gecodeerd, dat wil zeggen van alle persoonlijke gegevens ontdaan, aan het onderzoekende laboratorium ter hand gesteld. Onderzoekers in dit laboratorium hebben dus geen toegang tot uw gegevens. Het materiaal zal daarna weer aan de patholoog van uw ziekenhuis worden geretourneerd.

Vanwege praktische overwegingen vragen wij u apart van de eerder beschreven pathologie review die uitsluitend dient ter controle van de kwaliteit van de studie, ook toestemming te verlenen om erna eventueel overblijvend restmateriaal te gebruiken voor dergelijke goedgekeurde “side-studies”. Uiteraard kunt u ook toestemming geven voor uitsluitend de pathologie-review en niet voor een dergelijke “side-study”.

Voor- en nadelen

Op dit moment kan niet worden vastgesteld welke van de twee behandelingsarmen een betere kans op genezing biedt. Indien u besluit aan de studie deel te nemen brengt dit met zich mee dat er op regelmatige tijdstippen controles plaatsvinden. Er vindt geen extra onderzoek plaats, tenzij na uw uitdrukkelijke toestemming.

Vertrouwelijkheid (Privacy)

Onderzoeksgegevens kunnen slechts door daartoe geautoriseerde medewerkers van overheidsinstanties, medewerkers van het ziekenhuis en bevoegde instanties buiten de kliniek worden ingezien. Onderzoeksgegevens zullen worden gehanteerd met inachtneming van de wet becherming persoonsgegevens. Alle medische gegevens die tijdens deze studie worden verzameld zullen worden voorzien van een codenummer. De persoonsgegevens zullen niet gebruikt worden op studiedocumentatie.

Schade

Voor de deelnemers aan dit onderzoek is een verzekering afgesloten. Deze verzekering dekt schade door dood of letsel die het gevolg is van deelname aan het onderzoek, en die zich gedurende de deelname aan het onderzoek openbaart, of binnen vier jaar na beëindiging van de deelname aan het onderzoek. De schade wordt geacht zich te hebben geopenbaard wanneer deze bij de verzekeraar is gemeld.

(In geval van schade kunt u zich direct wenden tot de verzekeraar.)
De verzekeraar van het onderzoek is:

Naam:	Gerling Allgemeine Versicherungs-AG
Adres:	Postbus 2636
	1000 CP Amsterdam
Telefoonnummer:	020 – 54 92 213
Contactpersoon:	mr. P. Oosterveen

De verzekering biedt een maximum dekking van € 450.000 per proefpersoon en € 3.500.000 voor het gehele onderzoek. De dekking van specifieke schades en kosten is verder tot bepaalde bedragen beperkt. Dit is opgenomen in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Informatie hierover kunt u vinden op de website van de Centrale Commissie Mensgebonden Onderzoek: www.ccmo.nl.

Voor deze verzekering gelden een aantal uitsluitingen. De verzekering dekt niet:

- schade waarvan op grond van de aard van het onderzoek zeker of nagenoeg zeker was dat deze zich zou voordoen;
- schade aan de gezondheid die ook zou zijn ontstaan indien u niet aan het onderzoek had deelgenomen;
- schade die het gevolg is van het niet of niet volledig nakomen van aanwijzingen of instructies;
- schade aan nakomelingen, als gevolg van een nadelige inwerking van het onderzoek op u of uw nakomeling;
- bij onderzoek naar bestaande behandelmethoden: schade die het gevolg is van één van deze behandelmethoden;
- bij onderzoek naar de behandeling van specifieke gezondheidsproblemen: schade die het gevolg is van het niet verbeteren of van het verslechteren van deze gezondheidsproblemen.

Weigeren voor en tijdens het onderzoek

Het is, zoals gezegd, niet precies bekend welke van de twee behandelingen de beste is. Daarom heeft uw arts u verteld over het doel van dit onderzoek en u gevraagd om er aan mee te werken. U bent uiteraard vrij om uw medewerking aan dit onderzoek te weigeren. Als u besluit niet mee te doen, zal u de gebruikelijke “standaard”behandeling voorgesteld worden. Ook indien u nu toestemming geeft, kunt u die later zonder opgave van redenen weer intrekken. Wat u ook besluit, het zal geen consequenties hebben voor de verzorging en begeleiding van uzelf en uw familie. De behandeling zal zo nauwkeurig mogelijk volgens vooropgesteld plan verlopen. Het kan natuurlijk gebeuren dat uw lichamelijke reacties of nieuw ontdekte feiten ons tot veranderingen dwingen. Die

zullen direct met u besproken worden, zodat u de gelegenheid krijgt te overwegen al of niet met het onderzoek door te gaan. Wel vragen wij van u de voorschriften van uw behandelend arts goed op te volgen en u niet, zonder diens medeweten, elders te laten behandelen.
Tenslotte, u bent verzocht deel te nemen aan medisch wetenschappelijk onderzoek. De voor dit onderzoek internationaal vastgestelde richtlijnen zullen nauwkeurig in acht worden genomen.

Nadere informatie

Mocht u verdere vragen hebben, dan kunt u die voorleggen aan uw behandelend specialist of aan:
.....[naam/namen betrokken specialisten]
.....
.....
Voor meer informatie kunt u ook contact opnemen met een onafhankelijk arts die zelf niet bij het onderzoek betrokken is, maar wel deskundig is op het gebied van dit onderzoek:
.....[naam en telefoonnummer onafhankelijk arts]

Het onderzoek wordt gecoördineerd door Drs. G.W. van Imhoff van de afdeling hematologie van het UMC Groningen en Dr. L.F. Verdonck van het UMC Utrecht.

*Bijlagen: (Nederlandse Kankerbestrijding)

- Folder Wetenschappelijk onderzoek bij patiënten met kanker (Nederlandse Kankerbestrijding)
- Folder *Non-Hodgkin lymfomen* (Nederlandse Kankerbestrijding)
- Folder Instituut voor Gezondheidsethiek

TOESTEMMINGSVERKLARING
voor deelname aan het wetenschappelijk onderzoek:

Een vergelijkende studie tussen 6 R-iCHOP chemotherapie en 3 R-iCHOP gevolgd door hoge-dosis chemotherapie en autologe stamceltransplantatie (R-HDT+ASCT) bij volwassen patiënten (18-65 jaar) met een stadium II-IV hoog-intermediair en hoog risico diffuus grootcellig B-cel lymfoom.

Randomized phase III study of Rituximab with intensified CHOP chemotherapy (R-iCHOP-14) versus Rituximab with High-Dose Sequential Therapy and Autologous Stem Cell Transplantation (R-HDT+ASCT) in Adult Patients (18-65 yrs) with Stage II-IV High-intermediate and High risk Diffuse Large B-Cell Lymphoma.

Ik ben naar tevredenheid over het onderzoek geïnformeerd. Ik heb de schriftelijke informatie goed gelezen. Ik ben in de gelegenheid gesteld om vragen te stellen over het onderzoek. Mijn vragen zijn naar tevredenheid beantwoord. Ik heb goed over deelname aan het onderzoek kunnen nadenken. Ik heb het recht mijn toestemming op ieder moment weer in te trekken zonder dat ik daarvoor een reden behoef te geven.
Ik stem vrijwillig toe met deelname aan het onderzoek en verzoek hierbij dat tumorweefsel voor pathologie-review wordt opgestuurd naar het door HOVON aangewezen centrale pathologie laboratorium van deze studie.

Naam : .....

Adres : .....

Woonplaats : .....

Geboortedatum : .....

Handtekening : ..... Datum: .....

Los van bovengenoemde toestemming aan pathologie-review, geef ik ***WEL / NIET*** toestemming om overblijvend restmateriaal van de tumor dat van alle persoonlijke gegevens ontdaan zal worden, af te staan voor wetenschappelijk onderzoek in zogenaamde ‘side studies’.

Handtekening : ..... Datum: .....

Ondergetekende verklaart, dat de hierboven genoemde persoon zowel schriftelijk als mondeling over het bovenvermelde onderzoek geïnformeerd is. Hij/zij verklaart tevens, dat een voortijdige beëindiging van de deelname door bovengenoemde persoon, van geen enkele invloed zal zijn op de zorg die hem of haar toekomt.

Naam : .....

Functie : .....

Handtekening : ..... Datum: .....

Dit formulier is bestemd voor onderzoek met meerderjarigen, die wilsbekwaam zijn. Bij dit soort onderzoek moet door de betrokkenen zelf toestemming worden verleend.