Phase II study on the feasibility and efficacy of R-DHAP + HD-MTX, combined with intrathecal rituximab, followed by autologous stem cell transplantation in patients with a recurrent aggressive B-cell lymphoma with CNS localisation

PROTOCOL

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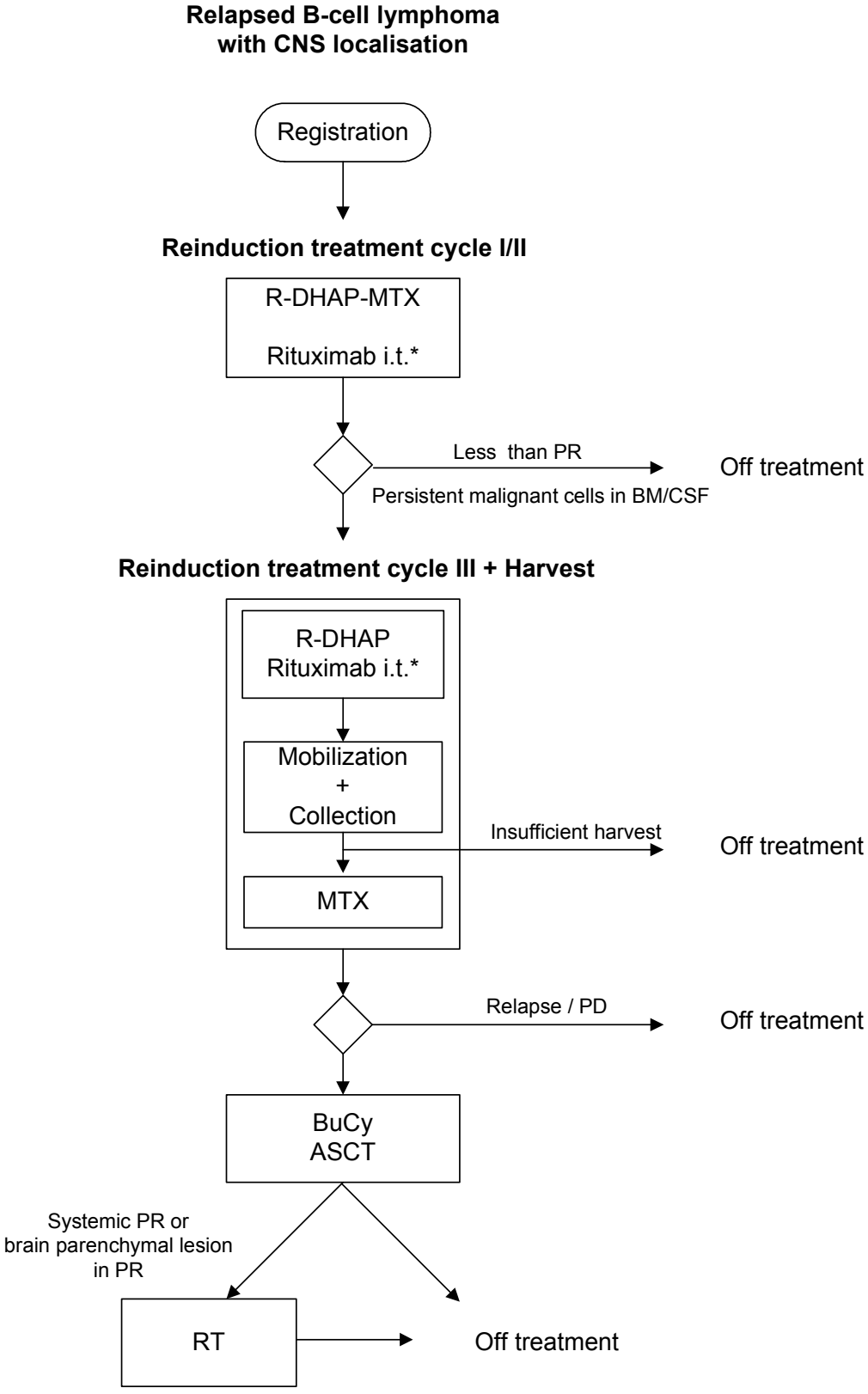
1 Scheme of study



*) In case the CSF is not cleared of lymphoma at the start of the 2nd R-DHAP-MTX cycle intrathecal treatment will be switched to MTX , cytarabine and dexamethasone

2 Table of contents

3 Synopsis

Study phase	Phase II
Study objectives	Evaluation of intensive therapy for relapsed B-cell lymphoma with CNS localisation. Treatment includes: a. intrathecal administration of rituximab b. combining R-DHAP with high dose methotrexate intravenously The following endpoints will be evaluated: progression free survival, response rate and overall survival.
Patient population	Patients with CD20 positive lymphoma (DLBCL, follicular lymphoma grade 3) in first relapse or progression, with central nervous system involvement with or without systemic disease, age 18-65 years inclusive
Study design	Prospective multicenter, phase II
Duration of treatment	Expected duration of treatment is about 5 months
Number of patients	35 patients registered
Planned start of recruitment	Start of recruitment III 2006
Planned end of recruitment	End of recruitment III 2009

4 Investigators and study administrative structure

Responsibility	Name	Affiliation/Address
Study Coordinators	J.E.C. Bromberg	Erasmus MC, Rotterdam
	J.K. Doorduijn	Erasmus MC, Rotterdam
Writing Committee	J. Baars	AvL, Amsterdam
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Datamanagement	F.M. Spoelstra	HOVON Data Center, Rotterdam
Serious Adverse Events (SAEs) notification	HOVON Data Center	Fax: +31.10.7041028

4.1 PA review

A central pathology review of the biopsy of the original diagnosis and the recurrence (if available) will be performed for each case by two review pathologists. The review analysis will be done without knowledge of the patient outcome. It will comprise:

- confirmation of the histological diagnosis according to 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-79a antibody

A review by more hemato-pathologists will be performed when judged appropriate.

Once a patient is registered in the study, the local pathologist as well as the review pathologist will be notified by e-mail. The local pathologist will be asked to send the reports (of the original diagnosis and the recurrence) together with a representative Hematoxylin & Eosin stained slide as well as a representative paraffin embedded block to the review pathologist. The block will be used for confirming immunohistochemistry as well as for the construction of tissue micro arrays (TMA). In case of insufficient material (endoscopic biopsy samples, needle biopsy samples) 10-15 unstained slides (APES coated glass slides) may be send for immunohistochemical confirmation. 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:
Dr. K.H. Lam
Department of Pathology
Josephine Nefkens Insititute
Erasmus MC Rotterdam
P.O. Box 2040
3000 CA Rotterdam

During the study a side study on tumor materials will be initiated. The aim is to perform tissue micro-array on tumor material and gene expression profiling studies on tumor material and CSF. The protocol concerning this side study will be initiated by the study coordinators, written separately and will be submitted for approval by the members of the HOVON lymphoma working party and the central medical ethics board of the trial.

5 Introduction

5.1 Secondary central nervous system lymphoma

A central nervous system (CNS) localisation of a systemic non-Hodgkin's lymphoma (NHL) is an infrequent event, reported to occur in 5-10% of all patients with NHL. [1-4] Patients with CNS localisation at presentation are generally treated similarly to patients without CNS localisation but with the addition of intrathecal chemotherapy with or without irradiation of the CNS. With this treatment, results are comparable to those achieved in patients with a similar extent of disease but without CNS localisation at diagnosis.[5] However, patients with a *relapsed* lymphoma with CNS localisation have a poor prognosis with a median survival of 2-4 months and less than 10% 1-year-survival after various conventional treatments.[2,4,6] Generally the CNS recurrence is concurrent with or soon followed by a systemic recurrence and prognosis is determined largely by the systemic disease.[6] In the context of the very poor prognosis of these patients more effective therapy is urgently needed.

5.2 Treatment of systemic relapsed or progressive disease

For the treatment of systemic NHL, high dose chemotherapy followed by infusion of autologous peripheral blood stem cells (PBSCT) is increasingly applied. In relapsed lymphoma that is still sensitive to conventional chemotherapy, myelo-ablative therapy followed by PBSCT is the treatment of choice and is able to increase the long-term survival rate.[7-9] Patients with relapsed or progressive B-cell NHL are currently treated with 3 courses of combination chemotherapy (DHAP, VIM, DHAP) followed by BEAM and PBSCT in case of sufficient response.[7] Since the successful introduction of the humanized mouse monoclonal anti CD20 antibody, rituximab, for the treatment of B-cell lymphoma, major improvements have been achieved in the outcome of patients. This has been documented in several multicenter phase III studies.[10;11;34] The value of rituximab in the treatment of progressive or relapsed lymphoma is less well documented. However, the HOVON-44 study that investigated this topic, was closed after an interim analysis that showed a significantly better failure free survival in favour of the rituximab treated patients (HR = 0.40 (95% CI 0.27-0.61, $p<0.01$). Patients with relapsed lymphoma with a CNS localisation have always been excluded from protocols studying intensive treatment including PBSCT and no prospective data are available concerning feasibility and efficacy of this treatment in these patients. Retrospective studies have shown that treatment with high dose chemotherapy and stem cell transplantation can result in long-term survival in selected patients.[3;12-14]

5.3 Treatment of CNS localisation

Intrathecal methotrexate (MTX) is the current standard treatment of meningeal relapse of NHL with or without radiation treatment. This results in symptomatic improvement and reduction of malignant cells in the cerebrospinal fluid (CSF) in 50-80% of patients, although the improvement is frequently transient.[3;4] Efficacy of intrathecal MTX is hampered by limited penetration into bulky leptomeningeal disease and intracerebral parenchymal lesions. High dose intravenous MTX penetrates well into the CNS and is an effective treatment of primary CNS lymphoma. Analogous to the treatment of primary CNS lymphoma it is likely that addition of high dose intravenous MTX (HD-MTX) will improve the efficacy of treatment of the CNS localisation of relapsed systemic NHL, although it is probably insufficiently active as monotherapy in treating the systemic disease.[15] Similarly, analogous to the treatment of systemic aggressive B-cell lymphomas, combination chemotherapy is likely to be more effective than monotherapy.

The optimal treatment of patients with a progressive or relapsed aggressive lymphoma with CNS localization should combine the best treatment of both systemic and central nervous system lymphoma. The addition of high dose MTX intravenously to a cisplatin-containing chemotherapy regimen (DHAP), which is the standard treatment for systemic relapsed or progressive aggressive B-cell lymphoma, requires intensive monitoring but has been shown to be feasible.[16-19] The preliminary results of the HOVON 44 study justify the addition of rituximab in relapsed CD20 positive B-cell lymphoma. The CSF-concentration of rituximab after intravenous administration, however, is only 0.1% of the serum concentration, and intravenous administration is probably insufficiently active to combat CNS disease.[20-23] Intrathecal administration of rituximab may be more effective, especially when combined with high dose intavenous MTX. Therefore, high-dose intravenous MTX will be combined with intrathecal administration of rituximab to treat the CNS localisation.

5.3.1 Intrathecal rituximab

The addition of intravenous rituximab to the standard treatment of systemic B-cell lymphomas has resulted in major improvement of the outcome. Unfortunately, after intravenous administration the CSF-concentration is low. The intrathecal administration in the case of CNS-localization of B-cell lymphomas therefore deserves further study. Monotherapy with intrathecal rituximab has been investigated in animal studies, and used in individual patients as well as a phase I study to treat central nervous system lymphoma.[20;21;35] Rubenstein et al found no toxicity after intrathecal administration of 10 mg rituximab to cynomolgus monkeys.[20] CSF concentration was maximal within 2 hours and minimal after 24 – 70 hours. The terminal half-life was 4.96 hours, considerably shorter than the serum half-life after intravenous administration which is reported to be 76-205 hours.[20;23] In humans the following side-effects have been described: mild and reversible nausea and chills, hypo- or hypertension, and a single case of severe backpain and temporary paraparesis probably

as a result of high tumorcell burden in the CSF and rapid tumorcell lysis after the first (25 mg) rituximab administration.[21;24] Subsequent administration in the same patient was uneventful. Dose-limiting toxicity was found to be grade III hypertension at a 50 mg dose level.[36] Thus doses up to 25 mg intrathecally seem safe. Clearing of meningeal tumor cells was achieved in the majority of patients. However, in a number of patients a temporary painful lumbosacral radiculopathy occurred after lumbar administration of 25 mg. Therefore the intrathecal dose will be limited to 10 mg.

5.3.2 Intrathecal treatment in case of failure of rituximab

Since high-dose therapy and stemcell transplantation seem worthwhile only in patients in whom CSF disease has been successfully treated,[14] salvage intrathecal therapy is incorporated into the protocol for those patients in whom the CSF is not cleared of malignant cells after the first course of R-DHAP-MTX and 5 intrathecal administrations of rituximab. Optimal treatment is required and therefore a combination of methotrexate, dexamethasone and cytarabine will be given, as previously used in patients with primary CNS lymphoma and CSF localisations of small noncleaved cell lymphoma/lymphoblastic lymphoma ALL.[25-28]

5.4 High-dose therapy

No data exist on the comparative efficacy of the various myelo-ablative regimens. Again the aim of this study is to treat both systemic and CNS compartments simultaneously. Busulfan is well known for its good penetration of the blood brain barrier. Busulfan with cyclophosphamide (BuCy) is a well known preparative regimen for autologous and allogeneic stem cell transplantation and has documented activity as a preparative regimen for patients with lymphoma.[29;30] BuCy has also been used effectively as myelo-ablative conditioning treatment before stemcell reinfusion in patients with primary CNS lymphoma.[31;32]

6 Study objective

To assess in a multicenter phase II study of patients with a recurrent or progressive B-cell lymphoma with CNS involvement:

- The progression-free survival after R-DHAP-MTX + rituximab intrathecally followed by myelo-ablative chemotherapy and autologous peripheral blood stem cell transplantation
- The response rate after R-DHAP-MTX + rituximab intrathecally
- The overall survival after R-DHAP-MTX + rituximab intrathecally followed by myelo-ablative chemotherapy and autologous peripheral blood stem cell transplantation

To evaluate the toxicity of R-DHAP-MTX + rituximab intrathecally followed by myelo-ablative chemotherapy and autologous peripheral blood stem cell transplantation

7 Study design

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

7.1 Reinduction chemotherapy cycles I and II

Patients with a secondary CNS localisation of an aggressive B-cell lymphoma after first line therapy (with or without a documented systemic relapse), meeting all eligibility criteria (see 8.1) will be treated with R-DHAP-MTX. In addition, the central nervous system will be treated by administration of rituximab intrathecally.
Patients will be evaluated for response after cycle II. After cycle I no complete restaging needs to be done, unless there are clinical signs of progressive disease. Patients who still have malignant cells in the cerebrospinal fluid after cycle I and 5 administrations of rituximab intrathecally will be switched to intrathecal treatment with methotrexate, cytarabine and dexamethasone. All patients with progressive disease or less than systemic and CNS parenchymal PR after the first two reinduction cycles will go off protocol. Furthermore, patients who still have evidence of malignant cells in the cerebrospinal fluid or bone marrow at this moment will go off protocol. In that case further treatment is at the discretion of the treating physician. However in case of less than PR in the brain immediate involved-field radiotherapy is strongly recommended

7.2 Reinduction chemotherapy cycle III

If a partial or complete remission is achieved after the first two cycles and the bone marrow and CSF are cleared of malignant cells, the patient is eligible for the third R-DHAP cycle in conjunction with intrathecal treatment, which will be followed by G-CSF administration in order to collect peripheral blood stem cells. After successful stem cell collection the patients will be treated with the third high-dose methotrexate.

7.3 Pretransplant conditioning and stem cell reinfusion

Chemotherapy responsive patients with adequate stem cell collection will be treated by myeloablative chemotherapy (busulfan/cyclophosphamide) and autologous blood stem cell transplantation.

7.4 Radiotherapy after stem cell transplantation

CNS consolidation radiotherapy will be omitted in patients with complete response because of the risk of neurotoxicity after high-dose intravenous MTX.
However, patients in partial remission after BuCy and stem cell transplantation, may be treated with radiotherapy (30-36 Gy). The radiotherapy will be restricted to nodal site(s) with residual tumor mass or focal radiotherapy in case of a brain parenchymal lesion in PR.

8 Study population

All eligible patients have to be registered before start of reinduction treatment (see chapter 16).

8.1 Eligibility for registration

8.1.1 Inclusion criteria

- Diagnosis of aggressive malignant B-cell lymphoma based upon a representative histology specimen according to the WHO classification (see appendix A):
  - Follicular lymphoma grade III
  - Diffuse large B-cell lymphoma

  Prior “low-grade” lymphoma with histologically proven transformation to follicular lymphoma grade III or DLBCL is also permitted.
- CD 20 positive
- First progression or relapse with CNS localisation (see below) without or with systemic relapse (preferably histologically proven). ‘Progressive’ includes patients who have progressive disease (PD), without prior response and patients who have progression after first PR.
- Diagnosis of CNS localisation based on **at least one** of the following:
  - Unequivocal morphological and/or immunophenotypical evidence of CSF lymphoma
  - clinical AND MRI evidence of leptomeningeal localisation
  - brain parenchymal lesion showing homogeneous contrast enhancement suspect for lymphoma, concurrently with systemic progression or recurrence
  - biopsy-proven brain parenchymal NHL localisation of previously diagnosed systemic NHL
- Age 18-65 years inclusive
- WHO performance status 0 – 2 (see appendix F) with or without administration of steroids
- Written informed consent according to the centre’s requirements
- Negative pregnancy test in women of reproductive potential

8.1.2 Exclusion criteria

- History of intolerance of exogenous protein administration
- Severe cardiac dysfunction (NYHA classification III-IV, appendix G, or LVEF < 45%)
- Severe pulmonary dysfunction (vital capacity or diffusion capacity < 50% of predicted value) unless clearly related to NHL involvement
- Hepatic dysfunction, bilirubin or transaminase ≥ 2.5 x upper normal limit, unless related to lymphoma.
- Renal dysfunction (serum creatinine ≥150 umol/l or clearance ≤ 60 ml/min)
- Prior cranial radiotherapy
- Active uncontrolled infection
- Known HIV-positivity
- (EBV) post-transplant lymphoproliferative disorder
- Documented CNS involvement during 1st line therapy (MTX intrathecal profylaxis during 1st line therapy is no exclusion criterium)

9 Treatments

9.1 Reinduction treatment

All patients will receive R-DHAP-MTX according to the following scheme:

Agent	Dose/day	Route	Day
Dexamethason	40 mg	Orally or i.v.	1, 2, 3, 4
Cisplatin	100 mg/m^2	24 hrs continuous infusion i.v.	1
Cytarabine*	2 g/m^2 q 12 hrs (2 doses)	3 hrs infusion for every administration of 2 g/m^2	2
Rituximab	375 mg/m^2	i.v.	5
Methotrexate	3000 mg/m^2	1 hr infusion i.v.	15**

* Cytarabine to be dissolved in 200-250 ml NaCl 0.9%

** **High dose MTX will be administered only if the conditions are met as described in chapter 9.1.3**
At cycle 3 MTX should be given within 14 days after harvest (see 9.2)

In addition intrathecal rituximab will be given.
Initially, i.t. rituximab will be given twice weekly. To avoid interaction with high dose MTX, **no i.t. rituximab will be given within 3 days before or after high dose MTX.** The schedule is designed to allow gradual tapering of i.t. rituximab dose-intensity after the first cycle, while maintaining

deliverance of i.t. rituximab on day –1 of each cycle and avoiding interaction with MTX as described above.

Agent	Dose/day	Route	Day
Rituximab* + dexamethasone	10 mg 4 mg	i.t./ i.ventr.	cycle 1: -1, 4, 8, 11, 21 cycle 2 -1, 5, 11, 21 cycle 3: -1, 11, 25

* i.t./ i.ventr rituximab to be diluted with NaCl 0.9% to achieve a concentration of 5 mg/ml

The next R-DHAP-MTX cycle is given 14 days after MTX i.v. (day 29) in the previous cycle unless:

- ANC < 1.5
- and/or platelets < 100
- and/or active infection

If the second cycle cannot be started 28 days after MTX i.v. the patient will go off protocol treatment.

9.1.1 Special management in conjunction with DHAP

Hyperhydration during DHAP is suggested to consist of 1000 ml saline 0.9% per 9 hours during 45 hrs starting 6 hours prior to the start of cisplatin. The 1000 ml saline will also contain 15 mmol KCl/l, 15 mg magnesium sulfate/l and 5 mg furosemide/l. Diuresis should be at least 300 ml every 3 hours. The bodyweight should be noted every 6 hours. If indicated, diuresis should be enforced by furosemide.

9.1.2 Special management in conjunction with i.v. rituximab

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, 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 rituximab 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 ^{o}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 1/2 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 next rituximab dose may be dissolved in 250 ml NaCL 0.9%. The first 50 ml may be infused in 30 minutes. If no adverse events occur, the remaining 200 ml may be infused in 1 hr. If the patient encounters an adverse event, the rituximab infusion should be interrupted until the symptoms have been resolved. Thereafter the infusion can be restarted according the following scheme:

The first 25 ml in 30 minutes, if no symptoms occur the infusion rate will be increased to 50 ml in 30 min, if no symptoms the infusion rate will be increased further to 75 ml in 30 min, and finally the rest will be infused with an infusion rate of 100 ml in 30 minutes.

9.1.3 High-dose methotrexate

Liver and renal function must be repeated before administration of high dose methotrexate and the patient should fulfill the following eligibility criteria before MTX is started:

- No significant renal dysfunction (creatinine > 1.5 upper limit of normal, or clearance ≤ 60 ml/min. Creatinine should not be more than 25% higher than before starting DHAP)
- Bilirubin/transaminases < 3 times upper limit of normal
- No evidence of extravascular fluid accumulations (peripheral edema, ascites, pleural fluid)
- No mucositis

Treatment should be postponed until the eligibility criteria are met. If high dose MTX cannot be given after a delay of 14 days the patient will go off protocol treatment.

Pancytopenia is no contraindication for high dose methotrexate.

9.1.4 Special management in conjunction with high-dose methotrexate

Hyperhydration during high-dose methotrexate is suggested to consist of 1000 ml glucose 2.5% / NaCl 0.45% with 20 mmol KCl/l and 10 mg furosemide/l per 6 hours, starting 6 hours prior to the start of methotrexate. MTX levels will be measured daily, starting 24 hrs after start of the infusion of methotrexate, until the MTX level is below 0.2 µmol/l. Hydration will be continued until the MTX level is below 0.2 µmol/l. The bodyweight should be noted every 6 hours. If indicated, diuresis should be enforced by furosemide.

Alkalinisation of the urine might consist of 100 ml sodium bicarbonate 8.4% i.v. administered in 15 min. The urine pH should be checked every 6 hours. The urine pH should be > 7 before the administration of methotrexate, and until the MTX level is below 0.2 µmol/l. If the pH is below 7, sodium bicarbonate should be repeated.

Leucovorin rescue (folinic acid) is started 24 hrs after the start of the MTX infusion. It will be administered once every 6 hrs according to the following scheme:

All patients receive 30 mg leucovorin i.v. 24 hrs after the start of the MTX infusion.

I. If the 24 hr MTX level is > 5 µmol/l or the serum creatinine has increased 150%: leucovorin 100 mg in 100 ml NaCl 0.9% infused in 30 minutes every 3 hrs until the MTX level is below 0,02 µmol/l.

II. If the 24 hr MTX level is < 5 µmol/l: leucovorin 30 mg/m^2 orally (intravenously in case of mucositis or diarrhoea) every 6 hrs until at least 96 hrs after the start of MTX infusion and thereafter until the MTX level is below 0,02 µmol/l.

Concomitant medication. During MTX therapy aspirin, NSAID's, sulfamethoxazole, co-trimoxazole, phenytoin, tetracyclins and benzimidazoles (omeprazole, pantoprazole) could increase toxicity and are preferably not used.

9.1.5 Special management in conjunction with i.t./ i.ventr. rituximab

All patients will receive rituximab 10 mg and dexamethasone 4 mg intrathecally, or intraventricularly if an Ommaya reservoir is in place, the day before the start of DHAP. The rituximab should be diluted with NaCl 0.9% to achieve a concentration of 5 mg/ml. If no side-effects ≥ CTCAE gr III occur then the rituximab will be continued at the dose of 10 mg. In case of side-effects ≥ CTCAE gr III i.t. treatment should be switched to MTX, cytarabine and dexamethasone as described in 9.1.6. **No i.t./i.ventr. rituximab will be given within 3 days before or after high dose MTX to avoid possible interactions.** Therefore, if MTX has to be postponed i.t/i.vent rituximab will be postponed accordingly. Analysis of CSF samples is specified in appendix H.

The first two intrathecal/intraventricular rituximab administrations should be given in in-patient setting. In the absence of side-effects > CTCAE grade II subsequent administrations may also be given in out-patient setting if applicable.

Premedication with paracetamol 1000 mg and anti-histaminics (e.g. clemastine 2 mg) will be given 30 min before every intrathecal treatment. The rituximab will be administered slowly, in 2 minutes, after removing at least an equivalent volume of CSF. Vital signs (blood pressure, pulse, respiration, temperature) should be monitored every 15 minutes after rituximab administration at least during the first hour or otherwise until stable. In case of adverse events patients should be observed and the severity of the adverse events should be evaluated. Hypertension should only be treated when

elevated > 200/120, mm Hg, or after 1 hour > 180/100 mm Hg. In case of other adverse events the patient should be treated according to the best available local practices and procedures.

9.1.6 Intrathecal treatment after failure of i.t./i.ventr. rituximab

In case the CSF is not cleared of lymphoma, as analysed by morphology and flowcytometry, at the start of the second R-DHAP-MTX cycle intrathecal treatment will be switched to MTX 15 mg i.t. (12 mg in the case of intraventricular administration), cytarabine 40 mg and dexamethasone 4 mg. These administrations will be given weekly during the first three weeks of the 2 remaining cycles, in total 6 administrations.

Salvage treatment ONLY to be administered in case of failure of it rituximab:

At 2nd R-DHAP-MTX

agent	Dose/day	route	Day
MTX	EITHER 15 mg OR 12 mg	i.t. i.ventr	4, 11, 18 (or ≥ 24 hrs after hd MTX)
Cytarabine	40 mg	i.t. / i.ventr	4, 11, 18 (or ≥ 24 hrs after hd MTX)
Dexamethasone	4 mg	i.t. / i.ventr	4, 11, 18 (or ≥ 24 hrs after hd MTX)

At 3rd R-DHAP-MTX

agent	Dose/day	route	Day
MTX	EITHER 15 mg OR 12 mg	i.t. i.ventr	-1,8,18 (or ≥ 24 hrs after hd MTX)
Cytarabine	40 mg	i.t. / i.ventr	-1,8,18 (or ≥ 24 hrs after hd MTX)
Dexamethasone	4 mg	i.t. / i.ventr	-1,8,18 (or ≥ 24 hrs after hd MTX)

9.2 Stem cell harvest

Patients with at least a partial response after the two reinduction cycles, no (persisting) lymphoma in the bone marrow on morphology and histology, and no evidence of lymphoma cells in de cerebrospinal fluid will receive a third R-DHAP cycle, 15 days after MTX i.v. in the second cycle, according to the scheme at chapter 9.1. After this third cycle peripheral blood stem cells will be harvested and cryopreserved according to standard institutional procedures. At least 2 x 10^6 viable CD34+ cells/kg (preferably 5 x 10^6 CD34+ cells/kg) as checked by standard institutional procedures should be harvested to proceed to the high dose chemotherapy followed by stem cell reinfusion. After stem cell harvesting the patients will receive their third high dose MTX infusion (as described in chapter 9.1.4) no later than 14 days after harvest.

9.3 Busulfan/cyclophosphamide followed by ASCT

Patients with a successful stem cell harvest will continue treatment with busulfan/cyclophosphamide conditioning preferably within 21 days, but no longer than 28 days after the last high dose MTX infusion.

Stem cells will be reinfused on day 0.

Agent	Dose/day	Route	Day
Busulfan	1 mg/kg q 6 hrs	Orally	-7, -6, -5, -4
Cyclophosphamide	60 mg/kg	1 hr infusion i.v.	-3, -2
Phenytoin	5 mg/kg q 6 hrs 5 mg/kg/day	Orally Orally	-9, -8, -7, -6, -5, -4
Infusion of stem cells			0

Busulfan 4 mg/kg/day is administered (total 16 mg/kg) divided into q 6 hrs (1 mg/kg/dose oral), or the equivalent intravenous dose, (0.8 mg/kg/day 4dd i.v., for 4 days). Since administration of high dose busulfan has been associated with the development of generalized seizures, prophylactic administration of phenytoin (5 mg/kg/dose p.o. q 6 hrs, beginning two days before the first dose of busulfan, then 5 mg/kg/day up to day –4) is recommended

9.3.1 Special management in conjunction with busulfan/cyclophosphamide and ASCT

Cyclophosphamide 60 mg/kg will be infused in 500 ml NaCl 09% or glucose 5% over 1 hour. Mesnum 25 mg/kg will be administered at –10 min prior to cyclophosphamide infusion, and at + 4 hrs, +8 hrs and + 12 hrs following cyclophosphamide infusion. Patients will also be hydrated intravenously at 200 ml/hr for 72 hrs, beginning at least 2 hrs before cyclophosphamide infusion. An average urinary flow of at least 100 ml/hr will be maintained for 48 hrs following cyclophosphamide infusion. The bodyweight should be noted every 6 hours. If indicated, diuresis should be enforced by furosemide. KCl will be supplemented in the case of hypokaliaemia.

BuCy conditioning and stem cell reinfusion will only be administered by an experienced team in a nursing ward with appropriate skills in hematologic intensive care. Patients will receive hematologic supportive care, including vigorous hydration, anti-emetics, irradiated platelet and red blood cell transfusions, prophylactic oral antibacterial and antifungal treatment as well as immediate treatment with intravenous broad spectrum antibiotics and/or antifungal treatment in case of fever and/or documented or suspected infection, according to guidelines of the participating institution.

9.4 Radiotherapy treatment

Patients in CR will not receive consolidation radiotherapy on the brain after completion of the protocol treatment because of the risk of neurotoxicity. Patients in partial remission after BuCy and stem cell transplantation, may be treated with radiotherapy (30-36 Gy). The radiotherapy will be

restricted to nodal site(s) with residual tumor mass and focal radiotherapy in case of a brain parenchymal lesion in PR.

10 End of protocol treatment

Reasons for going off protocol treatment are:

1. Normal completion of protocol treatment
2. Progressive disease or less than PR after the first two reinduction cycles
3. Less than CR in the CSF after the first two reinduction cycles
4. Less than CR in the bone marrow after the first two reinduction cycles
5. Progression/relapse after reinduction cycle III or stem cell collection
6. Inadequate collection of peripheral blood stem cells (<2 x 10^6 CD34+ cells/kg)
7. Excessive toxicity requiring stopping of protocol treatment
8. Intercurrent death
9. Lost to follow up
10. Major protocol violation
11. No compliance of the patient (especially refusal to continue treatment)

11 Required clinical evaluations

11.1 Observations prior to start of treatment

- history (including B symptoms)
- physical examination (including WHO performance, consultation ENT specialist)
- neurological examination including MMSE (appendix I)
- laboratory tests (including Hb, WBC and differential, platelet counts, sodium, potassium, calcium, creatinine, uric acid, bilirubin, AF, yGT, ALAT, ASAT, LDH, protein, albumin, glucose)
- CSF examination, including flowcytometry and sampling for translational research as detailed in appendix H
- routine urine analysis
- imaging (including CT thorax and abdomen and cervical region, brain MRI and MRI of other affected regions of the nervous system)
- when relevant lymph node biopsy for morphology and immunopathology of involved site
- bone marrow aspirate and biopsy
- ABO and RhD blood group, irregular antibody screening, HLA antibodies, HLA typing class I
- anti HIV, anti Hepatitis B and C
- left ventricular ejection fraction (LVEF) or cardiac ultrasound/Doppler

- preservation of tumor tissue and slides for central pathology review

11.2 Observations during treatment

Response will be formally evaluated

- after the second chemotherapy course
- after the third chemotherapy course
- after BuCy and stem cell transplantation
- after radiotherapy

Response will be evaluated according to the response criteria in appendix B. Response of the CNS localisation will be graded as defined in the report of the international workshop to standardise baseline evaluation and response criteria for primary CNS lymphoma (appendix C).[33] After cycle I no complete restaging needs to be done, unless there are clinical signs of non-responsive/ progressive disease. In that case additional staging procedures are required for the affected sites. Restaging will be done with special emphasis on initially involved sites by appropriate techniques. All relevant information regarding drug dose, measurable lesions, tumor response and treatment related toxicity will be collected, as well as:

- history (including B symptoms)
- physical and neurological examination (including WHO performance and MMSE)
- laboratory tests (including Hb, WBC and differential, platelet count, sodium, potassium, calcium, creatinine, uric acid, bilirubin, AP, γ-GT, ALAT, ASAT, LDH, protein, albumin, immuno-electrophoresis, glucose)
- CSF examination at each i.t. administration as detailed in appendix H
- routine urine analysis
- imaging of involved areas (including CT thorax, abdomen and cervical region, and CNS when initially abnormal)
- bone marrow aspirate and biopsy (if initially positive)

11.3 Observations during follow up

Follow up will be planned at least every 3 months during the first two years, every 6 months during the next 2 years and annually thereafter.

Follow up will include:

- physical and neurological examination (including WHO performance and MMSE)
- blood count, LDH
- any clinically indicated examination (thoracic and abdominal scan annually)
- 1 year after transplantation MRI brain in all patients

- in the case of abnormal brain or spinal MRI before treatment, MRI of involved area at 3,6,12,18 and 24 months and annually thereafter
- any documentation of abnormal events (e.g. secondary malignancies)
- any treatment off protocol
- 1 year after transplantation a neuropsychological examination in surviving patients

	At entry	After 2nd R-DHAP-MTX	After 3rd R-DHAP-MTX	After BuCy and TX	After RT	FU[1)]
Medical history	X	X	X	X	X	X
Physical examination incl. WHO performance	X	X	X	X	X	X
Neurologic examination incl. MMSE	X	X	X	X	X	X
Hematology	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X[2)]
CSF examination[3)]	X	X	X	o.i.	o.i.	o.i.
Routine urine analysis	X	X	X	X	o.i.	o.i.
CT thorax, abdomen, cervical region	X	X[4)]	X[4)]	X[4)]	X[4)]	o.i.[5)]
MRI CNS[6)]	X	X[7)]	o.i.	X[7)]	X[7)]	X[8)]
BM aspirate and biopsy	X	X[7)]	X[7)]	X[7)]	o.i.	o.i.
Lymph node biopsy	X					
Virological tests	X	o.i.	o.i.	o.i.	o.i.	o.i.
LVEF	X					

[1)] every 3 months during first 2 years, every 6 months during the next 2 years, annually thereafter

[2)] LDH mandatory, other parameters on indication

[3)] At each i.t. administration (see appendix H)

[4)] Initially involved sites.

[5)] In follow up at 1 year all patients complete restaging.

[6)] MRI brain and other affected areas

[7)] If initially abnormal / positive

[8)] All patients MRI brain at 1 year
If abnormal MRI before treatment, MRI of involved area at 3,6,12,18 and 24 months, annually thereafter

o.i. on indication

12 Toxicities

All the chemotherapeutic agents used in the protocol cause pancytopenia and can induce septic or hemorrhagic complications. Cisplatin and high-dose methotrexate are potentially nephrotoxic. Toxicities will be scored according to the NCI Common Terminology Criteria of Adverse Events, version 3.0 (Appendix E).

13 Safety evaluations and adverse events reporting

13.1 Definitions

Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical study subject during protocol treatment. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Adverse reaction (AR)

Adverse reactions (AR) are those AEs of which a reasonable causal relationship to any dose administered of the investigational medicinal product and the event is suspected.

Serious adverse event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose results in:

- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- significant / persistent disability
- a congenital anomaly / birth defect
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above)

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 SAE

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.

Suspected unexpected serious adverse reaction (SUSAR)

All suspected ARs which occur in the trial and that are both unexpected and serious.

Protocol treatment period

The protocol treatment period is defined as the period from the first study-related procedure until 30 days following the last dose of protocol treatment or until the start of another systemic anti-cancer treatment off protocol, if earlier.

13.2 Reporting of (serious) adverse events

Adverse event

AEs will be reported on the CRF. All adverse events of Grade 2 or higher, with the exception of progression of disease, occurring during the protocol treatment period will be reported. Adverse events occurring after that period should also be reported if considered related to protocol treatment. Follow up of ongoing adverse events ends at day 30 following the last dose of protocol treatment.

SAE and Unexpected serious adverse event

All SAEs occurring during the protocol treatment period must be reported to the HOVON Data Center by fax **within 24 hours of the initial observation of the event**, except hospitalizations for:

- a standard procedure for protocol therapy administration. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a Serious Adverse Event.
- the administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- a procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- prolonged hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- a procedure that is planned (i.e., planned prior to starting of treatment on study; must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the protocol treatment remains a reportable serious adverse 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 2 working 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 protocol treatment period, Serious Adverse Events that are considered to be at least suspected to be related to protocol treatment must also be reported to the HOVON Data Center using the same procedure, **within 24 hours after the SAE 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 to the protocol treatment (also include pre-existing conditions)
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 patient's 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 patient's 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.

13.3 Processing of serious adverse event reports

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 datamanager 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.

Any suspected unexpected serious adverse reactions (SUSARs), from any source, will be reported by HOVON Data Center to the investigators, the Ethics Committee which approved the study, and to all applicable Health Authorities within required timelines.

14 Endpoints

See appendix B for a complete definition of endpoints.

Primary endpoint

1. Progression-free survival measured from the date of registration. Patients still alive or lost to follow up are censored at the last day they were known to be alive.

Secondary endpoints

2. Response to R-DHAP-MTX.
3. Overall survival.
4. Toxicity
5. Percentage of patients transplanted.

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 namecode (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 authorised 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 timepoints. 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

The patient should be registered immediately after satisfactory completion of screening tests and obtaining informed consent, and before the start of chemotherapy.
Patients need to be be registered at the HOVON Data Center of the Erasmus MC - Daniel den Hoed by phone call: +31.10.4391568 or fax +31.10.4391028 Monday through Friday, from 09:00 to 17:00, or via the Internet through 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:

- Protocol number
- Institution name
- Name of caller/responsible investigator
- Patient's initials or code
- Patient's hospital record number (optional)
- Sex
- Date of birth
- WHO classification
- PA number (original, relapse and CNS if available)
- PA laboratory (original, relapse and CNS if available)
- Eligibility criteria

All eligibility criteria will be checked with a checklist.
Each patient will be given a unique patient study number, which will be given immediately by TOP or phone and confirmed by fax or email.

17 Statistical considerations

17.1 Sample size and accrual

Median survival in patients with CNS relapse of systemic NHL is reported to be 2-4 months with 1-year progression-free survival after conventional treatment estimated at ≤ 10%.[1;6] Since almost all recurrences occur within 1 year, and since such recurrences are generally rapidly fatal, 1-year progression-free survival is chosen as primary end-point.[3] Assuming that improving progression-free survival at 1 year to 30% is valuable, then 35 patients will be needed (a = 0.05, power 0.9). With an expected annual accrual of 15 patients, accrual will take 2.5 years.

17.2 Analysis

Progression free survival and overall survival at one year will be analyzed using an actuarial Kaplan-Meier estimate. The median and corresponding 95% confidence interval will be calculated. In addition, point estimates and corresponding confidence intervals of the response rate and toxicity rate will be estimated.

17.2.1 Efficacy analysis

The main endpoint will be progression-free survival at 1 year. Secondary endpoints will be response rate, transplantation rate and overall survival from registration.

17.2.2 Toxicity analysis

The analysis of treatment toxicity will be done primarily by tabulation of the incidence of side effects and infections with CTCAE grade 2 or more (appendix E) by cycle. Time to hematological recovery after each treatment cycle will be analyzed by actuarial methods.

17.3 Interim analysis and stopping rules

Toxicity and mortality of the first ten patients included in the study will be closely monitored by inspection of the SAE forms. Since toxicity of BuCy and PSCT is well-known, for the interim analysis, only toxicity of the first two reinduction courses will be taken into account. The trial will be terminated if either:

1) TRM is observed in 3 or more patients of the first ten patients within the first two reinduction cycles
2) Four or more patients of the first ten patients experience grade 4 or irreversible grade 3 toxicity (except nausea, vomiting, alopecia and hematological toxicity) within the first two reinduction cycles

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 and the ICH-GCP Guidelines. 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 registration.

19 Trial insurance

The HOVON insurance program covers all patients from participating centres 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.

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, the manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the study coordinator(s), investigators who have included more than 5% of the evaluable patients in the trial (by order of number of patients included), the statistician(s) and the HOVON datamanager in charge of the trial, and others who have made significant scientific contributions.

Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include an analysis of any of the study end-points unless the final results of the trial have already been published.

21 Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
AL(A)T	Alanine Amino Transferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
AR	Adverse reaction
AS(A)T	Aspartate Amino Transferase
ASCT	Autologous Stem Cell Transplantation
BEAM	BCNU Etoposide Ara-C Melphalan
BM	Bone Marrow
BuCy	Busalfan Cyclophophamide
CKTO	Commissie voor Klinisch Toegepast Onderzoek
CNS	Central nervous system
CR	Complete Remission
Cru	Complete Remission unconfirmed
CRF	Case Report Form
CSF	Cerebrospinal fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	Diffuse Large B-cell Lymphoma
EBV	Epstein Barr Virus
ECOG	Eastern Cooperative Oncology Group
ENT	Ear Nose Throat
FU	Follow up
G-CSF	Granulocyte Colony Stimulating Factor
GCP	Good Clinical Practice
γGT	Gamma Glutamyl Transferase
Hb	Hemoglobin
HD	High Dose
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte histocompatibility antigen
HOVON	Dutch/Belgian Hemato-Oncology Cooperative Group
HR	Hazard Ratio
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IT	Intrathecal
IV	Intravenous
IVENT	Intraventricular
KCl	Potassium Chloride

LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
METC	Medical Ethical review committee
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NaCl	Sodium Chloride
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NR	No response
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
PA	Pathology
PB	Peripheral Blood
PBSCT	Peripheral Blood Stem Cell Transplantation
PD	Progressive Disease
PO	Per Os
PPD	Product of the two largest Perpendicular Diameters
PR	Partial Response
R-DHAP	Rituximab- Dexamethason Cytarabin (High dose Ara-C) Cisplatin (Platinol)
SAE	Serious Adverse Event
SCT	Stem cell transplantation
SD	Stable disease
SPD	Sum of the Products of the two largest perpendicular Diameters
SUSAR	Suspected Unexpected Serious Adverse reaction
TOP	Trial Online Process
TRM	Treatment related mortality
US	Ultrasound
VIM	Etoposide (Vepesid) Ifosfamide Metotrexate
WHO	World Health Organization
WMO	Wet Medisch-Wetenschappelijk Onderzoek met mensen
WBC	White Blood Count

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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 Intravascular B cell lymphoma T cell rich B cell lymphoma Primary effusion lymphoma (not eligible in this trial)
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*

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.

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. Response criteria for CNS localisation of lymphoma

Response criteria for CNS localization of lymphoma adapted from:
response criteria for primary CNS lymphoma according to the report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma[33]

Response	**Brain imaging**	**Corticosteroid dose**	**CSF cytology / flowcytometry**
CR	No contrast enhancement	none	negative
CRu*	No contrast enhancement	any	negative
	Minimal abnormality	any	negative
PR	50% decrease in enhancing tumor	irrelevant	negative
	No contrast enhancement	irrelevant	persistent or suspicious
PD	25% increase in lesion Any new site of disease	irrelevant	recurrent or positive
SD	no change or minor changes not fulfilling the criteria for PR or PD.		

*Addendum
Minimal residual abnormality on brain MRI will be classified as CRu, unconfirmed complete response, since in primary CNS lymphoma this is frequently seen and does not necessarily infer a poor prognosis.[33]

D. 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.

E. 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.

F. 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

G. 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

H. Schedule and methods of CSF analysis and storage

Directly before each administration of i.t./i.ventr. rituximab CSF will be sampled.
At each sampling CSF should be:

- examined for cellular content and glucose and protein concentrations
- examined for lymphoma by morphology and flowcytometry

In addition on day –1 of each cycle CSF should be:

- frozen after centrifuging for determination of rituximab concentration (1.5 ml)
- frozen after centrifuging (preferably filled out in 5 aliquots) for translational research
  (For the translational research a separate protocol will be written by the study coordinators)

One hour after the first two administations an additional sample should be taken for the determination of rituximab concentration, cell count and translational research.

Samples should be frozen at –80˚C as soon as possible but no longer than 2 hours after collection. Frozen samples should be labeled such that they are traceable to the patient and the date and time of sampling.
When possible, frozen samples should be stored at the local centre until completion of the study. At completion of the study, or as otherwise agreed upon, samples will be collected and transported on dry ice to the Xendo laboratory for Pharmacokinetics in Groningen for rituximab concentration and to the Laboratory for Neuro-Oncology at the Josephine Nefkens Institute in Rotterdam for translational research. Addresses see below. Please contact Dr Luider before sending the samples for translational research to assure safe receipt (tel. 010-4087321 or 010-4638069 or 06-55324635, t.luider@erasmusmc.nl). When local storage is not possible please contact one of the study coordinators or T.Luider before collecting the CSF sample for transport arrangements.

Patients with an Ommaya reservoir
These patients will be asked to consent to additional CSF sampling to document changes in rituximab concentration and cell count
In these patients CSF will be sampled 2, 4, 8, 24, 48 and 72 hours after the first two administrations of rituximab in addition to the above sampling.

Addresses:

For translational research:

Dr. Th. M. Luider

Laboratory for Neuro-Oncology, Room BE 462

Josephine Nefkens Institute

Erasmus MC Rotterdam

Dr. Molenwaterplein 50

3015 GE Rotterdam

For ritumab concentrations

Xendo Laboratories B.V.

Attn to M. Putman

Hanzeplein 1, entrance 53

9713 GZ Groningen

I Folstein Mini Mental State Examination (MMSE)

Gestandaardiseerde MMSE

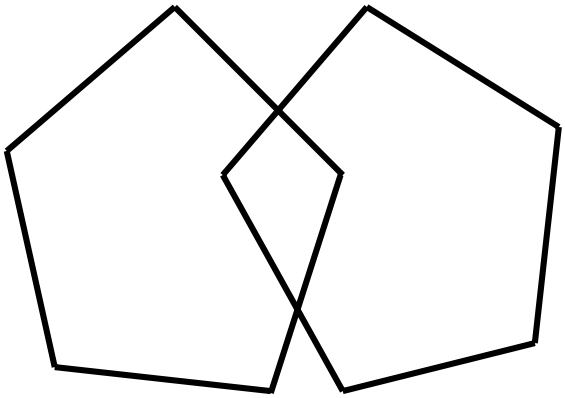
Naam patiënt :

Datum invullen : Naam invuller :

Ik ga u nu enkele vragen stellen en geef u enkele problemen om op te lossen. Wilt u alstublieft uw best doen om zo goed mogelijke antwoorden te geven.

	noteer antwoord		score:
1. a. Welk jaar is het? b. Welk seizoen is het? c. Welke maand van het jaar is het? d. Wat is de datum vandaag? e. Welke dag van de week is het?		(0-5)	_____
2. a. In welke provincie zijn we nu? b. In welke plaats zijn we nu? c. In welk ziekenhuis (instelling) zijn we nu? d. Wat is de naam van deze afdeling? e. Op welke verdieping zijn we nu?		(0-5)	_____
3. Ik noem nu drie voorwerpen. Wilt u die herhalen nadat ik ze alle drie gezegd heb? Onthoud ze want ik vraag u over enkele minuten ze opnieuw te noemen. (Noem "appel, sleutel, tafel", neem 1 seconde per woord) (1 punt voor elk goed antwoord, herhaal maximaal 5 keer tot de patiënt de drie woorden weet)		(0-3)	_____
4. Wilt u van de 100 zeven aftrekken en van wat overblijft weer zeven aftrekken en zo doorgaan tot ik stop zeg? (Herhaal eventueel 3 maal als de persoon stopt, herhaal dezelfde instructie, geef maximaal 1 minuut de tijd) Noteer hier het antwoord. of Wilt u het woord "'worst" achterstevoren spellen? Noteer hier het antwoord.		(0-5)	_____
5. Noemt u nogmaals de drie voorwerpen van zojuist. (Eén punt voor elk goed antwoord).		(0-3)	_____
6. Wat is dit? En wat is dat? (Wijs een pen en een horloge aan. Eén punt voor elk goed antwoord).		(0-2)	_____
7. Wilt u de volgende zin herhalen: " Nu eens dit en dan weer dat ". (Eén punt als de complete zin goed is)		(0-1)	_____
8. Wilt u deze woorden lezen en dan doen wat er staat'? (papier met daarop in grote letters: "Sluit uw ogen")		(0-1)	_____
9. Wilt u dit papiertje pakken met uw rechterhand, het dubbelvouwen en het op uw schoot leggen? (Eén punt voor iedere goede handeling).		(0-3)	_____
10. Wilt u voor mij een volledige zin opschrijven op dit stuk papier? (Eén punt wanneer de zin een onderwerp en een gezegde heeft en betekenis heeft).		(0-1)	_____
11. Wilt u deze figuur natekenen? (Figuur achterop dit papier. Eén punt als figuur geheel correct is nagetekend. Er moet een vierhoek te zien zijn tussen de twee vijfhoeken)		(0-1)	_____
	TOTALE TEST SCORE:	(0-30)	_____

Sluit uw ogen



J RTOG Neurologic Function Status

0 No neurologic symptoms; fully active at home/work without assistance

1 Minor neurologic symptoms; fully active at home/work without assistance

2 Moderate neurologic symptoms; fully active at home/work but requires assistance

3 Moderate neurologic symptoms; less than fully active at home/work and requires assistance

4 Severe neurologic symptoms; totally inactive requiring complete assistance at home or institution - unable to work