Randomized phase III study on the effect of early intensification of rituximab in combination with 2-weekly CHOP chemotherapy followed by rituximab maintenance in patients with diffuse large B-cell lymphoma

Published: 15-02-2007
Last updated: 11-05-2024

To evaluate the efficacy ofa. early intensification of rituximab combined with 2-weekly CHOP+G-CSF (R-CHOP14) in remission induction treatment in comparison to standard R-CHOP14b. maintenance treatment with rituximab in patients in remission after R...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON47490

Source
ToetsingOnline

Brief title
HOVON 84 NHL

Condition

- Lymphomas non-Hodgkin's B-cell
- Lymphomas non-Hodgkin's B-cell

Synonym
Diffuse large B-cell lymphoma; lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Hoffmann-La Roche,KWF

Intervention

Keyword: Diffuse large B-cell lymphoma, Early intensification rituximab, rituximab maintenance

Outcome measures

Primary outcome

First randomization:

Primary endpoint

* Response rate (complete remission and FDG-PET negative partial remission or

unconfirmed complete remission)

Second randomization:

Primary endpoint

* Failure free survival (measured from the date of second randomization)

The definition of failure used in failure free survival (whichever comes first)

will be:

- No response on induction treatment (whereby response is defined as CR or PET

negative

PR/CRu)

- Relapse

- Death (from any cause)

Secondary outcome

First randomization:

Secondary endpoints

* Failure 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

* Overall survival measured from the time of registration

* Time to reach response

* Toxicity

Second randomization:

Secondary endpoints

* Overall survival

* Toxicity

The definition of failure used in failure free survival (whichever comes first)

will be:

- No response on induction treatment (whereby response is defined as CR or PET

negative

PR/CRu)

- Relapse

- Death (from any cause)

Study description

Background summary

Diffuse large B-cell lymphoma is the most common lymphoma and occurs in both young and elderly patients, however most frequently in elderly patients. Current treatment with 2-weekly rituximab-CHOP courses results in an event free survival of 51%-70%. Therefore, a relapse is seen in a large part of the patients. Approximately 50% of the young patients with primary refractory disease or relapse can be salvaged with high dose chemotherapy followed by autologous stem cell transplantation. Elderly patients cannot be cured with salvage therapy. Most relapse patients die within two years. Current overall survival rate is 63% -80%. Thus, treatment results are not satisfactory. Therefore, novel strategies must be explored.

Study objective

To evaluate the efficacy of

a. early intensification of rituximab combined with 2-weekly CHOP+G-CSF (R-CHOP14) in remission induction treatment in comparison to standard R-CHOP14

b. maintenance treatment with rituximab in patients in remission after R-CHOP14 in comparison to no further treatment

Study design

Prospective, randomised, multi-center study.
The first part is the remission induction therapy and consists of 6 cycles (elderly patients) or 8 cycles (young patients) of CHOP given every 2 weeks. In addition rituximab will be given on day one or on day one and eight of the first 4 CHOP cycles. For young patients, rituximab will be given on day one of the last 4 CHOP cycles. For the elderly patients, rituximab will be given on day one of the 5th CHOP cycle, and on day 1, 15 and day 29 of the 6th CHOP cycle.

The second part of the study is the maintenance therapy and consists of 12x rituximab once every 8 weeks for 2 years for those who randomised for maintenance therapy. The other 50% of the patients will receive no maintenance treatment.

Intervention

intravenous rituximab

Study burden and risks

Patients in the experimental arm of the study must pay 4 more visits to the outpatient clinic to receive the 4 extra gifts of rituximab. This also applies to the patients randomising for the 12 gifts of rituximab during the maintenance phase. The extra rituximab gifts may induce a larger decrease of the serum immunoglobulins. This may result in an increased risk for infections. In the protocol mandatory measurements to prevent complications are described.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For first randomization:, - Patients with a confirmed histologic diagnosis of diffuse large B-cell lymphoma (DLBCL) based upon a representative histology specimen according to the WHO classification (see appendix A), - DLBCL must be CD20 positive, - Ann Arbor stages II-IV (see appendix C), - Age 18-65 years and age-adjusted IPI 1-3 OR age 66-80 years and age-adjusted IPI 0-3 , - WHO performance status 0 - 2 (see appendix E) , - Written informed consent, For second randomization:, Patients achieving a CR (or FDG-PET negative PR/CRu) after 6 (elderly) or 8 (young patients) cycles of R-CHOP14 will be randomized to maintenance treatment with rituximab or no further treatment., - Patients in complete remission or FDG-PET negative partial remission/unconfirmed complete remission at least 4 weeks after the last cycle of R-CHOP14 (including last rituximab administration), - Time interval since last cycle of R-CHOP14 (including last rituximab administration) between 4 and 8 weeks, - No rituximab-related adverse event necessitating stopping of rituximab administration, - No active infection, - Written informed consent

Exclusion criteria

-Age 18-65 (inclusive) years and aa-IPI 0 (no risk factors), -Intolerance of exogenous protein administration, -Severe cardiac dysfunction (NYHA classification III-IV, see appendix F) or LVEF < 45%, - Congestive heart failure or symptomatic coronary artery disease or cardiac arrhythmias not well controlled with medication. Myocardial infarction during the last 6 months , - Severe pulmonary dysfunction (vital capacity or diffusion capacity < 50% of predicted value) unless clearly related to NHL involvement, - Patients with uncontrolled asthma or allergy, requiring systemic steroid treatment , - Significant hepatic dysfunction (total bilirubin >= 30mmol/l or transaminases >= 2.5 x upper normal limit), unless related to NHL , - Significant renal dysfunction (serum creatinine >= 150 umol/l or clearance <= 60 ml/min), unless related to NHL, - Clinical signs of severe cerebral dysfunction, - Suspected or documented Central Nervous System involvement by NHL, - Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant and adversely affecting compliance to study drugs, - Testicular DLBCL, - Primary mediastinal B cell lymphoma, - Transformed indolent lymphoma, - (EBV) post-transplant lymphoproliferative disorder, - Secondary lymphoma after previous chemotherapy or radiotherapy, - Major surgery, other than diagnostic surgery, within the last 4 weeks, - Patients with active uncontrolled infections, - Patients known to be HIV-positive, - Active chronic hepatitis B or C infection, - Serious underlying medical conditions, which could impair the ability of the patient to participate in the trial (e.g. ongoing infection, uncontrolled diabetes mellitus, gastric ulcers, active

autoimmune disease), - Life expectancy < 6 months, - Prior treatment with chemotherapy, radiotherapy or immunotherapy for this lymphoma, except a short course of prednisone (< 1 week) and/or cyclophosphamide (< 1 week and not in excess of 900 mg/m2 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

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-10-2007
Enrollment:	460
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MabThera
Generic name:	rituximab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-02-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-08-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-05-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-05-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	22-03-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-08-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-08-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-005174-42-NL
Other	ISRTCN82286322
CCMO	NL15414.078.07