Efficacy of alternating immunochemotherapy consisting of RCHOP + R-HAD versus R-CHOP alone, followed by maintenance therapy consisting of additional lenalidomide with rituximab versus rituximab alone for older patients with mantle cell lymphoma

Published: 27-11-2014
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Primary objective:To evaluate whether the addition of lenalidomide to rituximab-maintenance improves progression free survival (PFS) compared to standard rituximab maintenance after response to induction chemotherapy in older patients with mantle...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's unspecified histology
Study type	Interventional

Summary

ID

NL-OMON54774

Source
ToetsingOnline

Brief title
HOVON 119 MCL R2 Elderly

Condition

- Lymphomas non-Hodgkin's unspecified histology

Synonym
Mantle Cell Lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: LYSARC (The Lymphoma Academic Research Organisation)
Source(s) of monetary or material Support: Celgene Corporation,Hoffmann-La Roche,KWF

Intervention

Keyword: Elderly patients, Lenalidomide, Mantle Cell Lymphoma, Rituximab

Outcome measures

Primary outcome

Progression free survival (PFS) from randomization for maintenance to

progression or death from any cause

Secondary outcome

• Time to event :

- overall survival from induction randomization to death from any cause

- overall survival from maintenance randomization to death from any cause

- time to treatment failure, progression-free survival from induction

randomization, remission duration

• PR/CRu to CR and PR to CRu conversion during maintenance

• Minimal residual disease (MRD) status and levels in peripheral blood and bone

marrow at midterm and at the end of induction, after one and two

years from end of induction and during follow-up until progression or up to 2.5

years of follow-up whichever comes first

• complete and overall response rates (based on Cheson 1999 criteria) at

midterm and end of induction,

• safety according to NCI CTCAE (v 4.0)

• secondary primary malignancies rates after lenalidomide vs. no lenalidomide

• Exploratory : response assessment according to Cheson 2007 criteria including

FDG-PET evaluation

Study description

Background summary

Based on several randomized trials and a systematic Cochrane review, combined immuno-chemotherapy represents the current standard of care in MCL (ESMO guidelines). However, even after immuno-chemotherapy only, a constant relapse pattern has been observed with the majority of patients relapsing within the first 3 years. Based on preliminary results from the recently closed phase III MCL elderly trial performed within the European MCL Network, Rituximab maintenance after 8 cycles of R-CHOP induction prolongs remission duration and overall survival and therefore represents the current standard of care for elderly patients with MCL. Still, no plateau has been observed, suggesting that maintenance with rituximab is not sufficient, but can be considered as a standard of care in MCL patients unable to received high-dose therapy with SCT consolidation.

Improving patient*s outcome can be reached by improving response rate before maintenance therapy. In younger patients, recent data from the MCL younger trial proved the superiority of alternating R-CHOP/R-DHAP (with high dose Ara-C) when compared to R-CHOP alone. These data suggest that incorporating cytarabine to induction therapy may improve patients* outcome in elderly patients with MCL.
An international phase II study suggested a longlasting impact of lenalidomide in relapsed MCL. These data suggest that incorporating lenalidomide to maintenance therapy with Rituximab could also improve MCL patients* outcome in patients unfit to receive HDT consolidation therapy.

Study objective

Primary objective:
To evaluate whether the addition of lenalidomide to rituximab-maintenance improves progression free survival (PFS) compared to standard rituximab maintenance after response to induction chemotherapy in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation

Secondary objective:
- to compare efficacy and safety of the maintenance regimens in terms of secondary endpoints
- to evaluate whether the introduction of cytarabine into induction improves clinical outcome compared to standard R-CHOP in older patients with mantle cell lymphoma not suitable for autologous stem cell transplantation

Study design

phase III randomized trial, international, multicentric, open labeled for induction and maintenance treatment

Intervention

addition of lenalidomide to maintenance treatment.

Study burden and risks

All study treatments have proven their efficacy in the treatment of MCL. It is expected that patients will achieve a high response rate in each of the induction arms consisting of 8 courses of R-CHOP or alternating 3 courses of R-CHOP and 3 courses of R-HAD. It is hoped that induction with alternating 3 courses of RCHOP and 3 courses of RHAD will improve the outcome. For the maintenance therapy, in patients who initially reach at least a partial response to induction, it is hoped that adding lenalidomide to standard Rituximab maintenance will be beneficial to the patients in term of PFS. It is possible that some patients may not reach a clinical response with the study treatment and will require other treatment outside this protocol.
Altogether, in this elderly MCL patient*s population, the benefit of this treatment program is expected to be superior to the potential short and long term toxicities. This study will help gain knowledge about this innovative treatment strategy in MCL based on new induction and maintenance strategies.

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

Randomization 1:
1. signed informed consent form
2. Biopsy-proven mantle cell lymphoma according to WHO classification, including evidence of cyclin D1 overexpression or the translocation t(11;14)(q13;q32),
3. >= 60 years of age and ineligible for autologous transplant
4. Ann Arbor stage II-IV
5. previously untreated (except for patients randomized directly for maintenance treatment who will receive 8 RCHOP before registration in the trial)
6. ECOG performance status <= 2
7. Male subjects must:
- agree to use a condom during sexual contact with a woman of childbearing potential, even if they have had a vasectomy, throughout lenalidomide therapy
- agree to not donate semen during lenalidomide therapy.
8. All subjects must:
- have an understanding that the lenalidomide could have a potential teratogenic risk.
- agree to abstain from donating blood while taking lenalidomide therapy
- agree not to share study medication with another person.
- be counseled about pregnancy precautions and risks of foetal exposure.,
Randomization 2:
To be randomized for maintenance, the patient must satisfy all inclusion / exclusion criteria for randomization 1 and the following criteria:
9. CR, CRu or PR after induction treatment, determined as per Cheson 1999

criteria by investigator
10. During the run-in period of 6 months starting from the date of the first randomization, in the case of direct randomization into maintenance phase, patient must have been treated in first line by 6-8 cycles of R-CHOP.

Exclusion criteria

Randomization 1:
1. Female of child-bearing potential (without natural menopause for at least 24 consecutive months, a hysterectomy or bilateral oophorectomy)
2. Any of the following laboratory abnormalities, if not related to lymphoma:
- Absolute neutrophils count (ANC) <1,000 /mm^3 (1.0 x 10^9/L) if not result of a BM infiltration.
- Platelet counts < 75,000/mm^3 (75 x 10^9/L) if not result of a BM infiltration.
- Serum aspartate transaminase (AST/SGOT) or alanine transaminase(ALT/SGPT) >3.0 x upper limit of normal (ULN).
- Serum total bilirubin > 1.5 UNL (except if due to Gilbert*s syndrome)
3. Calculated creatinine clearance (Cockcroft-Gault formula or MDRD) < 30 mL / min
4. Central nervous system involvement by lymphoma
5. Contraindication for medicamentous DVT prophylaxis for patients at high risk for DVT
6. Prior history of malignancies other than MCL unless the subject has been free of the disease for >= 5 years (Exceptions: Basal or squamous cell carcinoma of the skin, Carcinoma in situ of the cervix or of the breast, Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b).
7. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient to receive the study medication as planned.
8. Poor cardiac function (LVEF <50%) on echocardiography
9. Seropositivity for human immunodeficiency virus (HIV, mandatory test) Seropositivity for hepatitis C virus (HCV, mandatory test), Active viral infection with hepatitis B virus (HBV, mandatory test):
- HBsAg positive
- HBsAg negative, anti-HBs positive and anti-HBc positive
Patients with prior Hepatitis B must be given antiviral prophylaxis and HBV DNA monitored. Note: Patients who are HBsAg negative, anti-HBs positive and/or anti-HBc positive but viral DNA negative are eligible.
10. Uncontrolled illness including, but not limited to:
- Active infection requiring parenteral antibiotics
- Uncontrolled diabetes mellitus
- Chronic symptomatic congestive heart failure (Class NYHA III or IV).
- Unstable angina pectoris, angioplasty, stenting, or myocardial infarction within 6 months

- Clinically significant cardiac arrhythmia that is symptomatic or requires treatment, or asymptomatic sustained ventricular tachycardia.
11. Prior >= Grade 3 allergic hypersensitivity to thalidomide.
12. Prior >= Grade 3 rash or any desquamating (blistering) rash while taking thalidomide.
13. Subjects with >= Grade 2 neuropathy.
14. Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies
15. Prior use of lenalidomide.
16. Participation in another clinical trial within three weeks before randomization in this study., Randomization 2:
The presence of any exclusion criteria of randomization 1 or of the following criteria will exclude a subject from enrollment in the maintenance phase:
17. SD or PD after induction treatment determined as per Cheson 1999 criteria assessed by investigator.
18. Patients who had not received at least 6 cycles of R-CHOP21 or 2 cycles of R-CHOP21 / 2 cycles of R-HAD28 (alternating)
19. Patients with serious underlying medical conditions, which could impair the ability to receive maintenance treatment
20. Calculated creatinine clearance (Cockcroft-Gault formula or MDRD) of < 30 mL /min at screening for maintenance.
21. ANC < 1,000 cells/mm³ (1.0 X 10^9/L) at screening for maintenance;
22. Platelet count < 50,000 cells/mm³ (50 X 10^9/L) at screening for maintenance.

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: Recruiting

Start date (anticipated):	14-12-2015
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mabthera
Generic name:	Rituximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Revlimid
Generic name:	Lenalidomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-11-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-03-2019
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	17-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-08-2023
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	EUCTR2012-002542-20-NL
ClinicalTrials.gov	NCT01865110
CCMO	NL43749.078.14