ReBeL study: a randomized phase I/II trial of lenalidomide and rituximab with or without bendamustine in patients >= 18 years with relapsed follicular lymphoma
A HOVON/GLSG/ NCRI study

Published: 10-06-2011
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The objective of the study is to investigate the feasibility and efficacy of treatment with lenalidomide and rituximab with or without bendamustine in patients with relapsed follicular lymphoma.

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

Summary

ID

NL-OMON47678

Source
ToetsingOnline

Brief title
HOVON 110 FL / GLSG/ NCRI

Condition

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

Synonym
FL or non hodgkin lymphoma (NHL), Follicular lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Celgene Corporation,KWF,Mundipharma

Intervention

Keyword: Bendamustine, Follicular lymphoma, Lenalidomide, Relapse

Outcome measures

Primary outcome

Phase I:

• dose limiting toxicity

• recommended dose level of lenalidomide and of bendamustine in combination

with rituximab (for arm B of the phase II of the study)

Phase II:

• complete remission rate

• rate of severe toxicity.

Secondary outcome

• Overall response rate following induction treatment and at the end of

maintenance rituximab

• Molecular response rate.

• Event free survival (EFS; i.e. time from registration to induction failure,

progression, relapse or death, whichever occurs first). A patient counts as

induction failure if no PR or CR was achieved after induciton.

• progression free survival (PFS; i.e. time from registration to disease

progression, relapse or death, whichever occurs first);

• disease free survival (DFS; i.e. time from CR to relapse or death, whichever

comes first)

• time to next antilymphoma treatment

• overall survival (O.S.; i.e. time from registration until death)

• relative dose intensity of lenalidomide and, if applicable, bendamustine

Study description

Background summary

Follicular lymphoma (FL) is an indolent type of lymphoma. After diffuse large B cell lymphoma, it is the most frequently occurring type of lymphoma. In the Netherlands, 800 new cases are diagnosed yearly. Although the disease is exquisitely sensitive to both chemotherapy, immunotherapy and radiotherapy, there are no curative options. Currently, there is no standard treatment for patients with relapsed FL. Lenalidomide, rituximab and bendamustine have shown promising activity in FL, both in first line and in relapse. Since the toxicity of both drugs is relatively minor , combination of these drugs is an attractive option.The hypothesis is that both treatment arms will be effective with acceptable toxicity.
This phase I/II prospective multicenter trial will be performed in the Netherlands, Germany and UK (phase II only).

Study objective

The objective of the study is to investigate the feasibility and efficacy of treatment with lenalidomide and rituximab with or without bendamustine in patients with relapsed follicular lymphoma.

Study design

Phase I/II trial; the phase II trial is a multicenter, prospective, randomized phase II trial with two experimental arms

Intervention

All patients will be treated with 6 induction cycles followed by 2 years of

maintenance treatment with rituximab, once every three months.

Study burden and risks

The treatment will be given on an outpatient basis. Most visits are according to standard treatment. Extra is the bendamustine infusion on day 1 and 2 in arm B of the study for 6 cycles. Bendamustin on day 1 will be combined with the rituximab administration. An ECG will be made at screening. In next induction cycles there is an extra visit on day 14.
Also for all patients extra blood will be taken 7 times on set times. The extra material is taken when the standard bloodsamples are taken. There are no extra bone marrow biopsies.
2 PET-scans will be done in combination with the CT scan. The CT-scan is standard patient care.
20-30 patients are asked to participate in an additional investigation. In this investigation a lymph node biopsy will be taken once and a fine needle aspirate (FNA) twice. For this, the patient gives consent seperately.
In all premenopausal women a pregnancy test will be performed frequently as defined in the Lenalidomide Pregnancy Prevention Risk management plan that applies to all patients that are treated with lenalidomide.
Men being treated with bendamustine are advised not to father a child during and for up to 6 months following end of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with bendamustine.
Side effects to be expected from lenalidomide and bendamustine are the usual side effects of chemotherapy e.g. bone marrow suppression resulting in anemia, thrombocytopenia and leukopenia. This gives an increased infection risk. Furthermore there is a slightly increased risk of thrombosis due to the use of lenalidomide and a risk of skin rash due to the use of both drugs. At the long-term there is a slightly increased risk of secundairy malignancies (comparable to the risk following treatment with other cytostatic drugs). Rituximab is known to pass the placenta and may get into breast milk. As a result, it may possible cause a temporary lymphopenia in the unborn baby, up to now is has not been described that the risk of infections for the baby is increased.
Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Relapsed FL grade 1, 2, 3a, see appendix A;
• Ann Arbor stage II-IV at relapse, see appendix B;
• A biopsy or FNA to show CD20 postivity is required. A biopsy/FNA performed at any time since the most recent therapy is acceptable as long as this shows FL and there is no clinical concern for transformation at the time of study entry. In case clinically transformation is suspected, a biopsy should be obtained at the time of study entry to exclude transformation;
• A maximum of five prior systemic treatment regimens (patients who have had a prior allogeneic SCT are excluded; prior autologous SCT (if > 1 year ago) is allowed);
• Prior bendamustine is allowed, under the following conditions:
* Only one prior treatment (with a maximum of 6 cycles) with bendamustine is allowed
* Patients must have had a PR or CR following prior use of bendamustine
* Prior treatment with bendamustine must have taken place >=24 months ago (measured from the start of prior bendamustine treatment, i.e. approximately 18 months from the end of prior bendamustine treatment)
• Subjects must have an indication for treatment based on one or more of the following criteria:

- Involvement of at least 3 nodal sites, each with a diameter > 3 cm
- Symptomatic splenomegaly
- Bulky disease at study entry according to the GELF criteria: nodal or extranodal mass (except spleen) > 7 cm in its greatest diameter
- B-symptoms (absence or presence of fever and/or night sweats and/or unexplained loss of 10% of body weight or more in the 6 months preceding diagnosis)
- Hb < 10 g/dl (6.2 mmol/l) (if caused by bone marrow infiltration and not otherwise explained)
- Thrombocytopenia: platelets < 100x109/l caused by bone marrow infiltration
- Organ compression syndrome (e.g. hydronephrosis caused by lymphadenopathy)
- Pleural/peritoneal effusion
- Symptomatic extranodal manifestations;
• Measurable disease as defined in appendix C (patients with only bone marrow involvement are therefore not eligible);
• Age >= 18 years;
• Able to adhere to the study visit schedule and other protocol requirements;
• WHO performance status of 0-2;
• Laboratory test results within these ranges: absolute neutrophil count >= 1.5x 109/l (unless bone marrow infiltration), platelet count >= 100x 109/l (unless bone marrow infiltration), creatinine clearance >= 50 ml/min, total bilirubin <= 30 µmol/l (1,75 mg/dl), AST & ALT <= 3x ULN;
• Females of childbearing potential must have a negative serum or urine pregnancy test within 10 - 14 days prior to and again within 24 hours of starting lenalidomide treatment;
• Patients must be willing and capable to use adequate contraception during and after the therapy (all men, all pre-menopausal women; see 10.2 and 12.5). Patients must be able to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan;
• Written informed consent.

Exclusion criteria

• Rituximab-refractory patients (definition: progression during or within 6 months after rituximab containing immunochemotherapy. Patients relapsing under rituximab maintenance treatment are eligible, if at biopsy or FNA CD20 positivity is confirmed);
• Clinical or histologic signs of transformation. Patients with a prior transformed phase of FL are eligible IF there are currently no signs of transformation and there is histologic proof that the current phase is not transformed AND the transformed phase occurred >2 years ago;
• Prior allogeneic SCT;
• Prior autologous SCT less than one year ago;
• Any prior use of an immunomodulatory agents such as lenalidomide, pomalidomide or CC-122;
• Concurrent use of other anti-cancer agents or treatments;
• The use of prednisolone for any other indication than lymphoma treatment is allowed at a maximum dose of or equivalent to 20 mg prednisolone;
• Concurrent use of allopurinol, e.g. because of gout. Patients with gout are advised to switch

to another anti-gout medication, because of the risk of Stevens-Johnson Syndrome observed in patients using bendamustine and allopurinol;
• Use of any other experimental drug or therapy within 28 days of baseline;
• Hepatitis B (including HBcAb) positive, Hepatitis C positive and/or HIV positive patients;
• Patients with uncontrolled autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (ITP);
• Active fungal, bacterial, and/or viral infection;
• Recent vaccination for yellow fever (within 4 weeks before registration)
• Pregnant or breast-feeding females (lactating females must agree not to breast feed while taking lenalidomide);
• Known hypersensitivity and/or serious adverse reactions to lenalidomide or similar drugs;
• Intolerance of exogenous protein administration, or known allergy to murine products;
• Uncontrolled hyperthyroidism or hypothyroidism;
• Neuropathy >= grade 2 at time of inclusion;
• Clinically symptomatic severe cardiac dysfunction (NYHA III-IV, see appendix G);
• Clinically symptomatic severe pulmonary dysfunction;
• Severe neurologic or psychiatric diseases;
• Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection);
• History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast, prostate cancer (TNM stage of T1a or T1b);
• Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-09-2011
Enrollment:	99

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Levact
Generic name:	Bendamustine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	n.v.t.
Generic name:	rituximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Revlimid
Generic name:	lenalidomide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-06-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-04-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2011-000097-56-NL
CCMO	NL36781.018.11