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 study.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22769

Source
NTR

Brief title
HOVON 110 FL / GLSG

Health condition

Relapsed CD20+ follicular lymphoma

Sponsors and support

Primary sponsor: Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON)
P/a HOVON Data Center
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Source(s) of monetary or material Support: - Stichting Hemato-Oncologie voor

Volwassenen Nederland (HOVON)
-KWF
-Celgene
-Mundipharma

Intervention

Outcome measures

Primary outcome

For the phase I part of the study: To determine the dose limiting toxicity (DLT) and recommended dose level (RDL) of lenalidomide and bendamustine given in combination with rituximab for the phase II part of the study.

For the phase II of the study: To determine the efficacy and toxicity of the two arms of the study (arm A: lenalidomide and rituximab, and arm B: lenalidomide, rituximab and bendamustine) in patients with relapsed follicular lymphoma (FL) and to identify the most promising of these two treatment arms.

Secondary outcome

In the phase II part of the study:

1. To determine the value of PET-CT scanning in response assessment of FL patients;

2. To identify predictive factors for response. For this purpose various tissue–associated markers will be explored both on tumor cells and on non-malignant cells of the tumor microenvironment using tissue microarrays or primary lymphoma biopsy samples. These studies will be supported by gene expression profiling in a selection of the patients. Results will be correlated to clinical outcome as well as PET-CT results and circulating subsets of T cells and NK cells;

3. To specifically explore treatment-induced alterations in non-malignant immune cell populations. For this purpose, alterations during treatment in these populations in the peripheral blood and at the tissue level of involved lymh nodes will be performed. For the latter analysis sequential fine needle aspirations and biopsies will be performed in a selection of patients. The sequential biopsies will also be used to study the biological mechanisms of tumor cell kill.

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 and Germany. In the phase I part the optimal dose of bendamustine and lenalidomide will be established. In the phase II parts, patients aged 18 years or older with FL will be treated with 6 monthly cycles of lenalidomide and rituximab, with or without bendamustine, followed by 2 years of rituximab maintenance treatment (once every 3 months). Patients will be followed until 8 years after registration.The target number of patients during the phase I and II part will be 15-24 and 150 respectively. Expected duration of the study will be 11 years.
The primary endpoints for the phase I part are: Dose-Limiting toxicity (DLT) and recommended phase II dose (RDL) of lenalidomide and bendamustine given in combination with rituximab. For the phase II part the primary endpoints are CR rate and severe toxicity during induction treatment.

Study objective

In this trial the efficacy and toxicity is tested of treatment with lenalidomide and rituximab (arm A), and lenalidomide, rituximab and bendamustine (arm B) in patients with relapsed follicular lymphoma (FL).

Study design

1. At entry;

2. Prior to each cycle;

3. 6-8 weeks after start of induction cycle 6;

4. Before each administration of rituximab maintenance treatment;

5. After 12 and 24 months of maintenance treatment;

6. End of protocol treatment;

7. During follow up every 3 months for 2 years and every 6 months thereafter, up to 8 years after registration;

8. At progressive disease.

Intervention

All patients will be treated with 6 induction cycles followed by 2 years of maintenance treatment with Rituximab, once every three months.

In the induction cycles in the phase I part of the study, lenalidomide, rituximab and bendamustine are given using up to three dose levels of lenalidomide (10, 15 or 20 mg on day 3-21 of a 28-day schedule) with up to two dose levels of bendamustine (70 or 90 mg/m2 on day 1,2) and rituximab (375 mg/m2 on day 1), in order to establish the RDL of lenalidomide and bendamustine given in combination with rituximab for the phase II of the study.

In the phase II part of the study, in the induction cycles lenalidomide in combination with rituximab with or without bendamustine is given.

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Eligibility criteria

Inclusion criteria

1. Relapsed FL grade 1, 2, 3a;

2. Ann Arbor stage II-IV at relapse;

3. The lymphoma at relapse must be CD20+. To establish this, and to exclude transformation to aggressive lymphoma, a biopsy at relapse is strongly recommended;

4. A maximum of three prior treatment regimens (patients that have had a prior allogeneic SCT are excluded; prior autologous SCT (if > 1 year ago) is allowed);

5. Subjects must have an indication for treatment based on one or more of the following criteria:

A. Involvement of at least 3 nodal sites, each with a diameter > 3 cm;

B. Symptomatic splenomegaly;

C. Bulky disease at study entry according to the GELF criteria: nodal or extranodal mass (except spleen) > 7 cm in its greatest diameter;

D. 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);

E. Hb < 10 g/dl (6.2 mmol/l) (if caused by bone marrow infiltration and not otherwise explained);

F. Thrombocytopenia: platelets < 100x109/l caused by bone marrow infiltration;

G. Organ compression syndrome (e.g. hydronephrosis caused by lymphadenopathy);

H. Pleural/peritoneal effusion;

I. Symptomatic extranodal manifestations.

6. Measurable disease as defined in appendix C (patients with only bone marrow involvement are therefore not eligible);

7. Age ≥ 18 years;

8. Able to adhere to the study visit schedule and other protocol requirements;

9. WHO performance status of 0-2;

10. Laboratory test results within these ranges: absolute neutrophil count ≥ 1.5x 109/l, platelet count ≥ 100x 109/l, creatinin clearance ≥ 50 ml/min, total bilirubin ≤ 30 µmol/l (1,75 mg/dl), AST & ALT ≤ 3x ULN;

11. 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;

12. Patients must be willing and capable to use adequate contraception during the therapy (all men, all pre-menopausal women). Patients must be able to adhere to the requirements of the Lenalidomide Pregnancy Prevention Risk Management Plan;

13. Written informed consent.

Exclusion criteria

1. Rituximab-refractory patients (definition: progression during or within 6 months after rituximab containing immunochemotherapy or rituximab maintenance treatment);

2. Clinical or histologic signs of transformation;

3. Prior allogeneic SCT;

4. Prior autologous SCT less than one year ago;

5. Any prior use of lenalidomide or bendamustine;

6. Concurrent use of other anti-cancer agents or treatments;

7. Use of any other experimental drug or therapy within 28 days of baseline;

8. Hepatitis B sAg positive, Hepatitis C positive and/or HIV positive patients;

9. Patients with uncontrolled autoimmune hemolytic anemia (AIHA) or autoimmune thrombocytopenia (ITP);

10. Active fungal, bacterial, and/or viral infection;

11. Pregnant or breast-feeding females (lactating females must agree not to breast feed while taking lenalidomide);

12. Known hypersensitivity and/or serious adverse reactions to lenalidomide or similar drugs;

13. Intolerance of exogenous protein administration, or known allergy to murine products;

14. Uncontrolled hyperthyroidism or hypothyroidism;

15. Neuropathy ≥ grade 2 at time of inclusion;

16. Clinically symptomatic severe cardiac dysfunction (NYHA III-IV);

17. Clinically symptomatic severe pulmonary dysfunction;

18. Severe neurologic or psychiatric diseases.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-09-2011
Enrollment:	174
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	18-08-2011
Application type:	First submission

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
NTR-new	NL2882
NTR-old	NTR3028
Other	HOVON / METC : HO110 / 2011-000097-56;
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A