A Phase 3, Open-label, Multicenter, Randomized Study of Sequential Zevalin (ibritumomab tiuxetan) versus Observation in Patients at Least 60 Years of Age with Newly Diagnosed Diffuse Large B-cell Lymphoma in PET-negative Complete Remission After R-CHOP or R-CHOP-like Therapy

Published: 03-04-2013
Last updated: 23-04-2024

To evaluate the efficacy and safety of Zevalin compared with observation alone in patients who are in PET-negative complete remission (CR) after first-line R-CHOP or R-CHOP like therapy.

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

Summary

ID

NL-OMON40206

Source
ToetsingOnline

Brief title
Zevalin in patients with Diffuse Large B-cell Lymphoma

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Cancer of the blood

Research involving
Human

Sponsors and support

Primary sponsor: Spectrum Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Spectrum Pharmaceuticals Inc.

Intervention

Keyword: DLBCL, Observation, Survival, Zevalin

Outcome measures

Primary outcome

Efficacy: Primary endpoint is overall survival.

Secondary outcome

Efficacy: Secondary endpoints are 24-month overall survival rate post randomization, and progression-free survival.

Safety: Treatment-emergent adverse events (AEs), deaths and other serious adverse events (SAEs), AEs resulting in withdrawal of patient, and laboratory abnormalities.

Study description

Background summary

The addition of the antibody Rituximab to a chemotherapy regimen of R-CHOP, improved the outcome for older DLBCL patients (over the age of 60) for the first time in over 25 years and 6-8 cycles of R-CHOP has now become the standard of care (Coiffier et al. 2002; 346:235-42). Despite this development, many patients relapse and there are no effective salvage options for older

patients. Further improvements and novel therapies are therefore required to improve outcomes further.
The patient population for this study is DLBCL patients 60 years old and above who have achieved a complete response following R-CHOP therapy. At the completion of 6 cycles of R-CHOP it is routine practice to assess the response to therapy with a PET CT scan. Patients who have undergone a complete response or CR, are then eligible to be randomised into the trial. The study drug is called 90Y Ibritumomab tiuxetan or *Zevalin* and is a form of targeted treatment called radioimmunotherapy.
It has been demonstrated that there is unrealised residual disease that exists in this patient population, despite them achieving a CR. In patients demonstrating a CR following R-CHOP treatment, one study has shown the relapse rate at 5 years to be 20% (Feugier et al. J Clin Oncol 2005;23:4117-26).
Phase 2 studies have demonstrated the potential efficacy of Zevalin in the treatment of this patient population (refer to protocol section 3.2).
Furthermore, the rationale for adding Zevalin to the completion of chemotherapy is provided by a phase 3, multicentre study carried out on 414 patients with follicular NHL, in which the addition of Zevalin was not only safe but provided an improvement in the median progression free survival (PFS) of 38 months in the Zevalin arm, compared with 18 months in the observation arm. This study led to US and EU approval of Zevalin consolidation in patients with follicular NHL who are in first remission (Hagenbeek A et al., 2010: Blood).
In summary, Zevalin has been tested extensively in other NHL, in DLBCL, promising activity has been demonstrated to potentially improve outcome for older patients. The use of Zevalin in DLBCL requires rigorous Phase III testing.

Study objective

To evaluate the efficacy and safety of Zevalin compared with observation alone in patients who are in PET-negative complete remission (CR) after first-line R-CHOP or R-CHOP like therapy.

Study design

Methodology:
Patients will be stratified by age-adjusted International Prognostic Index (aaIPI) risk group (1, versus 2, versus 3 IPI risk factors), and geographical region, and randomly assigned (1:1), to receive the Zevalin Regimen or observation.

Duration of Treatment:
Two treatment days one week apart followed by a 13-week safety period. Patients will be followed until the appropriate number of events (death or relapse) is observed. Patients will be followed for a median observation period of 5 years. Estimated duration of the study, including accrual period, is 75 months.

Reference Therapy:
Observational control arm

Intervention

Dose Regimen - pretreatment with rituximab followed by Y-90-Zevalin treatment.

Day 1 Rituximab 250 mg/m2 intravenous infusion.

Day 7-9 Rituximab 250 mg/m2 intravenous infusion, followed 4 hours later by Y-90-Zevalin 0.4 mCi/kg 10-minute intravenous push (0.3 mCi/kg in patients with a platelet count in 100,000/microL to 149,000/microL.

Study burden and risks

Burden and risks:
There are risks and side effects for the bone marrow biopsy procedure which can include pain, bleeding, bruising or infection. Bone marrow biopsy is only required for patients in the Zevalin arm.
The electrocardiogram patches put on the patient's chest for an ECG may cause a short-term skin reaction, irritation, and/or rash in the patch area. ECG is required in Zevalin and observation arms.
Placement of a needle into a vein in the arm to obtain blood samples may cause irritation or perforation of the vein, bleeding, bruising, dizziness or infection. Venupuncture s required in both the observation and Zevalin arms.
Side effects to both rituximab and Zevalin may occur but patients will be carefully monitored in order to lessen side effects. The full listing of side effects is provided in the reference safety information (IB for Zevalin and summary of product characteristics for rituximab). Rituximab and Zevalin treatment is only required in the Zevalin arm.
CT scans: Contrast dye may cause patient to feel warm, sick or get a metallic taste in the mouth or develop an allergic response. In patients with low kidney function, this dye can temporarily or permanently decrease kidney function. The frequency of CT scans is identical in the observation and Zevalin arms.
The Zevalin administration and CT scans all involve exposure to radiation. The risk of this additional radiation is to slightly increase the chance of a patient developing cancer at a later date. However for this patient population this risk is considered negligible.
Patients will be closely monitored to identify and minimize any side effects throughout the study.

Potential benefits:
The patient population for this study is DLBCL patients who have achieved a complete response following R-CHOP therapy. It has been shown that there is unrealised residual disease that exists in this patient population, despite these patients achieving a complete response. In patients demonstrating a

complete response following R-CHOP treatment, one study has shown the relapse rate at 5 years to be 20% (Feugier et al. J Clin Oncol 2005;23:4117-26).
Elderly patients that experience relapse have few available treatment options.
Zevalin is approved in Europe, the USA and other countries for consolidation therapy in patients with follicular NHL who are in first remission. Phase 2 data demonstrate the potential of Zevalin in the patient population involved in this study (protocol section 3.2).
The favourable results from Phase 2 studies warrant confirmation in a Phase 3 randomized trial, in which the effect of treatment with Zevalin on overall survival is compared with observation.

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

1. Patient is 60-years of age or older at time of randomization
2. Histologically confirmed Ann Arbor stage II, III, or IV DLBCL; or FL Grade 3B according to the REAL/WHO classification (from initial diagnosis made prior to starting R-chemotherapy).
3. An H&E stained slide and unstained slides must be available for confirmatory pathology review, as per the separate Pathology Guidance document. Patients may be randomized based on the local diagnosis.
4. Presence of at least one IPI risk factor. The aaIPI is defined by one point for each factor: a. LDH> upper limit of normal (ULN); b. Stage III or IV; and c. WHO/ECOG performance status >1.
5. First-line treatment must have been 6 cycles of standard R-CHOP or RCHOP-like chemotherapy (e.g. R-CHOP21, R-CHOP14, or DA-EPOCH-R). Patients who received pre-phase therapy for the purpose of improving performance status prior to initiating R-CHOP are eligible. Standard dose reductions for toxicity are allowed.
6. Complete remission (CR) according to the Revised Response Criteria for Malignant Lymphoma after first-line treatment.
a. Diagnostic CT scans with contrast of chest, abdomen, and pelvis must have been performed within 8 weeks after the first dose of the last cycle of R-chemotherapy. PET-CTs obtained elsewhere before and after R-CHOP are acceptable for evaluating response to R-CHOP, but a diagnostic CT pre-randomization is requested as reference for post randomization interval change. A neck CT will be applicable if the patient had involvement of the neck region by palpation / physical examination at initial diagnosis. The CT portion of an FDG PET that includes the neck will be acceptable if the neck had involvement.
b. A negative FDG-PET scan performed within 8 weeks after the first dose of the last cycle of R-chemotherapy and confirming CR, with negative defined as a score of 1-3 on the Deauville 5-point scale used to quantify radionucleotide density in PET scans as determined locally [23]. PET positive/indeterminate lesions which are confirmed on biopsy to harbor no active lymphoma will be considered negative for determination of CR status.
c. If positive bone marrow involvement at initial diagnosis the patient must have a negative bone marrow biopsy following R-chemotherapy to confirm the CR.
7. WHO/ECOG performance status of 0, 1 or 2.
8. Adequate hematopoietic functions unsupported by transfusion within the last 2 weeks: Absolute neutrophil count (ANC) >= 1.5 x 109/L, Hemoglobin (Hgb) >= 9 g/dL, Platelets >= 100 x 109/L. Patients with blood counts close to recovery towards these values after R-CHOP should be discussed with the study Medical Monitor prior to randomization, but blood counts must have met these thresholds prior to treatment with Y-90 Zevalin.
9. In patients who had a post R-chemotherapy bone marrow biopsy performed, the marrow must show cellularity >15%. For patients without a post R-chemotherapy bone marrow biopsy (i.e. those patients with negative marrow at diagnosis), a repeat biopsy to assess bone marrow cellularity of >15% will be required only for patients randomized to the Zevalin Regimen.
10. Life expectancy of 6 months or longer.
11. Written informed consent obtained according to local guidelines.

Exclusion criteria

1. Presence of any other malignancy or history of prior malignancy within 5 years of study entry. Within 5 years, patients treated with curative intent for Stage I or II cancers are eligible provided they have a life expectancy of >5 years. The 5-year exclusion rule does not apply to non-melanoma skin tumors and in situ cervical cancer.
2. Prior radioimmunotherapy, including radiation therapy for NHL, or any other NHL therapy.
3. Presence of central nervous system (CNS) involvement, or testicular lymphoma at first diagnosis.
4. DLBCL as histological transformation of previously diagnosed indolent B-cell lymphoma. Patients with De Novo Transformed DLBCL, defined as DLBCL on lymph node biopsy and a "discordant marrow" with small cells at initial diagnosis, are eligible.
5. Known seropositivity for hepatitis C virus (HCV) or hepatitis B surface antigen (HbsAg). Patients who are positive for HbsAg but without active disease (Hep B PCR below the limits of detection) and who receive adequate prophylaxis may be enrolled, but should continue prophylaxis for at least 6 months after the last dose of rituximab or Zevalin.
6. Known history of HIV infection.
7. Abnormal liver function: total bilirubin >2 × ULN unless secondary to Gilbert disease.
8. Abnormal renal function: serum creatinine >2.0 × ULN.
9. Ongoing toxic effects of chemotherapy >grade 2 and expected to interfere with Zevalin treatment.
10. Known hypersensitivity to murine or chimeric antibodies or proteins.
11. Colony stimulating factor therapy administered more than 8 weeks after last dose of R-chemotherapy or within 4 weeks prior to planned administration of Zevalin.
12. Concurrent severe and/or medically uncontrolled disease (e.g. uncontrolled diabetes, congestive heart failure, myocardial infarction within 6 months of study, unstable and uncontrolled hypertension, chronic renal disease, or active uncontrolled infection) which could compromise participation in the study.
13. Treatment with investigational drugs less than 4 weeks prior to randomization.
14. Major surgery less than 4 weeks prior to randomization.
15. Concurrent systemic corticosteroid use for any reason except as premedication in case of known or suspected allergies to contrast media or as premedication for potential side effects of rituximab treatment. Patients on a chronic dose of prednisone for a medical condition (e.g. Asthma or autoimmune disease) less than or equal to 20mg daily, stable for 4 weeks, are permissible.
16. Unwillingness or inability to comply with the protocol.
17. Pregnant women or women who are breastfeeding

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):	05-05-2014
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MabThera
Generic name:	Rituximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Zevalin
Generic name:	Ibritumomab Tiuxetan

Ethics review

Approved WMO

Date:	03-04-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	01-10-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	27-01-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-03-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-05-2014
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	EUCTR2011-004916-51-NL
ClinicalTrials.gov	NCT01510184
CCMO	NL42935.078.13