A phase III study of lenalidomide maintenance after debulking with gemcitabine or liposomal doxorubicin +/- radiotherapy in patients with advanced cutaneous T-cell lymphoma not previously treated with intravenous chemotherapy.

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To determine if maintenance treatment with lenalidomide prolongs progression free survival in patients with advanced stage CTCL that has notbeen previously treated with intravenous chemotherapy except the chemotherapy received in the preceeding...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Lymphomas non-Hodgkin's T-cell
Study type	Interventional

Summary

ID

NL-OMON38396

Source
ToetsingOnline

Brief title
Lenalidomide maintenance therapy in cutaneous T-cell lymphoma patients.

Condition

- Lymphomas non-Hodgkin's T-cell
- Skin neoplasms malignant and unspecified

Synonym

Cutaneous lymphoma, Mycosis Fungoides

Research involving
Human

Sponsors and support

Primary sponsor: European Organisation for Research in Treatment of Cancer (EORTC)
Source(s) of monetary or material Support: Celgene Corporation,EORTC

Intervention

Keyword: Cutaneous T-cell lymphoma, lenalidomide, Phase III

Outcome measures

Primary outcome

Disease assessment will be performed every 8 weeks according to the EORTC-ISCL

criteria.

The primary (efficacy) endpoint is progression free survival.

Secondary outcome

Toxicity is assessed as a secondary endpoint. This study will use the

International Common Terminology Criteria (CTCAE), version 4.0, for toxicity

and adverse event reporting.

Study description

Background summary

Primary cutaneous T-cell lymphomas (CTCLs) are a heterogenous group of lymphomas, classified according to the WHO/EORTC classification of cutaneous lymphomas. Collectively, they are rare, with a prevalence of approximately 1-2/100,000 persons. Mycosis fungoides is the most common type, accounting for nearly 50% of primary CTCL. Classical mycosis fungoides, its variants and subtypes usually run an indolent course. However, patients with advanced stages of the disease have a poorer prognosis. Erythrodermic CTCL with various degrees of blood involvement, including Sézary syndrome, also have a more aggressive course. Several studies have shown the stage-dependant prognosis of this

disease. A revised staging and classification of mycosis fungoides and Sézary syndrome has been recently published by ISCL and EORTC.
Due to the rarity of CTCL, very few randomized trials have been performed in this disease. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome have been published. Treatment of advanced stage disease is largely empirical, based on small non-randomized, uncontrolled studies with response data. Depending on extent and staging of cutaneous lymphoma, the age and physical condition of the patient, and the presence of concurrent disease, treatment strategies can be topical or systemic. Available topical treatment strategies include glucosteroids, retinoids, Carmustin or HN2, available systemic treatments options include interferon alpha, oral re(x/t)inoids, and low dose methotrexate or other chemotherapeutical drugs, either as single agents or in combination. These treatments can be combined with phototherapy, radiotherapy or photopheresis in erythrodermic stage. In patients with advanced stage disease, treatments frequently induce partial responses or complete responses with relapse after a few months, but the prognosis becomes increasingly poor with subsequent lines of therapy.
Recently developed treatments include histone deacetylase inhibitors, proteosome inhibitors, monoclonal antibodies and lenalidomide.
Lenalidomide is related to thalidomide, and like thalidomide it has both immunomodulatory and anti-angiogenic properties which may confer antitumor and antimetastatic effects. Lenalidomide more potently regulates cellular immune and cytokine responses, while having a
better clinical risk-benefit profile than thalidomide. In early phase II trials, Lenalidomide seems to have more anti-tumor activities than thalidomide. Lenalidomide has an antiproliferative effect on several cell types, and has immunomodulatory, anti-inflammatory, and anti-angiogenic effects. Lenalidomide has been studied in a number of clinical trials, predominantly in the indication of multiple myeloma (MM), but also for myelodysplastic syndrome (MDS), lymphomas, Crohn's disease and solid tumors. More than 5,000 patients have received the drug for multiple myeloma, alone.
Lenalidomide was selected for this study because it showed activity in other hematological maligancies (multiple myeloma and 5q- myelodysplatic syndrome), is reasonably well tolerated, and in a 25 patient open phase 2 trial, demonstrated activity in CTCL, achieving a 28% PR responses. In that study, lenalidomide was administered orally on an outpatient basis. The first fifteen patients received 25 mg daily for 21 days with 7 days rest of a 28-day cycle, the same schedule which is proposed in the present protocol. The remaining ten patients in that protocol began with a dose of 10 mg and escalated as tolerated in 5 mg increments to a maximum of 25 mg. The median patient age was 60 years (range, 47-83) andpatients received a median of 6 prior treatment regimens (range, 2-9). All but seven of the patients had advanced stage disease. All responses were seen within the group that started at the 25 mg dose. Seven patients in that study achieved a partial response which was defined as a Composite Assessment of Index Lesion Disease Severity ratio less than or equal to 0.5, with no new clinically abnormal lymph nodes, no progression of existing clinically abnormal lymph nodes, and no new cutaneous tumors. Patients who

responded did so after a median of 9 cycles of therapy, with a median time to best response of 6 months. Seven patients went off protocol due to toxicity. The most common side effects reported were anemia, fatigue/malaise, skin burning, pruritis, diarrhea, and lower leg edema.

This prospective, multi-center study will determine the benefit of maintenance treatment with lenalidomide in this difficult to treat group of patients. The importance of this study is that if this maintenance treatment is indeed effective it will give considerable health-gain for these patietns.

Study objective

To determine if maintenance treatment with lenalidomide prolongs progression free survival in patients with advanced stage CTCL that has not been previously treated with intravenous chemotherapy except the chemotherapy received in the preceeding debulking stage. Patients will be randomized to either receive the maintenance therapy or not, and these two study arms will be compared in terms of the difference in progression free survival.

Study design

Debulking
All patients must receive one of the two permitted debulking regimens:
* Gemcitabine administered on days 1, 8, and 15 of a 28-day cycle at a dose of 1000 to 1200 mg/m2 intravenously over 30 minutes for a total of four cycles.
(or)
* Liposomal Doxorubicin administered on days 1 and 15 of a 28-day cycle at a dose of 20 mg/m2 intravenously over one hour for a total of four cycles.
* Local low-dose/energy ionizing radiation therapy may be used as part of the debulking process to treat tumor lesions that do not respond after three cycles of debulking chemotherapy.

Lenalidomide
This study centers on the ability of maintenance treatment with lenalidomide to prolong the response achieved by these debulking regimens.
Arm 1: Observation
Arm 2: Lenalidomide, 25mg po d1-21, q 28 days.
Treatment in arm 2 continues until progression, toxicity, patient refusal or death, or maximum treatment duration.
Maximum treatment duration: 560 days.

Intervention

Half of the patietns will be assigned to treatmetn with Lenalidomide. During

treatment of these patietns blood samples will be drawn to monitor for tocicity.

Study burden and risks

The extenst of the burden associated with participation will be the visits of the hospital, pregnancy testing and blood drawing.

Hospital visits
The hospital visits will include a pretreatment visit (complete work-up including: physical exam, medical history, WHO perfprmance status, pregnancy test, blood count, blood chemistry, thyroid test, 12 lead ECG, disease assesment), every 4 weeks (to assess adverse events), every 8 weeks (physical exam, medical history, WHO performance status, blood count, disease assesment) and a post treatment visit (complete work-up including: physical exam, medical history, WHO perfprmance status, pregnancy test, blood count, blood chemistry).

Pregnancy testing
Before each cycle pregnancy testing will be performed if applicable (only in lenalidomide arm)

Blood drawing
Blood drawing is performed routinously on the following days:
Cyclus 1: day 1,2,4,8,15, 22.
Cyclus 2: day 1,8,15,22.
Cyclus 3: day 1,15.
Cyclus 4 and all subsequent cycli: day 1.

Riscs associated with participationa are the potential adverse effects of Lenalidomide:

Side Effects of any grade occurring in about 10% or more of patients
* Fatigue or feeling tired;
* Anemia or a decrease in red blood cells that can cause tiredness;
* Neutropenia or a decrease in white blood cells;
* Thrombocytopenia or a decrease in platelets;
* Constipation or infrequent or difficult bowel movements;
* Diarrhea or loose/frequent bowel movements;
* Nausea;
* Loss of appetite;
* Back pain;
* Joint pain;
* Muscle cramps;
* Swelling of the arms and legs;
* Problems falling asleep or staying asleep;
* Fever;
* Cough;

* Shortness of breath or difficulty catching your breath;
* Upper respiratory infection;
* Rash;
* Itching and dry skin;
* Lack or loss of strength;
* Dizziness;
* Headache.

Serious side effects occurring in about 1% or more of patients and not listed above
* Neutropenia or a decrease in white blood cells that can make the patient prone to infection associated with a fever;
* Pulmonary embolism or blood clot in or around the lungs;
* Deep vein thrombosis or blood clots in a larger blood vessel;
* Atrial fibrillation or irregular heartbeat;
* Progression of the disease being studied;
* Pneumonia or an infection of the lungs;
* Sepsis or an infection of the blood;
* Dehydration;
* Kidney failure.

Rare cases of the following events have been reported:
* Angioedema- an allergic skin disease characterized by patches of swelling involving the skin and/or the lining of the nose, mouth, and gastrointestinal tract.
* Stevens-Johnson syndrome and toxic epidermal necrolysis- serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to detachment of the top layer of skin (could be body-wide).
* Tumor lysis syndrome- metabolic complication that can occur during or without treatment of cancer. These complications are caused by the break-down products of dying cancer cells and include hyperkalemia (high potassium), hyperphosphatemia (high phosphorus), hyperuricemia and hyperuricosuria (high uric acid in blood and urine) , hypocalcemia (low calcium), and consequent acute uric acid nephropathy and acute renal failure (kidney damage).
* Rhabdomyolysis, a serious condition involving the destruction of skeletal muscle that can lead to kidney failure. Signs and symptoms include dark, red, or cola colored urine and muscle tenderness, stiffness, aching (myalgia) or weakness.

Possibly there is a slightly increased risk for the development of secondary malignancies.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

At registration
* Advanced stage mycosis fungoides (stage IIB-IV), or Sézary Syndrome.
* Prior debulking therapy with either gemcitabine or liposomal doxorubicin, resulting in complete or partial response as defined in this protocol's "Evaluation criteria" chapter. At the time of registration, patients provide consent for the collection of this pre/post debulking assessment information.
* For patients with Sezary syndrome, Sezary cell burden has to be decreased by at least 50 percent after debulking.;All patients must receive one of the two permitted debulking regimens:
* Gemcitabine administered on days 1, 8, and 15 of a 28-day cycle at a dose of 1000 to 1200 mg/m2 intravenously over 30 minutes for a total of four cycles.
(or)
* Liposomal Doxorubicin administered on days 1 and 15 of a 28-day cycle at a dose of 20 mg/m2
intravenously over one hour for a total of four cycles.

* Local low-dose/energy ionizing radiation therapy may be used as part of the debulking process to treat lesions that do not respond after three cycles of debulking chemotherapy.
* No other drug may be part of the debulking regimen. The use of low-dose steroids as premedication is allowed at the investigator*s discretion.
* Disease not appropriate for skin-directed therapy, per local institution standards.
* Disease not previously treated with intravenous chemotherapy (except for the permitted debulking agents, used for that purpose immediately prior to this protocol, as described above).
* In addition to antineoplastic cytotoxic agents, for purposes of this protocol, the definition of intravenous chemotherapy also includes:
* Denileukin diftitox
*Antibodies or antibody conjugates
* Age > 18 years.
* WHO performance status 0-2.
* Life expectance greater than 12 months
* Adequate organ function
* Cardiovascular status <= New York Heart Association (NYHA) category II (refer to Appendix D).
* Hepatic: Total Bilirubin <= 1.5 x UNL, alkaline phosphatase (ALP) <= 3 x UNL, alanine aminotransferase (ALT, SGPT) <= 3 x UNL, aspartate aminotransferase (AST, SGOT) <= 3 x UNL
* Renal: Electrolytes including sodium, potassium, chloride, blood urea nitrogen (all creatinine < UNL, creatinine clearance >= 60 ml/min (measured or calculated according to the method of Cockcroft and Gault, Appendix E), uric acid, phosphorus, calcium (all * Hematological: Hemoglobin >= 10 g/dl, absolute neutrophil count >= 1.5 x 109/L, platelets >= 60 x 109 /L.
* Thyroid testing: free T4 and TSH anti-coagulation therapy (e.g. Vitamin K) to keep the International normalized ratio (INR) in the range of 2-3;* Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial.;* Female subjects of childbearing potential (defined as any female subject unless she meets at least one of the following criteria: Age >=50 years and naturally amenorrheic for >= 1 year {amenorrhea following cancer therapy does not rule out childbearing potential}, premature ovarian failure confirmed by a specialist gynacologist, previous bilateral salpingo-oophorectomy or hysterectomy, XY genotype, Turner syndrome or uterine agenesis.) must:
* Understand that the study medication could have an expected teratogenic risk
* Agree to use, and be able to comply with, effective contraception without interruption, 4 weeks
before starting study drug, throughout study drug therapy (including dose interruptions) and for 4
weeks after the end of study drug therapy, even if she has amenorrhea. This applies unless she
commits to absolute and continued abstinence confirmed on a monthly basis. Note: Combined oral contraceptive pills are not recommended. If she was using combined oral contraception, she must switch to one of the methods below. The increased risk of VTE continues for 4 to 6 weeks after stopping combined oral contraception. The following are

considered effective methods of
contraception:
1. Implant or levonorgestrel-releasing intrauterine system (IUS). Note: for either, prophylactic antibiotics should be considered at the time of insertion particularly in patients with neutropenia due to risk of infection.
2. Medroxyprogesterone acetate depot
3. Tubal sterilization
4. Sexual intercourse with a vasectomized male partner only; vasectomy must be confirmed by
two negative semen analyses
5. Ovulation inhibitory progesterone-only pills (i.e., desogestrel)

Agree to have a medically supervised pregnancy test with a minimum sensitivity of 25 mIU/ml not
more than 3 days before the start of study medication once the subject has been on effective contraception for at least 4 weeks. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.
* Agree to have a medically supervised pregnancy test every 4 weeks including 4 weeks after the end of study treatment, except in the case of confirmed tubal sterilization. These tests should be
performed not more than 3 days before the start of next treatment. This requirement also applies to women of childbearing potential who practice complete and continued abstinence.;* Male subjects must:
* Agree to provide to their female partners the Brochure for women who may come into contact with Revlimid.
* Agree to use condoms throughout study drug therapy, during any dose interruption and for one
week after cessation of study therapy if their partner is of childbearing potential and has no contraception.
* Agree not to donate semen during study drug therapy and for one week after end of study drug
therapy.;* All subjects must:
* Agree to abstain from donating blood while taking study drug therapy and for one week following
discontinuation of study drug therapy.
* Agree not to share study medication with another person and to return all unused study drug to the investigator.;* Before patient registration, written informed consent must be given according to ICH/GCP, and
national/local regulations.
At randomization
* At randomization, the above eligibility criteria evaluated at registration will be verified. In addition, it must be assured that no disease progression has taken place between registration and randomization.
* Patients can only be randomized in this trial once.

Exclusion criteria

* Central nervous system involvement.
* Uncontrolled infectious disease, autoimmune disease, immunodeficiency, or history of either
splenectomy or splenic irradiation.
* Second malignancies in the 3 years prior to study entry with the exception of surgically cured
carcinoma in situ of the cervix, in situ breast cancer, incidental finding of stage T1a or T1b prostate
cancer, and basal/squamous cell carcinoma of the skin.
* Pregnant or breast feeding subjects.
* Lapp lactase deficiency or history of glucose-galactose malabsorption.
*Radiation or drug-based therapy (including steroids) between registration and randomization.

Study design

Design

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

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	20-12-2010
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Caelyx

Generic name:	liposomal doxorubicin
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:	09-04-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	30-05-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-08-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-10-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	02-08-2013

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-011020-65-NL
CCMO	NL31427.058.10