A Randomized, Open-Label, Multinational Phase 3 Trial Comparing Amrubicin Versus Topotecan in Patients With Extensive or Limited and Sensitive or Refractory Small Cell Lung Cancer After Failure of First-Line Chemotherapy

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory tract neoplasms
Study type	Interventional

Summary

ID

NL-OMON33958

Source
ToetsingOnline

Brief title
AMR PH GL 2007 CL 001

Condition

- Respiratory tract neoplasms

Synonym
Lungcancer, Small Cell Lung Cancer

Research involving

Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Celgene Corporation

Intervention

Keyword: Extensive disease, Limited disease, Lung Cancer, Small Cell Lung Cancer

Outcome measures

Primary outcome

The primary efficacy variable for this study is overall survival.

Key secondary efficacy variables include:

• ORR based on RECIST (complete response [CR] + partial response [PR]); and

• PFS.

Duration of response and time to tumor progression will also be analyzed as

secondary efficacy variables.

The safety variables for this study are:

• Adverse events;

• Clinical laboratory variables;

• 12-lead ECGs;

• Left ventricular ejection fraction (LVEF) assessed by echocardiograms (ECHOs)

or multiple gated acquisition scans (MUGAs); Study sites in Germany and UK will

use ECHO to measure LVEF.

• Physical examinations; and

• Vital signs.

The quality-of-life variables for this study are health status and quality of

life in patients with lung cancer.

The pharmacoeconomic variables for this study are:

• Medication use;

• Hospital/clinic visits;

• Medical procedures; and

• Use of community resources.

Secondary outcome

NA

Study description

Background summary

Japanese clinical trials in relapsed SCLC patients have demonstrated encouraging response and survival data for this population. It appears that treatment with amrubicin leads to a survival advantage when compared with historical data on treatment with standard topotecan therapy in relapsed SCLC patients. The current trial is designed to test the hypothesis that in a Western population, treatment with amrubicin leads to a survival benefit when compared with treatment with topotecan in patients with SCLC after failure of first-line chemotherapy.

Study objective

The primary objective is to demonstrate superiority in overall survival of amrubicin (40 mg/m2 administered as a 5-minute infusion once daily for 3 consecutive days starting on Day 1 of a 21-day course) compared with topotecan hydrochloride (topotecan) (1.5 mg/m2 administered as a 30 minute infusion once daily for 5 consecutive days starting on Day 1 of a 21-day course) in patients with extensive or limited and sensitive or refractory small cell lung cancer (SCLC) after failure of first-line chemotherapy.
The important secondary objectives are to further characterize the clinical benefit of amrubicin compared with topotecan in terms of the following:
• Objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST); and
• Progression-free survival (PFS).
Additional secondary objectives are to assess or compare the effect of

amrubicin relative to topotecan in terms of the following:
• Duration of response;
• Time to tumor progression (TTP);
• Quality of life (assessed using EuroQol [EQ-5D] and the Lung Cancer Symptom Scale [LCSS]);
• Safety; and
• Pharmacokinetics (plasma and whole blood concentrations) in amrubicin-treated patients only.

Study design

This is a Phase 3, randomized, open-label, multinational study to determine the superiority in overall survival of amrubicin compared with topotecan when administered to patients with extensive or limited and sensitive or refractory SCLC after failure of first-line chemotherapy. Sensitive will be defined as a best response to first-line platinum-based chemotherapy of complete response, partial response, or stable disease, with subsequent progression * 90 days after completing first-line chemotherapy; refractory will be defined as progressive disease as best response to first-line platinum-based chemotherapy or progression < 90 days after completing first-line chemotherapy.
Patients randomized prior to the effective date of Amendment 5 (03October2008) were stratified by type of response to first-line therapy (sensitive versus refractory), Eastern Cooperative Oncology Group (ECOG) score, and disease stage. Effective with the implementation of Amendment 5, randomized patients are stratified by type of response to first-line therapy (sensitive versus refractory), and the disease stage (limited versus extensive). Patients randomized to the amrubicin study arm (Arm A) will receive 40 mg/m2 amrubicin as a 5-minute intravenous infusion once daily for 3 consecutive days starting on Day 1 of a 21-day course. Patients randomized to the topotecan study arm (Arm B) will receive 1.5 mg/m2 topotecan as a 30-minute intravenous infusion once daily for 5 consecutive days starting on Day 1 of a 21-day course.
Patients in both treatment arms will be treated for up to 6 cycles, unless there is disease progression, unacceptable toxicity, the patient withdraws consent for further treatment, or the physician decides to discontinue treatment. Patients who continue to experience stable disease or better at Cycle 6 may receive 6 additional cycles, for a total of 12 cycles over a duration of approximately 8 months, using the same study events schedule (see Table 1), after discussion with the sponsor. Once a patient completes treatment, the patient will enter the follow-up period. Follow-up will continue until the patient dies, withdraws consent for further follow-up or is lost to follow-up.
A data monitoring committee (DMC) will assess the ongoing conduct of the study with a frequency sufficient to monitor patient safety as described in the DMC charter. CT scans or MRI will be collected and archived by the sponsor or their representative in the event that an independent review is needed to verify response to treatment. All 12 lead electrocardiograms (ECGs) will be collected and archived by the sponsor or their representative and centrally reviewed.

ECHO/MUGA scans for patients showing confirmed significant LVEF reductions will be collected for later central independent review. Details will be provided in the Statistical Analysis Plan (SAP).
In addition to efficacy and safety assessments, quality-of-life (all patients) and medical resource-use (subset of patients) data will be gathered prior to dosing at Cycle 1, during treatment (even cycles), and at follow-up for both treatment arms. Sparse blood sampling will be performed on amrubicin patients for whole blood and plasma pharmacokinetic analyses. One blood sample will be collected from each patient for pharmacogenomic research to evaluate variants in genes involved in metabolism and transport of amrubicin. Blood samples for pharmacogenomic research are optional and are collected from both amrubicin and topotecan patients to help distinguish between the predictive and prognostic value of any genetic variants.
One interim analysis of the efficacy variables is planned during the study. The DMC will review data as part of the interim analysis. The interim analysis is to occur when the total number of patient deaths reaches 294. The final analysis is planned after 490 deaths have occurred.

Intervention

This is an open-label study. Patients will be randomized to receive one of 2 treatments, amrubicin or topotecan, at a ratio of 2:1 (amrubicin to topotecan). Treatment should be started within 7 days of randomization; each cycle is 21 days. Patients in both treatment arms will be treated for up to 6 cycles, unless there is disease progression, unacceptable toxicity, the patient withdraws consent for further treatment, or the physician decides to discontinue treatment. Patients who continue to experience stable disease or better at Cycle 6 may receive 6 additional cycles, using the same study events schedule (see Table 1), after discussion with the sponsor. Two dose reductions are permitted for each patient.
Amrubicin for injection is supplied as 50-mg vials. Patients will receive 40 mg/m2 amrubicin as a 5-minute infusion once daily for 3 consecutive days starting on Day 1 of a 21-day course.
Topotecan for injection is supplied as 4-mg vials. Patients will receive 1.5 mg/m2 as a 30-minute infusion once daily for 5 consecutive days starting on Day 1 of a 21-day course.

Study burden and risks

Side Effects of Amrubicin
We have learned from the use of Amrubicin in Japan that there are anticipated side effects. These effects include:
• decrease in white blood cells which can lead to increased chance of infection, and in rare cases can be serious and could result in death,
• decrease in platelets (blood clotting cells) that could result in a risk of bleeding, decrease in red blood cells (anemia - which may cause tiredness and

lack of energy)
• Nausea and/or vomiting
• Loss of appetite
• Loss of hair
• Sores on the inside of the mouth
• Diarrhea
• Fever
• vein inflammation
• Changes to the electrical activity of the heart (shown on ECG)
• Red-colored urine
• Elevations in some liver function tests, which may indicate damage to the liver
• Elevations in kidney function tests, which may indicate damage to the kidneys
• aggravation of a kind of pneumonia has occurred in patients with lung cancer and lymphoma.
• There have also been rare occurrences of gastrointestinal ulcer or irritation, which can lead to serious bleeding.

A decrease in the heart*s ability to pump blood to all parts of the body, of uncertain significance has occurred in some Japanese patients. Therefore, your heart function status will be monitored closely during your participation in the study.

When a person receives chemotherapy after having had radiation therapy, skin or tissue damage from the prior radiation therapy can become damaged again (may involve redness, peeling, pain, and swelling). This is referred to as radiation recall. Skin changes have been noted to range from mild redness to tissue death. Radiation recall may also occur in the lungs and other internal organs. A variety of chemotherapeutic agents, including anthracyclines, such as doxorubicin, can cause radiation recall reaction Radiation recall has not been reported with Amrubicin, however, it is a potential risk with Amrubicin since other anthracyclines have caused this reaction.

Chemotherapy agents, such as Amrubicin, are often followed by treatment with a certain type of growth factor (pegylated granulocyte-colony-stimulating factor, pegylated G CSF, pegfilgrastim). When chemotherapy agents are followed by treatment with this certain type of growth factor, a reaction called hand-foot syndrome (HFS) is sometimes seen. Hand-foot syndrome is a condition that may involve painful swelling, redness and tenderness over the palms and soles that may result in blistering and shedding of the skin. Growth factors are sometimes used to increase production of white blood cells. If HFS occurs, your doctor may change your treatment to use a different type of growth factor.

In addition, when receiving amrubicin, it is very important to let your study nurse know if
the
medication is causing any redness, swelling, pain or discomfort at the

injection site.

Side Effects of Topotecan
Common side effects for topotecan include:
• Neutropenia or leucopenia - decrease in white blood cells which can lead to increased chance of infection, and in rare cases be serious and could result in death. Possibly this may require antibiotics and/or a drug to increase your white blood cell count
• Thrombocytopenia - decrease in platelets (blood clotting cells) that could result in a risk of bleeding
• Anaemia - decrease in red blood cells which may cause tiredness and lack of energy
• Nausea and/or vomiting
• Sores on the inside of the mouth
• Loss of appetite
• Loss of weight
• Feeling unwell
• Loss of hair
• Diarrhoea
• Fever
• Constipation
• abdominal pain
• difficulty breathing
• coughing
• tiredness
• weakness
• rash (allergic reaction)
• headache
• numbness/tingling.
• Yellow skin
• Itching sensation
• Muscle pain
• Rare side effects include sepsis and elevations in some liver function tests, which may indicate damage to the liver, and elevations in kidney function tests, which may indicate damage to the kidneys.

Other Possible Risks and side effects.
Low white blood cell counts can lead to an increased chance of infection and may require antibiotics and/or a drug to increase your white blood cell count. There is a risk of infection or swelling at the injection/catheter site. The risks of having blood drawn include pain, bruising, and rarely, infection. MRI or CT scans can be associated with extremely rare allergic reactions to contrast agents used to see things during the procedure. When you have this type of scan, you will be checked carefully by the radiologist for these allergic reactions and will be treated immediately if one happens.

Duration of Side Effects:

While on study, you can experience the above described side effects. You should discuss your concerns with your doctor. There also may be other side effects that we cannot predict. Let your doctor know about the side effects that you are experiencing. Your doctor may be able to give you other drugs to make side effects less serious or uncomfortable. Many side effects go away after the investigational drug is stopped, but in some cases, these side effects may be serious and/or long lasting. Rarely, side effects could be fatal.

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

Key inclusion criteria include the following:
1. Histological or cytological diagnosis of SCLC at study entry according to the International Association for the Study of Lung Cancer (IASLC) histopathologic classification. Mixed or

combined subtypes according to the IASLC are not allowed;
2. SCLC that is either sensitive (defined as a best response to first-line platinum-based chemotherapy of complete response, partial response or stable disease, with subsequent progression * 90 days after completing first-line chemotherapy) or refractory (defined as progressive disease as best response to first-line platinum-based chemotherapy or progression < 90 days after completing first-line chemotherapy);
3. Extensive or limited disease; patients with limited disease who are candidates for local or regional salvage radiation therapy must have been offered such treatment prior to participation in this study;
4. Radiographically documented progression after first-line treatment with platinum-based chemotherapy;
5. No more than 1 prior chemotherapy regimen;
6. At least 18 years of age;
7. ECOG performance status (PS) of 0 or 1.

Exclusion criteria

Key exclusion criteria include the following:
1. Chest radiotherapy with curative intent to the primary disease complex <= 28 days prior to first dose; cranial radiotherapy <= 21 days prior to first dose; radiotherapy to all other areas <= 7 days prior to first dose;
2. Prior anthracycline, topotecan, or irinotecan treatment.
3. Patients with known history of seropositive human immunodeficiency virus (HIV) or patients who are receiving immunosuppressive medications that would, in the opinion of the investigator, increase the risk of serious neutropenic complications.

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):	09-03-2009
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Product type:	Medicine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-03-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2008
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-11-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2009

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-11-2009
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	EUCTR2007-003989-18-NL
ClinicalTrials.gov	NCT00547651
CCMO	NL20870.078.08