A Phase 2 Trial of Single-Agent Amrubicin in Patients with Extensive Disease Small Cell Lung Cancer that is Refractory or Progressive within 90 Days of Completion of First Line Platinum-based Chemotherapy

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON30587

Source
ToetsingOnline

Brief title
Amrubicin in SCLC patients refractory to Platinum based Chemotherapy

Condition

- Respiratory disorders NEC

Synonym
extensive Small Cell Lung Cancer, lung cancer

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Amrubicin, Extensive Small Cell Lung Cancer, Platinum-based Chemotherapy, refractory

Outcome measures

Primary outcome

Efficacy:

The efficacy-evaluable population (primary efficacy population) includes all patients who received at least one full cycle of amrubicin (Day 1-3 administration) and had at least one response assessment or discontinued before having a response assessment due to rapid disease progression or death. Tumor response will be assessed according to the RECIST criteria. Reassessment of tumor will be done by the same methods used to establish baseline tumor measurements. All responding patients (CR and PR) must have their response confirmed no less than 4 weeks after the first documentation of response.

Safety:

All patients who received at least one dose of amrubicin on this study will be considered evaluable for safety. Common Terminology Criteria for Adverse Events (CTCAE) table, Version 3, will be used to grade toxicities. Duration and treatment of toxicity will be recorded. The safety measures will be assessed on an ongoing basis. The safety variables will be assessed by body system. Both

hematological and nonhematological adverse events that are considered definitely, probably, or possibly drug-related will be monitored until resolution.

Secondary outcome

Pharmacokinetics:

Secondary objectives of this study include determining the basic pharmacokinetic parameters and between-subject variability of amrubicin and its active metabolites at a dose of 40 mg/m2 given as an intravenous infusion over approximately 5 minutes on Days 1, 2, and 3. Full PK data will be collected for 18 patients. Patients selected for full PK sampling will have blood samples collected on Days 1 through 5 and Day 8 of Cycle 1.

Study description

Background summary

In Europe, platinum-based combination chemotherapy has become the standard for the treatment of extensive disease SCLC (ED SCLC). Results of treatment remain far from satisfactory since virtually all patients die of disease and long term survivors are very few (under 10%).
Two studies in Japan with patients with refractory SCLC have shown the anti-tumor activity of amrubicine when administered as monotherapy. In order to confirm the promising results for refractory Japanese patients in US and European patients, the same schedule used in Japan will be used in this trial.

Study objective

The primary objective is the Objective tumor response rate (RECIST).
Secondary objectives are: duration of overall response, time to tumor progression (TTP), progression free survival (PFS), overall survival, toxicity profile, incidence of cardiomyopathy, incidence of CNS progression, pharmacokinetic parameters.

Study design

This is a Phase 2, open-label, non-randomized, multicenter, single-agent study of amrubicin for the treatment of patients who have ED-SCLC that is considered refractory to prior platinum-based first-line therapy.

Patient sample size determination is based on the Fleming Single-Stage Design methodology. Efficacy will be measured by the overall response rate (complete and partial responses). Amrubicin will be considered promising if the true overall response rate is 18% or higher, and will be considered unworthy of further investigation if the true overall response rate is 6% or less in this refractory population.

Patient accrual will continue until at least 63 refractory patients receive at least one full cycle of amrubicin (Day 1-3 administration) and either had the Cycle 2 tumor assessment performed or had early tumor progression. If 7 or fewer responses (CR + PR) are observed in this group of 63, the hypothesis that the true response rate is less or equal to 6% cannot be rejected. If 8 or more responses are achieved, the hypothesis that the true response rate is less than or equal to 6% is rejected and this regimen will be considered worthy of further testing. This design yields 0.90 probability of a positive result if the true response rate is 18% or higher and 0.05 probability of a positive result if the true response rate is 6% or lower.

Intervention

Patients will receive 40 mg/m2 amrubicin as a slow IV push or infusion over approximately 5 minute once daily for 3 consecutive days starting on Day 1 of every 21 day cycle.

Study burden and risks

Screening:·complete medical, surgical and prior chemotherapy history (including all medications), Physical examination, Blood sample, Pregnancy test for women of childbearing potential, 12-lead electrocardiogram and Urinalysis.
Radiographic measurement of the tumors will be done before start of treatment and then every 6 weeks.
On Day 1: a physical examination, an ECG, Blood samples, questions any medications the patient might be taking or have taken since the last visit and side effects.
On each treatment day (Day 2-3):vital signs and patient will be asked about all medications the patient might be taking or has taken since the last visit and about side effects.
Days 8 and 15. blood sample, vital signs and the patient will be asked about any medications the patient might be taking or has taken since your last visit and about side effects.

Before treatment, after cycle 3 and cycle 6 (and thereafter every 2 cycles) a echocardiogram or MUGA scan will be taken.
end-of-study: physical examination, vital signs, blood samples, ECG electrocardiogram and the patient will be asked about any medications the patient might be taking or has taken since your last visit and about side effects.
For patients consenting to pharmacokinetic research extra blood samples will be taken on days 1, 2, 3, 4, 5, 8 and also ECG will be taken.
For patients consenting to pharmacogenetic research, an extra blood sample will be taken on Day 1 of start of the study.

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

- Histological or cytological diagnosis of SCLC; extensive-disease (ED) at the time of study entry
- Refractory to first-line platinum-based chemotherapy (i.e., has received one prior platinum-based chemotherapy regimen) defined as one of the following:
a. Best response to first-line chemotherapy is radiographically documented progression (refractory disease)
b. Best response to first-line chemotherapy is radiographically documented response or stable disease, with subsequent documented progression during continuing chemotherapy (resistant relapse)
c. Documented progression within 90 days of completion of first-line chemotherapy (last dose of chemotherapy), regardless of best response to treatment (resistant relapse)
- At least 18 years of age
- ECOG Performance Status of 0, 1, or 2
- Measurable disease defined by RECIST criteria:
a. Measurable disease: The presence of at least one measurable lesion. If only one lesion is present, the neoplastic nature of the disease site should be confirmed by histology and/or cytology
b. Measurable lesion: Lesions that can be accurately measured in at least one dimension with the longest diameter ><= 20 mm using conventional techniques or ><= 10 mm using spiral CT scans. CT (including spiral CT) scans and MRI are the preferred methods of measurement; however, chest x-rays are acceptable if the lesions are clearly defined and surrounded by aerated lung. Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is required.
- Adequate organ function including the following:
a. Adequate bone marrow reserve: absolute neutrophil (segmented and bands) count (ANC) ><= 1500 cells/uL, platelet count ><= 100,000 cells/uL and hemoglobin ><= 9 g/dL
b. Hepatic: bilirubin <<= 1.5 X ULN; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <<= 3.0 X ULN.
c. Renal: serum creatinine < 2.0 mg/dL or calculated creatinine clearance > 60 mL/min
d. Cardiac: Left ventricular ejection fraction (LVEF) ><= 50% by MUGA or echocardiography (intra-patient reassessment of LVEF should be performed via the same method throughout the study).
- Negative serum pregnancy test at the time of enrollment for women of child-bearing potential. For men and women of child-producing potential, use of effective contraceptive methods during the study.
- Ability to understand the requirements of the study, provide written informed consent and authorization of use and disclosure of protected health information, and agree to abide by the study restrictions and to return for the required assessments

Exclusion criteria

- Pregnant or nursing women
- Chest radiotherapy within the previous 28 days or other radiotherapy within the previous 14 days. Recovery from the acute toxic effects of radiation required prior to study enrollment. Measurable lesions that have been previously irradiated must be enlarging to be considered target lesions. Prior radiation therapy allowed to < 25% of the bone marrow.
- More than 1 prior chemotherapy regimen for SCLC.
- Prior anthracycline treatment.
- treatment with any investigational agent within 28 days or standard chemotherapy with 21 days prior to first dose. patients must have recovered from all acute adverse events of prior therapies, excluding alopecia
- Patients with second primary malignancy (except in situ carcinoma of the cervix or adequately treated nonmelanomatous carcinoma of the skin or other malignancy treated at least 2 years previously with surgery and/or radiotherapy and no evidence of recurrence since that time).
- Concurrent severe or uncontrolled medical disease (i.e., active systemic infection, diabetes, hypertension, coronary artery disease, congestive heart failure) that, in the opinion of the Investigator, would compromise the safety of the patient or compromise the ability of the patient to complete the study.
- Symptomatic central nervous system metastases. Patients with asymptomatic brain metastases are allowed. The patient must be stable after radiotherapy for >= 2 weeks and off corticosteroids for >= 1 week.
- History of interstitial lung disease or pulmonary fibrosis.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-12-2006

Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	amrubicin
Generic name:	amrubicin

Ethics review

Approved WMO Date:	09-11-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-01-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-06-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-08-2008
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	EUCTR2006-004785-14-NL
CCMO	NL14576.029.06