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A phase I dose escalation study of cisplatin, pemetrexed and radiotherapy for inoperable stage III non-small cell lung cancer

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22/11/2006

Recruitment status
No longer recruiting

Registration date
22/11/2006

Overall study status
Completed

Last Edited
06/01/2021

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
NL742, NTR752

Study information

Scientific Title

A phase I dose escalation study of cisplatin, pemetrexed and radiotherapy for inoperable stage III non-small cell lung cancer

Study objectives
The optimal management of loco-regionally advanced Non-Small Cell Lung Cancer (NSCLC) is evolving. Multimodality treatment is rapidly becoming the most common approach to stage III NSCLC. The American Society of Clinical Oncology (ASCO) guidelines recommend initial chemotherapy (platinum-based, two or three cycles) combined with radiotherapy in patients with adequate performance status and lung function.

For patients with inoperable stage III disease, concomitant chemoradiotherapy appears to provide an additional survival advantage. Although no single drug combination has been established as best, nor has the optimum radiation dose been defined. Pemetrexed is a new agent with promising activity in NSCLC and with potential radiosensitising activity. Pemetrexed has activity as a single agent in NSCLC and in combination therapy. The combination of cisplatin and pemetrexed has been explored in phase I, II and III settings. A phase I trial of pemetrexed with radiation has been explored. Radiosensitising activity of pemetrexed in vitro, its activity in combination with cisplatin provide the rationale for combining radiotherapy and pemetrexed in a phase I trial.

Attempts at radiation dose escalation in patients with stage III disease have not succeeded in escalating significantly beyond 66 Gy. However this has been in 1.8 to 2.25 Gy fractions given over six to seven weeks, and overall treatment time is also known to be a significant factor in determining radiation response in many tumours.

In this study we propose to investigate independent dose escalation of all three agents - of the chemotherapeutic agents cisplatin and pemetrexed in conventional fashion, and of the radiotherapy by shortening overall treatment time.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from the local medical ethics committee

Study design
Open-label, non-randomised phase I study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Lung cancer

Interventions
All patients will receive one cycle of pemetrexed 500 mg/m^2 and cisplatin 80 mg/m^2 (standard systemic dose) before concurrent radiotherapy starts. One cycle is three weeks.

Patients should have recovered fully from the first cycle of chemotherapy before they continue with the concurrent chemo radiation part. Patients will be entered in cohorts of three.

The first cohort of patients will receive three-weekly infusions of pemetrexed at a dose of 400 mg/m^2 and cisplatin 60 mg/m^2 which will be administered on the morning of day one of the second course of chemotherapy. Radiotherapy will be administered two hours after the chemotherapy administration, at an initial dose of 66 Gy in 33 fractions over 45 days. Each agent will be escalated independently, to allow further cohorts to be treated while allowing at least six weeks after the completion of radiotherapy to assess acute toxicity.

At any dose level, before escalation of the dose of that agent, all three patients treated in the previous cohort in which that agent was escalated, or in cohort one, must have completed the entire six weeks of treatment and have been assessed for acute toxicity six weeks after completing radiotherapy. In case of grade four dose-limiting toxicity no further treatment or escalation is allowed. If one patient experiences a grade three dose-limiting toxicity, a further three patients will be treated at that dose level. If no patients in the second trio experience a dose-limiting toxicity, dose escalation may continue.

If one additional instance of dose-limiting toxicity occurs (total two of six patients within one cohort), dose escalation will be stopped and the cohort will be expanded to nine patients. If no more than three of nine patients experience dose-limiting toxicity the maximum tolerated dose is confirmed.

Intervention Type
Mixed

Primary outcome(s)
The primary objective of this study is to determine the Maximum Tolerated Dose (MTD) of pemetrexed, cisplatin and radical involved-field radiotherapy in the treatment of patients with unresectable Stage III NSCLC. Two MTDs will be determined:
1. MTD of pemetrexed and cisplatin in combination with conventional radiotherapy.
2. MTD of pemetrexed and cisplatin with hypofractionated radiotherapy.

Key secondary outcome(s))
The secondary objectives of this study are the following:
1. The incidence and nature of acute toxicities.
2. The incidence and nature of delayed toxicity at three, six and 12 months after final radiotherapy treatment.
3. Objective tumour response.
4. Progression free survival.
5. Overall survival.

Completion date
01/03/2009

Eligibility

Key inclusion criteria
1. Histologically or cytologically confirmed diagnosis (bronchial brushings and washings or Computed Tomography (CT)-guided fine needle aspiration) of NSCLC, stage III which is not amenable to surgical resection

2. Uni-dimensional or bi-dimensional disease on CT scans of the chest. Measurable tumour and /or nodal mass not exceeding 6 cm in largest diameter
3. Received no prior chemotherapy or radiation therapy
4. Performance Status zero to one on the World Health Organisation (WHO) scale
5. Estimated life expectancy of at least 24 weeks
6. Patient compliance and geographic proximity that allow adequate follow-up
7. Adequate bone marrow reserve:
a. White blood count (WBC) more than or equal to 3.0 x 10^9/L
b. platelets more than or equal to 100 x 10^9/L
c. haemoglobin more than or equal to 6 mmol/L (³ 9.6g/dl)
8. Adequate respiratory function: Forced expiratory volume in one second (FEV1) more than or equal to 1.0 L/s (more than 30%) and transfer factor for carbon monoxide (DLCO) more than or equal to 40% of predicted
9. Aged 18 years or over
10. Written informed consent from patients
11. Effective use of contraception for both males and females if appropriate during and for three months following end of study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Not Specified

Total final enrolment
4

Key exclusion criteria
1. Evidence of active infection at the discretion of the investigator
2. Inadequate liver function: bilirubin more than 1.5 times normal, Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) more than three times normal
3. Inadequate renal function: calculated creatinine clearance using Cockcroft-Gault formula of less than 60 ml/min
4. Hypercalcemia
5. Evidence of extrathoracic metastases/Stage IIIB with supraclavicular lymph nodes
6. Uncontrolled superior vena cava syndrome, haemoptysis causing a decrease of blood haemoglobin of more than or equal to 1 g/L (more than or equal to 0.062 mmol/L) in 24 hours, or other situations which make complete staging or treatment planning impossible
7. Pleural effusion with positive cytology
8. Pregnancy
9. Breast feeding
10. Serious concomitant systemic disorder incompatible with the study

11. Second primary malignancy (except in situ carcinoma of the cervix or adequately treated non-melanomatous skin cancer), unless off treatment and in remission for greater than five years
12. Use of any investigational agent in the month before enrolment into the study
13. Any co-morbid pulmonary disease that may put the patient at risk of toxicity, specifically interstitial lung disease (fibrosis) and serious chronic pulmonary disease
14. Patients who are unable to interrupt aspirin, other nonsteroidal anti-inflammatory drugs for a five day period starting two days before administration of pemetrexed (eight-day period for long acting agents such as piroxicam). Patients that cannot be treated with folic acid and vitamin B12 and dexamethasone
15. Presence of clinically detectable (by physical examination) third-space fluid collections, for example ascites or pleural effusions that cannot be controlled by drainage or other procedures prior to the study entry
16. Use of growth factors

Date of first enrolment
01/03/2006

Date of final enrolment
01/03/2009

Locations

Countries of recruitment
Netherlands

Study participating centre
Erasmus mc-Daniel den Hoed
Rotterdam
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Sponsor information

Organisation
Erasmus Medical Center (The Netherlands)

ROR
https://ror.org/018906e22

Funder(s)

Funder type
Industry

Funder Name
Eli Lilly

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/09/2010	06/01/2021	Yes	No