EORTC randomized phase II study of pleurectomy/decortication preceded or followed by chemotherapy in patients with early stage malignant pleural mesothelioma.

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To investigate the feasibility of immediate P/D followed by cisplatin/pemetrexed chemotherapy (or carboplatin/pemetrexed chemotherapy) or deferred P/D after cisplatin/pemetrexed chemotherapy (or carboplatin/pemetrexed chemotherapy) in patients with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Mesotheliomas
Study type	Interventional

Summary

ID

NL-OMON53100

Source
ToetsingOnline

Brief title
Pleurectomy/decortication in mesothelioma

Condition

- Mesotheliomas
- Pleural disorders
- Respiratory tract therapeutic procedures

Synonym
'Mesothelioma' and 'pleural tumor'

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chemotherapy, Decortication, Mesothelioma, Pleurectomy

Outcome measures

Primary outcome

Primary end-point

Rate of success to complete the full treatment (P/D + chemotherapy or chemotherapy + P/D) within 20 weeks (± 2 weeks) after treatment start.

Treatment start is defined as day 1 of the first chemotherapy cycle in the deferred surgery arm and the day of operation in the immediate surgery arm.

A patient is considered to be a *treatment success* if he/she meets all of the following criteria:

1. Patient has received the full protocol treatment, defined as 3 cycles of pemetrexed and cisplatin (allowing for the dose adjustments described in section 5.3), preceded/followed by pleurectomy/decortication (P/D) (as described in section 5.3).

2. Patient alive and has no evidence of progression/relapse at week 20 (±2 weeks) after the first day of starting protocol treatment (chemotherapy followed by P/D or P/D followed by chemotherapy).

3. Patient has no persisting grade 3-4 treatment side-effects (CTCAE V 4.0) at

week 20 (±2 weeks) after the first day of starting protocol treatment

(chemotherapy followed by P/D or P/D followed by chemotherapy)

Secondary outcome

Secondary end-points

* Process indicators of the quality and uniformity of P/D and outcome: The

following measures were thought to ensure quality of surgery:

* Loco-regional failure free survival

* Progression free and overall survival.

* Treatment side-effects and perioperative mortality and morbidity at 30 and 90

days.

Study description

Background summary

The role of surgery in the treatment of malignant, pleural mesothelioma is controversial. Concerning this subject, evidence in the form of randomized controlled trials is scarce. There are two surgical options in treating mesothelioma: pleurectomy/decortication (P/D) versus extra-pleural pneumonectomy (EPP). Previously, patients standardly underwent the more extensive surgery: the EPP. However, outcomes of (the less invasive) P/D seem to be better than outcomes of EPP. Furthermore, survival outcomes of EPP are known to be better when surgery is combined with chemotherapy. The combination of P/D and chemotherapy has not yet been studied. However building on the knowledge concerning EPP, a combination of P/D and chemotherapy could lead to better survival outcomes, while also leading to less perioperative mortality and morbidity.

In this study, the feasibility of the combination of P/D and chemotherapy is assessed. More specifically: is it more feasible to treat mesothelioma with chemotherapy in a neoadjuvant setting or is it more feasible to administer chemotherapy postoperatively. The primary endpoint is the rate of successfully completed treatments, surgically as well as chemotherapeutically; independent of the order it is administered in and within 20 weeks of commencing said treatment. Further endpoints include 20 week-survival, without signs of

progression, relapse or 'related adverse events' over grade 2 according to the 'Common Terminology Criteria for Adverse Events' (CTCAE). If patients progress at any point before or during the three cycles of chemotherapy, this will be considered as treatment failure. Further anti cancer treatment can only proceed outside of the protocol. In the future, the results of this study can be used to compare the combination of P/D and chemotherapy versus a combination of chemotherapy and EPP or even no surgery as a control.

Study objective

To investigate the feasibility of immediate P/D followed by cisplatin/pemetrexed chemotherapy (or carboplatin/pemetrexed chemotherapy) or deferred P/D after cisplatin/pemetrexed chemotherapy (or carboplatin/pemetrexed chemotherapy) in patients with early stage malignant pleural mesothelioma.

Study design

This is a multicenter, randomized, 1:1, non-comparative phase II trial.
Patients with early stage MPM will be randomized between

ARM A: immediate P/D followed by three cycles of chemotherapy (pemetrexed 500mg/m2 and cisplatin 75 mg/m2 or carboplatin AUC 5 as IV, both drugs given on day 1, every three weeks) for non-progressing patients

ARM B: three cycles of chemotherapy (same regimen) followed by P/D, for non-progressing patients.

Four weeks (±2 weeks) will be allowed between the baseline tumor assessment and the start of treatment (surgery or chemotherapy).
Randomization should be done as soon as possible after baseline tumor assessment.

Intervention

Surgery
The minimal *default* procedure to which all thoracic and oncological surgeons participating in this trial will conform is *parietal and visceral pleurectomy to macroscopically remove all tumor*.

Chemotherapy
On day 1 of each cycle, pemetrexed 500 mg/m2 should be administered as IV infusion over 10 minutes followed 30 minutes later by cisplatin 75 mg/m2 (or carboplatin AUC 5) as IV over approximately 2 hours.

The three cycles of chemotherapy should start at four weeks (±2 weeks) after baseline CT scan in the deferred surgery arm and at four weeks (min 3 - max 6

weeks) after surgery in the immediate surgery arm. Chemotherapy cycles are defined as a 3 week period.

Study burden and risks

Patients participating in this study will not experience any extra risks. The burden during participation in this study is low en mainly consists of standard interventions and standard care. Six, standard outpatient visits wil take place. The blood collection necessary for this study will be done during regular blood collection, thus does not carry extra risk.

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. Patients are aged 18 years or older, with pathologically proven malignant pleural mesothelioma (MPM). All histological subtypes are accepted.
2. Stage cT1-3, N0-2, M0 according to UICC TNM classification. FDG-PET-CT scan showing absence of M1, N3, supraclavicular and coeliac node involvement is required. No clinical or radiological invasion of mediastinal structures (heart, aorta, spine, esophagus, etc.) and no widespread chest wall invasion (T4) are acceptable. Focal chest wall lesions are acceptable.
3. No prior treatment of any kind for mesothelioma is allowed, especially prophylactic track irradiations after diagnostic procedures.
4. WHO performance status 0-1.
5. Fit to receive chemotherapy and undergo a P/D with optional removal of hemidiaphragm and pericardium. The responsible surgeon and chest physician should judge the required fitness prior to registration, taking into account the results of all the relevant (i.e. pulmonary, cardiac) examinations.
6. No history of other malignancy within the last three years, except for carcinoma in situ of the cervix or basal cell or spinocellular carcinoma of the skin.
7. No pre-existing peripheral sensory or motor neuropathy > grade I according to CTCAE v4.0.
8. No clinically significant pleural effusion that cannot be managed with thoracentesis or pleurodesis (according to institutional practice). If pleurodesis is considered, it should be done before randomization.
9. No significant cardiovascular morbidity (assessed by cardiologist) precluding surgery.
10. Adequate organ function, evidenced by the following laboratory results within two weeks (+/- 3 days) prior to randomization with a buffer range from the normal values of +/- 5% for hematology and +/- 10% for biochemistry [with the EXCEPTION of Glomerular Filtration Rate] are acceptable):
*absolute neutrophil count >1500/l;
*Platelet count >100,000/l;
*Hemoglobin >11.0g/dL or 7 mmol/L;
*Total bilirubin <=1.5 upper limit of normal (ULN);
*SGOT (AST), SGPT (ALT), and alkaline phosphatase <=2.5×ULN;
*Glomerular Filtration Rate (GFR)>= 50 ml/min according to Cockcroft and Gault Formula.
11. No current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease, wound healing disorders; ulcers; or bone fractures, known infection with HIV, active hepatitis B and/or hepatitis C virus).
12. No major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery (other than P/D) during the course of study treatment.
13. No history of receiving any investigational treatment within 28 days of randomization.

14. No known hypersensitivity to pemetrexed or cisplatin or carboplatin or their components.
15. Women of child bearing potential (WOCBP) must have a negative serum (or urine) pregnancy test within 3 days prior to the start of chemotherapy/surgery. Patients of childbearing/reproductive potential should use adequate birth control measures, as defined by the investigator, during the study treatment period and for at least three months after the last study treatment. A highly effective method of birth control is defined as those which result in low failure rate (i.e. less than 1% per year) when used consistently and correctly. Female subjects who are breast feeding should discontinue nursing prior to the start of chemotherapy/surgery and until three months after the last study treatment.
16. Absence of any psychological, familial, sociological or geographical donation potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial. Absence of any other inability or unwillingness to comply with the requirements of the protocol as assessed by the investigator.
17. Before patient registration written informed consent must be given according to ICH/GCP, and national/local regulations.

Exclusion criteria

Mentioned earlier (inclusion criteria).

Study design

Design

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):	29-01-2018

Enrollment:	18
Type:	Actual

Ethics review

Approved WMO Date:	18-05-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-09-2022
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
ClinicalTrials.gov	NCT02436733

Register	ID
CCMO	NL59830.078.17