Circulating tumour cells by diagnostic leukapheresis mirror primary tumour heterogeneity in non-small cell lung cancer

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Primary aim: Frequency of identifying CTCs and their numbers in apheresis product before and after (during) treatment.Secondary aim: Prediction of response to therapy in different stages of NSCLC patient groups with the change in CTC numbers.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON43511

Source
ToetsingOnline

Brief title
CANCER-ID UMCG CTC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, lung carcinoma, non small cell lungcarcinoma, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: Europese unie;innovative medicine initiative (IMI-JU) financial contribution

Intervention

Keyword: circulating tumour cells (CTC), Diagnostic leukapheresis (DLA), Non small cell lung carcinoma (NSCLC), tumour heterogeneity

Outcome measures

Primary outcome

Primary outcome is the amount of CTC's and the percentage of patients that we

can isolate CTC's in, respective to their disease stage.

Secondary outcome

Change in CTC count related to response to therapy measured as decrease in size

of the tumour, or survival.

Study description

Background summary

Circulating tumour cells (CTCs) are a strong predictor of prognosis(1-3) and can be used as a biomarker for early detection of systemic cancer spread, therapy monitoring, and nowadays also for single cell genomics. Obtaining relevant information from blood by so called *liquid biopsies* is thus a simple method to detect tumour cells. Therapeutic decisions in lung cancer are increasingly dependent on adequate tumor tissue biopsies. However, amongst others, tumour heterogeneity and technical issues with the handling of tissue allow adequate diagnosis in only part of patients. CTCs may help to bypass these problems: CTCs do not have the issue of contamination with normal cells and DNA/RNA from leukocytes that come with this technique can be harvested in the same run(4).
Therefore, CTCs may replace current tumour biopsy practices when an adequate numbers of tumour cells can be detected, while also giving the option for further mutation analysis(5,6).
Immunomagnetic enrichment of cancer cells from blood samples expressing membranous epithelial cell adhesion molecule (EpCAM) protein led to the development of the FDA approved CellSearch system, nowadays the most widely used standard for CTC detection. The relevant detection rate is set on >2 or >5

CTCs per 7.5 ml blood sample. Clinical use of CTCs is currently limited in NSCLC because all systems fail to detect CTCs at an acceptable rate and at a sufficient high yield (for mutation analysis) in a large fraction of patients.
For NSLC, CTCs are observed in 26 to 49% of patients with metastatic disease. In nonmetastatic disease one CTC per 7.5 ml is observed in only 5 to 24% of patients. Extrapolation of CTC frequency distribution in 7.5 ml of blood from patients with metastatic breast, colon and prostate cancer showed that probably all these patients had CTCs in circulation, but the sample volume was not sufficient to detect them in all patients(7). A possible solution for this problem would be to significantly increase the blood volume. This can be achieved with leukapheresis that has been specified to increase CTC detection by means of a filter (e.g. Vycap). We hope this would provide a more reliable detection of CTCs at a higher frequency, and that by using this technique CTC*s can be found in sufficient high yield, even in nonmetastatic disease. We will study these issues within the European CANCER-ID consortium, a public-private partnership supported by Europe*s Innovative Medicines Initiative (IMI) with currently 38 partners aiming at clinical validation of blood borne biomarkers and establishing standard protocols for these. Leukapheresis, a standard clinical method to isolate mononuclear cells (MNCs) from blood, is currently used as routine practice in hematological diseases. Usually one to five liters of blood is processed in adults. Diagnostic leukapheresis (DLA) has previously been studied in solid cancer patients. Median total processed blood volume for lung cancer was 2,6 l (1,4 - 11,0). This resulted in 56 mL (40 - 156) volume of DLA product with 40.108 MNCs. The detection rate of CTCs in peripheral blood was 22% versus 56% in DLA. The procedure took one hour without adverse events(8).
In this study we will first explore the frequency and number of CTCs in all stages of NSCLC. Our hypothesis is that CTCs mirror the primary tumour heterogeneity at different stages of disease. Therefore, we will combine diagnostic leukapheresis with single cell genetics to study tumour heterogeneity for the prediction of therapy response in different stages of NSCLC patient groups.

Study objective

Primary aim: Frequency of identifying CTCs and their numbers in apheresis product before and after (during) treatment.
Secondary aim: Prediction of response to therapy in different stages of NSCLC patient groups with the change in CTC numbers.

Study design

2.1. Study design:
The clinical value of diagnostic leukapheresis (DLA), a more invasive and more time consuming procedure than a venapuncture, will be related to the molecular and functional characterization of CTCs in the context of personalized

molecular therapies. Screening high volumes of blood will enable a true liquid biopsy for patients with NSCLC and may open the possibility of using CTCs as biomarkers to guide and monitor systemic therapies even in the adjuvant therapy setting. Therefore, we want to study the enumeration of CTCs by DLA and determine whether CTCs can be used to detect single cell DNA abarrations and mutations to determine treatment strategies in four different clinical situations.

2.2. Study groups:
1. Patients with advanced NSCLC with mutations before and 3 weeks after the first treatment of any treatment line (n=20).
2. Patients with advanced NSCLC without detectable mutations before and 3 weeks after the first treatment (n=20).
3. Patients before and after chemoradiotherapy 3 weeks after the first treatment in stage III NSCLC (n=20).
4. Patients with resectable NSCLC before and after surgery (n=20).

Ad 1 to 4. In case no CTCs will be determined in the first 3 patients with 3 L DLA, we will extend the apheresis time to extract 5 L blood. If this doesn*t produce results in the next 5 patients then no new patients will be included in that group.
Ad 4. CTCs will be collected before surgery from a peripheral venipuncture (7.5 mL blood), DLA will be collected just before surgery, during operation before the clamps are placed on the pulmonary vein from the pulmonary vene coming from the lobe harboring the malignancy and 14 days after surgery, before adjuvant treatment is initiated.
Ad 1-4. Before and after DLA, a routine peripheral venipuncture for CTC (7.5 mL blood) will be performed.
Ad1-4. If no CTC*s can be found in the first procedure, then no second apharesis will be performed.

2.3. Statistics:
Assuming a prevalence of CTCs in apheresis products at baseline of 80% and 26% (effect size 0,67) after or during treatment, in 20 patients we should detect this difference at a significance level of 0.05 (two-sided) and with a power of 80%. Thus, we will study 40 diagnostic leukapheresis products (20 baseline and 20 during or after treatment).
For testing the hypothesis that the decrease in CTCs will determine a prolonged survival, the change in CTCs (using either median changes, using logistic regression or using a ROC curve(9)) will be associated with the progression-free survival and overall survival using Kaplan-Meier survival curves. Cox regression analysis will be performed with correction for covariates such as disease stage, performance status and therapy.
Exploratory studies will be performed with descriptive statistics with DNA and RNA blood-borne biomarkers.

Study burden and risks

During the investigation the patient will receive a moderate drain on their energy, as the apharesis will take about one hour of time and two needles will be inserted in their arms, which might be painfull or stressfull for the patients. The pain is not severe however. Also we don't expect the complications to occur that often, and the consequences of these complications should be limited. Complications that can occur are strange sensations in extremities, face of lips, bruises at the injection sites, or bleeding. An infection of the insertion site is the only severe complication.

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

Patients with a histologically proven pulmonary malignancy (all disease stages)
Performance status 0-2
Patients using anticoagulants such as fraxodi or acenocoumarol are allowed, unless they have had recent hemorrhagic events
Written informed consent

Exclusion criteria

Patients with insufficient peripheral venes to undergo leukapheresis
Haemorrhagic diathesis: recent CVA, major bleeding, ulcus duodeni
Cardiac failure, LVEF<40%
No growth factors are allowed

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2016
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO

Date:	09-03-2016
Application type:	First submission

Review commission: METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 19904
Source: NTR
Title:

In other registers

Register	ID
Other	Nederlands Trial Register 5540
CCMO	NL55754.042.15
OMON	NL-OMON19904