Immunological effects of stereotactic radiotherapy - An exploratory trial (iDOSE)

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Objective: To identify immunological responses elicited by different schedules of SABR in ES-NSCLC. Expression rates and activation states of immune effector subsets will be assessed in peripheral blood and liquid biopsies (plasma/serum).Hypothesis...

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

Summary

ID

NL-OMON54820

Source
ToetsingOnline

Brief title
iDOSE

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: stichting Amsterdam Infection & Immunology Institute (AI&II)

Intervention

Keyword: immunology, molecular, SABR, SBRT

Outcome measures

Primary outcome

The primary endpoints of this study are the immunological responses in the peripheral blood. The endpoints will be assessed by examination of the liquid biopsies and peripheral blood to detect immunomodulation.

Secondary outcome

No secundary parameters

Study description

Background summary

SABR is a form of hypofractionated radiotherapy where a biologically effective dose (BED) of >=100 Gy is delivered in 1-8 fractions. SABR is currently standard of care in early stage non-small cell lung cancer (ES-NSCLC) for patients who are not fit for surgery or decline surgery, with a local-regional tumor control of 85-90% in five years. Analysis of nearly 1600 patients from both the VU University medical center and MD Anderson showed that the risk of distant metastases within 5 years of SABR treatment is twice as high as that of loco-regional recurrences, warranting further research on combinations of therapy to improve the systemic efficacy of treatment. SABR has proved to be superior to conventional radiotherapy, with less toxicity. Radiotherapy is a rational modality to combine with immunological therapies (e.g. checkpoint-inhibitors), due to its limited toxicity and durable responses of combined treatment in preclinical studies. SABR can induce tumor-directed immune responses, as was shown both preclinical and clinical by the systemic T-cell activation accompanied by an increase in PD-1 expression identified in a major fraction of ES-NSCLC patients. Interestingly, enhanced immune activation was not induced by surgery, indicating that the immune modulatory effect of SABR was not merely a result of reduced tumor load and associated immune suppression. The abscopal effects was first described by Mole in 1953, and describes the regression of tumor lesions outside the radiation field following local radiotherapy. Abscopal effects are rarely seen after radiotherapy alone, probably due to the suppressive effects of the TME. The combination of immune

checkpoint inhibitors (ICI) can overcome this suppressive milieu and induce abscopal effects in combination with radiotherapy, supporting the rationale for combined modality treatment. Adjuvant Durvalumab (PD-L1 antibody) in addition to chemo-radiotherapy, improves progression-free survival in patients with locally advanced, unresectable stage III lung cancer, according to the results from the phase III PACIFIC trial. Furthermore, local objective response enhanced from 16% to 28.4% with Durvalumab, suggesting that a local immune response was initiated. These results support the concept of SABR as an in-situ vaccination therapy, which can be potentiated by concurrent treatment with ICI. Yet, much remains unknown concerning radiotherapy-induced immunological responses in vivo, especially with regards to SABR. Different SABR schedules may have comparable outcomes concerning local control, but may be quite different in immunological outcomes (e.g. MHC expression, activation of effector T cells, T cell infiltration), as demonstrated in preclinical studies. Many clinical trials are exploring the efficacy of these combination therapies in NSCLC. Nevertheless, the optimal schedule of immunotherapy, as well as optimal SABR dose and fractionation schedules, remain to be elucidated. It has been suggested that current cancer immune-radiotherapy trials may not use optimal schedules for optimizing immunological responses. Preclinical models show a correlation between fractionation dose and abscopal effects and biologically effective dose (BED) and abscopal effects, with a 50% chance of gaining abscopal effects with a BED of 60 Gy. Recent preclinical data show that a high fractionation dose induces expression of TREX1, an intracellular nuclease that interferes with signaling through the STING pathway and potently abrogates type-I interferon (IFN) secretion by irradiated cancer cells, subsequently preventing the activation of an adaptive immune response. Despite the large amount of preclinical data available, clinical data on immune effects of radiotherapy, especially SABR, is limited, justifying the initiation of the exploratory trial laid out in our proposal. This exploratory trial could also be an important trial for future studies in oligometastatic disease, since chemotherapy is being replaced by immune-oncology (I-O) treatment in stage IV disease. Given the number of positive trials a rising number of different I-O drugs are approved for treatment of stage IV disease. Since SABR has a significant effectivity in oligometastatic disease too, integrating both approaches is logical. Patients with synchronous or metachronous metastases can experience benefit in terms of disease free survival from systemic therapy in combination with radial local treatment (SABR), however this occurred with a huge variety in the fractionation dose of radiotherapy. For optimal understanding and application of SABR in these cases, it is of major importance that the immunological effects of SABR are being elucidated. We aim to use the data from this clean, low tumor volume early stage NSCLC SABR trial, for developing future trials in oligometastastic disease.

Study objective

Objective: To identify immunological responses elicited by different schedules of SABR in ES-NSCLC. Expression rates and activation states of immune effector

subsets will be assessed in peripheral blood and liquid biopsies (plasma/serum).

Hypothesis: We anticipate that some SABR schedules may alter the immune activation status more than other schedules, leading to changes in cellular composition in blood as a consequence of local and/or systemic switches from a suppressive immune content to a more activated immune content.

Study design

This is a hypothesis generating trial evaluating immunological and molecular effects of SABR for ES-NSCLC. Patients with early stage (T1N0-T3N0/Nx) peripherally and centrally located, pathology confirmed NSCLC or suspicion on early stage NSCLC, and eligible for SABR, will be enrolled in this study. Patients will be treated with the appropriate SABR schedule defined in departmental protocols. Translational research to explore the immune mechanism of action will include FACS analyses, ctDNA and NanoString analyses to assess expression rates and activation states of immune effector subsets in peripheral blood. Blood samples will be taken before, during and several times after SABR. The primary endpoints of this study are the immunological responses in the peripheral blood. The endpoints will be assessed by examination of liquid biopsies and peripheral blood to detect immunomodulation.

Study burden and risks

Burden and riks are limited, since we ask only for peripheral blood samples 5 times during this trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Have a diagnosis of cytologically proven or suspicion on early stage (T1N0-T3N0/Nx) NSCLC, for which SABR has been recommended following discussions within a multi-disciplinary tumor board.
2. Be willing and able to provide written informed consent for the trial.
3. Be 18 years of age on day of signing informed consent.

Exclusion criteria

1. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 30 days prior to the planned SABR.
2. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 30 days prior to SABR.
3. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
4. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen*s syndrome will not be excluded from the study.
5. Has a history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.
6. Has an active infection requiring systemic therapy.

7. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject*s participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
8. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) or a known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-05-2019
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	09-04-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	16-08-2023
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
CCMO	NL65585.029.18