Decoding predictors of Colitis induced by Immune checkpoint blockade therapy

Published: 14-04-2022
Last updated: 05-04-2024

Our main objective is to determine the factors that increase susceptibility to IMC in order to find predictive biomarkers.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON53776

Source
ToetsingOnline

Brief title
DECIPHER

Condition

- Gastrointestinal inflammatory conditions
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Immune-checkpoint inhibitor induced colitis

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Immune checkpoint mediated colitis, Immune related adverse events, Immunotherapy

Outcome measures

Primary outcome

1. Incidence of any grade and grade 3/4 IMC within 12 weeks.

2. Development of grade 3 or 4 IMC with corresponding interval (start immune checkpoint inhibition until symptom onset).

3. Frequencies and phenotype of immune cell populations and cytokine production in the colon of patients prior to and during ICI treatment.

4. Differences in immune cell populations and cytokine production prior to and during ICI treatment, in patients who eventually develop grade 3 or 4 IMC as compared to those who do not develop IMC.

Secondary outcome

5. Differences in the microbiome and metabolome prior to and during ICI treatment, in patients who eventually develop IMC as compared to those who do not develop IMC

6. Differences in circulating immune cell populations and cytokines prior to and during ICI treatment, in patients that eventually develop IMC as compared to those who do not develop IMC.

7. Differences in immune cell populations, cytokine production, microbiome and metabolome composition in patients undergoing different types of ICI-treatment (anti-PD-1/ anti-CTLA-4).

8. Transcriptome of intestinal tissue prior to and during ICI treatment

Study description

Background summary

One of the biggest breakthroughs within oncology in the recent years has been the development of immunotherapy: drugs that enhance the strength of immune system to attack tumor cells. Immune cells do this naturally, however many tumors have evolved by disabling anti-tumor immunity through cancer immunoediting. Examples of this are anti-inflammatory cytokine production or the upregulation of proteins that lead to T cell inactivation/exhaustion, such as oncogenic PD-L1 (Programmed cell Death Ligand 1) expression. When PD-1 (Programmed cell Death 1) on activated T cells binds to PD-L1, the T cell will stop proliferating and becomes exhausted. Similar anergic responses in T cells are observed when CTLA-4 (Cytotoxic T-lymphocyte-associated 4) on T cells binds ligands like CD80/CD86.

Over the past decades, antibodies against CTLA-4 and PD-1 or PD-L1 have been developed aiming to unleash these breaks on exhausted T cells. Intriguingly, this indeed leads to anti-tumor immune responses and in subgroups of patients even to complete responses even in metastasized cancer. Given this unprecedented potential to cure cancer, many scientists are now focusing on finding ways to improve anti-cancer immune responses using several immunomodulatory drugs.

Unfortunately, the use of immune checkpoint inhibitors is not completely harmless. As can be envisioned, generalized immune activation is accompanied by considerable immune-related adverse events (irAEs). These side effects include ICI-associated thyroiditis, - hepatitis and colitis among others.
ICI-mediated colitis (IMC) is one of the most commonly observed irAEs which may cause discontinuation of therapy. Often, patients with severe IMC require hospitalization and anti-inflammatory therapies to resolve intestinal inflammation, such as systemic prednisone, anti-TNF therapy or anti-integrin antibodies. The interruption of the treatment and the start of anti-inflammatory treatments that may promote tumor growth, is obviously deleterious for the patient.

Therefore, the major challenge and largely unmet clinical need is predicting which patients are susceptible to develop IMC. This would greatly advance the field of immunotherapy, as patients with a high probability of IMC could be prophylactically treated with intestinal-specific anti-inflammatory drugs to prevent severe irAE*s and continue anti-cancer treatments.

In this proposal, we aim to unravel the factors that increase susceptibility to IMC, including the intestinal immune composition and the microbiome composition, in order to find predictive biomarkers for IMC susceptibility. In

parallel, we hope to find signals that keep the colonic immune response *silent*, information that may eventually also be useful to understand immune exhaustion in inflammatory bowel disease (IBD).

Study objective

Our main objective is to determine the factors that increase susceptibility to IMC in order to find predictive biomarkers.

Study design

Investigator initiated prospective cohort study

Study burden and risks

Burden: Patients will visit the coordinating investigator four to six times after recruitment, depending on whether the patient develops IMC or not. During these visits, procedures such as an IUS or sigmoidoscopy will be performed. The goal is to schedule these assessment visits on the day of ICI-treatment or outpatient clinic visits for standard routine care to lessen patient burden. Venapunctures will be combined with routine testing if possible and stool samples may be prepared at home before visiting the hospital.

Risks: A sigmoidoscopy is usually well tolerated and is performed in daily clinical practice without use of analgesics and/or anaesthesia. Preparation for sigmoidoscopy includes the administration of an enema prior to the sigmoidoscopy.

Intestinal ultrasonography is a well-tolerated and non-invasive diagnostic tool. This will be optional for all participating patients to undergo. We expect that our study procedures will not inflict additional burden to the subjects.

Benefit: There is no evident benefit for patients who choose to participate in this study. It is aspired to gain new insights on the pathophysiology of IMC and to further assess methods to predict, thus prevent the occurrence and severity in patients undergoing ICI-treatment.

Contacts

Public
Amsterdam UMC

Meibergdreef 9

Amsterdam 1105AZ
NL
Scientific
Amsterdam UMC

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients fom 18 years diagnosed with a malignancy
- Indication for systemic ICI-treatment with nivolumab or pembrolizumab (anti-PD-1), atezolizumab, ipilimumab (anti-CTLA-4) monotherapy or the combination of nivolumab with ipilimumab.
- WHO performance score 0-2

Exclusion criteria

- Patients, who are not able to provide informed consent.
- History of IBD
- Life expectancy < 6 months
- Viral or bacterial infection within the past week
- Recent use of antibiotics (<3 months)
- Use of anti-inflammatory drugs (for example prednisolone, anti-TNF, anti IL12/23)
- Patients who are undergoing chemotherapy treatment

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-09-2022
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	14-04-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	NL79489.018.21