Sequential diagnostics of pulmonary fungal infections

Published: 01-05-2024
Last updated: 18-11-2024

To determine the clinical utility of sequential computational assisted CT-guided treatment of PFI in the hemato-oncology population.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haematological disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON56740

Source
ToetsingOnline

Brief title
SIGNALS

Condition

- Haematological disorders NEC
- Fungal infectious disorders
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
invasive fungal infection, pulmonary fungal infection

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Ct-scan, fungal infection, hematological malignancies, stem cell transplantation

Outcome measures

Primary outcome

1. Incidence of possible or probable PFI using this diagnostic protocol

2. Rate and diversity of pathological imaging findings suggestive of PFI

3. Compare diagnostic performance of standardized conventional radiological assessment (IPARADS) versus computer aided assessment

Secondary outcome

(a) Describe imaging features that are not associated with PFI: number of lesions/events

(b) Describe the development and reduction of PFI features during aplasia and neutropenia recovery.

(c) Exploration of the imaging kinetics and response kinetics during fungal infections with computer aided analysis of target lesions

(d) Describe treatment duration and outcome following CT-guided response evaluation

Study description

Background summary

Invasive pulmonary aspergillosis- or mucormycosis are the most common pulmonary fungal infections (PFI) diagnosed in patients receiving intensive chemotherapy for myeloid malignancies or as a conditioning regimen for allogeneic stem cell transplantation. Prolonged neutropenia, mucosal damage and reduced cellular immunity are risk factors that contribute to the high incidence of mold infections in these patients. Several studies have proven the efficacy of

primary mold active azole prophylaxis in reducing the incidence and mortality of PFI in these patients and prophylaxis is recommended by various guidelines during cytotoxic treatment up until immunological recovery which can take weeks to months. However, there are negative effects of prophylaxis that were not studied in the aforementioned trials. For example, there are important bidirectional drug interactions with new targeted antileukemic and antiviral drugs that were introduced after these trials were published and that were not studied in the registration trials. There is also increasing azole resistance in Europe and breakthrough infections with azole susceptible or resistant molds are also frequently reported. The alternative to universal prophylaxis is a pre-emptive or diagnostic driven approach to PFI management, where mold active treatment is started only when an invasive mold infection is suspected because of clinical sings of infection (e.g. fever during neutropenia or pulmonary symptoms) or positive serum aspergillus antigenemia while results of definitive diagnostic testing are pending. We have applied this approach in our institution; using serial aspergillosis antigenemia monitoring and low dose CT-imaging for persistent fever has led to a reduction of the use of azole drugs to just 15% of our population which would have otherwise all received universal azole prophylaxis, thus preventing overtreatment in the majority of the patients. Surprisingly, all of our PFI cases were diagnosed primarily by CT-imaging and subsequent CT-directed bronchoalveolar lavage of suspected pulmonary lesions, while serum antigenemia remained negative. These findings indicate that we cannot rely on positive antigenemia as an early marker for PFI, at the same time they point to the advantage of CT-imaging in the early detection of PFI . This is in line with current studies supporting the role of CT-imaging as a screening tool for PFI even before the start of chemotherapy given that around 20% of patients already have a PFI before starting treatment. Moving forward with our diagnostic approach to PFI we will integrate an early CT-scan of the chest as a screening tool before the start of chemotherapy starting in 2023. While this baseline CT will offer early diagnosis of PFI to some, we foresee some important questions that have remained unanswered in the current literature. First, even though early CT-imaging is already routine practice in several institutions, there are no known reports of the evolution kinetics of PFI lesions early during the course of chemotherapy-induced neutropenia, before fever or positive serum antigenemia appear. In fact we do not know when fungal lesions first become apparent on CT-imaging nor do we know at what speed they develop or when they incite fever. Similarly, response to treatment currently relies on follow up imaging but there are no recommendations on lesion response criteria. In this diagnostic strategy protocol we want to explore computational assisted sequential CT-pulmonary imaging as a tool for early detection and quantification of PFI lesions and also to guide early initiation and continuation of antifungal treatment during intensive chemotherapy courses for myeloid malignancies or allogeneic stem cell transplantation.

Study objective

To determine the clinical utility of sequential computational assisted CT-guided treatment of PFI in the hemato-oncology population.

Study design

non-randomised prospective feasibility study with additional diagnostic intervention

Intervention

One additional non contrast enhanced low dose CT thorax.
Routine of care follow up or clinically triggered CT thorax will be performed following a weekly interval if feasible

Study burden and risks

CT scanning is an imaging modality that is extensively used in standard care. Low dose CT scans are performed at 100kV with automated exposure control (Sure Exposure). Image reconstruction is performed using AiCE deep learning reconstruction with a slice thickness of 0.5 in lung and mediastinal window. Average dose-length-product (DLP) is estimated at 40.In this study one additionalCT scan will be performed which is needed to better understand the kinetics of development of invasive pulmonary fungal infections and the combined strategy will identify patients that have fungal infections earlier and also identify patients that are in need of antifungal treatment even in the absence of fever. On the other hand it also contributes to safety, in patients that have no lesions it is safe to (continue to) withhold antifungal treatment even when there is persistent fever. In the future this study will provide evidence to decrease the number of patients that are unnecessarily exposed to antifungal drugs, decrease the duration in which they are exposed to these drugs and also standardize radiological reporting for the clinician and future research.

Contacts

Public
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL
Scientific
Radboud Universitair Medisch Centrum

Geert Grooteplein Zuid 10
Nijmegen 6525 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Age 18 yrs and older • Inclusion within 1 day before start of cytoreductive treatment or remission induction chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) OR for myeloablative conditioning of allogeneic stem cell transplantation (HSCT) including FLAMSA conditioning • Expected absolute neutrophil count of <0.5 x109 for at least 10 days • No previous or current history of proven or probable IMD • No current diagnosis of pneumonia • No current respiratory distress or ventilation support (low flow oxygen is permitted ie by nasal canula) • Patients must be able to be transferred to the radiology department for scanning • Female subjects with childbearing potential must have a negative serum (or urine) pregnancy test within 3 days prior to inclusion • Absence of any psychological, familial , sociological condition potentially hampering compliance with the study protocol and follow up; those conditions should be discussed with the patient before registration in the trial • Before registration patients should give written informed consent according to ICH/GCP regulations

Exclusion criteria

• Pregnant female subjects
• Current or previous history of primary or metastatic lung malignancy
• Treatment for pulmonary fungal infection in preceding 3 months
• Inflammatory bowel disease or any inflammatory bowel condition

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-08-2024
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	01-05-2024
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-06-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL84290.091.23