From September 19th to 21st 2019

8th

EUROPEAN CONFERENCE ON INFECTIONS IN LEUKAEMIA

ECIL

Mycobacteria Group

(adults)

Tuberculosis (TB)

FINAL SLIDE SET
CONFIDENTIAL

Mercure Sophia Antipolis
Sophia Antipolis France

Latent TB infection (LTBI) in Haematology

ECIL recommendations: patients to target

- Only high risk population of HM/HSCT patients should be considered for a preventive treatment for active TB development **AIIu**
- Factors associated with high risk of developing future active TB in HM/HSCT are:
  - Patients from countries or communities with a high incidence of TB as specified by eCDC https://ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2019 **CIII**
  - People referring exposure to a patient with contagious TB **AIIt**
  - People with pleuro-parenchymal imaging abnormalities (mainly on the upper lobes) suggestive of previous TB in patients who had not received an appropriate anti-TB treatment **BIIt**
  - Patients who receive ruxolitinib if epidemiological risk factors are significant (history, endemic areas). (Maschmeyer, 2019, ECIL 2017) **BIIu**
- Special attention should be paid to the risk of primary infection or re-infection throughout the haematological follow-up **AIII**

ECIL recommendations: which patients to treat ?

- Three strategies are available for the high risk patients defined before. Based on the limited available data, the group could not reach a consensus on the preferred strategy
  1. Provide preventive therapy without screening
  2. Screening patients with immune-based tests keeping in mind their limitations:
     - Provide preventive therapy to those scored positive after excluding active TB
     - Exclude active TB in those that are indeterminate and accurate estimation of the risk for future active TB should be considered for treatment decision
     - Do not treat if scored negative after accurate estimation of the risk for future active TB
  3. Not providing any preventive treatment considering the benefit/risk ratio

ECIL recommendations: which patients to treat ?

- For decision of screening or initiating TB preventive therapy consider the prognosis of the haematological malignancy and patients' characteristics especially age **BIII**
- Preventive treatment should be administered if there has been close, and prolonged contact with active pulmonary or laryngeal TB, regardless of the HM/HSCT patient's TST or IGRA status **AIIt**
- Patients who had prior active TB treated correctly do not need to be screened or be offered preventive treatment **AIIt**
- For patients who had prior active TB treated inappropriately, seek expert advice and consider full TB treatment or preventive treatment based on the history of TB **AIIt**

ECIL recommendations: How to screen ?

- IGRA should be preferred to TST for patients previously vaccinated with BCG **BIIt** For other patients, either TST or IGRA can be used **CIIu**
- TST positivity should be defined as an induration of ≥ 5 mm **BIIt**
- Either T SPOT TB or Quantiferon can be used equally well **BIIu**
- In case of doubt about the extent of a TB sporadic contact, IGRA conversion could be helpful and should probably be repeated after 8-12 weeks from the last exposure, if initially negative **BIIt**
- In case of indeterminate IGRA, data in HM/HSCT population do not support repeating IGRA or TST **BIIt**

ECIL recommendations: How to treat ?

- Before starting a preventive treatment, active TB must be ruled out (investigate clinical symptoms and perform a lung imaging) **AIII**
- Initiating a TB preventive treatment should not delay HM treatment/HSCT procedure **AIII**
- Recommended drugs:
  - First, rifampicin if possible taking into consideration drug-drug interactions (especially cyclosporine/tacrolimus in HSCT) 4 months of daily treatment with 10 mg/kg/d rifampicin (max 600 mg) **BIIt**
  - In case rifampicin cannot be used, isoniazid should be administered at the dose of 5 mg/kg/d (maximum 300 mg) for 9 months **BIIt**
- Drug-drug interactions and toxicities should be discussed on a case by case basis **AIII**
- Pyridoxine 25-50mg/day should be added in case of treatment with INH **BIIt** For patients with pre-existing peripheral neuropathy, increasing pyridoxine dose to 100 mg/day can be considered **BIII**
- Preventive treatment should be given with caution during HSCT conditioning therapy/antineoplastic chemotherapy **CIII**

ECIL recommendations: How to monitor the treatment ?

- Baseline liver function test (AST, ALT, bilirubin, GGT, AP) monitoring before initiation treatment is recommended: **AIIt**
  - AST, ALT should be < 3xULN
  - Relative contra-indications for INH are ALT>3x ULN, alcohol use, and viral hepatitis
- Prevention and management of hepatotoxicity
  - Depending on benefit/risk considerations, consider deferring TB preventive treatment if pre-existing liver enzymes increase or concomitant hepatotoxic drugs **BIII**
  - Monitor transaminases every 2-4 weeks: ALT, AST, BILI, AP, GGT for both INH and RIF. INR-PTT monitoring recommended if preexisting liver disease **AIIt**
  - Withhold INH if ALT,AST at least 5 times ULN, or at least 3 times ULN with symptoms **BIII**
  - Do not challenge again if signs and symptoms undoubtely linked to TB preventive treatment **AIII**
- Patients must be advised that rifampicin will cause an orange-red discoloration of body fluids (urine, sweat, tears, saliva) and that contact lenses may become stained **AIII**

Active TB disease in haematology

ECIL recommendations: active TB disease diagnosis

- Expert advice for both clinical, microbiological and treatment management of active TB is strongly recommended
- A high level of clinical suspicion is required to ask for specific microbiological tests (microscopy, culture and nucleic acid amplification test), especially for TB high risk patients with suggestive clinical symptoms and radiological signs
- Appropriate drug susceptibility testing should be performed on all initial *M. tuberculosis* isolates
- If the strain is susceptible to first line drugs, drug susceptibility testing for second line drugs is not required unless rifampicin is not used in the regimen **BIII**
- Molecular identification and detection of drug resistance against rifampicin (e.g Xpert) should be performed on respiratory specimen **AIIt**
- Comprehensive phenotypic and genotypic drug susceptibility testing in case of MDR isolate should be performed **AIIt**

ECIL recommendations: TB treatment

- Treat TB in HM/HSCT patients similarily to general population: daily 2 months of HRZE followed by 4 months of HR for most cases **BIIt**; Ethambutol can be stopped before 2 months if no resistance for HR **BIIt**
- DDIs between anti-TB drugs and all other drugs should be carefully considered **AIIu**, and if possible, concomitant drugs should be changed when alternatives are available **BIII**
- Longer duration treatment must be considered according to the location of the disease, the host's immune status or the evolution under treatment **AIIt**
- Longer duration treatment should be considered when rifamycins are not part of the treatment regimen **AIIt**
- Supplementary pyridoxine for all HM/HSCT patients treated with isoniazid **BIIt**
- Treatment of MDR/XDR must rely on comprehensive phenotypic and genotypic drug susceptibility testing and it requires a longer duration treatment; Evaluation depends on the choice of drugs and specific schedules do monitor adverse events **AIIt**
- Careful evaluation of the timing of chemotherapy for the underlying haematological disease with the respect of treatment of active tuberculosis should take into consideration that a delay/ or reduction in antineoplastic chemotherapy has been associated with poor overall outcome **BIIu**
- Reduction of immunosuppression is recommended if feasible, with particular attention to the risk of IRIS as well as the risk for ruxolitinib withdrawal syndrome and the need for corticosteroids in case of central nervous system TB **BIII**

ECIL recommendations: Monitoring

- Evaluation and monitoring of treatment toxicity should include
  - liver test (ALT, AST, GGT/AP, BILI) at baseline, every 2 weeks for 2-3 months then every 2-4 weeks (if abnormal hepatic status continue every 2 weeks) and INR-PTT in case of underlying liver disease or abnormal liver test during FU **AIIt**
  - when ethambutol is given, visual acuity and red-green color discrimination at treatment initiation; monthly questioning concerning visual disturbance; monthly ophthalmological evaluation if treatment for longer than 2 months, dose ≥ 15-20mg/kg, or renal insufficiency **BIII**
- For patients with positive sputum cultures, the specimen should be monitored closely by microscopy and culture during therapy until at least 2 negative culture results are available **BIII**
- Sequential PCR monitoring is not recommended during therapy **AIIt**
- If the patient is able to produce sputum, a sample should be collected and evaluated by microscopy and culture and at the end of therapy **BIII**
- Imaging (preferably a lung HRCT scan in pulmonary TB) at the end of therapy is helpful as a baseline for possible future questions on relapse **CIII**

ECIL recommendations

Management of hepatotoxicity **AIII**

- Consider other causes if liver enzymes increase have increased
- Withhold treatment if AST/ALT or GGT/AP are at least 5 times ULN or at least 3 times with symptoms
- If TB treatment cannot be interrupted: change to a less hepatotoxic regimen, eg. Quinolone-EMB-injectable (eg.Amikacin); the FQ should be preferably NOT include moxifloxacin or ofloxacin but can include levofloxacin
- After AST/ALT or GGT/AP returns to less than 2 times ULN, restart drugs one by one every 3-7 days
- In case of severe hepatotoxicity, consider permanent discontinuation of PZA

Prevention

- BCG vaccination is contraindicated in HM/HSCT recipients *Cordonnier, 2019, ECIL 2017*
- Appropriate isolation from contagious patients should be applied
- TB contact investigation should be performed

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Mycobacteria Group

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Nontuberculosis mycobacteria (NTM)

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ECIL recommendations for NTM infection

DIAGNOSTIC CONSIDERATIONS AIII

- Specifically ask for a mycobacterial search
- Samples that are microscopically positive for acid fast bacilli should be investigated by molecular methods to rule out TB
- Prolonged culture is required to identify NTM (up to 63 days)
- The following drug-NTM combination susceptibility results can be correlated with clinical outcome and are the only ones that should be systematically tested :
  - Macrolides and amikacin susceptibility for MAC and *M. abscessus*
  - Rifampicin susceptibility for *M. kansasii*

GENERAL TREATMENT CONSIDERATIONS AIII

- Seek expert advice for management and to discuss whether treatment should be initiated
- Treatment has to be adjusted to the causative NTM species and the resistance to the above mentioned drugs -NTM combination
- Recommended anti-NTM treatment might not be feasible due to DDIs (especially for clarithromycin, azithromycin, rifamycins) in association with the haematological treatment and evidence base for therapy with second line anti NTM agents is very limited

ECIL Recommendations: NTM pulmonary disease

- Interhuman transmission of NTM has not been described; NTM infection does not usually require specific transmission precautions
- For pulmonary disease
  - Differentiating NTM infection from colonisation, is a crucial point for treatment decision. Consider the pathogenicity of the NTM, clinical/lung CT scan picture and number and type of positive samples **AIIt**
  - Do not rely on a single NTM positive sputum to retain the diagnosis of NTM pulmonary disease **AIIt**; repeat sputum or do bronchoscopy (bronchial aspirate specimen may lead to superior positivity compared to BAL for mycobacterial search) **BIII**
  - Diagnostic criteria for pulmonary NTM should rely on ATS/ERS/IDSA/ESCMID guidelines
  - Initiation of treatment for NTM is rarely a medical emergency **BIII** Repeated clinical, microbiological and radiological (HRCT) evaluations should be considered for decision of treatment **AIIt**
- A single positive respiratory sample for NTM with no clinical or lung CT scan abnormalities does not require a specific treatment pre-HSCT. However, a careful monitoring should be done after HSCT **BIIu**
- Multidrug treatment regimen against NTM should rely on ATS/ESCMID/ERS/IDSA recommendations; it should be prolonged for at least 12 months based on culture conversion
- For monitoring the efficacy of treatment, a sputum specimen should be cultured every 1-2 months until end of therapy even if the these cultures become negative **BIIt**
- Treatment outcome definition should follow international consensus *(ERJ, 2018)*

ECIL recommendations: NTM extrapulmonary disease

- The duration of treatment for skin/soft tissue NTM infection depends on NTM species and requires expert advice **BIII**
- In NTM infection of a central catheter, the device should be removed **AIIu**; antimicrobial treatment should be discussed according to the extent of the infection and the causative NTM species **BIII**
- A NTM positive culture from other extrapulmonary sterile sites usually requires antimicrobial treatment; M. gordonae is an exception as is M. chelonae in certain circumstances **AIIt**
- Treatment of extrapulmonary NTM should follow the same principles as pulmonary disease (ATS 2007); Source control should be done **AIIt**