

September
22th & 23th



2017

7th EUROPEAN
CONFERENCE
ON INFECTIONS IN
LEUKAEMIA

Mercure Sophia Antipolis Sophia Antipolis ♦ France

Infectious Complications of New Drugs and Biotherapies in Hematology

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2017



General Decision

- Aim at Expert Report rather than guideline
 - *Infections*
 - *Approach to latent TB*
 - *Differential diagnosis and management of immune-related adverse events*



Ibrutinib: Treatment Recommendations

- For documented infections: see previous ECIL guidelines
- For non-infectious pneumonitis: withdrawal of ibrutinib and steroids
 - *See the part on grading and management of pneumonitis*



Ibrutinib: Burning Questions and Areas for Further Research

- Urgent need for prospective and high quality data on infectious AEs
- Pre-ibrutinib assessments:
 - Hepatitis B and C (E? no data for ibrutinib) serology => *ECIL guideline if seropositive*
 - TB => *specific slides*
- Antimicrobial prophylaxis
 - Anti-mould prophylaxis in patients receiving concomitantly high dose steroids (e.g. CNS lymphoma) (*drug-drug interaction with voriconazole; dose reduction and TDM? L-AmB?*)
 - Anti-PcP in patients with additional risk factors (e.g. recent FCR therapy)
 - Latent tuberculosis => *specific slides*
 - Role and effectiveness of vaccination in ibrutinib-treated patients unclear
- Monthly intravenous immunoglobulin therapy in patients with low IgG levels in pts with ≥ 1 previous serious infection



Idelalisib: Recommendations

- PcP: prophylaxis with trimethoprim-sulfamethoxazole (included in the label now, but weak evidence)
- CMV serostatus for all patients before treatment administration
- For CMV-negative patients: CMV-negative **or** filtered blood products
- CMV-pos.: CMV antigen/PCR monitoring
- If positive PCR/ag with increasing viral load: pre-emptive anti-CMV treatment
 - No recommendation for idelalisib discontinuation
- Symptoms consistent with CMV disease
 - Anti-CMV **treatment**
 - Discontinuation of idela until CMV resolution should be considered



Infections in Ruxolitinib-Treated Patients

Recommendations (1)

- **Patients presenting with fever** should be carefully evaluated for serious infections
 - Think of bacterial infection first: urinary tract, pneumonia, sepsis
 - No routine AB prophylaxis
 - Apart from Zoster, no increased risk of opportunistic infections by ruxolitinib
 - **Usually no ruxolitinib discontinuation** in a patient with typical bacterial infection
 - In case of discontinuation, keep in mind “Ruxolitinib withdrawal syndrome” (respiratory distress, progression of splenomegaly, fever or pruritus, mimicking an infection)



Infections in Ruxolitinib-Treated Patients

Recommendations (2)

- HBV screening in all patients
- In patients with indication for treatment or prophylaxis: ECIL guideline (*Mallet et al*)
- Screening for latent tuberculosis
 - *See specific slides*



Venetoclax: Summary and Recommendations

Patients with fever/infection and neutropenia

- Standard supportive care measures. G-CSF used with good response in this setting

Discontinuation or dose reduction of the drug (package insert)

- Neutropenia without infection: dose reduction or interruption; permanent discontinuation is rare.
- Infection without neutropenia: usually manageable without dose adjustment

Deeks ED. Drugs 2016

Freise KJ et al. Clin Pharmacokinet 2017

Roberts AW et al. N Engl J Med 2016



mTOR Inhibitors (Sirolimus, Temsirolimus, Everolimus) and Infection: Recommendations

- High level of alertness for infections
- No specific measures for prophylaxis
- No specific diagnostic approach in case of fever
- Consider drug-induced lung disease



Infections in Patients on HDAC Inhibitors: Recommendations

- **No** clear evidence of HDACi – attributable increase in the risk of infection or infection-related mortality
- **No** rationale for specific prophylaxis
- **No** rationale for specific diagnostic procedures in case of fever after treatment including HDACi in pts with hematologic malignancies
- **No data** indicating the need for screening for HBV
- **No evidence to withhold** treatment including HDACi in pts with active infection
- HDACi use in **HIV**-positive pts with hematological malignancies does **not** seem to increase the risk of HIV activation



Brentuximab Vedotin: Recommendations for Screening

- JC serology: insufficient negative predictive value
- No specific BV-related risk for CMV, but patient group in general
- CMV => consistency with CMV group
- Take risk into consideration, but no routine CMV monitoring



Recommendations for BV Drug Discontinuation

- PML => discontinue
- DILD => discontinue => re-challenge (individual decision)
- Pneumonia => no data to support recommendation of discontinuation
- Herpesvirus reactivation => no data to support recommendation of discontinuation
- Febrile neutropenia => stop until resolution of G3-4 neutropenia



Blinatumomab: Prophylaxis and Drug Discontinuation

- **No specific signals** of increased infection rate
 - *Double-check with the Würzburg group if we missed something*
- Discontinuation or dose reduction in case of infection according to package insert
- **Ig level monitoring** for ≥ 2 years **and IgG supplementation** in case of low IgG concentration after ≥ 1 serious infection



Anti-PD1 & Anti-CTLA4 Antibodies: Diagnosis and Treatment of Fever/Infection

- In case of fever, rule out infectious cause
- **Usually** infection results from immunosuppression given for immune-mediated complication
 - Consider different background of patient affected
- If infection is diagnosed, treat accordingly and **continue drug**



Anti-PD1 & Anti-CTLA4 Antibodies: Recommendations for Prophylaxis

- PcP prophylaxis in patients with secondary **immunosuppression (IrAE)** for at least 4 weeks (*=> ECIL guideline*)
- No data on vaccination available (consistent with vaccination group)



Approach to Latent Tuberculosis

- **Evaluation** before: generally recommended, but routine only for ruxolitinib
- **Screening**: history of active TB in household contacts; suspect finding indicating prior/latent TB on imaging (CT scan; chest radiograph); social background; patient reporting new TB contact; profession
- Complete **work-up**: positive IGRA or TST; history of TB not adequately treated; suspect finding indicating active TB



Which Patients Should Receive Preventive TB Therapy

- No active TB in work-up, but
 - Positive IGRA, positive TST in a non-vaccinated patient
 - History of TB not fully treated
 - Abnormal chest imaging suggesting past TB inadequately treated
- No need for preventive TB therapy after active TB treatment completion



Preventive TB Treatment

- Options: isoniazide 6 months; rifampicin 3 months*
 - Consider drug toxicity (liver, drug interactions)
 - Consider TB multi-drug resistance
- Delay the start of hematological drug 3-4 weeks if possible (e.g., ruxo for MF)

**Getahun H et al, N Engl J Med 2015*

**Meta-Analysis: Zenner D et al, Ann Intern Med 2017*

2017



Hepatitis:

Viral Reactivation or Immune-Related?

Recommendation for all drugs addressed

- Rule out (reactivation of) viral infection
- If negative, consider biopsy



Diagnostic Guidelines for Lung CT Scan in Hematology Pts

Consolidation

Ground-glass opacities

Bronchial/-olar

Nodules > 1 cm

Reversed halo sign

Lymphatic

Lymph nodes

Fibrotic

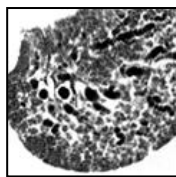
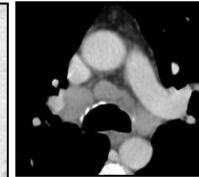
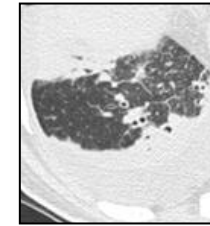
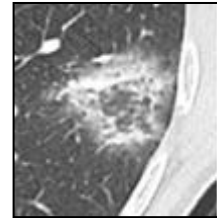
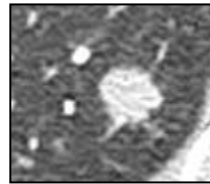
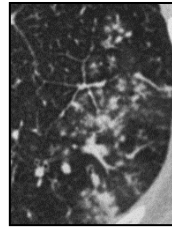
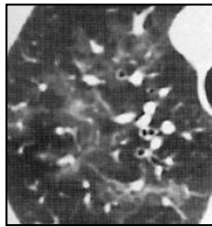
Tree in bud
Centrilobular
micronodules

Halo sign
or not

Septal thickening
Peribronchovascular
thickening
Pleural effusion
Lymph nodes

Necrotizing
or not

Traction
bronchiectasis
Honeycomb
Reticulations



Bacteria
Filamentous
fungi

Pneumocystis
Respiratory virus

Community
respiratory virus
Bacteria
Mycobacteria
Filamentous
fungus
(bronchoinvasive)

Filamentous
fungus
Slow-growing
bacteria
Mycobacteria

Mucormycosis
Aspergillosis

Mycobacteria

Diffuse alveolar
damage
Drug-induced
(OP)

Drug-induced
Pulmonary
edema
Intraalveolar
hemorrhage
Diffuse alveolar
damage

Hematological
disease
Cancer

Drug-induced
(OP)

Pulmonary
edema
Lymphangitis

Hematological
disease
Drug-induced
(sarcoid-like)

Drug-
induced
Diffuse
alveolar
damage

Look for relevant elementary abnormality
« Pathological reading » (correlations CT scan / histopathology)
Check consistency of associated lesions



Management of Lung Infiltrates in Hematological Pts

Lung infiltrates on lung CT scan

Develop hypotheses

Assess immunosuppression profile

Consider antiinfectious prophylaxis

Appreciate susceptibility to different pathogens

Clinical data
Little discriminating

Lung + other organ?

Fever

Control of hemopathy

Blood biology according to diagnostic hypotheses

Blood cultures, PCR CMV, HSV, fungi, *Aspergillus* galactomannan, β -D glucan, BNP, CRP, blood cell count

Evaluate respiratory condition

Risk/benefit ratio for Bronchoscopy-BAL

Favorable:
Broncho-BAL

Bronchial biopsies if abnormalities
Extensive search for pathogens: bacteria, mycobacteria, fungi (including PCR PcP), multiplex for respiratory viruses
BAL cell count

Unfavorable:
Noninvasive tests

Sputum examination for bacteria, mycobacteria and fungi; Induced sputum (*P. jirovecii*); nasopharyngeal aspirate for viral multiplex

Check consistency of all data

Lung biopsy should be an exception; discuss case by case
CT scan guided

Management of lung infiltrates in suspected drug-induced pneumonitis

Management

Lung infiltrates

Recommend interpretation by radiologist /pulmonologist
See next HRCT interpretation chart

Consider: **Infection**
pulmonary edema,
disease specific
involvement, others

Consider drug imputability: idelalisib, mTor inhibitors,
checkpoint inhibitors, ibrutinib > brentuximab, ruxolitinib
(after withdrawal) > blinatumomab, BCL2 inhibitors,
HDAC inhibitors

O2 requirement

If drug-induced lung
disease suspected

No O2
requirement

Immediate drug
withdrawal

+

Investigations

Alternative
diagnosis ruled out

Consider steroids 1 mg/kg/d
Or pulse steroids 2-4 mg/kg/d
according to severity

Consider
rechallenge
according to
risk/benefit ratio
± steroids

Investigations

No alternative diagnosis
Evaluate risk/benefit ratio

Pursue/dechallenge
Inform patient
Control low dose CT scan 2-4 weeks