ASPERGILLUS AND BTK INHIBITOR USE
A CASE REPORT

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CASE

- Patient is 70 year old male
- Chronic Lymphatic Leukemia (CLL) diagnosed 2011
  - Rituximab-bendamustine x4 (R-B)
    - Neutropenic infection after first dose
    - Wide erythema reaction after third rituximab dose
- 4/2018 cytopenias related CLL (anemia, thrombocytopenia and neutropenia (0.5-0.9x10E9/l)
  - Because of skin problems with R-B treatment, ibrutinib started 5/2018
    - Ibrutinib is an oral Brutons tyrosinokinase inhibitor: inhibits malignant B-cell proliferation
  - Although anemia relieved and neutropenia disappeared, overall condition worsened during summer 2018
    - Patient was admitted to hospital

CASE

- CT-guided lung biopsy from lesion was tried, but failed
- BAL:
  - Pneumocystis jirovecii PCR was positive
  - Bacterial culture: normal flora, no pathogens
  - Fungal culture and native preparate were negative for fungi (Aspergillus antigen or fungal PCR were not taken?)
  - Aspergillus antigen twice from blood negative
  - Pneumocystis treatment with co-trimoxazole started
- Patient collapsed and CT of the brain ordered

BIOPSY FINDINGS

- Fungal structures were detected in biopsy specimen already in freeze sample and in culture grew
  - ASPERGILLUS FUMIGATUS +
    - AMFOTERB S 0.38
    - ISAVUKON S 0.25
    - ITRAKONA S 1
    - POSAKONA S 0.064
    - VORIKONA S 0.125
- Voriconazole was started
- Ibrutinib was discontinued

CASE

- After diagnosis of aspergillosis patient did not receive treatment to CLL
- CLL has been quite stabile, patient has been free of symptoms until April 2019
- Voriconazole is continued
- Voriconazole trough levels high (normal range 2.0-5.5. mg/l)
  - no signs of toxicity
  - **9.4** mg/l voriconazole dose reduced to 100 mgx2
  - **8.3** mg/l
  - **14** mg/l voriconazole dose reduced to 100mgx1
  - **8.4** mg/l
  - **8.9** mg/l
  - **11** mg/l
  - **7.4** mg/l

CASE

- April 2019
  - Patient was hospitalized because of a collapse
  - CT: no signs of infections in lungs or brain

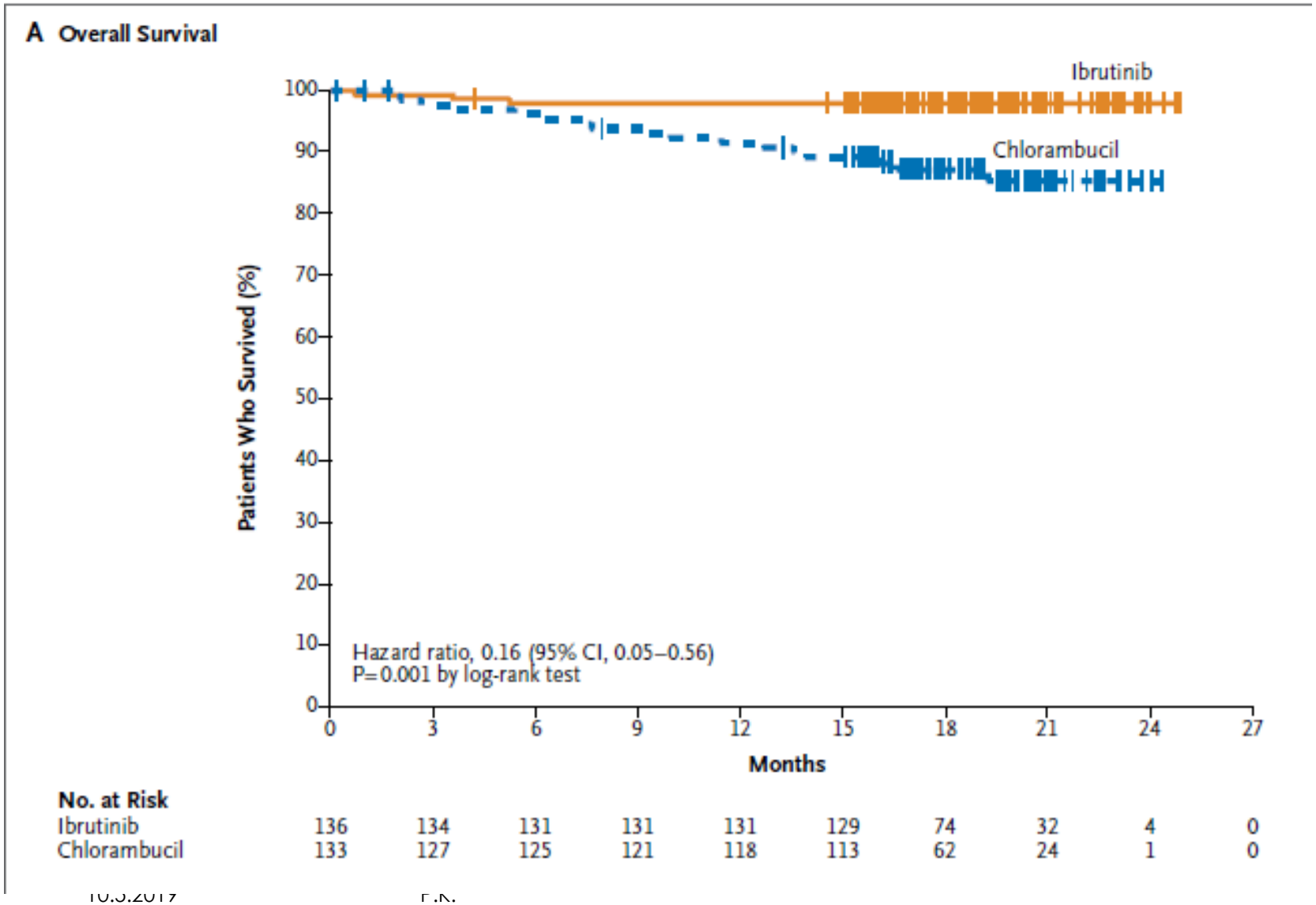
IBRUTINIB (IMBRUVICA™)

- Bruton's tyrosine kinase (BTK) inhibitor
  - BTK is a key signaling molecule of the B-cell receptor signaling complex that plays an important role in the survival of malignant B cells. Ibrutinib blocks signals that stimulate malignant B cells to grow and divide uncontrollably.
- Indications
  - Chronic graft-versus-host (cGVHD) disease after failure of one or more prior lines of systemic therapy.
  - Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.
  - Mantle cell lymphoma (MCL) who have received at least one prior therapy.
  - Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.
  - Waldenstrom's macroglobulinemia

IBRUTINIB (IMBRUVICA™)

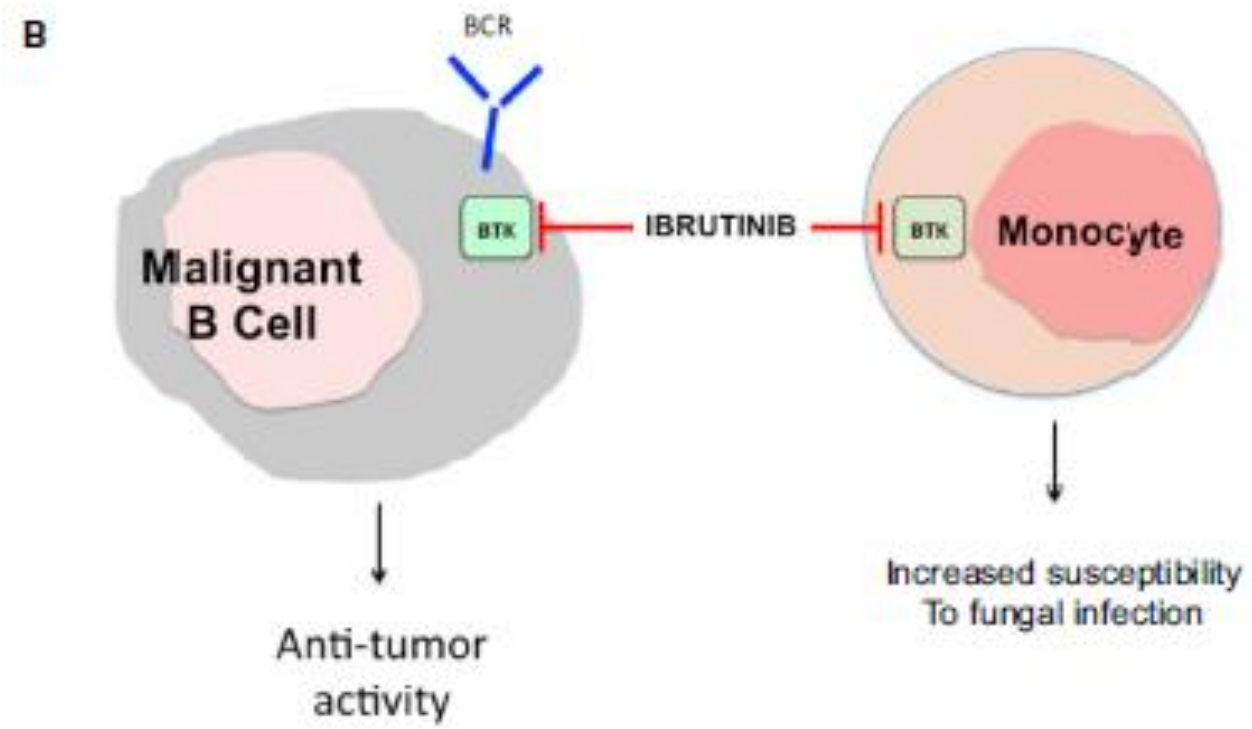
- Dose (tablets 140 mg)
  - CLL and Waldenström's disease 3 tablets/day=420 mg/day
  - Mantle cell lymphoma 4 tabl/day =560 mg/day
  - Treatment until disease progression (if tolerable)
- Most common side-effects
  - Decreased platelets, neutrophilsor hemoglobin
  - DiarrheaFatigue, Musculoskeletal pain, Swelling, Upper respiratory tract infection, Nausea, Bruising
  - About 20 % patients discontinue drug because of toxicity:
    - Atrial fibrillation, infection, pneumonitis, bleeding, arthralgia. (Mato ER et al Ann Oncol 2017;28:1050-1056)
- Metabolized by CYP3A4

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia



Burger JA et al NEJM 2015; 373:2425-37

IBRUTINIB: SIMPLIFIED MECHANISM OF ACTION



Crommes C, Yunes A. Cancer Cell 2017;;31:731-3

IBRUTINIB AND FUNGAL INFECTIONS

- Ibrutinib has been used about 5 years
- There are several publications concerning fungal infections in patients on ibrutinib treatment
- Opportunistic infections rate 8.1 % in patients receiving in first line BTK inhibitors has been published (Issa N et al Open Forum Infect Dis 2017;4(suppl 1):S699)
- In primary CNS lymphoma 5-27 % of patients had aspergillus infection (Grommes C, Younes A Cancer Cell 2017;31:731-733)
- A review of 17 cases of aspergillosis and 10 cases of CNS aspergillosis has published (Swan CD, Gottlieb T. BMJ Case Rep 2018.doi:10.1136/bcr-2018-224786)
  - 4/10 survived

IBRUTINIB AND FUNGAL INFECTIONS

- Other published opportunistic fungal infections
  - Cryptococcosis 7 cases
  - Pneumocystis 7
  - Zygomycosis 3 (one Aspergillus+Zygomycosis)
  - Fusariosis 1
  - Histoplasmosis 1

P.K. (Swan CD, Gottlieb T. BMJ Case Rep 2018.doi:10.1136/bcr-2018-224786)

Ibrutinib in PCNSL: The Curious Cases of Clinical Responses and Aspergillosis

Study 1st author	Grommes et al.	Choquet et al.	Leonakis et al.
n	20	18	18
Disease inclusion	Relapsed refractory PCNSL 65% or secondary CNSL 35%	Relapsed/refractory PCNSL 61% or relapsed/refractory primary vitreo-retinal lymphoma 39%	PCNSL 28% previously untreated, 72% relapsed/refractory
Ibrutinib dose	560-840 mg daily	560 mg daily	560-840 mg daily
Ibrutinib schedule	Monotherapy until disease progression	Monotherapy until disease progression	Monotherapy for 2 months, followed by ibrutinib + chemo
Concomitant steroids	Yes (n=10)	Yes (n=5)	Yes (n=11)
Pretreatment DNA sequencing results available	Not reported	Not reported	4 patients
% PR + CR to ibrutinib monotherapy	75%	55%	83%
% with Aspergilus infection	5%	11%	27% on ibrutinib monotherapy (39% during the entire study)
Median PFS/EFS achieved with single agent ibrutinib	7.5 months	3 months	Not assessable for ibrutinib alone, 15.5+ months for the combination regimen

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IBRUTINIB

- Increases risk of fungal infections
  - Aspergillosis
    - Higher incidence to CNS involvement than in other patient groups ?
      - Reason unknown
  - Fungal prophylaxis problematic
    - CYP3A4 inhibition (voriconazole, posaconazole ?, isavuconazole?) increases blood levels
      - De Jong et al Leukemia &Lymphoma 2018;59:https://doi.org/10.1080/10428194.2018.1460474
        - Voriconazole 200 mg bid+ibrutinib 140 mg exposure was 143.3 % when compared to ibrunitinib alone 560 mg
          - Cost of ibrutinib about 9000 €/month (560 mg daily), voriconazole about 400 €/month (200 mgx2)
            - Cost saving potential with voriconazole 9000 €-2650 €=6350 €/month
  - No recommendation of fungal prophylaxis so far

ASPERGILLUS CASE REPORT AND BTK INHIBITOR USE

Remember the increased risk of fungal infections in patients using BTK inhibitors

Thank You