VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

Terapie target e innovative: il ruolo di BTKi nei linfomi mantellari, a piccoli linfociti e marginali. Razionale, applicazioni cliniche e resistenza

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Janssen			X		X		
Novartis			X		X		
Lilly			X		X		
BMS			X		X		
SOBI			X				
Sanofi - Regeneron			X		X	X	
Abbvie			X		X		

Resistance Mechanisms: Classification

BTK-Dependent

C481S mutations

PLCG2 mutations

Other kinase mutations

BTK-Independent

PI3K/AKT pathway

NF-κB activation

BCR signaling bypass

Pharmacokinetic

Drug efflux

Low drug levels

Metabolism variations

1. Brown JR, et al. Resistance mutations in BTK that confer profound resistance to ibrutinib. NEJM. 2021; 2. Woyach JA, et al. Resistance mechanisms for CLL therapies. Blood. 2021;138(23):2422-2436.; 3. Furman RB, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. NEJM. 2015; 4. Burger JA, Barr PM. Long-term follow-up of BTK inhibitors. Semin Hematol. 2021; 5. Mato AR, et al. Optimal sequencing of BTK inhibitor therapy in CLL. Nature Rev Cancer. 2022; 6. Sharman JP, et al. Pirtobrutinib (LOXO-305), a next-generation BTK inhibitor for patients with relapsed/refractory B-cell malignancies. NEJM. 2021.

BTK-Dependent Resistance: C481S Mutations

C481S is the most common mutation causing BTK inhibitor resistance (~50% of resistant cases)

Cysteine at position 481 is the covalent binding site for irreversible BTK inhibitors

Serine substitution prevents ibrutinib, acalabrutinib, and zanubrutinib binding

Non-covalent BTK inhibitors (pirtobrutinib) can overcome C481S mutations

Other BTK mutations: T474I, L528W, F311L, E501K - less frequent but clinically significant

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Secondary Pathway Mutations

PLCγ2 mutations (~20% of resistant cases): R665W, R665Q, S707F

Enhance downstream BCR signaling activation independent of BTK

SYK mutations: alternative kinase activation pathway

PRKCB mutations: protein kinase C β activation

These mutations can occur alone or in combination with BTK mutations

Accumulation of multiple mutations increases resistance complexity

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BCR-Independent Signaling Pathways

PI3K/AKT/mTOR

PTEN loss

PIK3CA mutations

Increased mTOR signaling

NF-κB Pathway

CARD11 mutations

Canonical/non-canonical NF-κB

TNFAIP3 (TNFα Induced Protein 3) loss

Other Pathways

MEK/ERK activation

JAK/STAT signaling

Wnt/β-catenin pathway

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Microenvironmental Resistance

Lymphoid microenvironment provides survival signals bypassing BTK inhibition

Stromal cell-derived factors: CXCL12, BAFF, APRIL support CLL survival

T-cell derived cytokines: IL-4, TNF-α enhance cell survival

Increased CAF (cancer-associated fibroblast) interactions in resistant clones

Hypoxic conditions in lymphoid tissues promote resistance gene expression

Combination therapies targeting microenvironmental support may overcome resistance

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Pharmacokinetic Resistance Mechanisms

MDR1/P-glycoprotein upregulation: active drug efflux from resistant cells

BCRP (breast cancer resistance protein) also mediates BTK inhibitor efflux

Variable drug absorption and metabolism between patients

CYP3A4 interactions affect BTK inhibitor bioavailability

Altered drug distribution in sanctuary sites (CNS, bone marrow niches)

Combination with MDR1 inhibitors shows promise in overcoming efflux-mediated resistance

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BTK Inhibitor Drug-Drug Interactions

BTK inhibitors are substrates and inhibitors of CYP3A4 and P-glycoprotein

Significant pharmacokinetic interactions with numerous commonly used drugs

Most relevant in ibrutinib and acalabrutinib; less with pirtobrutinib

Interactions can increase or decrease BTK inhibitor levels

Clinical management requires careful drug selection and dose adjustments

Patient age, comorbidities, and polypharmacy increase interaction risk

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CYP3A4 Drug Interactions with BTKi

Drug Category	Examples	Interaction Type	Clinical Impact
Strong CYP3A4 Inhibitors	Azole antifungals, protease inhibitors, macrolides	Increased BTK-I levels	Toxicity risk
Moderate CYP3A4 Inhibitors	Diltiazem, verapamil, fluconazole	Increased BTK-I levels	Monitor closely; dose reduction may be needed
Strong CYP3A4 Inducers	Rifampicin, phenytoin, carbamazepine	Decreased BTK-I levels	Impaired or loss of efficacy
Moderate CYP3A4 Inducers	St. John's Wort, efavirenz	Decreased BTK-I levels	Monitor closely; response may be impaired

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P-Glycoprotein Transport Interactions

BTK inhibitors are P-gp substrates: ibrutinib, acalabrutinib, zanubrutinib

P-gp inhibitors increase BTK-I bioavailability: cyclosporine, verapamil, quinidine

P-gp inducers decrease BTK-I bioavailability: rifampicin, phenytoin

Combined CYP3A4 + P-gp interactions significantly increase drug levels

Pirtobrutinib has lower P-gp affinity - fewer interactions

Monitor carefully when combining with multiple interacting agents

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Common Drug Combinations: Risk Assessment

HIGH RISK

- Azole antifungals
- Protease inhibitors
- Clarithromycin
- Cyclosporine
- Strong inducers

MODERATE RISK

- Diltiazem, verapamil
- Fluconazole
- Amiodarone
- Ritonavir-boosted drugs
- Moderate inducers

LOW RISK

- Penicillins, cephalosporins
- Acetaminophen
- Most anticoagulants
- SSRIs (except fluoxetine)
- Beta-blockers (metoprolol)

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Clinical Management of DDI with BTK Inhibitors

Comprehensive medication review at baseline and with each new drug

Consider non-interacting alternatives: antibiotic selection, antifungals

Dose adjustments: Reduce BTKi dose with strong CYP3A4 inhibitors (as per SmPC)

Timing separation: Space BTK inhibitor from some drugs (e.g., antacids, PPIs)

Monitor for toxicity: Increased AEs, bleeding, infections with high-risk combinations

Pirtobrutinib has lower CYP3A4 dependency

Regular LFTs, CBC, and clinical assessment when adding interacting agents

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Conclusions

BTK inhibitor resistance is multifactorial - monitor closely for emerging resistance patterns

Routine deep sequencing at disease progression identifies resistance mechanisms and guides therapy

C481S mutations and BCR-independent pathways represent major mechanisms—tailor treatment accordingly

Drug-drug interactions significantly impact BTK inhibitor efficacy and toxicity in polypharmacy patients

Early MRD detection enables intervention before overt resistance development