Ruxolitinib: JAK of all trades
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Disclosures
• I have no relevant financial or nonfinancial relationships to disclose

Objectives
1. Explain the mechanism of action and indications for ruxolitinib
2. Evaluate the literature supporting ruxolitinib use in various indications
3. Formulate a conclusion for the place of ruxolitinib in therapy

Poll question
• At your institution, what indications are you using ruxolitinib for?
A. ALL
B. GVHD
C. Other
D. More than one of the above
E. None of the above

Ruxolitinib’s mechanism of action

Ruxolitinib Dosing
• Dosing
  ≫ Adult:
    • Myelofibrosis
      • 5 to 20 mg twice daily
    • Dose dependent on platelet counts
    • Polycythemia vera: 10 mg twice daily
    • Graft-versus-host disease (GVHD): 5 to 10 mg twice daily
  ≫ Pediatric: not established

GVHD: graft-versus-host disease
Ruxolitinib Pharmacokinetics

- Highly protein bound (~97%)
- Extensively metabolized by CYP3A4 to active metabolites
  - Dosing adjustments for concomitant strong CYP3A4 inhibitors and fluconazole
- Metabolites excreted in urine (74%)
  - Dosing adjustments for renal impairment

Ruxolitinib Indications

- FDA approved indications:
  - Myelofibrosis
  - Polycythemia vera
- Off label use (adult): GVHD
- Pediatric off-label uses
  - Acute lymphocytic leukemia (ALL)
  - GVHD

Ongoing clinical trials include several indications in pediatric patients

- Acute GVHD (aGVHD)
- Chronic GVHD (cGVHD)
- Relapsed/refractory ETP-ALL
- Ph-like ALL
- Cutaneous cGVHD
- Salvage therapy for hemophagocytic lymphohistiocytosis (HLH)
- Atopic dermatitis

GVHD in pediatric patients

- Incidence
  - Acute: 20-80%
  - Chronic: 20-50%
- Response rate to corticosteroids: 50%
  - Durable response rate remains low at 30%
- No standard recommendations for second line therapy or steroid-refractory GVHD (SR-GVHD)

References:

Ruxolitinib shows improved survival in mice with GVHD

Ruxolitinib 30 mg/kg twice daily administered from day -1 until day 20 of allo-HSCT vs. control group

- Reduced proliferation in effector T-cells
- Suppression of proinflammatory cytokine production
- Mice receiving ruxolitinib had improved survival compared to control group (40% vs. 0% at day 35)
- Reduced histopathological grading and serum proinflammatory cytokines


Ruxolitinib for steroid‐refractory acute GVHD (aGVHD)

- Design: Retrospective, single center review
- Population:
  - Pediatric HSCT patients
  - Received ruxolitinib between 2013 – 2016
  - Biopsy proven (when applicable) aGVHD
  - Steroid refractory: ≥ 1 site worsening by ≥ 1 stage 72 hours after or failure to improve 7 days after treatment
- Intervention:
  - ≥ 25 kg: 5 mg twice daily (adult dosing)
  - < 25 kg: 2.5 mg twice daily
  - Max dose: 10 mg
  - Decreased by 50% if administered with azoles
- Patient characteristics (n=13):
  - Median age = 8.5 years (range 1.6‐16.5)
  - Included GVHD grades II –IV
  - Organs involved: skin, liver, GI, eye
  - Median agents used prior to ruxolitinib = 4
  - Dose escalation in 9/13 patients


Ruxolitinib for steroid‐refractory acute aGVHD (continued)

- Response (n=11):
  - Complete response (CR): 1
  - Partial response (PR): 4
  - No response: 2
  - Treatment failure: 4 (1 due to toxicity)
  - Overall response rate (ORR): 45%
  - CR: 9%
- Toxities:
  - ≥ Grade 3 elevated alanine transaminits: 7
  - ≥ Grade 3 neutropenia: 5
  - Grade 4 thrombocytopenia: 1
- Conclusion:
  - Empiric dosing may have affected overall and CR rates
  - Toxicities were reversible, yet significantly impacted ruxolitinib therapy
  - Larger studies necessary to assess correct dosing and efficacy


Multicenter survey for ruxolitinib use in SR-GVHD

- aGVHD N=54
  - Previous therapies: 3 (median)
  - ORR 81.5%
  - CR 46.3%
  - Median time to response: 1.5 weeks
- cGVHD N=41
  - Previous therapies: 3 (median)
  - ORR 85.4%
  - CR 7.3% (PR 78%)
  - Median time to response: 3 weeks
- Toxicities:
  - Cytopenias: 33.3% of aGVHD and 14.5% of cGVHD
  - CMV reactivation: 33.3% of aGVHD and 14.6% of cGVHD
- Conclusion:
  - Authors concluded ruxolitinib has a potential place in therapy for SR-GVHD and is well tolerated

Khandelwal, et al. Leukemia. 2015;29(10):2062‐2068

Current ongoing clinical trials for ruxolitinib use for GVHD in patients 12 years and older

- REACH1 trial:
  - Phase 2 study, single cohort
  - Ruxolitinib + steroids for treatment of SR-GVHD
  - Press release reported ORR of 55% at day 28
- REACH2 trial:
  - Phase 3 study study, randomized open label
  - Ruxolitinib vs. best available therapy for SR-aGVHD
- REACH3 trial:
  - Phase 3 study, randomized open label
  - Ruxolitinib vs. best available therapy for SR-cGVHD


Ruxolitinib for acute lymphoblastic leukemia (ALL)
Poll Question

Which patient is most likely to benefit from ruxolitinib therapy?

a. 13 year old male with Ph+ B-ALL  
b. 12 year old female with Ph-like B-ALL  
c. 4 year old female with low risk B-ALL  
d. 7 year old male with T-ALL

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Targetable Lesions in Ph-like ALL

- 264 patients with Ph-like ALL were studied to identify genetic alterations resulting in activation of kinases.

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Phase I study of ruxolitinib in relapsed/refractory solid tumors, leukemias, or myeloproliferative neoplasms: CGG Study (ADV1011)

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<th>Patient Population</th>
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<th>Results</th>
<th>Conclusion</th>
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| Children with solid tumors (n=28) or hematologic malignancies (n=21) | Ruxolitinib dose escalation 15 mg/m²/dose → 50 mg/m²/dose | Dose limiting toxicities: 2 neutropenia, 1 AKI, and 1 CPK  
Non-dose limiting toxicities: cytopenias, nausea, and elevated transaminases and creatinine  
Greatest pSTAT5 inhibition at 50 mg/m²/dose | Recommended dose is 50 mg/m² PO BID |

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Case study: ruxolitinib in a child with Ph-like ALL

- 10 year old Caucasian male presented with high risk ALL  
- Novel GOLGA5-JAK2 fusion identified  
- MRD 40% on day 29 of induction  
- Induction failure  
- Ruxolitinib 40 mg/m² initiated day 7 of consolidation  
- MRD ≥ 0.01% at the end of consolidation  
- Ruxolitinib discontinued  
- Achieved remission with CAR T-cell therapy  
- Underwent allogeneic HSCT  
- Mouse model confirmed intense treatment response of GOLGA5-JAK2 ALL with ruxolitinib use  
- Ruxolitinib shown to be safe and effective in combination with multi-drug regimen

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Two current major clinical trials include ruxolitinib with standard leukemia treatment

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| • St. Jude Children’s Research Hospital  
• Ruxolitinib initiated at day 45 in patients with:  
  • Activation of JAK-STAT signaling  
  • Day 15 MRD ≥ 5% or day 42 MRD ≥ 1%  
  • All ETP and Llly patients w/o complete response at end of induction  | • Children’s Oncology Group  
• Pilot and efficacy phases  
• 4 groups  
  • A: CRLF2-R + JAK mutation and + MRD  
  • B: CRLF2-R - JAK mutation and + MRD  
  • C: JAK mutation – CRLF2-R mutation and + MRD  
  • D: Any genetic changes in group A, B, or C + negative MRD |

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Ruxolitinib in Hemophagocytic lymphohistiocytosis (HLH)

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Available from:

- https://clinicaltrials.gov/ct2/show/NCT02723994?term=aall1521&rank=1
Ruxolitinib in murine models with Hemophagocytic lymphohistiocytosis (HLH)

- **Background**
  - Inflammation in HLH is contributed to release of cytokines (INFγ, IL-2, and IL-6)
  - These cytokines stimulate the JAK-STAT pathway
- 2 murine models assessed (primary and secondary HLH)
- Treatment: ruxolitinib 90 mg/kg BID vs. control group
- Ruxolitinib group showed promising results
  - Significantly reduced spleen size, WBC, RBC, Hgb, and Plt
  - Decreased serum cytokine levels and tissue inflammation
  - Enhanced survival

**Case Report: Ruxolitinib for Refractory HLH**

- 11 year old previously healthy boy admitted with HLH
- Standard treatment (dexamethasone and etoposide) initiated
- Clinical deterioration at day 10 → refractory HLH
- Ruxolitinib 2.5 mg BID initiated
- Clinical improvement within 24 hours (extubated within 3 days)
- Etoposide discontinued
- Patient bridged to HSCT
- HLH trigger unknown (genetic mutations negative)

**Poll Question**

A mom is picking up her 3 year old son’s ruxolitinib for treatment of GVHD. The following are important counseling points except:

- A. Handle the medication with appropriate personal protective equipment
- B. Ruxolitinib should be stored at room temperature
- C. Ruxolitinib cannot be mixed with water to make a suspension
- D. Grape juice should be avoided when taking ruxolitinib

**Clinical Pearls**

- Ruxolitinib suspension may be prepared
  - Mix 1 tablet with 40 mL water and stir ~10 minutes
  - Must use within 6 hours
- Dosage forms: 5, 10, 15, 20, and 25 mg tablets
- Consider monitoring lipid panel and performing skin examinations
- Be aware of drug and food (grapefruit juice) interactions
- Gloves should be worn when handling medication

**Conclusions**

- Ruxolitinib shows promising results for utility in ALL, GVHD, and potentially refractory HLH
- Further studies are needed to confirm place in therapy
  - First line therapy for targeted therapies in each indication
  - Long term efficacy and safety needs established
- Pharmacists need to be aware of monitoring parameters and counseling pearls