Ruxolitinib: JAK of all trades

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Disclosures

- I have no relevant financial or nonfinancial relationships to disclose

Objectives

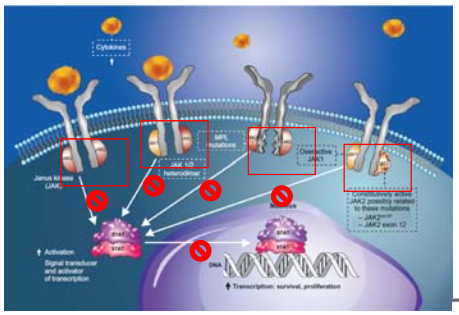
1. Explain the mechanism of action and indications for ruxolitinib
2. Evaluate the literature supporting ruxolitinib use in various indications
3. Formulate a conclusion for the place of ruxolitinib in therapy

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



Mughal, TI, et al. Int J Gen Med. 2014 Jan 29;7:89-101

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

Ruxolitinib. Lexicomp Online, Lexi-Drugs. Hudson, Ohio: Lexicomp, Inc.; 2018; July 5, 2018.
Jakafi (ruxolitinib) [package insert]. Wilmington: Incyte Corporation, DE; 2011.
GVHD: graft vs. 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. Lexicomp Online, Lexi-Drugs. Hudson, Ohio: Lexicomp, Inc.; 2018; July 5, 2018.
Jakafi (ruxolitinib) [package insert]. Wilmington: Incyte Corporation, DE; 2011.

Ruxolitinib Indications

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

Ruxolitinib. Lexicomp Online, Lexi-Drugs. Hudson, Ohio: Lexicomp, Inc.; 2018; July 5, 2018.
Jakafi (ruxolitinib) [package insert]. Wilmington: Incyte Corporation, DE; 2011.

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

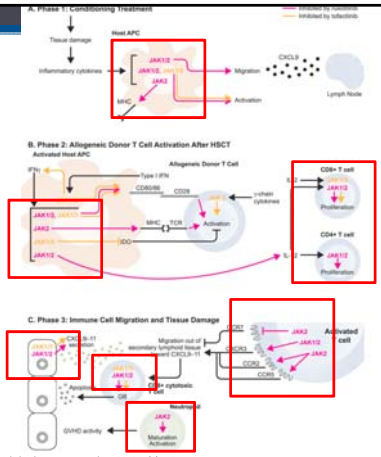
Retrieved from:
https://clinicaltrials.gov/ct2/results?cond=ruxolitinib&Search=Apply&age_v=&age=0&gndr=&type=&rslt=
ETP: early T-cell precursor ALL

Ruxolitinib for pediatric GVHD

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)

Baird K, et al. Pediatr Clin North Am. 2010;57(1):297-322



Schroeder, et al. Biol Blood Marrow Transplant. 2018;24(6):1125-1134.

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

Spoerl S, et al. Blood. 2014; 123(24):3832-32

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

Khandelwal, et al. Biol Blood Marrow Transplant. 2017;23(7):1122-1127.

Ruxolitinib for steroid-refractory acute aGVHD (continued)

Response (n=11)	• Complete response (CR): 1 • Partial response (PR): 4 • No response: 2 • Treatment failures: 4 (1 due to toxicity) • Overall response rate (ORR): 45% • CR: 9%
Toxicities	• ≥ Grade 3 elevated alanine transaminitis: 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

Khandelwal, et al. Biol Blood Marrow Transplant. 2017;23(7):1122-1127.

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

Zeiser, 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

Available from: https://clinicaltrials.gov/ct2/results?cond=ruxolitinib+reach&term=&cntry=&state=&city=&dist=
BusinessWire (21 June 2018). Retrieved from: https://www.businesswire.com/news/home/20180621005159/en/

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

Targetable Lesions in Ph-like ALL

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

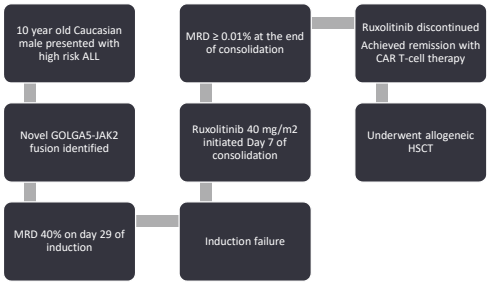
Kinase Gene	Tyrosine Kinase Inhibitor	Fusion Partners	Patients
		number	
ABL1	Dasatinib	6	14
ABL2	Dasatinib	3	7
CSF1R	Dasatinib	1	4
PDGFRB	Dasatinib	4	11
CRLF2	JAK2 inhibitor	2	30
JAK2	JAK2 inhibitor	10	19
EPOR	JAK2 inhibitor	2	9
DGKH	Unknown	1	1
IL7R	JAK1 inhibitor, JAK3 inhibitor, or both	1	1
NTRK3	Crizotinib	1	1
PTK2B	FAK inhibitor	2	1
TSLP	JAK2 inhibitor	1	1
TYK2	TYK2 inhibitor	1	1

Roberts KG, et al. N Engl J Med. 2014;371(11):1005-15.

Phase I study of ruxolitinib in relapsed/refractory solid tumors, leukemias, or myeloproliferative neoplasms: COG Study (ADVL1011)	
Patient Population	Children with solid tumors (n=28) or hematologic malignancies (n=21) Median age: 14.4
Intervention	Ruxolitinib dose escalation 15 mg/m2/dose → 50 mg/m2/dose
Results	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
Conclusion	Recommended dose is 50 mg/m2 PO BID

Loh ML, et al. Pediatr Blood Cancer. 2015;62(10):1717-1724
CPK: creatine phosphokinase
AKI: acute kidney injury

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



- 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

Ding YY, et al. Haematologica. 2018. : haematol.2018.192088; doi:10.3324/haematol.2018.192088

Two current major clinical trials include ruxolitinib with standard leukemia treatment

TOT17

- 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 Lly patients w/o complete response at end of induction

AALL1521

- 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

Available from:
https://clinicaltrials.gov/ct2/show/NCT03117751?term=st.+jude+children%27s+research+hospital+leukemia&draw=2&
https://clinicaltrials.gov/ct2/show/NCT02723994?term=aall1521&rank=1

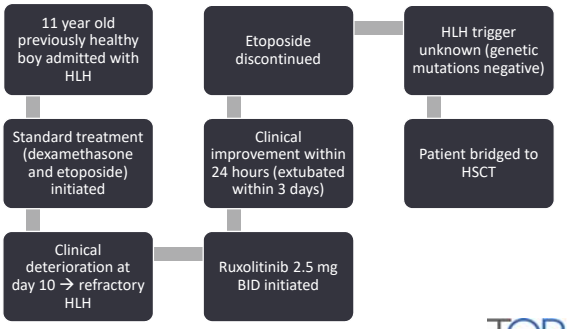
Ruxolitinib in Hemophagocytic lymphohistiocytosis (HLH)

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

Das R, et al. Blood. 2016;127(13):1666-1675.

Case Report: Ruxolitinib for Refractory HLH



Broglie, et al. Blood Adv. 2017;1(19):1533-1536.

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

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Jakafi (ruxolitinib) [package insert]. Wilmington: Incyte Corporation, DE; 2011.

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