Specificities in transplantation in myelofibrosis (Liver Toxicity and splenomegaly)

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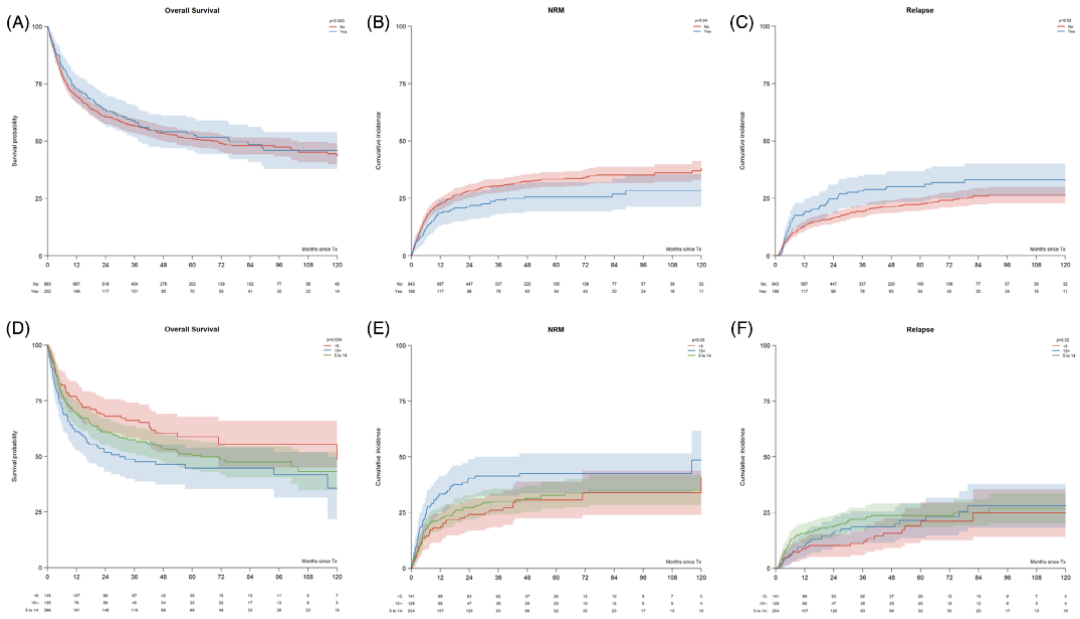
Impact of spleen size and splenectomy on transplant outcomes

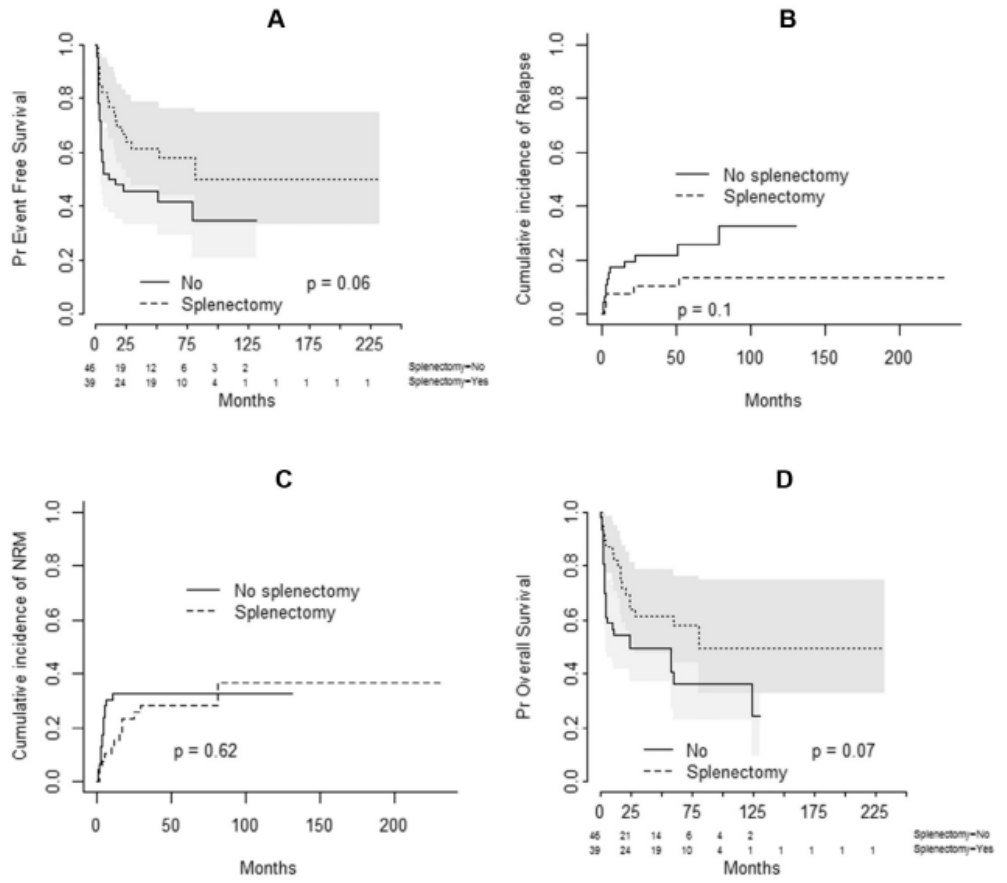
- EBMT
  - 1195 transplants
  - 202 with splenectomy
- Splenectomy
  - Multivariate analysis for splenectomy: lower NRM, increased relapse risk and change is OS
- Subset analysis of splenectomy vs spleen size (>15 cm)
  - Improved OS
  - Reduced NRM
  - No change in relapse risk



Polverelli N et al. Impact of spleen size and splenectomy on outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis: A retrospective analysis by the chronic malignancies working party on behalf of European society for blood and marrow transplantation (EBMT). Am J Hematol. 2021 Jan;96(1):69-79.

Impact of splenectomy in Myelofibrosis before allogeneic SCT

- 85 patients underwent allogeneic SCT for MF
  - 39 patient underwent splenectomy
  - Splenectomy patients had spleens >20cm
- Significant complication rate following splenectomy
  - Thrombosis or haemorrhage
- No difference in NRM, relapse or OS
  - Faster neutrophil recovery



Robin M et al. The Impact of Splenectomy in Myelofibrosis Patients before Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2017 Jun;23(6):958-964.

JAK inhibition prior to allogeneic SCT

Conditioning	N	Spleen Response	Stop of Ruxolitinib	Graft Failure	GVHD II-IV	TRM
MAC/RIC NMA[1]	14	64%	Tapering, off at conditioning	7%	14%	7%
RIC[2]	22	45% (>50%) 24% (<50%)	At conditioning	None	36%	14% (at 14)
RIC[3]	11	72%	Different	None	45%	NR
RIC[4]	23	n = 16; 50%	Tapering, off at conditioning	NR	NR	2 deaths (GVHD)
RIC/MAC[5]	6	NR	Tapering, off at conditioning	None	48%	16%
RIC/MAC[6]	28	NR	Tapering off at conditioning	None	78%	7%

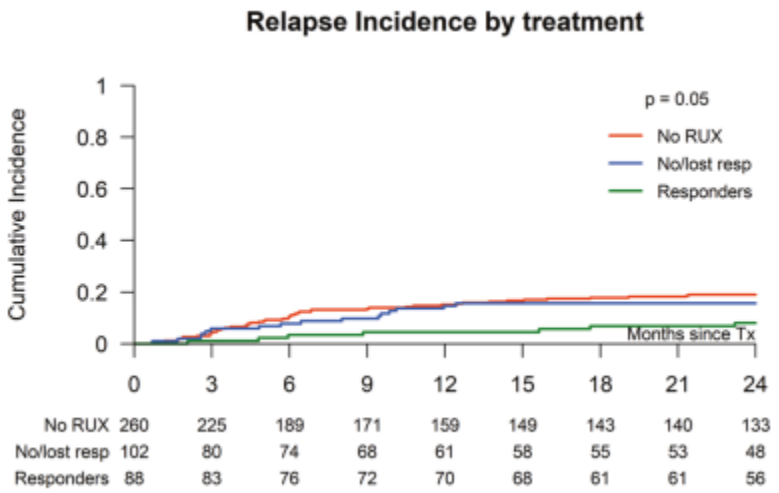
1. Jaekel N et al. *Bone Marrow Transplant*. 2014;49:179-184. 2. Stübig T et al. *Leukemia*. 2014;28:1736-1738. 3. Lebon et al. 55th American Society of Hematology Annual Meeting (ASH 2013). Abstract 2111. 4. Robin M et al. ASH 2013. Abstract 306. 5. Shanavas M et al. *Bone Marrow Transplant*. 2014;49:1162-1169. 6. Salit RB et al. *Bone Marrow Transplant*. 2020;55:70-76.

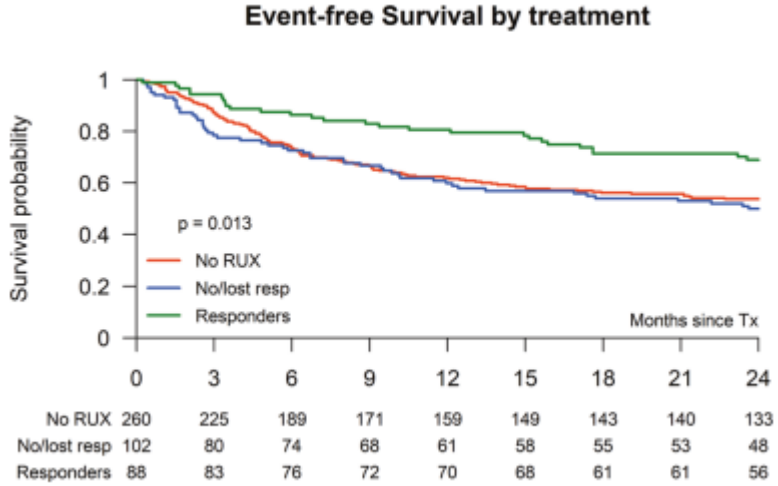
Impact of prior JAK inhibitor therapy with Ruxolitinib on outcome after allogeneic SCT: A study of the CMWP of EBMT

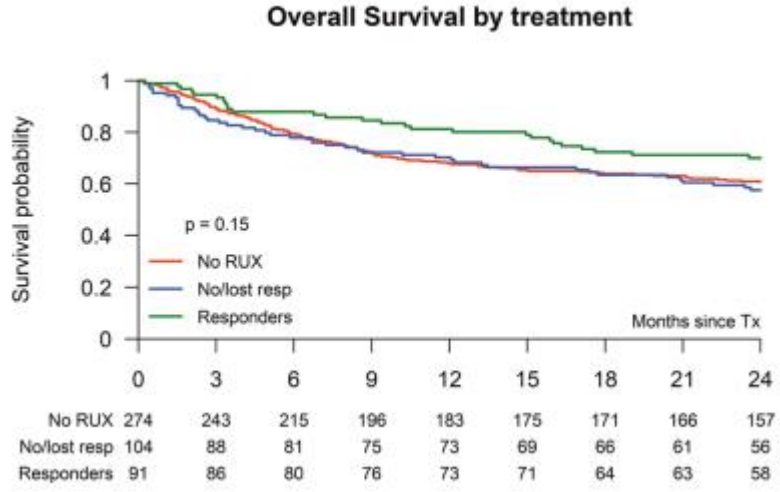
- EBMT registry study
- 586 patients (277 prior Ruxolitinib, 274 no Ruxolitinib)
- Well matched groups
- Higher risk patients and JAK2 mutated more common in Ruxolitinib arm
- Higher numbers of MUDs in prior Ruxolitinib arm
- No difference in GVHD rates
- 23% stopped Ruxolitinib prior to SCT
- 15% of patients in Ruxolitinib arm had >50% reduction in spleen size
- 54% had no spleen response or were losing response pre allograft

Kröger N. Impact of prior JAK-inhibitor therapy with ruxolitinib on outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis: a study of the CMWP of EBMT. Leukemia. 2021 Dec;35(12):3551-3560.

Impact of Ruxolitinib on spleen response determines outcome







Ruxolitinib responders have
- improved OS and EFS
- Relapse incidence is reduced
- lower risk of graft failure 6% (compared to 15% with no response/loss of response to Ruxolitinib)

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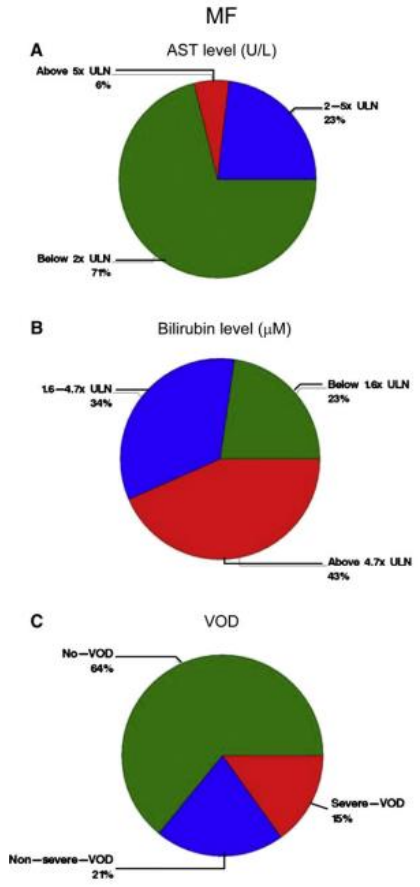
Early Liver toxicity in SCT for Myelofibrosis

- Retrospective analysis of 53 patients transplanted for Myelofibrosis
- Assess liver toxicity
- Control sample of MDS allogeneic SCT

Wong KM. Incidence and risk factors for early hepatotoxicity and its impact on survival in patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012 Oct;18(10):1589-99.ll transplantation. Biol Blood Marrow Transplant. 2012 Oct;18(10):1589-99.

Early hepatotoxicity in Myelofibrosis SCT

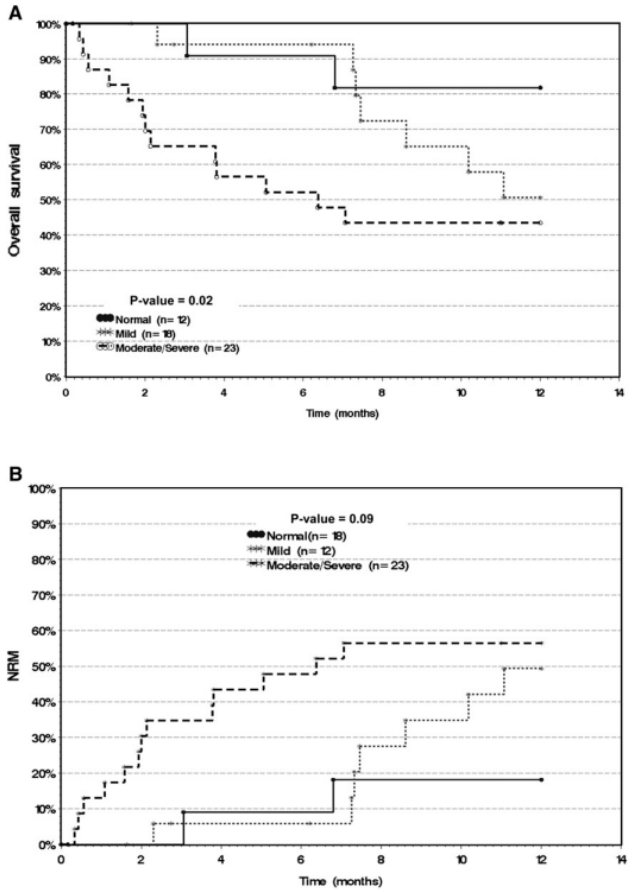
- 79% of patient developed transaminitis or hyperbilirubinaemia
- Rise in AST levels in the 1st 6 weeks
  - 29% patients AST>2 ULN
  - 6% AST >10 ULN
- Bilirubin increase
  - Mild 34%
  - Moderate 40%
  - Severe 4%
- VOD
  - Defined by Baltimore criteria
  - 36% features of VOD



Wong KM et al. Incidence and risk factors for early hepatotoxicity and its impact on survival in patients with myelofibrosis undergoing allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2012 Oct;18(10):1589-99.

Impact of hyperbilirubinemia in 1st 6 weeks on outcomes

- Acute hepatocellular injury with moderate/severe bilirubin associated with inferior survival at 12 months
- Predictors of high bilirubin
  - Portal hypertension
  - Biopsy proven iron overload
  - Splanchnic thrombosis



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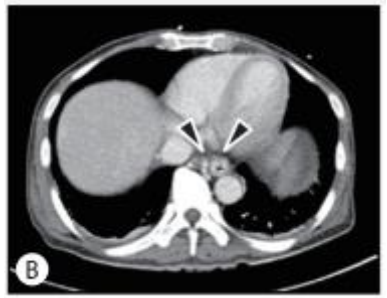
Investigations pre transplant for Liver disease

- Screening MRI to assess liver iron burden
- If significant iron overload
  - Risk assess patient
    - Disease risk
    - Patient comorbidities
    - Presence of other factors asso

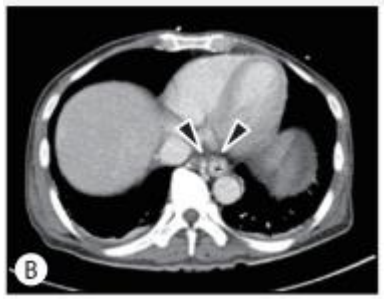


  - Delay transplant and iron chelate
- Consider the type of antifungal agent if severe iron overload

Perram J et al. Innovative strategies to improve hematopoietic stem cell transplant outcomes in myelofibrosis. Am J Hematol. 2022 Nov;97(11):1464-1477.

Portal hypertension in Myelofibrosis

- Portal hypertension reported in upto 18% of patients with MPN
- Studies have identified 3.6% of Myelofibrosis patients have gastro oesophageal varices
- Varices can confer a high risk of bleeding peri/post allogeneic SCT



Investigations pre transplant for suspected portal hypertension

- Screening for portal hypertension and varices
  - Assists in patient eligibility
- CT can detect varices
  - Validity of this method is unknown
- Endoscopic screening in asymptomatic patients is not recommended
  - If bulky spleen then gastroscopy should be considered
- Prophylactic banding is recommended in high-risk cases
- Screen for non-cirrhotic portal hypertension
  - Doppler ultrasound with liver elastography

Perram J et al. Innovative strategies to improve hematopoietic stem cell transplant outcomes in myelofibrosis. Am J Hematol. 2022 Nov;97(11):1464-1477.

Thank you