Outcomes of myelofibrosis patients in The Era of using JAK2 Inhibitor with allogeneic-HSCT at the University of Southern California, a retrospective study

Vincent Louie Mendiola[1], MD, MPH; Krithika Chennapan[2], MD; Denaly Chen[1], MD; Jack Rodman[3], MPH; Abdullah Ladha[1] ,MD; Amir Ali[1] PharmD; Karrune Woan[1], MD, PhD; Eric Tam[1], MD; Preet Chaudhary[1], MD, PhD; George Yaghmour[1], MD
[1]Division of Hematology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA 90033, USA
[2]Department of Internal Medicine, University of Southern California, Los Angeles, CA 90033, USA
[3]Department of Biostatistics Epidemiology Research Design, University of Southern California, Los Angeles, CA 90033, USA

Introduction

- In myelofibrosis (MF) patients, the standard of care curative option is with allogeneic-hematopoietic stem cell transplantation (allo-HSCT) but no clear standard of care pre- and post-allo-HSCT management exists
- Use of JAK inhibitors in pre-transplant MF patients showed serious adverse events from a prospective study (JAK ALLO) with a resulting hypothesis that the abrupt discontinuation of JAK inhibitor prior to HCT and splenectomy may have contributed to this (1). However, several retrospective studies did not observe these serious SAEs, and no harmful effect on early posttransplant outcomes was observed in these studies (2-5)
- Questions then arise such whether use of JAK inhibitors pre- or post-transplant lead to better outcomes
- In addition, further elucidation of patient characteristics/risks/response are needed due to scarcity of data post-transplant
- In this study, we aim to provide further data concerning this field.

Objectives

- **Primary Outcomes:**
  - OS and EFS since transplant, stratified by risk, peri-transplant JAK2 inhibitor, and type of combination of conditioning and associated graft versus host disease prophylaxis (GVHD ppx) used
- **Secondary Outcomes:**
  - Patient/treatment/transplant characteristics, response, survival and GVHD rates

Materials & Methods

- This is a single institution, retrospective study which included patients aged ≥18 years with MF diagnosed in 2012-2020 and received allo-HSCT at our institution
- Distribution of time-to-event end points/outcomes were calculated with Kaplan-Meier (KM) method and OS and EFS reported through KM curves
- Patient demographics, treatment, response, and adverse event characteristics presented with descriptive statistics
- Two-sided p value ≤0.05 was considered significant

Table 1. Patient Characteristics and Risk Category for all Patients (n=21)

Variable	Frequency (%)/ Mean (SD) [min, max]
Age at Transplant	61.1 (9.2) [41, 71]
Gender	
Male	11 (52.4%)
Female	10 (47.6%)
Race/Ethnicity	
White/non-Hispanic	13 (61.9%)
Hispanic	5 (23.8%)
Asian	3 (14.3%)
Black/African American	0
Type of MF	
Primary	15 (71.4%)
Secondary	6 (28.6%)
Type of Secondary MF	
MPN (ET/PCV)	6 (100%)
MDS related	0
Other	0
NA	15
Disease Status at Transplant	
CR/PR	2 (9.5%)
PD	9 (42.9%)
SD	10 (47.6%)
JAK2 v617F Mutation	
No	10 (47.6%)
Yes	11 (52.4%)
Pre-HCT Spleen Size (cm)	20.62 (5.9) [9.3, 29.0]
Pre-Treatment JAK2 Inhibitor	
No	7 (33.3%)
Yes	14 (66.7%)
Any Pre-transplant Cytopenia	
No	0
Yes	21 (100%)
Presence of CALR Mutation	
No	18 (85.7%)
Yes	3 (14.3%)
Presence of MPL Mutation	
No	20 (95.2%)
Yes	1 (4.8%)
Triple Negative Mutation	
No	15 (71.4%)
Yes	6 (28.6%)
Presence of ASXL1, EZH2, SRSF2, IDH1/2, or U2AF1 Mutations	
No	16 (76.2%)
Yes	5 (23.8%)
13q del	
No	17 (81.0%)
Yes	4 (19.0%)
20q del	
No	19 (90.5%)
Yes	2 (9.5%)
Trisomy 8	
No	18 (85.7%)
Yes	3 (14.3%)
Monosomy 7	
No	20 (95.2%)
Yes	1 (4.8%)
Del(20)	
No	20 (95.2%)
Yes	1 (4.8%)
Unfavorable or High-Risk Karyotype/Cytogenetics	
No	19 (90.5%)
Yes	2 (9.5%)
DIPSS Plus Risk Score	
Low risk	0
Intermediate risk #1	3 (14.3%)
Intermediate risk #2	10 (47.6%)
High risk	8 (38.1%)
MIPSS70+ v2.0 Risk Score	
Low risk	0
Intermediate risk	7 (33.3%)
High risk	8 (38.1%)
Very high risk	6 (28.6%)

Table 2. Transplant Characteristics for all Patients (n=21)

Variable	Frequency (%)/ Mean (SD) [min, max]
JAK2 Inhibitor Tapered Pre-transplant	
No	4 (33.3%)
Yes	8 (66.7%)
NA/missing	9
JAK2 Inhibitor Resumed post-transplant	
No	10 (83.3%)
Yes	2 (16.7%)
NA/missing	9
Day Post-transplant Resumed	92.3 (32.6) [71, 130]
Peri-transplant JAK2 Inhibitor Use	
No	8 (42.1%)
Yes	11 (57.9%)
Peri-transplant non-JAK2 Inhibitor Use	
No	11 (57.9%)
Yes	8 (42.1%)
Type of Transplant	
MSD	7 (33.3%)
MUD	8 (38.1%)
Haplo	6 (28.6%)
Conditioning Regimen	
Flu/mel	4 (20.0%)
Flu/mel/TBI	4 (20.0%)
Flu/Cy/atg/Bu400	5 (25.0%)
Flu/Bu	5 (25.0%)
Flu/bu/atg	1 (5.0%)
Flu/TBI	1 (5.0%)
NA/Missing	1
Type of Regimen	
RIC	16 (80.0%)
MAC	4 (20.0%)
NMA	0
NA/missing	1
Stem Cell Source	
PBSC	21 (100%)
BM	0
Umbilical cord	0
GVHD PPX	
Tacro/MTX	11 (55.0%)
Tacro/Cy/MMF	7 (35.0%)
Tacro/Sirolimus	1 (5.0%)
Tacro/MMF	1 (5.0%)
NA/missing	1
Length of Stay after Transplant	47.8 (51.0) [16, 244]
Days to Engraft ANC	16.9 (4.5) [9.0, 28.0]
Days to Engraft PLTs	42.3 (52.8) [3.0, 180.0]
Received MSD+PTCY	
No	19 (95.5%)
Yes	1 (5.0%)
Received MUD+PTCY	
No	18 (90.0%)
Yes	2 (10.0%)
Received HAPLO+PTCY	
No	14 (70.0%)
Yes	6 (30.0%)

Table 3. Adverse Events & GVHD Characteristics for all Patients (n=21)

Variable	Frequency (%)
D+30 days Pancytopenia	
No	2 (9.5%)
Yes	19 (90.5%)
D+6 months Pancytopenia	
No	1 (5.9%)
Yes	16 (94.1%)
NA/missing	4
D+1 year Pancytopenia	
No	6 (42.9%)
Yes	8 (57.1%)
NA/missing	7
Any Infection Post-transplant up to 1-year	
No	13 (61.9%)
Yes	8 (38.1%)
Hepatomegaly after Transplant	
No	11 (68.8%)
Yes	5 (31.2%)
NA/missing	5
Leukemic Transformation Pre-transplant	
No	21 (100%)
Yes	0
Leukemic Transformation Post-transplant	
No	21 (100%)
Yes	0
Blood Transfusion Dependent by D+3 months	
No	8 (40.0%)
Yes	12 (60.0%)
NA/missing	1
Blood Transfusion Dependent by D+6 months	
No	10 (62.5%)
Yes	6 (37.5%)
NA/missing	5
Blood Transfusion Dependent by D+1 year	
No	11 (73.3%)
Yes	4 (26.7%)
NA/missing	6
Any Acute GVHD (pre d+100)	
No	12 (57.1%)
Yes	9 (42.9%)
Type of Acute GVHD	
Skin	2 (25.0%)
GI	1 (12.5%)
Liver	1 (12.5%)
Other	0
Skin & GI	2 (25.0%)
GI & Liver	1 (12.5%)
Skin, GI, & Liver	1 (12.5%)
Any Chronic GVHD (post d+100)	
No	11 (57.9%)
Yes	8 (42.1%)
Type of Chronic GVHD	
Skin	1 (12.5%)
GI	1 (12.5%)
Liver	1 (12.5%)
Other	0
Skin & GI	1 (12.5%)
Skin, GI & Liver	2 (25.0%)
Skin, Liver & Other	1 (12.5%)

Table 4. Response and Outcomes for all Patients (n=21)

Variable	Frequency (%)
Readmitted within 30-days of transplant	
No	14 (82.4%)
Yes	3 (17.7%)
Patient never discharged	4
Splenomegaly D+1-30	
No	1 (33.3%)
Yes	2 (66.7%)
NA/missing	18
Splenomegaly D+30-100	
No	1 (25.0%)
Yes	3 (75.0%)
NA/missing	17
Splenomegaly D+>100	
No	0
Yes	9 (100%)
NA/missing	12
Clinical improvement by 3 months	
No	14 (66.7%)
Yes	7 (33.3%)
Patient Disease Status by 3 months	
CR/PR	1 (5.0%)
Relapsing/PD	2 (10.0%)
SD by d+3 months	13 (65.0%)
Died before 90 days	1 (5.0%)
Failed engraftment	3 (15.0%)
Clinical improvement by 6 months	
No	7 (41.2%)
Yes	10 (58.8%)
NA/missing	4
Patient Disease Status by 6 months	
CR/PR	1 (4.8%)
Relapsing/PD	1 (4.8%)
SD by d+6 months	9 (42.9%)
Died before 6 months	9 (42.9%)
Failed engraftment	1 (4.8%)
Clinical improvement by 12 months	
No	3 (21.4%)
Yes	11 (78.6%)
NA/missing	7
Patient Disease Status by 12 months	
CR/PR	6 (28.6%)
Relapsing/PD	0
SD by d+1 year	2 (9.5%)
Died before 1-year	12 (57.1%)
Failed engraftment	1 (4.8%)
Relapsed/PD anytime post SCT	
No	18 (85.7%)
Yes	3 (14.3%)
Primary Graft Failure anytime post-transplant	
No	5 (62.5%)
Yes	3 (37.5%)
NA/missing	13
Any Death post-transplant	
No	14 (66.7%)
Yes	7 (33.3%)
Alive by 100 days post-transplant	
No	0
Yes	21 (100%)
Alive at 1-year post-transplant	
No	3 (15.8%)
Yes	15 (78.9%)
Lost to follow-up by 1-year	1 (5.3%)

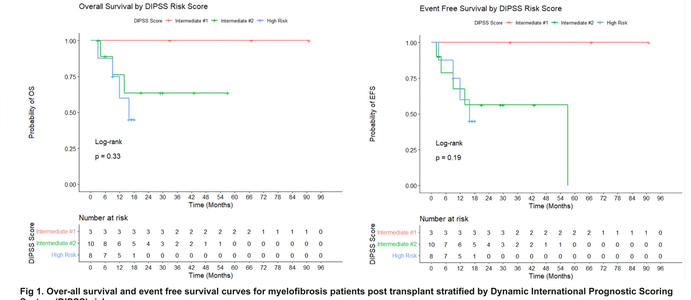


Fig 1. Over-all survival and event free survival curves for myelofibrosis patients post transplant stratified by Dynamic International Prognostic Scoring System (DIPSS) risk score

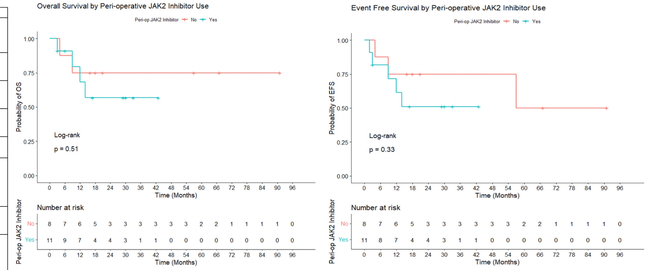


Fig 2. Over-all survival and event free survival curves for myelofibrosis patients post transplant who received a peri-transplant (within 3 months of allo-HSCT) JAK2 inhibitor

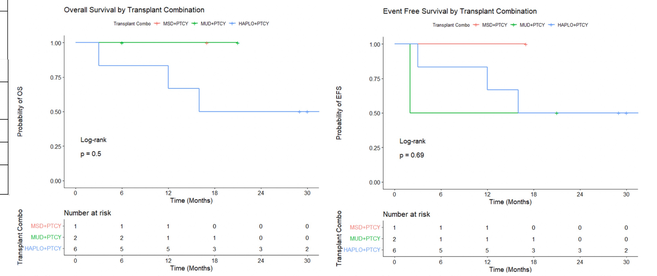


Fig 3. Over-all survival and event free survival curves for myelofibrosis patients post transplant stratified by matched sibling donor (MSD), matched unrelated donor (MUD) and haploidentical (HAPLO) transplant types combined with post-transplant Cytoxan (PTCY)

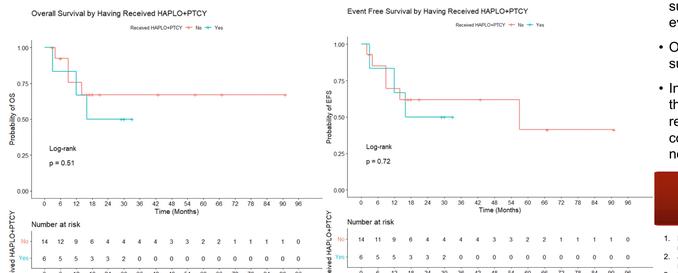


Fig 4. Over-all survival and event free survival curves for myelofibrosis patients stratified by patients who received haploidentical (HAPLO) transplant combined with post-transplant Cytoxan (PTCY) vs those who did not

Results

- 21 MF patients reviewed, median age 61.1 years. 71.4% had primary MF. 38.1% at high risk per DIPSS Plus and 28.6% very high-risk per MIPSS 70+ v2.0. 52.4% had JAK2 V617F mutation, 28.6% triple negative (lacked JAK2/MPL/CALR mutations). 23.8% as having any positivity in either ASXL1, EZH2, SRSF2, IDH1/2 and U2AF1 mutations. Pre-transplant, 100% had pancytopenia requiring transfusions. 9.5% had CR/PR, 42.9% PD and 47.6% SD. 57.9% had any peri-transplant JAK2 inhibitor use (Table 1).
- 33.3% underwent MSD, 38.1% MUD and 28.6% underwent HAPLO allo-HSCT. 80% had RIC. In terms of GVHD ppx, 55% received tacrolimus+ methotrexate, 35% had post-transplant cyclophosphamide (PTCY). 30% underwent HAPLO + PTCY (Table 2).
- Pancytopenia improved, 90.5% d+30 to 57.1% d+365. Transfusion dependency decreased, 60% d+90 to 26.7% d+365. Clinical improvement rates increased, 33.3% d+30 to 78.6% by d+365. CR/PR rates increased, 5% d+90 to 28.6% d+365 (Table 3).
- 14.3% had relapsed/PD, 37.5% had primary graft failure with 33.3% any deaths post allo-HSCT. 42.9% had any acute GVHD pre-d+100, 42.1% had any chronic GVHD post d+100. 100% alive at d+100, 78.9% alive by d+365 (Table 4).
- Since transplant, 3y OS 62.6%, 3y EFS 59.2% with worsening OS/EFS with higher DIPSS (p=0.19-0.33). 3y OS (40%) (p=0.29) and EFS (40%) (p=0.41) in patients with very-high risk per MIPSS 70+ v2.0 (Fig 1).
- With peri-transplant JAK2 inhibitor use, 3y OS was 56.8% vs 75%; 3y EFS was 51.1% vs 75% (p=0.33-0.51) (Fig 2).
- For patients who underwent HAPLO+PTCY GVHD ppx, OS, EFS reached at 16 months while non-HAPLO+ any GVHD ppx did not reach median OS while EFS median was 57 months. 2y OS, EFS was at 50% for those who underwent HAPLO+PTCY vs 67.1% OS and 61.9% EFS if underwent non-HAPLO+ any GVHD ppx (p=0.51-0.72) (Fig 3-4).

Discussion & Conclusion

- Given that most of our patients had high/very high-risk scores, we achieved a good rate of clinical improvement with less transfusion dependency. A good survival rate was also achieved (100% survival at d+100 and 78.9% at 1y). Our 3y OS of 62.6% and 3y EFS of 59.2% is also appreciable even with the rates of GVHD.
- Our data also further supports that having a higher risk score per DIPSS/MIPSS leads to poorer survival.
- Interestingly, there may be no difference in OS/EFS with peri-transplant JAK2 inhibitor use. Also, those who underwent HAPLO+PTCY had their median OS/EFS reached first (16 months vs not reached for OS/ 57 months for EFS) and may portend to a possible lower survival trend compared to those who underwent MSD/MUD + any GVHD ppx combination treatment, though not statistically significant.

References

1. Robin, Marie, Francois, Sylvie et al. . Ruxolitinib before allogeneic hematopoietic stem cell transplantation (HSCT) in patients with myelofibrosis: a preliminary descriptive report of the JAK ALLO study, a phase II trial sponsored by Goelams-FIM in collaboration with the SFgmtc [abstract]. Blood. 2013;122(21). Abstract 306.
2. Jaekel N, Behre G, Behning A, et al. . Allogeneic hematopoietic cell transplantation for myelofibrosis in patients pretreated with the JAK1 and JAK2 inhibitor ruxolitinib. Bone Marrow Transplant. 2014;49(2):179-184.
3. Rondelli D, Goldberg JD, Isola L, et al. . MPD-RC 101 prospective study of reduced-intensity allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis. Blood. 2014;124(7):1183-1191.
4. Shanavas M, Popat U, Michaelis LC, et al. . Outcomes of allogeneic hematopoietic cell transplantation in patients with myelofibrosis with prior exposure to Janus kinase 1/2 inhibitors. Biol Blood Marrow Transplant. 2016;22(3):432-440.
5. Kennedy JA, Atenafu EG, Messner HA, et al. . Treatment outcomes following leukemic transformation in Philadelphia-negative myeloproliferative neoplasms. Blood. 2013;121(14):2725-2733.

Copyright to the Division of Hematology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA 90033, USA