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ORIGINAL ARTICLE

Ruxolitinib therapy is associated with improved renal function in patients with primary myelofibrosis

Paolo Strati[1] · Maen Abdelrahim[2] · Umut Selamet[3] · Valda D. Page[4] · Sherry A. Pierce[5] · Srdan Verstovsek[5] · Ala Abudayyeh[4]

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Abstract

Recent evidence suggests that renal dysfunction may be a direct consequence of primary myelofibrosis (PMF). We performed a retrospective analysis of 100 patients with previously untreated PMF, receiving frontline treatment with single agent ruxolitinib, and compared them to 105 patients, receiving frontline treatment with a non-ruxolitinib-based therapy, matched by age, sex, DIPSS plus, and estimated glomerular filtration rate (eGFR). Use of ruxolitinib associated with a significantly higher rate of renal improvement (RI) $\geq$ 10% (73% vs 50%, $p = 0.01$) confirmed on multivariate analysis (MVA) [odds ratio 3, 95% confidence interval (CI) 1.6–5.5, $p < 0.001$]. After a median follow-up of 41 months (range, 1–159 months), median failure-free survival (FFS) was 14 months (range, 1–117 months). Achievement of a RI $\geq$ 10% maintained its independent association with prolonged FFS on MVA (hazard ratio 1.4, 95% CI 1.1–2, $p = 0.02$). Ruxolitinib can significantly improve renal function in patients with PMF, significantly impacting failure-free survival.

Keywords PMF · Ruxolitinib · Renal function

Introduction

Renal dysfunction is commonly observed in primary myelofibrosis (PMF), being reported in up to 33% of patients [1]. Its etiology is commonly assumed to be secondary to patients' age and comorbidities [2], treatment-associated complications (such as infections and tumor lysis syndrome) [3, 4], or extramedullary hematopoiesis (EMH) causing post-renal obstruction [5–11] and/or renal parenchymal infiltration [12–19].

However, recent evidence shows that the most common cause of renal dysfunction in PMF may be represented by myeloproliferative neoplasms-related glomerulopathy (MPN-RG), an entity characterized by mesangial expansion and hypercellularity, with variable degree of features of chronic thrombotic microangiopathy (TMA) and/or intra-capillary EMH, in the absence of immune-mediated glomerulonephritis [20–22].

To date, the optimal treatment of MPN-RG has not been defined, as kidney biopsies are rarely performed in patients with PMF developing renal dysfunction, frequently limited by the presence of concurrent thrombocytopenia. Case reports have shown that ruxolitinib may significantly improve renal function in patients with PMF diagnosed with MPN-RG [22, 23], but published evidence is limited and sometimes conflicting [24].

We present here a retrospective single-center analysis of 100 patients with PMF receiving frontline ruxolitinib, and compare changes in their renal function to those of 105 patients with PMF receiving frontline non-ruxolitinib-based therapy.

✉ Srdan Verstovsek
sverstov@mdanderson.org

✉ Ala Abudayyeh
aabudayyeh@mdanderson.org

[1] Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[2] Institute of Academic Medicine and Weill Cornell Medical College, Houston Methodist Cancer Center, Houston, TX, USA

[3] Division of Nephrology, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA

[4] Section of Nephrology, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 1468, Houston, TX 77030, USA

[5] Department of Leukemia, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 428, Houston, TX 77030, USA

Methods

Study population

We performed a retrospective analysis of 100 patients with previously untreated PMF followed at MD Anderson Cancer Center (MDACC) who received frontline single agent ruxolitinib between July 2004 and November 2011. A group of 105 patients with PMF, receiving frontline treatment with a non-ruxolitinib-based therapy during the same time range and matched by age, sex, Dynamic International Prognostic Scoring System (DIPSS) plus, and estimated glomerular filtration rate (eGFR), was used as control. PMF was diagnosed according to the 2008 World Health Organization criteria [25], and the DIPSS plus score was assigned to each patient as previously described [26]. Demographic and clinical information at the time of treatment initiation were extracted from the MDACC Enterprise Information Warehouse (EIW) databases. This study was approved by the Institutional Review Board of MDACC and conducted in accordance with our institutional guidelines and the principles of the Declaration of Helsinki.

Renal function

Estimated GFR values were calculated by Modification of Diet in Renal Disease Study (MDRD) equation at baseline and serially during treatment. Renal improvement (RI) was defined as best percentage change in eGFR during treatment as compared to baseline value.

Statistical analysis

Categorical and continuous variables were compared using the $\chi 2$ or Fisher exact tests and the Mann-Whitney test, as appropriate. Logistic regression was used for multivariate analysis (MVA) of categorical variables. Failure-free survival (FFS) was defined as time from treatment initiation to treatment failure or last follow-up. Survival curves were calculated using the Kaplan-

Table 1 Patients' baseline characteristics

Patients ($N = 205$)	Number (%), median [range]		
	Ruxolitinib-treated ($n = 100$)	Non ruxolitinib-treated ($n = 105$)	p value
Demographic characteristics			
Age (years)	65 [40–83]	64 [37–82]	0.91
Males	59 (59)	63 (60)	0.89
Caucasian	94 (94)	95 (90)	0.44
Baseline laboratories			
White blood cells (10^9/L)	18 [3–159]	21 [4–187]	0.30
Peripheral blasts (%)	0 [0–9]	0 [0–8]	0.94
Hemoglobin (g/dL)	10.2 [7.2–16.9]	10.6 [7.5–16]	0.65
Platelet (10^9/L)	273 [13–1195]	291 [25–1205]	0.46
Creatinine (mg/dL)	1 [0.5–2.1]	1 [0.4–1.8]	0.45
eGFR (mL/min/1.73 m^2)	67 [31–175]	70 [38–160]	0.81
Albumin (g/dL)	4.1 [2.4–4.8]	4 [2.6–4.5]	0.41
Myelofibrosis characteristics			
Constitutional symptoms	82 (82)	89 (85)	0.71
Palpable spleen (cm BCM)	19 [0–35]	14 [0–33]	0.16
Palpable liver (cm BCM)	0 [0–30]	0 [0–23]	0.23
Unfavorable cytogenetics	23 (23)	26 (25)	0.87
$JAK2^{V617F}$ allele (%)	61 [0–98]	53 [0–97]	0.17
Bone marrow blasts (%)	1 [0–15]	1 [0–16]	0.76
Transfusion-dependent	24 (24)	26 (25)	0.86
DIPSS Plus			
Low	0 (0)	0 (0)	0.75
Intermediate-1	13 (13)	11 (10)	
Intermediate-2	53 (53)	50 (48)	
High	34 (34)	44 (42)	

eGFR, estimated glomerular filtration rate (eGFR); *BCM*, below the costal margin; *DIPSS*, dynamic international prognostic system score

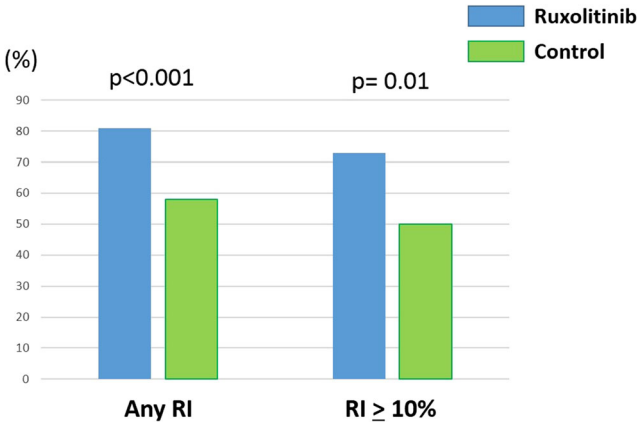

Fig. 1 Renal improvement (RI) in study group compared to a control group matched by age, sex, DIPSS plus, and baseline estimated glomerular filtration rate

Meier method; univariable comparisons were made using the log-rank test, and MVA was performed using Cox regression. All p values were two-sided and considered significant if ≤ 0.05. Statistical analyses were completed using SPSS 21.

Results

Patients' baseline characteristics and renal improvement

The baseline characteristics of 100 patients with previously untreated PMF, receiving frontline single-agent ruxolitinib, and included in the study are shown in Table 1. A group of 105 patients with PMF, matched by age, sex, DIPSS plus, and eGFR, receiving frontline therapy with non-ruxolitinib-based therapy, was used as control; in the control group, regimens included immunomodulatory drugs in 46 patients, small molecule inhibitors in 33, and epigenetic modifiers in 26 patients.

Table 2 Univariate analysis of factors associated with response improvement (RI) ≥ 10%

Patients ($N = 205$)	Number (%), median [range]		
	RI ≥ 10% ($n = 125$)	RI < 10% (80)	p value
Demographic characteristics			
Age (years)	65 [40–83]	68 [48–86]	0.18
Males	75 (60)	47 (59)	0.89
Caucasian	110 (88)	79 (99)	**0.006**
Baseline laboratories			
White blood cells (10^9/L)	13 [1–152]	12 [1–159]	0.93
Peripheral blasts (%)	1 [0–20]	1 [0–15]	0.28
Hemoglobin (g/dL)	9.6 [6–16.9]	9.9 [7.6–26.6]	0.63
Platelet (10^9/L)	232 [10–1600]	210 [11–1350]	0.79
Creatinine (mg/dL)	1 [0.5–2.1]	0.9 [0.5–2.1]	**0.05**
eGFR (mL/min/1.73 m^2)	66 [28–124]	78 [32–175]	**< 0.001**
Albumin (g/dL)	4.1 [2.4–5.1]	4.1 [3.2–4.9]	0.61
Myelofibrosis characteristics			
Constitutional symptoms	108 (86)	63 (79)	0.18
Palpable spleen (cm BCM)	15 [0–30]	12 [0–35]	0.19
Palpable liver (cm BCM)	0 [0–20]	0 [0–30]	0.43
Unfavorable cytogenetics	31 (25)	18 (23)	0.87
$JAK2^{V617F}$ allele (%)	54 [0–98]	45 [0–97]	0.12
Bone marrow blasts (%)	1 [0–17]	2 [0–14]	0.93
Transfusion-dependent	43 (34)	35 (44)	0.19
DIPSS plus			
Low	0 (0)	0 (0)	0.18
Intermediate-1	13 (10)	3 (4)	
Intermediate-2	55 (44)	42 (53)	
High	57 (46)	35 (43)	
Ruxolitinib therapy	73 (58)	27 (34)	**0.001**

Significant p-values are indicated in bold

eGFR, estimated glomerular filtration rate (eGFR); *BCM*, below the costal margin

Eighty-one (81%) patients receiving frontline ruxolitinib had an increase in eGFR while on treatment (as compared to baseline) vs 61 (58%) in the control group ($p < 0.001$) (Fig. 1). A renal improvement (RI) ≥ 10% was achieved in 73 (73%) patients in the ruxolitinib group and 52 (50%) patients in the control group ($p = 0.01$) (Fig. 1), after a median time of 11 and 7 months, respectively ($p = 0.32$). A RI ≥ 25% was achieved in a small population sample (33% and 23%, respectively).

Factors associated with renal improvement ≥ 10%

The association between baseline characteristics (including type of treatment) and achievement of a RI ≥ 10% was evaluated for all the 205 patients included in the study. On univariate analysis (UVA), factors associated with a RI ≥ 10% were non-Caucasian race (99% vs 88%, $p = 0.006$), elevated baseline serum creatinine (1 mg/dL vs 0.9 mg/dL, $p = 0.05$), low baseline eGFR (66 ml/min/1.73 m^2 vs 78 mL/min/1.73 m^2, $p < 0.001$), and use of ruxolitinib (58% vs 34%, $p = 0.001$) (Table 2). On MVA, use of ruxolitinib maintained its independent association with a RI ≥ 10% [odds ratio 3, 95% confidence interval (CI) 1.6–5.5, $p < 0.001$].

Failure-free survival and associated factors

After a median follow-up of 41 months (range, 1–159 months), all 205 patients failed frontline treatment, and median FFS was 14 months (range, 1–117 months). The association between all baseline characteristics (including type of treatment), quality of RI, and FFS was evaluated. Factors associated with prolonged FFS on UVA were intermediate-1 DIPSS plus score as compared to intermediate-2 and high score (53 months vs 24 months and 6 months, $p < 0.001$), use of ruxolitinib (39 months vs 6 months, $p < 0.001$), and achievement of a RI ≥ 10% (24 months vs 8 months, $p = 0.01$) (Fig. 2). Achievement of a RI ≥ 10% maintained its independent association with prolonged FFS on MVA (hazard ratio 1.4, 95% CI 1.1–2, $p = 0.02$).

Discussion

This is the first study showing that ruxolitinib, as compared to other therapies, can significantly improve renal function in patients with PMF, significantly impacting FFS.

In our analysis, RI was significantly more prevalent in patients receiving frontline ruxolitinib, than in patients receiving frontline non-ruxolitinib-based therapy, despite patients in the control group were matched by age, sex, DIPSS plus score and baseline eGFR, and treated during the same time range at the same institution. The association between the use of ruxolitinib and RI was also confirmed on MVA.

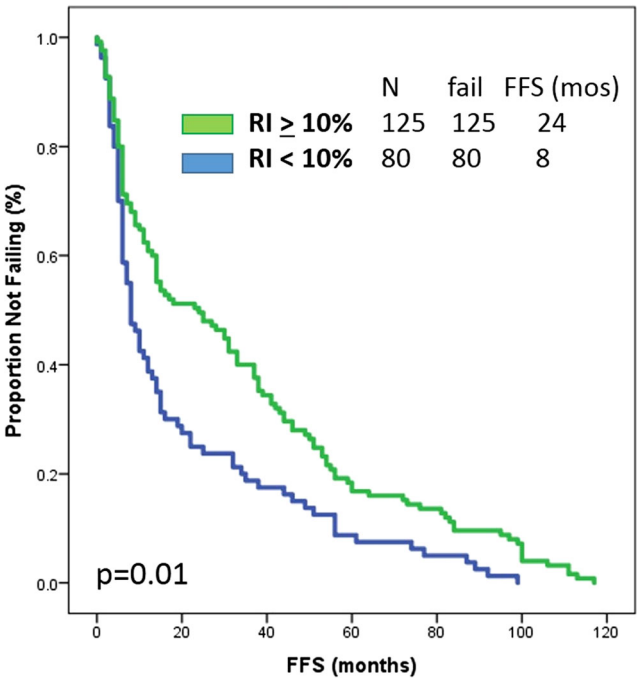

Fig. 2 Association between quality of renal improvement (RI) and failure-free survival (FFS)

Observed results are unlikely to be due to ruxolitinib's intrinsic nephroprotective properties. An open label single-dose study assessing the pharmacokinetics and the pharmacodynamics of ruxolitnib in healthy subjects and subjects with various degree of renal impairment has in fact shown that ruxolitinib is cleared predominantly by hepatic metabolism, with renal excretion being the primary elimination route for its metabolites, with no direct nephrotoxicity neither nephroprotection [27].

It is more likely, then, that the observed renal improvement may have been secondary to the effect exerted by ruxolitinib on the specific etiology of renal dysfunction in this population. Recent data have shown that the most common cause of renal dysfunction in patients with PMF may be represented by MPN-RG, a PMF-induced glomerulopathy, characterized by mesangial expansion and hypercellularity with variable degree of features of chronic TMA [20–22]. While the etiology of MPN-RG remains largely unknown, many of the cytokines typically overproduced by megakaryocytes in patients with PMF [28, 29] have been described as potential drivers of mesangial expansion and proliferation in other disease models [30, 31]. To this regard, ruxolitinib is able to disrupt the production of several cytokines, representing a potential therapeutic strategy for several immune-mediated diseases, including rheumatoid arthritis and graft versus host disease [32, 33], and potentially explaining the higher rate of RI observed in patients with PMF treated with this agent as compared to those treated with alternative molecules in our study. Our findings are supported by case reports and case series, showing also an improvement in renal function in

patients with PMF treated with ruxolitinib [22, 23], along with rebound inflammatory symptoms and worsening renal function in patients who discontinue this agent [34]. This is unique to ruxolitinib in PMF, as other kinase inhibitors have instead shown to favor renal dysfunction in other MPN [35, 36]. To this regard, given the role played by the JAK/STAT pathway in the regulation of glomerular permeability, ruxolitinib has been proposed as a potential treatment also for non-MPN-associated glomerulopathies [37]. We acknowledge a major limit to our study, which is the lack of kidney biopsies providing information about the etiology of renal dysfunction in evaluated patients.

The RI produced by the use of ruxolitinib in our study was mostly represented by an increase in eGFR on treatment $\geq$10% as compared to pre-treatment values, with only a minority of patients enjoying an improvement $\geq$25%. While this may be considered a small change, it significantly associated with prolonged FFS, and it maintained its independent association with FFS even on a MVA, similarly to what observed in other hematological malignancies [38, 39]. We acknowledge another major limit to our analysis, which is the variability of eGFR in patients with PMF, and the heterogeneous timing of serial blood collections for eGFR assessment, due to the retrospective nature of this study.

In conclusion, this is the first study showing that the use of ruxolitinib is associated with improved renal function in patients with PMF. Similarly to what is already done in plasma cell dyscrasia and more recently in chronic lymphocytic leukemia [40, 41], routine kidney biopsies in patients with PMF and unexplained renal dysfunction may shed light on its etiology, and help assess the efficacy on ruxolitinib for the treatment of MPN-RG.

Authorship contributions PS designed the study, analyzed data, and wrote the paper; SV provided clinical care to patients and coauthored the paper; MA and US provided clinical care to patients and coauthored the paper; VDP and SAP collected clinical data and coauthored the paper; AA designed the study, analyzed the data, provided clinical care to patients, and wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Baek SW, Moon JY, Ryu H, Choi YS, Song IC, Lee HJ, Yun HJ, Kim S, Jo DY (2018) Chronic kidney disease in the BCR-ABL1-negative myeloproliferative neoplasm: a single-center retrospective study. Korean J Intern Med 33(4):790–797. https://doi.org/10.3904/kjim.2016.263
2. Newberry KJ, Naqvi K, Nguyen KT, Cardenas-Turanzas M, Florencia Tanaka M, Pierce S, Verstovsek S (2014) Comorbidities predict worse prognosis in patients with primary myelofibrosis. Cancer 120(19):2996–3002. https://doi.org/10.1002/cncr.28857
3. Shimono J, Tsutsumi Y, Ohigashi H (2015) Acute renal tubular damage caused by disseminated Trichosporon infection in primary myelofibrosis. Rinsho Ketsueki 56(1):21–24. https://doi.org/10.11406/rinketsu.56.21
4. Sile S, Wall BM (2001) Acute renal failure secondary to spontaneous acute tumor lysis syndrome in myelofibrosis. Am J Kidney Dis 38(4):E21
5. Tuite MJ, Weiss SL (1991) Ultrasound and computed tomographic appearance of extramedullary hematopoiesis encasing the renal pelvis. J Clin Ultrasound 19(4):238–240
6. Oesterling JE, Keating JP, Leroy AJ, Earle JD, Farrow GM, McCarthy JT, Silverstein MN (1992) Idiopathic myelofibrosis with myeloid metaplasia involving the renal pelves, ureters and bladder. J Urol 147(5):1360–1362
7. Gryspeerdt S, Oyen R, Van Hoe L, Baert AL, Boogaerts M (1995) Extramedullary hematopoiesis encasing the pelvicalyceal system: CT findings. Ann Hematol 71(1):53–56
8. La Fianza A, Torretta L, Spinazzola A (2005) Extramedullary hematopoiesis in chronic myelofibrosis encasing the pelvicaliceal system and perirenal spaces: CT findings. Urol Int 75(3):281–284. https://doi.org/10.1159/000087809
9. Cvetkovic ZP, Cvetkovic BR, Celeketic D, Milenkovic D, Perunicic-Pekovic G (2010) Bilateral ureteral obstruction due to primary myelofibrosis caused hyperuricaemia. Acta Chir Iugosl 57(2):79–83
10. Ganguli A, Chalokia RS, Kaur BJ (2016) Obstructive Uropathy as an initial presentation of primary myelofibrosis: case report and review of literature. Indian J Hematol Blood Transfus 32(Suppl 1):117–120. https://doi.org/10.1007/s12288-016-0679-6
11. Imai K, Aoi T, Kitai H, Endo N, Fujino M, Ichida S (2017) A case of perirenal extramedullary hematopoiesis in a patient with primary myelofibrosis. CEN Case Rep 6(2):194–199. https://doi.org/10.1007/s13730-017-0274-1
12. Panda A, Chandrashekhara SH, Nambirajan A, Mishra P (2016, 2016) Idiopathic myelofibrosis with disseminated hepatosplenic, mesenteric, renal and pulmonary extramedullary haematopoeisis, portal hypertension and tuberculosis: initial presentation and 2 years follow-up. BMJ Case Rep. https://doi.org/10.1136/bcr-2016-217854
13. Chen G, Ali R, Shuldberg MM, Bastani B, Brink DS (2013) Extramedullary hematopoiesis in renal allograft. Clin Kidney J 6(5):491–494. https://doi.org/10.1093/ckj/sft101
14. Sukov WR, Remstein ED, Nascimento AG, Sethi S, Lewin M (2009) Sclerosing extramedullary hematopoietic tumor: emphasis on diagnosis by renal biopsy. Ann Diagn Pathol 13(2):127–131. https://doi.org/10.1016/j.anndiagpath.2007.12.003
15. Semple D, Kingdon E, Holt S (2004) Dialysis independence following radiotherapy of renal extramedullary haemopoeisis. Nephrol Dial Transplant 19(5):1310–1312. https://doi.org/10.1093/ndt/gfh049
16. Remstein ED, Kurtin PJ, Nascimento AG (2000) Sclerosing extramedullary hematopoietic tumor in chronic myeloproliferative disorders. Am J Surg Pathol 24(1):51–55
17. Schnuelle P, Waldherr R, Lehmann KJ, Woenckhaus J, Back W, Niemir Z, van der Woude FJ (1999) Idiopathic myelofibrosis with extramedullary hematopoiesis in the kidneys. Clin Nephrol 52(4):256–262
18. Xiao JC, Walz-Mattmuller R, Ruck P, Horny HP, Kaiserling E (1997) Renal involvement in myeloproliferative and lymphoproliferative disorders. A study of autopsy cases. Gen Diagn Pathol 142(3–4):147–153
19. Holt SG, Field P, Carmichael P, Mehta A, Jarmulowicz M, Clarke D, Hilson A, Burns A (1995) Extramedullary haematopoeisis in the

renal parenchyma as a cause of acute renal failure in myelofibrosis. Nephrol Dial Transplant 10(8):1438–1440
20. Said SM, Leung N, Sethi S, Cornell LD, Fidler ME, Grande JP, Herrmann S, Tefferi A, D'Agati VD, Nasr SH (2011) Myeloproliferative neoplasms cause glomerulopathy. Kidney Int 80(7):753–759. https://doi.org/10.1038/ki.2011.147
21. Alexander MP, Nasr SH, Kurtin PJ, Casey ET, Hernandez LP, Fidler ME, Sethi S, Cornell LD (2015) Renal extramedullary hematopoiesis: interstitial and glomerular pathology. Mod Pathol 28(12):1574–1583. https://doi.org/10.1038/modpathol.2015.117
22. Strati P, Glass WF, Abdelrahim M, Selamet U, Tchakarov A, Workeneh BT, Verstovsek S, Abudayyeh A (2018) Renal complications of primary myelofibrosis. Leuk Lymphoma 60:1–4. https://doi.org/10.1080/10428194.2018.1474525
23. Rajasekaran A, Ngo TT, Abdelrahim M, Glass W, Podoll A, Verstovsek S, Abudayyeh A (2015) Primary myelofibrosis associated glomerulopathy: significant improvement after therapy with ruxolitinib. BMC Nephrol 16:121. https://doi.org/10.1186/s12882-015-0121-6
24. Del Sordo R, Brugnano R, Covarelli C, Fiorucci G, Falzetti F, Barbatelli G, Nunzi E, Sidoni A (2017) Nephrotic syndrome in primary myelofibrosis with renal extramedullary hematopoiesis and glomerulopathy in the JAK inhibitor era. Clin Nephrol Case Stud 5:70–77. https://doi.org/10.5414/CNCS109100
25. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, Harris NL, Le Beau MM, Hellstrom-Lindberg E, Tefferi A, Bloomfield CD (2009) The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 114(5):937–951. https://doi.org/10.1182/blood-2009-03-209262
26. Gangat N, Caramazza D, Vaidya R, George G, Begna K, Schwager S, Van Dyke D, Hanson C, Wu W, Pardanani A, Cervantes F, Passamonti F, Tefferi A (2011) DIPSS plus: a refined dynamic international prognostic scoring system for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol 29(4):392–397. https://doi.org/10.1200/JCO.2010.32.2446
27. Chen X, Shi JG, Emm T, Scherle PA, McGee RF, Lo Y, Landman RR, Punwani NG, Williams WV, Yeleswaram S (2014) Pharmacokinetics and pharmacodynamics of orally administered ruxolitinib (INCB018424 phosphate) in renal and hepatic impairment patients. Clin Pharmacol Drug Dev 3(1):34–42. https://doi.org/10.1002/cpdd.77
28. Martyre MC, Magdelenat H, Bryckaert MC, Laine-Bidron C, Calvo F (1991) Increased intraplatelet levels of platelet-derived growth factor and transforming growth factor-beta in patients with myelofibrosis with myeloid metaplasia. Br J Haematol 77(1):80–86
29. Martyre MC (1995) TGF-beta and megakaryocytes in the pathogenesis of myelofibrosis in myeloproliferative disorders. Leuk Lymphoma 20(1–2):39–44. https://doi.org/10.3109/10428199509054751
30. Iida H, Seifert R, Alpers CE, Gronwald RG, Phillips PE, Pritzl P, Gordon K, Gown AM, Ross R, Bowen-Pope DF et al (1991) Platelet-derived growth factor (PDGF) and PDGF receptor are induced in mesangial proliferative nephritis in the rat. Proc Natl Acad Sci U S A 88(15):6560–6564
31. Jiang T, Che Q, Lin Y, Li H, Zhang N (2006) Aldose reductase regulates TGF-beta1-induced production of fibronectin and type IV collagen in cultured rat mesangial cells. Nephrology (Carlton) 11(2):105–112. https://doi.org/10.1111/j.1440-1797.2006.00553.x
32. Kontzias A, Laurence A, Gadina M, O'Shea JJ (2012) Kinase inhibitors in the treatment of immune-mediated disease. F1000 Med Rep 4:5. https://doi.org/10.3410/M4-5
33. Zeiser R, Burchert A, Lengerke C, Verbeek M, Maas-Bauer K, Metzelder SK, Spoerl S, Ditschkowski M, Ecsedi M, Sockel K, Ayuk F, Ajib S, de Fontbrune FS, Na IK, Penter L, Holtick U, Wolf D, Schuler E, Meyer E, Apostolova P, Bertz H, Marks R, Lubbert M, Wasch R, Scheid C, Stolzel F, Ordemann R, Bug G, Kobbe G, Negrin R, Brune M, Spyridonidis A, Schmitt-Graff A, van der Velden W, Huls G, Mielke S, Grigoleit GU, Kuball J, Flynn R, Ihorst G, Du J, Blazar BR, Arnold R, Kroger N, Passweg J, Halter J, Socie G, Beelen D, Peschel C, Neubauer A, Finke J, Duyster J, von Bubnoff N (2015) Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey. Leukemia 29(10):2062–2068. https://doi.org/10.1038/leu.2015.212
34. Tefferi A, Pardanani A (2011) Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc 86(12):1188–1191. https://doi.org/10.4065/mcp.2011.0518
35. Yilmaz M, Lahoti A, O'Brien S, Nogueras-Gonzalez GM, Burger J, Ferrajoli A, Borthakur G, Ravandi F, Pierce S, Jabbour E, Kantarjian H, Cortes JE (2015) Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. Cancer 121(21):3894–3904. https://doi.org/10.1002/cncr.29587
36. Molica M, Scalzulli E, Colafigli G, Fegatelli DA, Massaro F, Latagliata R, Foa R, Breccia M (2018) Changes in estimated glomerular filtration rate in chronic myeloid leukemia patients treated front line with available TKIs and correlation with cardiovascular events. Ann Hematol 97(10):1803–1808. https://doi.org/10.1007/s00277-018-3375-9
37. Savin VJ, Sharma M, Zhou J, Genochi D, Sharma R, Srivastava T, Ilahe A, Budhiraja P, Gupta A, McCarthy ET (2017) Multiple targets for novel therapy of FSGS associated with circulating permeability factor. Biomed Res Int 2017:6232616. https://doi.org/10.1155/2017/6232616
38. Strati P, Chaffee KG, Achenbach SJ, Slager SL, Leung N, Call TG, Ding W, Parikh SA, Kay NE, Shanafelt TD (2017) Renal insufficiency is an independent prognostic factor in patients with chronic lymphocytic leukemia. Haematologica 102(1):e22–e25. https://doi.org/10.3324/haematol.2016.150706
39. Gonsalves WI, Leung N, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Dingli D, Kapoor P, Go RS, Lin Y, Russell SJ, Lust JA, Zeldenrust S, Kyle RA, Gertz MA, Kumar SK (2015) Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma. Blood Cancer J 5:e296. https://doi.org/10.1038/bcj.2015.20
40. Fermand JP, Bridoux F, Kyle RA, Kastritis E, Weiss BM, Cook MA, Drayson MT, Dispenzieri A, Leung N, International K, Monoclonal Gammopathy Research G (2013) How I treat monoclonal gammopathy of renal significance (MGRS). Blood 122 (22): 3583–3590. doi:https://doi.org/10.1182/blood-2013-05-495929, 2013
41. Strati P, Nasr SH, Leung N, Hanson CA, Chaffee KG, Schwager SM, Achenbach SJ, Call TG, Parikh SA, Ding W, Kay NE, Shanafelt TD (2015) Renal complications in chronic lymphocytic leukemia and monoclonal B-cell lymphocytosis: the Mayo Clinic experience. Haematologica 100(9):1180–1188. https://doi.org/10.3324/haematol.2015.128793