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Treatment approaches to polycythemia vera and myelofibrosis.

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Abstract

Myeloproliferative neoplasms consist of a diverse group of disorders. Over the last 10 years, with better understanding of pathophysiology of these disorders, there are many more treatment options available to patients with these diseases. Further, improved understanding of the underlying genetic landscape has led to improved prognostication which helps identify appropriate therapeutic options. For polycythemia vera, initial therapy generally includes aspirin and phlebotomy. However, in patients who do not achieve an appropriate response to phlebotomy, hydroxyurea or ruxolitinib can be considered. In patients who have myelofibrosis, therapy is determined by symptom burden. In patients who have significant constitutional symptoms, a JAK inhibitor, such as ruxolitinib is an appropriate choice. There are many novel therapies under investigation for patients with myelofibrosis, including anti-fibrotic agents, novel JAK inhibitors, telomerase inhibitors and allogeneic stem cell transplant.

KEYWORDS: polycythemia vera; myelofibrosis; treatment

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Enfoques terapéuticos de policitemia vera y mielofibrosis

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Resumen

Las neoplasias mieloproliferativas consisten en un diverso grupo de enfermedades. En los últimos 10 años, con mejor comprensión de estas enfermedades, hay mas opciones de tratamiento disponibles para los pacientes que las padecen. Además, el mejor entendimiento del panorama genético detrás de estas enfermedades ha contribuido a mejorar el pronóstico, lo que ayuda a identificar las opciones terapéuticas adecuadas. El tratamiento inicial de la policitemia vera generalmente incluye aspirina y flebotomía. Sin embargo, en pacientes que no tienen respuesta adecuada a la flebotomía, puede considerarse la administración de hidroxiurea o ruxolitinib. En pacientes con mielofibrosis, el tratamiento está determinado de acuerdo con la magnitud de los síntomas. En pacientes con síntomas constitucionales significativos, un inhibidor de JAK, como ruxolitinib, es la opción adecuada. Hay muchos tratamientos nuevos en investigación para pacientes con mielofibrosis, que incluyen agentes antifibróticos, nuevos inhibidores de JAK, inhibidores de telomerasa y trasplantes alogénicos de células progenitoras.

PALABRAS CLAVE: policitemia vera, mielofibrosis, tratamiento.

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BACKGROUND

Myeloproliferative neoplasms are a diverse group of myeloid disorders characterized by a either a high production of blood cells, or excessive fibrosis leading to multiple complications. In polycythemia vera (PV), excessive production of red blood cells is noted. These patients often experience bone pain, itching, and complications related to increased blood volume such as headache, shortness of breath, and leg cramping. Disease manifestations of patients with myelofibrosis (MF) include significant scar tissue and fibrosis in the bone marrow, enlarged spleen and/or liver from extramedullary hematopoiesis, and may include significant constitutional symptoms such as bone pain, night sweats, pruritis, and cachexia. MF can present de novo, and it is considered idiopathic myelofibrosis, or secondary to PV or essential thrombocytosis.

These disorders provide substantial challenges to hematologists as the patients may often have a significant symptom burden. Historically, there were limited options with regards to treatment, but in the last ten years, there has been progression in the understanding of the diseases, and more potential treatment strategies available for symptom relief.

Genetics and molecular studies

The identification of Janus-activated kinase 2 (JAK 2) mutations in myeloproliferative neoplasms provided insight into the biology of the disease. JAK2 V617F[1-4] were initially identified in PV, essential thrombocythemia (ET) and MF patients. Not only did this provide a diagnostic test, but also shed light on the biology of the disease. This mutation constitutively activates the JAK2 tyrosine kinase, which results in downstream signaling through STAT, Ras–MAPK, and phosphatidylinositol-3′-kinase (PI3K)–AKT pathways. These signaling pathways converge at the nucleus and regulate gene expression.[5] Overtime, the continuous activation of these pathways result in oncogenesis, and the phenotype of the disease.

Since then, the field has grown rapidly and many more mutations have been identified. Shortly after the JAK2V617F mutation, myeloproliferative leukemia virus oncogene (MPLW515L) was described[6,7] followed by JAK exon 12.[8,9] It was several years after that calretuculin (CALR) mutation was described.[10] The majority of patients with PV carry the JAK2V617F mutation. Presence of a driving mutation is present in 90% of patients with PMF.[11] (11) As well as providing information about the biology of the disease, the presence of any one of these mutations, or absence of mutations also provides prognostic information.[11]

A current interest in the field is to understand other underlying mutations that may predict response to different agents,[12] progression to leukemia and survival (Table 1).[13] These genetic mutations are detected through next generation sequencing, which allows for examination of multiple different genetic mutations. Mutations in genes such as *ASXL1, EZH2, SRSF2* or *IDH1/2* have been found important predictors of outcome in several studies (Table 1).

Treatment options for polycythemia vera

When choosing therapy for patients with PV, it is important to consider the fact that some of these patients will experience a survival similar to that of the general population.[14] Treatment strategies should be aimed at lowering the risk for thrombotic events and mitigation of symptoms.[15,16] Initial therapy should be aimed at reduction of the hematocrit to less than 45%[17] and initiation of aspirin 81 mg daily in patients with no other contraindication.[16,18] However, many patients are unable to achieve satisfactory disease control with this regimen, characterized by persistent leukocytosis, thrombocytosis, splenomegaly,

Table 1. Genetic mutations in myeloproliferative neoplasms

Author	Mutation	Results	Misc
Non driver mutations			
Tefferi et al. 2014[60]	CAL-R ASXL-1	Survival: CAL-R+/*ASXL1*-: Median survival 20 y CAL-R-/*ASXL1*+ or CAL-R+/ASXL1-: 9 y CALR-/*ASXL1*+: 4 y	Predictive value independent of DIPSS score
Guglielmelli et al 2014[27]	*ASXL1* *EZH2* *SRSF2* *IDH1/2*	In MVA: presence of 2 or more mutations increased risk of transformation to acute leukemia and death	
Vannucchi et al 2013[13]	*ASXL1* *EZH2* *SRSF2* *IDH1/2*	Two cohorts: Mayo cohort: *ASXL1, SRSF2* or *IDH1* detrimental for survival European cohort: *ASXL1, SRSF2* and *EZH2* detrimental for survival	*ASXL1* predictive value independent of DIPSS
Driver mutations			
Tefferi et al[26]	JAK2 MPL CALR	CALR mutation: median survival 15.9y MPL mutation: median survival 9.9y JAK-2 mutation: median survival 5.9 y Triple negative: median survival 2.3y	
Rumi et al.[25]	JAK2 MPL CALR	CALR mutation: median survival 17y MPL mutation: median survival 9.1y JAK-2 mutation: median survival 9.2 y Triple negative: median survival 3.2y	

or need for frequent phlebotomy. In such situations, alternative therapies such as hydroxyurea, pegylated interferon alpha-2a, and ruxolitinib can be considered (Figure 1).[15,16]

Hydroxyurea

Hydroxyurea (HU) is a widely excepted treatment for symptomatic PV. Response to therapy is seen in a high proportion of patients. In a large study in Spain, a 90% overall response rate was noted in patients treated with HU, 24% complete response, and 66% partial response.[19] (19) The side effects are minimal and generally controlled by dose adjustment, and the data supporting the leukemogenic potential of HU are limited.

Interferon-alpha 2α

The use of pegylated interferon alpha 2a (PEG-IFNα) has shown both hematologic responses as well as molecular responses in patients with PV. PEG-IFN_ achieved a hematologic response rate of 76%-100% of patients treated,[12,20,21] of the patients with a median follow up of 31- 42 mo.[12,20,21] The overall response rate was 60%[12]-72%[21] with 18%[12]-24%[21] achieving a complete molecular response. The most common toxicities included neutropenia, infection, elevated LFTs, diarrhea, depression, and musculoskeletal complaints. There were very few grade 3 or greater toxicities reported, and up to 92% of the patients were able to tolerate the medication for at least 12 months.[21]

Ruxolitinib

Ruxolitinib (RUX) is an attractive therapeutic option for myeloproliferative neoplasms. Initially this medication was tested extensively in patients with MF, however, there is now data for its use in PV. The RESPONSE trial enrolled patients who

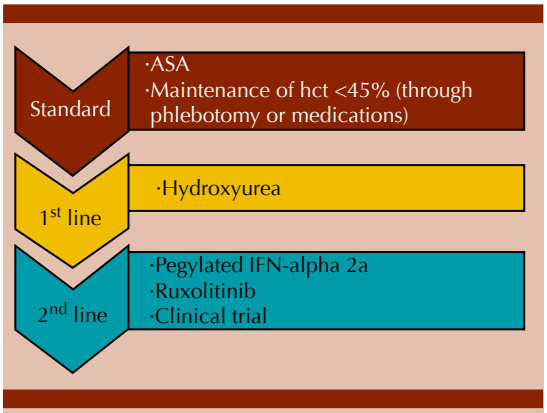

Figure 1. Treatment options for PV.

were not adequately controlled or not tolerant of HU to receive RUX versus best available care, which could include phlebotomy, lower doses of HU, interferon or PEG-IFNα, pipobroman, anagrelide or immunomodulatory agents such as lenolidomide or thalidomide.[22] The primary endpoints included hematocrit control, and reduction of spleen size by at least 35%, secondary endpoints included quality of life measures. Crossover was allowed at 32 weeks if both primary endpoints were not met. More patients in the RUX arm *vs* BAT arm achieved the composite primary endpoint (21% *vs* 0.9%, p<0.001), higher proportion of patients in RUX arm had hematocrit control (60% *vs* 20%), and a 35% reduction in spleen size (38% *vs* 0.9%).[22] More patients in the RUX arm (49% *vs* 5%) had greater than 50% reduction in their symptoms burden as measured by MPN-SAF total symptom score.[22]

Myelofibrosis

MF is classified as either primary myelofibrosis (PMF), post-PV (PPV-MF) or post-ET myelofibrosis (PET-MF). The median survival at diagnosis of MF is 10 years, but varies greatly depending on the disease characteristics. The only curative therapy is allogeneic stem cell transplant, but there are many other symptomatic therapies that improve symptoms and may prolong survival.

Prognosis

Prognosis of MF varies greatly. There have been several predictors of survival. Dynamic International Prognostic Scoring System (DIPSS) determines the prognosis based on the presence of absence of five risk factors, including: age greater than 65 (1 point), hemoglobin of less than 10g/dL (2 points), constitutional symptoms (1 point), white blood cell count of greater than 25 (1 point) and a blast percentage of greater than 1% (1 point). A score of 0 denotes low risk, 1-2 intermediate 1 risk, 3-4 intermediate 2 risk, and 5-6 high risk. Survivals of low, intermediate-1, intermediate-2 and high risk MF are 15.4, 6.5, 2.9, and 1.3 years respectively.[23] Other indicators of higher risk disease include platelets of less than 100, transfusion dependence, and poor risk cytogenetics characterized by a complex karyotype or any sole or two abnormalities including +8, -7/7q-, -5/5q-, inv(3), i(17q), 12p-, 11q23 rearrangement.[24]

The driver mutation present may also define prognosis. Two studies have evaluated the implication of the specific driver mutation present on survival.[25,26] CAL-R mutation as a favorable prognostic indicator, with median survival in the range of 15-17 years. JAK-2 and MPL mutations confer a median survival of 5-9 years.[25,26] Patients who do not harbor any of the driver mutations appear to have the worse prognosis, with a median survival of 2-3 years.[25,26]

Prognosis can be further defined by evaluating genetic mutations using next generation sequencing. That allows analysis of many genes on one platform. Using this, several other genes have been identified as carrying a poor prognosis in patients with MF.[27] In one study, using both a test cohort and validation cohort, identified the following genes as carrying a higher risk: *ASXL1,*

EZH2, SRSF2 or *IDH1/2*. Survival was clearly better in those patients having none of these mutations, and became progressively worse with either one, or two or greater mutations.[27] These mutations also may help predict outcomes following transplant, in that worse outcomes following transplant are seen in patients carrying more poor prognostic genetic mutations.[28]

Ruxolitinib

Ruxolitinib (RUX) is a potent JAK1/2 inhibitor that was approved in 2012 for use in MF after it was shown to rapidly reduce spleen size and provide a marked improvement in quality of life in two phase III clinical trials: **CO**ntrolled **M**yelo**F**ibrosis Study with **OR**al JAK Inhibitor **T**herapy (COMFORT)-I (www.clinicaltrials.gov NCT00952289) and COMFORT-II (www.clinicaltrials.gov NCT00934544).

The COMFORT-I study, which was done in America, Canada and Australia, compared RUX therapy with placebo.[29] This study enrolled 309 patients with INT-2 or high risk DIPSS, the median spleen volume was 2500 cm^3. At 24 weeks, 41.9% of patients in the RUX arm had a spleen reduction of >35% as compared to the placebo arm (0.7%). They also had an improvement in the MF-SAF. This response was not dependent on presence of JAK2 mutation. The most common adverse events included anemia and thrombocytopenia. The COMFORT-II study, which was done in Europe, compared RUX with best available therapy (BAT).[30] In this study, 219 patients were enrolled, 146 received RUX and 73 received BAT. At 24 weeks, 32% of patients in the RUX arm had a spleen reduction of >35% as compared to none in the BAT arm. Additionally, improved quality of life was noted in the RUX arm. As in the COMFORT-I study, the most common adverse events were anemia and thrombocytopenia. Neither of these studies demonstrated an overall survival benefit, however, it is important to note that patients were eligible for crossover. Further, as the drug was approved shortly after publication of the studies, many patients who were not on the study drug were able to obtain it. However, there was an analysis done on patients who had received the RUX in early phase I/II studies, compared to a matched historical cohort, which demonstrated a survival advantage in those patients who experienced reduction in spleen size of >50%.[31,32] With longer follow up, this beneficial effect of RUX appears to be durable, with 51% maintaining their spleen response at 3 years, and 48% at 5 years.[33] Despite the crossover design, intention to treat analysis demonstrated that median survival in the BAT arm was 4.1 years, and the median survival of the RUX arm has not yet been reached with a median follow up of 4.3 years.[33] The median response or RUX is 3.2 years.[33]

Pacritinib

The use of RUX in MF is limited by cytopenias. It currently is only approved for patients whose platelets are greater than 50. Pacritinib is a novel JAK2/FLT-3 inihibitor that appears to be better tolerated in patients with cytopenias. The PERSIST-1 study enrolled patients with intermediate or high risk disease and a palpable spleen ≥5 cm.[34] Patients are randomized in a 2:1 ratio to either pacritinib 400 mg daily *vs* BAT. Endpoints are similar to those in the COMFORT studies, symptom management and reduction in spleen size at 24 weeks. In the intention to treat analysis, response was observed in 19.1% in the pacritinib arm versus 4.7% in the BAT arm (p=0.0003).[34] Currently, PERSIST 2 is underway which evaluates the use of pacritinib in patients whose platelets are consistently less than 100,000.

Other JAK inhibitors

The only JAK inhibitor currently FDA approved is RUX. Pacritinib is very close to approval, and

in phase III studies, but not yet approved. Momelotinib is another JAK inhibitor that is in phase III trials. Momelotinib has the advantage of being less suppressive on erythropoiesis, so being better tolerated in patients with anemia. In a phase I/II study, patients experienced improvement in their anemia (53%), reduction in spleen size (39%) and reduction in constitutional symptoms (>50%).[35] However, a significant treatment induced peripheral neuropathy has been described in patients receiving this medication.[36] Other JAK inhibitors that are currently in phase II studies include NS-018 and INCB039110.

Ruxolitinib combinations

RUX has also been tested in combination with other agents designed to mitigate the toxicities and improve efficacy. Such combinations include danazol,[37] pomolidomide,[38] LDE-225 (hedgehog inhibitor),[39] IFN-alpha.[40] All of these combinations have shown promise, but require more data prior to incorporating them into routine clinical practice.

PEG-Interferon-α-2a

IFN-α-2a has been used in hematologic malignancies for many years.[41] Its use has been limited by the need for daily administration and the side effect profile. However, when the pegylated formulation became available, and injection was reduced to weekly, it became a more attractive option. There is an ongoing trial evaluating its use in early MF (NCT02370329).

Novel therapeutic approaches

One unique approach to MF is telomerase inhibition. Imetelstat is a telomerase inhibitor which has shown activity in multiple malignancies.[42] Telomers are protein bound repetitive DNA sequences that reside at the end of linear chromosomes and protect coding DNA from genetic damage.[42] Telomerase, a holoenzyme made up of human telomerase reverse transcriptase (hTERT), a RNA template, and specialized proteins helps maintain telomere length in rapidly dividing cells.[42] Telomerase appears to be more active in cancer cells compared to somatic tissue. Imetelstat is a 13-mer lipid-conjugated oligonucleotide that targets the RNA template of telomerase, effectively inhibiting telomerase activity and cell proliferation.[42]

Tefferi et al published the results of 33 intermediate 2 and high risk patients treated with imetelstat. In this cohort, 7 (21%) of patients achieved a complete response, which occurred at a median of 3.5 months and lasted for a median of 18 months.[42] Of the 7 with a CR, transfusion independence was achieved in 3 of them. Four of the patients with a CR also had clearance of their clonal population, and reversal of the fibrosis. Reduction of spleen size by at least 35% occurred in 35% of patients. The response occurred primarily in patients who had JAK2 V617 mutation present, and did not harbor *ASXL1* mutation.[42] This drug is also undergoing further study in a larger group of patients.

Anti-fibrotic agents are also being considered. One such agent is PRM-151.[43] This is a humanized serum amyloid protein that modulates monocytes to take on a more anti-fibrotic phenotype rather than a pro-fibrotic phenotype. Over this time, reduction of fibrosis leads to improved spleen size and blood counts. Another approach is tumor growth factor-beta inhibition. TGF-beta is a cytokine that promotes fibrosis.[44] This has been shown to be safe and tolerable in patients with MF[44] and is being tested in a larger population (NCT NCT01291784).

Bone marrow transplant

Bone marrow transplant is the only curative option for patients with MF. Table 1 reviews

Table 2. Transplant outcomes for myelofibrosis

Study	N	Myeloablative/RIC conditioning	TRM	Relapse	OS
Kerbauy et al[47] FHCRC	103	MA-94 RIC-9	35%	8%	61% at five years
Ballen et al[57]	280	MA-229	18% MRD- 1 yr 35% MUD- 1 yr	32% MRD-5 yr 23% MUD-5 yr	37% MRD- 5yr 30% MUD- 5yr
Patriarca et al.[46]	100	Both	35%- 1 yr	41%-2 yr	28%- 5 yr
Kroger et al.[58]	100	RIC	16%- 1 yr	29%- 5 yr	67%- 5 yr
Robin et al.[56]	147	MA-46 RIC-101	39%- 4 yr	29%- 4 yr	39%- 4 yr
Stewart et al.[45]	51	MA-27 RIC-24	41%- MA 3 yr 32%- RIC 3 yr	15%- MA 46%- RIC	44%- MA 3yr 31%- RIC 3yr
Abelsson et al.[55]	92	MA-42 RIC-50	17.5% - MA 100d 5.8%- RIC 100d	nr	49%- MA 5 yr 59%- RIC 5yr
Rondelli et al.[52]	66	RIC-Flu/Mel	30%- 2 yr	69% RR*	75%- MRD 2 yr 32%- MUD 2 yr
Gupta et al.[53]	233	RIC	24%- 5 yr	48%- 5 yr	56%- MRD 48%- MUD 34%- MMUD

MA: myeloablative; RIC: reduced intensity conditioning; MRD: matched related donor, MUD: matched unrelated donor; MMUD: mismatched unrelated donor; RR: response rate.
*Relapse not reported, only response rate.

transplant studies done over the last 10 years. Historically, due to the treatment related toxicities, transplants were reserved for patients who were younger.[45-48] In earlier studies, there was a high treatment related mortality, but they did provide proof of concept that transplant was a curable treatment for patients with MF. In more contemporary times, with reduced intensity conditioning, patients are able to undergo allogeneic stem cell transplant well into their 70s.[49,50] Transplant in MF has many challenges. First, patients will often have a large spleen, and significant marrow fibrosis, both of which can impact engraftment. Additionally, patients will frequently have significant cardiac and liver dysfunction as a result of their MF. Finally, over half the patients who are diagnosed with MF are greater than 65 years of age, and may have significant comorbidities that preclude transplantation.

When to transplant?

Given the significant morbidity and mortality associated with transplant, it is generally reserved for patients with a DIPSS score of Int-2 or high risk.[51] Earlier transplant can be considered in patients who have other molecular markers of high risk disease, including mutations of *ASXL1*, *EZH2*, *SRSF2* and *IDH*.[13] As these markers can predict a shortened survival, independent of DIPSS, they may provide valuable prognostic information to help in decisions regarding transplant.

Complications of transplant

Patients with MF who undergo transplant have several unique risks following transplant. In addition to the standard risks including graft versus host disease, and infection, their organ dysfunction secondary to myeloproliferative neoplasm

can be significant. For example, the scar tissue present in the bone marrow can lead to a failure to engraft in up to 10% of patients. Additionally, due to the hepatic extramedullary hematopoiesis, there is a higher risk of sinusoidal obstructive syndrome. As such, the risk of treatment related mortality ranges from 16-40%.[46,46,52-58]

Survival

Survival following transplant can range from 30-75% at 1-5 years.[45,46,52,53,56-59] With allo outcomes may improve with *SRSF2, EZH2, IDH1* mutations, however, those with *ASXL1, U2AF1, IDH2, DNMT3A* may not experience a benefit.[28] Although it may take up to a year, reversal of fibrosis can be observed in patients undergoing transplant, suggesting a cure.

CONCLUSIONS

PV and MF are challenging diseases to treat, but there are many advances in the treatment of these diseases and more on the horizon.

Front line therapy for PV includes aspirin and phlebotomy (Figure 1). In patients who continue to have difficulties or do not tolerate these treatments, HU is the first line therapy. If adequate control is still not obtained, PET-IFN2a or RUX can be considered.

In MF (Figure 2), the treatment largely depends on the symptoms and potential side effects of treatment. In patients with constitutional symptoms, and painful splenomegaly, RUX is an excellent choice for patients whose platelets are >50. In cases where platelets are not adequate or persistent anemia is present, other JAK inhibitors can be considered, though at the present time, only in a clinical trial. Novel approaches are being considered such as telomerase inhibitors, anti-fibrotic agents such as PRM-151 and anti-TGF beta antibodies.

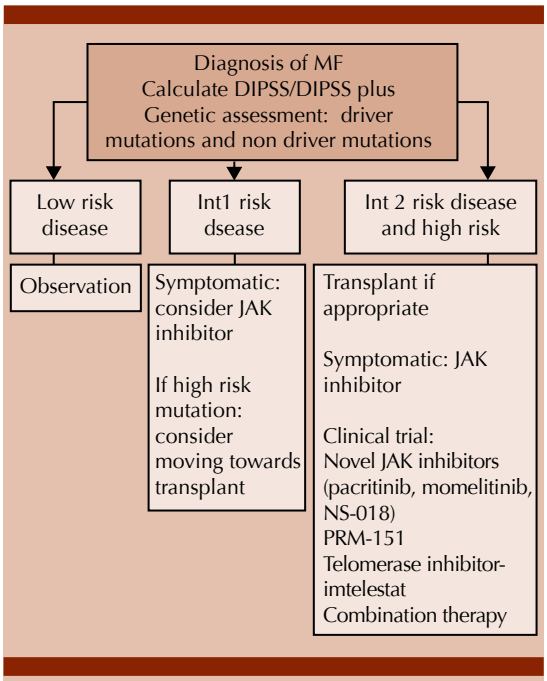

Figure 2. Treatment options for MF.

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