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Review Article

Immunotherapy and myeliod metaplasia

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Abstract

The past few decades have witnessed significant advances in our understanding of the etiology, diagnosis and treatment of Myeloproliferative disorders (MPDs). Although the causes of chronic MPDs remain unknown, Janus kinase 2 (JAK 2) gene mutation is found to be associated. Myelofibrosis with Myeloid metaplasia (MMM) is a rare MPD, characterized by splenomegaly, immature peripheral blood granulocytes and erythrocytes, and teardrop-shaped red blood cells. The identification of the JAK2–V617F mutations in chronic MPDs has stimulated a great deal of effort in screening and developing specific inhibitors for clinical use. Currently, immunotherapies options for MMM include kinase inhibitors, anti-fibrotic therapy, stem cell transplantation, mTOR inhibitor and immunomodulators. While allogeneic stem cell transplantation is curative, rest of the treatment are mostly supportive. This review contributes to existing knowledge of recent therapeutic advances by encapsulating various immunotherapeutic modalities. However, further research is mandated on the effects of such modalities in combination with immunotherapy to witness improved quality of life and better prognosis in patient.

Keywords: MPDs; Myeloid metaplasia; Kinase inhibitors; Stem cells; Immunomodulators

Introduction

Myeloproliferative disorders (MPDs) are classified according to the most affected type of blood cells. There are four main types of MPDs, namely, Polycythemia Vera (PV), Essential thrombocythemia (ET), Myelofibrosis with Myeloid metaplasia (MMM), and Chronic myelomonocytic leukemia (CMML).

MMM (also known as chronic idiopathic myelofibrosis, myelosclerosis with MMM, and idiopathic myelofibrosis) is a rare myeloproliferative disorder, characterized by splenomegaly, immature peripheral blood granulocytes and erythrocytes, and teardrop-shaped red blood cells [1]. The cause of death in MMM includes leukemic transformation (LT) that occurs in 8% to 23% of patients in the first 10 years of diagnosis [2,3]. Annually, it occurs in about 1.5 out of every 100,000 people in the United States. The disease affects both men and women and is usually diagnosed in people over the age of 50. However, MF can occur at any age.

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Etiology/Predisposing Factors

The causes of chronic MPDs remain unknown. However, a mutation of a particular gene known as Janus kinase 2 (JAK 2) is found in a large proportion of people with MPDs implying a plausible association. There are several risk factors associated with chronic MPDs. Some of them are [4-7]

Age and Sex

PV is more common in men than in women. The condition is rarely seen in people under the age of 40, but a few cases have been diagnosed among children. CMML is about twice as common in men as in women. The risk of CMML increases with age., with most cases found in people aged 60 and above. The disease is rare in those below 40.

Cancer Treatment

Prior treatment with chemotherapy seems to increase the risk of CMML. The risk of CMML post cancer chemotherapy, however, is not as high as the risk of other blood problems, such as myelodysplastic syndromes and acute myeloid leukemia.

Exposure to petrochemicals

Benzene and Toluene, and ionizing radiation increase the risk of MMM.

Pathophysiology/Molecular basis of MMM

Cytogenetic abnormalities originating on the progenitor cell level are found in MMM, particularly deletions of chromosomes 13q and 20q, trisomy 8 and abnormalities in chromosomes 1, 7 and 9 [8,9]. Several molecular mutations have also been identified.

The JAK2–V617F mutation is present in 50 to 65% of patients with MF [10-12]. Although, JAK2–V617F murine models can summarize a myelofibrotic myeloproliferative disease intricately, experiments done on primary myelofibrosis patient samples suggest that this mutation may not be a disease-initiating event in humans. Other molecular mutations, present to a lesser extent, have been reported in the following genes: myeloproliferative leukemia virus (MPL), LNK, Casitas B-lineage lymphoma (CBL), ten-eleven-translocation 2 (TET2), additional sex-combs-like 1 (ASXL1), isocitrate dehydrogenase (IDH) 1 and 2, IKAROS family zinc finger-1 (IKZF1) and enhancer of zeste homolog 2 (EZH2) [13, 14].JAK2 and MPL mutations and loss of function of LNK result in the activation of JAK signal transducer activator of transcription (STAT), and induction of MPN-like disease in mice [15, 16]. An activated JAK–STAT pathway promotes the transcription of a plethora of pro-proliferative and antiapoptotic genes [17-19]. MMM is also characterized by bone marrow changes induced by cross-communication among clonal stem cells, megakaryocytes, and monocytes with stromal cells, leading to inappropriate cytokine release, myeloproliferation, neoangiogenesis and fibrosis [9]. Excessive releases of cytokines may further result in JAK–STAT activation, resulting in the propagation of the cycle [20].

Immunotherapy in MMM

Kinase Inhibitors

FDA Approved Drug

Ruxolitinib: It is a JAK inhibitor, approved by the FDA. Ruxolitinib specifically binds to and inhibits protein tyrosine kinases JAK 1/2, leading to reduced inflammation and inhibition of cellular proliferation [21].

Indication and Uses: Ruxolitinib is indicated for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-PV myelofibrosis and post-ET myelofibrosis.

PD/PK: Ruxolitinib is rapidly absorbed orally and C_{max} is achieved within one to two hours post the dose. The mean volume of distribution at a steady-state is 72 L with an inter-subject variability of 23%, metabolized by CYP3A4, and the mean elimination half-life is approximately three hours.

Contraindication: None

Warning: Thrombocytopenia, anemia and neutropenia, risk of infection, and non-melanoma skin cancer

AE: The most common hematologic adverse reactions are thrombocytopenia and anemia. The most common non-hematologic adverse reactions are bruising, dizziness and headache.

Non-FDA Approved Drug

Momelotinib: It is an orally bioavailable small-molecule inhibitor of JAK1/2 with potential antineoplastic activity. Momelotinib competes with JAK1/2 for ATP binding, inhibits JAK1/2 activation and the JAK–STAT signaling pathway, thereby inducing apoptosis and reducing proliferation of JAK1/2-expressing tumor cells.

Pacritinib: It is an orally bioavailable inhibitor of JAK2 and the JAK2 mutant JAK2–V617F with potential antineoplastic activity. Pacritinib competes with JAK2 for ATP binding, inhibiting JAK2 activation and the JAK–STAT signaling pathway, resulting in caspase-dependent apoptosis. JAK2 is the most common, mutated gene in Bcr-Abl-negative MPDs; the JAK2–V617F gain-of-function mutation involves a valine-to-phenylalanine modification at position 617. The JAK–STAT signaling pathway is a major mediator of cytokine activity.

NS-018: It is an orally bioavailable, small molecule inhibitor of JAK2 and Src-family kinases, with potential antineoplastic activity. The JAK2/Src inhibitor NS-018 competes with ATP for binding to JAK2 as well as the mutated form JAK2–V617F, thereby inhibiting the activation of JAK2 and downstream molecules in the JAK2/STAT3 signaling pathway that plays an important role in normal development, particularly hematopoiesis. In addition, NS-018 inhibits the Src family tyrosine kinases. This eventually leads to the induction of tumor cell apoptosis. JAK2 is the most common, mutated gene in Bcr-Abl-negative MPDs; JAK2–V617F is a constitutively activated kinase that activates the JAK/STAT signaling pathway and dysregulates cell growth and function, and its expression transforms hematopoietic cells to cytokine-independent growth [22-24] (Table 1).

Anti-fibrotic therapy

Non-FDA Approved Drug

PRM-151: It is a fully recombinant form of the human pentraxin 2 (PTX2) proteins with potential anti fibrotic activity. PTX2 is a circulating plasma protein that belongs to the class of pattern recognition receptors (PRR) of the innate immune system. Upon intravenous administration, recombinant human serum amyloid P/pentraxin 2 (PRM-151) may inhibit the generation of myofibroblast, by preventing the differentiation of circulating monocytes into fibrocytes and profibrotic macrophages [25] (Table 2).

Stem Cell Transplantation: Allogeneic stem cell transplantation (ASCT) is the treatment with the potential to cure

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Momelotinib (CYT387)	NCT01236638	Phase II	Non Randomized, Safety/Efficacy study, open label	JAK1/2
Pacritinib	NCT02055781	Phase III	Randomized, Safety/Efficacy study, open label	JAK2, JAK2–V617F
NS-018	NCT01423851	Phase I, Phase II	Safety/Efficacy study, open label	JAK2 and Src-family kinases

Table 1: Non-FDA Approved kinase inhibitor.

Drug	Clinical trial identifier no.	Phase	Study Design	Target
PRM-151	NCT01981850	Phase 2	Non-Randomized, Safety/Efficacy study, open label	Inhibit myofibroblast generation

Table 2: Non-FDA approved Anti-fibrotic therapy.

myelofibrosis. In this procedure, the patient receives high doses of chemotherapy or radiation therapy to destroy the diseased bone marrow. Then, healthy hematopoietic (blood-forming) stem cells from a compatible donor (a sibling or unrelated person whose stem cells "match" the patient's) are infused into the patients of MMM. The transplanted healthy cells travel to the patient's bone marrow, replacing the defective stem cells. The new cells grow and provide a supply of red cells, white cells (including immune cells) and platelets [26].

Allogeneic stem cell transplantation can be used for the elderly, when medically appropriate. There is no specific age cutoff for stem cell transplantation. Compared to a standard ASCT, a reduced-intensity transplant delivers lower doses of chemotherapy drugs and/or radiation to the patient undergoing preparation for the transplant. The success of reduced-intensity transplantation is a result of the graft-versus-tumor effect of the donor stem cells, rather than high doses of chemotherapy. This approach benefits older and sicker patients, and other selected patients. Reduced-intensity transplants are now done with results, which are an increasingly encouraging sign for MMM patients [27].

mTOR Inhibitor

Non-FDA Approved Drug

Everolimus (RAD-001): It is a derivative of the natural macrocyclic lactone Sirolimus with immunosuppressant and anti-angiogenic properties. In cells, Everolimus binds to the immunophilin FK Binding Protein-12 (FKBP-12) to generate an immunosuppressive complex that binds to and inhibits the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory kinase [28] (Table 3).

Drug	Clinical trial identifier no.	Phase	Study Design	Target
Everolimus (RAD-001)	NCT00081874	Phase I, II	Safety/ Efficacy Study Open Label	mTOR

Table 3: Non-FDA Approved mTOR inhibitor.

Immunomodulators

Non-FDA Approved Drug

Prednisone (PRED): In anemic patients, who are not candidates for Erythropoiesis-stimulating agents (ESA) therapy or in whom such therapy was unsuccessful, one has a choice of several potentially effective conventional drugs, including corticosteroids (e.g., PRED 0.5 mg/kg/d) [29], androgens (e.g., fluoxymesterone 10 mg three times daily) [30], danazol (600 mg/d) [31],thalidomide (THAL) (50 mg/d) with or without PRED (0.25 mg/d) [32, 33],or lenalidomide (10 mg/d) with or without PRED [34-36]. Response rates and durations for each one of these treatment modalities are somewhat similar and estimated at 20% and one year respectively.

Lenalidomide: A phase II study of Lenalidomide (CC-5013) in combination with PRED for the treatment of MMM has been conducted, in which forty-eight subjects with anemia (42 evaluable) received lenalidomide, 10 mg/d, with a 3-month low-dose PRED taper. Ten subjects received three months and 25 received six months of therapy. There were responses in ten subjects (23%), clinical improvement of anemia in eight (19%) and/or decreased spleen size in four (10%). Serial bone marrow analysis showed no resolution of disease-related fibrosis or angiogenesis. With a median follow-up of 2.3 years, 23 subjects are alive [37].

Thalidomide (THAL): A phase II treatment trial of combination low-dose THAL and PRED was conducted in 21 symptomatic patients (hemoglobin level < 10 g/dL or symptomatic splenomegaly) with MMM with low-dose THAL (50 mg/d) along with a three month oral PRED taper (beginning at 0.5 mg/kg/d). The THAL–PRED treatment was well tolerated in all enrolled patients, with 20 patients (95%) completing three months of treatment. An objective clinical response of improvement in anemia was demonstrated in 13 (62%) patients. Among ten

patients who were dependent on erythrocyte transfusions, seven (70%) improved and four (40%) became transfusion independent. Among eight patients with thrombocytopenia (platelet count < 100 x 10(9)/L), six (75%) experienced a 50% or higher increase in their platelet count. In four of 21 patients (19%), the spleen size decreased by more than 50%. Responses observed were mostly durable after discontinuation of the PRED. The dose of THAL in this study (50 mg/d) was better tolerated than the higher doses used in previous studies [38].

Pomalidomide: A phase1/2 study of Pomalidomide in myelofibrosis was conducted to study if higher doses of Pomalidomide increased anemia responses (previously, Pomalidomide was shown to be safe and effective for myelofibrosis associated anemia, with a dose of 0.5 mg/day [with PRED] or 2.0 mg/day). The dose of 3.0 mg/d, given for 21 out of the 28 consecutive days was the maximum-tolerated dose (MTD), with myelosuppression being dose limiting. Non-responders at the MTD had their dose decreased and the therapy interval was increased regularly. Seven of the 19 subjects had an anemia-response and two had a spleen response. Most responses occurred after the dose-reduction to 0.5 mg/d, suggesting the association of higher doses with increasing myelosuppression without increasing (or possibly decreasing) efficacy [39].

Cytokine therapy

Non-FDA Approved Drug

PEG-proline-interferon Alpha-2b: It is a long-acting formulation of recombinant interferon alpha subtype 2b (IFN-a2b) protein, in which IFN-a2b is coupled, via proline, to polyethylene glycol (PEG), with antiviral, immunomodulating and antineoplastic activities. Upon subcutaneous administration, IFN-a2b binds to specific interferon cell-surface receptors. This activates interferon-mediated signal transduction pathways and induces the transcription and translation of genes with interferon-specific response elements (ISREs); the protein products mediate antiviral, antiproliferative, anticancer and immune-modulating effects. The PEG moiety inhibits proteolytic breakdown and clearance of IFN-a2b, which prolongs its half-life, extends the duration of its therapeutic effects and allows less frequent dosing. The proline linker facilitates the synthesis of a predominant (90%) positional isomer which allows for further increases in stability and a longer half-life than previous PEG conjugates [40] (Table 4).

Drug	Clinical trial identifier no.	Phase	Study Design	Target
PEG-proline-interferon alpha-2b	NCT02370329	Phase II	Efficacy Study Open Label	Interferon cell surface receptor

Table 4: Non-FDA Approved interferon alpha.

Conclusion

The success rate in treating hematological malignancies is increasing and advancing day-by-day with the enhancing knowledge on the function of the immune system. The identification of the JAK2–V617F mutations in chronic MPDs has stimulated a great deal of effort in screening and developing specific inhibitors for clinical use. It is certain that the next few years will bring further developments in this fast-evolving field. Researchers are still challenged when exploring innate and adaptive immune systems. Immunotherapy is a promising development in the past few years in the field of cancer. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapies (like chemotherapy with immunotherapy). The effects of such modalities in combination with immunotherapy in cancer patients are still in the exploratory phase. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

Abbreviations

ADP – Adenosine Di Phosphate

AMP – Adenosine Mono Phosphate

ASCT – Allogeneic stem cell transplantation

ASXL1 – Additional sex-combs-like 1

CBL – Casitas B-lineage lymphoma

C_{max} – Peak plasma concentration

CMML – Chronic Myelomonocytic Leukemia

CYP3A4 – Cytochrome P450 3A4

ESA – Erythropoiesis-stimulating agents

ET – Essential Thrombocythemia

EZH2 – Enhancer of zeste homolog 2

FDA – Food and Drug Administration

FKBP-12 – FK Binding Protein-12

IDH – Isocitrate dehydrogenase

IFN – Interferon

IFN-a2b – interferon alpha subtype 2b

IKZF1 – IKAROS family zinc finger-1

ISREs – Interferon-specific response elements

JAK – Janus Kinase

JAK-STAT – Janus kinase/signal transducers and activators of transcription

LT – Leukemic Transformation

MMM – Myelofibrosis with Myeloid Metaplasia

MPDs – Myeloproliferative disorders

MPL – Myeloproliferative leukemia virus

MPNs – Myeloproliferative Neoplasms

MTD – Maximum-tolerated dose

mTOR – mammalian Target of Rapamycin

PEG – Polyethylene glycol

PRED – Prednisone

PRR – Pattern recognition receptors

PTX2 – Pentraxin 2

PV – Polycythemia Vera

TET2 – ten-eleven-translocation 2

THAL – Thalidomide

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