Management of Advanced Phase Myeloproliferative Neoplasms

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Abstract: The *BCR-ABL1*–negative myeloproliferative neoplasms (MPNs), including polycythemia vera, essential thrombocythemia, and primary myelofibrosis, can evolve into a form of secondary acute myeloid leukemia termed MPN in blast phase (MPN-BP). MPN in accelerated phase (MPN-AP), which is defined by 10% to 19% myeloid blasts in the peripheral blood or bone marrow, is a precursor to MPN-BP. Alternative definitions of MPN-AP exist based on studies identifying clinical variables that portend a poor prognosis and high risk for progression to MPN-BP. Allogeneic hematopoietic stem cell transplant remains the only curative therapeutic option; however, advanced age and high comorbidity index preclude the majority of patients from receiving this treatment modality. This article reviews management considerations for the advanced-phase MPNs (MPN-AP and MPN-BP), with a special focus on MPN-AP, and highlights novel experimental therapies.

Introduction

The *BCR-ABL1*–negative myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), although primarily chronic in nature, have the potential to evolve into a form of secondary acute myeloid leukemia (AML) termed MPN in blast phase (MPN-BP). MPN-BP is defined as 20% or more myeloid blasts in the bone marrow or peripheral blood compartment of a patient with a documented history of an MPN.[1] At 10 years from the time of diagnosis, approximately 1%, 4%, and 20% of patients with ET, PV, and myelofibrosis (MF) will progress to MPN-BP, respectively.[2] MPN-BP has a dismal prognosis, with a median overall survival of approximately 3 to 5 months.[3,4] The mechanisms driving progression of chronic MPNs to MPN-BP remain elusive but are hypothesized to involve acquisition of genomic mutations, epigenomic alterations, and a pro-inflammatory microenvironment supporting malignant hematopoiesis. A complex karyotype and mutations involving *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*, and *TP53* are associated with an increased risk of leukemic transformation.[5]

MPN-BP is generally preceded by an accelerated phase (AP), which is defined as 10% to 19% myeloid blasts in the peripheral blood or bone marrow compartment. This defining feature correlates

with the definitions of advanced phases in other myeloid neoplasms, including the accelerated phases of chronic myelogenous leukemia and myelodysplastic syndrome (MDS) with excess blasts (category 2).[6] However, recent findings suggest that the defining blast percentage for MPN-AP should be widened. In a retrospective study of 1099 patients with MF, those patients with at least 4% peripheral blood blasts or at least 5% bone marrow blasts were found to have equivalent survival to those patients with at least 10% peripheral blood or bone marrow blasts.[7] MPN-AP has been alternatively defined by Tam and colleagues in a multivariable analysis of clinical features associated with poor outcome in a cohort of 370 patients with MF seen at MD Anderson Cancer Center. Chromosome 17 aberrations, platelet count less than 50 $\times$ 10^9/L, and peripheral blood or bone marrow blasts between 10% and 19% were found to be associated with a survival of 12 months or less. This study also revealed that the majority of patients with chronic-phase MPN who underwent leukemic transformation transitioned through an MPN-AP.[8] Adverse prognostic factors for overall survival in patients with MPN-AP/BP include mutated *TP53*, at least 4 mutations, low albumin, increased peripheral blood blasts, at least 3 cytogenetic abnormalities, and supportive care only.[9]

All patients with chronic-phase MPN should be monitored regularly for signs and symptoms of leukemic transformation. Those patients with known complex karyotype, high-risk cytogenetic abnormalities (gain of 1q, deletion 17p), and/or high-risk mutations (*ASXL1*, *EZH2*, *SRSF2*, *IDH1/2,* and *TP53*) warrant the highest level of concern for disease evolution. In a Mayo Clinic study, peripheral blood blasts of at least 3% was identified as a risk factor for leukemic transformation in patients with PMF. Additionally, all patients found to have at least 10% marrow blasts had at least 2% blasts in the peripheral blood.[10] This suggests that patients with MPN who have consistent peripheral blood blasts of at least 2% should undergo a baseline bone marrow pathology evaluation, with repeat evaluation performed when clinical status changes. When performing bone marrow aspirate and biopsy, cytogenetic and mutational analysis should be performed to assess for the acquisition of high-risk cytogenomic features.

MPN-AP and MPN-BP are part of a dynamic spectrum of progressive disease. At this time, treatment options for MPN-AP are in large part the same as those for MPN-BP. It is prudent to consider treatment once MPN-AP is diagnosed rather than delaying treatment until progression to MPN-BP, given its dismal prognosis. Because AP is an obligatory step to BP and portends a poor outcome in itself, the rationale for delayed treatment is poor. However, the consensus on optimal therapy for MPN-AP, enabling clear disease course modification and prolongation of survival, is not established.

Here we focus on the current therapeutic landscape for management of patients with advanced-phase MPNs, with a special focus on MPN-AP, including cytotoxic chemotherapy, hematopoietic stem cell transplant (HSCT), hypomethylating agents (HMAs), and molecular-based therapeutics. These approaches are discussed within the context of determining the optimal treatment strategy based on patient age, performance status, and disease characteristics (Figure). In addition, we provide an overview of current investigational therapies for MPN-AP/BP.

Chemotherapy and HSCT

At this time, HSCT is the only potentially curative therapy for MPN-AP/BP. Long-term survival is achieved in approximately one-third of patients with MPN-AP/BP who undergo HSCT.[11] A single-center study evaluating 75 patients with leukemic transformation revealed the superiority of HSCT vs other treatment options in producing durable remissions. Of the patients treated with curative intent (induction chemotherapy + HSCT), 26% were alive at 2 years vs only 3% of the patients who were treated with noncurative intent (single-agent chemotherapy or supportive care). Of the 17 patients who underwent HSCT, 5 were still alive at last follow-up, with a median overall survival of approximately 4 years from the time of leukemic transformation. Those patients who underwent induction chemotherapy but did not undergo HSCT had an outcome similar to that of patients treated with noncurative intent, indicating the lack of benefit with induction chemotherapy in the absence of consolidation HSCT. HMA treatment in this study also yielded benefit, with 1 out of 3 azacitidine-treated patients achieving stable disease for 14 months, and 1 out of 3 decitabine-treated patients achieving an incomplete remission, allowing for a 40-month survival.[12]

Cytotoxic chemotherapy alone without consolidation HSCT does not afford appreciable benefit to patients with MPN-BP. This was also exemplified in a retrospective study evaluating 91 patients with MF that had transformed to MPN-BP. Although 41% of patients attained a remission after induction, these remissions were not sustained and the median overall survival was a discouraging 3.9 months, which was comparable to those treated with supportive therapy or low-intensity chemotherapy.[3]

The most important predictor of long-term survival after HSCT is a leukemia-free state, or complete remission, at the time of transplant. The leukemia-free state is usually defined as less than 5% blasts in the bone marrow and the absence of circulating blasts.[11,13-15] This was illustrated by Alchalby and colleagues in a retrospective study evaluating HSCT outcomes in 46 patients with MPN-BP.

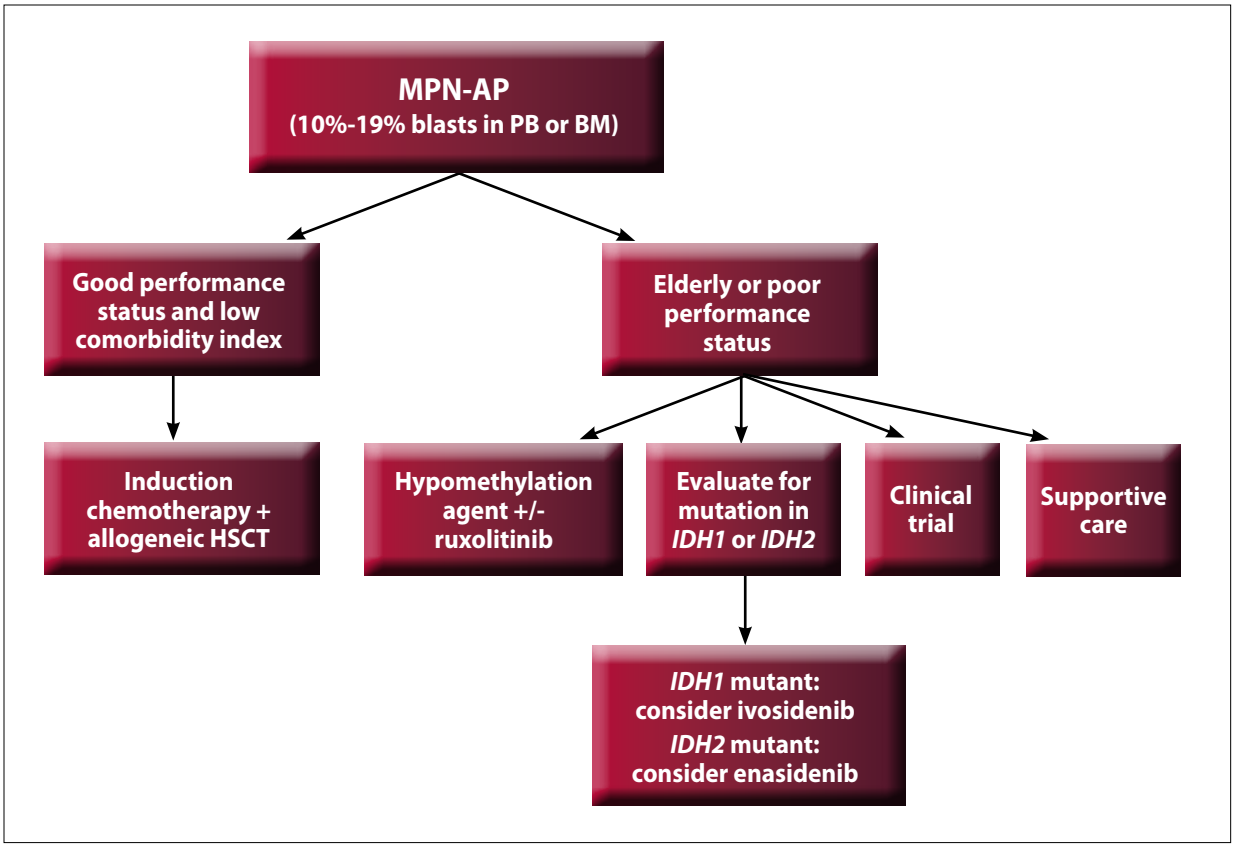

Figure. Treatment paradigm for MPN-AP.

BM, bone marrow; HSCT, hematopoietic stem cell transplant; MPN-AP, myeloproliferative neoplasm in accelerated phase; PB, peripheral blood.

At 3 years after HSCT, 69% of patients transplanted in complete response were alive, vs only 22% of patients transplanted with residual disease.[13]

Although no prospective trials have directly compared myeloablative vs reduced intensity conditioning (RIC) regimens for MPN-AP/BP, retrospective data suggest these regimens are comparable in terms of survival endpoints.[11,13] No clear superiority among the RIC regimens is evident. In a retrospective study comparing 61 patients with MF who received busulfan-containing vs melphalan-containing regimens, no difference in overall survival between the groups was observed.[16] The conditioning regimen should be chosen based on the patient's comorbidities and performance status.

Data regarding the optimal donor hematopoietic stem cell source are largely extrapolated from MF studies and small retrospective HSCT studies in MPN-BP. Currently, the preferred donor option is an HLA-matched sibling donor. Whether HLA-matched unrelated donors are inferior to HLA-matched related donors is questionable. In a retrospective study performed at the Icahn School of Medicine that evaluated HSCT in 42 patients with chronic and advanced-phase MF (12 having MPN-BP), the median progression-free survival was 11 months for the unrelated donor graft recipients and not yet reached for the related graft recipients (P=.0332).[17] A multicenter, retrospective study performed by the Center for International Blood and Marrow Transplant Research analyzed the outcome of 233 patients with MF undergoing reduced intensity HSCT and found that unrelated donor source was the only transplant variable associated with poor outcome. Five-year overall survival was 56% in the recipients of related donor grafts vs 48% in well-matched unrelated donor graft recipients and 34% in partially-matched/mismatched unrelated donor graft recipients (P=.002).[18] Furthermore, in a Myeloproliferative Disorders Research Consortium (MPD-RC) prospective study evaluating 66 patients with MF receiving RIC followed by transplant, 2-year survival was superior in the matched related donor group (75%) compared with the matched unrelated donor group (32%).[19] However, in a prospective study evaluating 103 patients with MF receiving RIC therapy followed by HSCT, no difference in overall survival occurred between patients with related

vs unrelated matched donors.[20] Umbilical cord blood, although still an option, is not preferred owing to delayed and reduced engraftment.[11] A recent retrospective analysis suggested that haploidentical donor transplants may be superior to matched related donor transplants in patients with MF, although further validation is necessary.[21]

A paucity of data exist regarding other clinical parameters associated with transplant outcome in patients with MPN-BP. Lancman and colleagues reported that in a combined cohort of patients with MPN-BP who received HSCT, transfusion dependence prior to HSCT was a negative predictor of survival after transplant, with these patients having an overall survival comparable to that of patients not receiving HSCT. Although transfusion dependence is associated with increased disease severity and risk of poor outcome in the case of chronic-phase MF, in this study transfusion dependence was associated with decreased survival owing to HSCT complications such as sepsis and graft-versus-host disease (GVHD) rather than disease-related reasons, such as relapse. This may indicate that transfusion dependence in MPN-BP serves as a clinical marker for decreased overall fitness.[15] Certain cytogenomic aberrations can also be highly indicative of poor outcome. Retrospective data from MPN-BP transplant studies, coupled with transplant data in the MF and AML settings, indicate that patients who harbor a complex karyotype, *TP53* mutation, *ASXL1* mutation, or 17p perturbation are at high risk for relapse after HSCT.[12]

Prognostic scoring systems can help determine when to consider transplant in MF, but currently have little utility in the MPN-AP setting. Owing to the inherently poor prognosis associated with MPN-AP, patients should be considered for HSCT. Although the development of risk scoring systems may add value to HSCT prognostication in MPN-AP, such a system would have to clearly discern distinct outcomes. Even if a scoring system predicts limited benefit with HSCT, many patients and physicians alike may still choose the procedure owing to the lack of alternatives. Importantly, most patients in the MPN-AP/BP population will not be viable candidates for HSCT owing to advanced age, poor performance status, comorbidities, and in some cases, the lack of suitable donor options.

Hypomethylating Agents

Chronic-phase in comparison to advanced-phase MPNs have been noted to possess distinct methylation signatures and epigenetic changes of inflammatory and cell signaling gene subsets hypothesized to drive MPN pathogenesis.[22,23] The class of genes hypermethylated depends on the MPN subset. For instance, ET/PV cases exhibit hypermethylation of genes controlling transcriptional regulation, whereas PMF cases exhibit hypermethylation of genes encoding inflammatory mediators.[23] Additionally, patients with MPN harboring high-risk mutations in *ASXL1* and *TET2* have their own methylomic signatures that may predispose to leukemic transformation.[23]

Azacitidine and decitabine have shown activity in MPN-AP/BP and are currently employed with the goals of alleviating symptom burden and prolonging survival. The initial study evaluating outcomes with HMA therapy in MPN-AP/BP patients was a retrospective analysis of 54 patients with MPN who had progression to MPN-AP/BP or MDS and were treated with azacitidine. After 4 to 6 cycles of azacitidine treatment, the overall response rate was 52%, with 24% of patients achieving a complete response. The median duration of response was 9 months, and overall survival was 11 months.[24]

A retrospective study performed at MD Anderson evaluated the outcomes of high-risk MF and MPN-AP/BP treated with single-agent decitabine. Twenty-one patients with MPN-BP were included in the study, and 6 responded (29%), with a median duration of response of 7 months. In those who responded to treatment, the median overall survival was significantly improved compared with nonresponders (10.5 vs 4 months). Thirteen patients with MPN-AP were included in the analysis, and 8 (62%) of them responded, with a median duration of response of 6.5 months. Median overall survival for MPN-AP was 11.8 months in responders and 4.7 months in nonresponders.[25] A retrospective study at Mount Sinai revealed similar findings, with 67% of MPN-BP patients alive at 9 months.[26] Guadecitabine (SGI-110) has a longer half-life than azacitidine and decitabine, which allows for prolonged exposure of tumor cells to the active metabolite. Its efficacy is currently being assessed in patients with MPNs, including MPN-AP, in an ongoing single-center phase 2 study (NCT03075826). To date, no prospective comparison of intensive chemotherapy vs HMA therapy has been conducted in MPN-AP/BP.

Inactivating *TP53* mutations are found in approximately 20% of patients with MPN-AP/BP.[27] Although *TP53* mutations at a low variant allele frequency can be detected in chronic-phase MPN, loss of heterozygosity and increase in mutational burden have been associated with transformation to MPN-BP.[27] Mutant *TP53* AML is associated with a poor prognosis, and this is in part due to inherent chemoresistance.[28] In a single-center prospective trial evaluating a 10-day course of decitabine in patients with AML and MDS, response rates were elevated in patients with a *TP53* mutation. The activity of HMA therapy in patients with MPN-AP/BP harboring mutant *TP53* will be evaluated in an ongoing multicenter phase 2 trial (NCT03063203).

Currently, we recommend HMA therapy for patients with MPN-AP/BP who are not candidates for

HSCT, or for those patients who are candidates for HSCT but require bridging therapy with less-intense treatment than cytotoxic chemotherapy. No prospective comparative studies of azacitidine and decitabine have been conducted in MPN-AP/BP; however, results are extrapolated from studies in MDS. In treatment of MDS, low-dose decitabine resulted in greater myelosuppression than low-dose azacitidine.[29] Therefore, decitabine may be more advantageous in the setting of proliferative disease and azacitidine may be preferred in those patients with baseline cytopenias. Importantly, HMA therapy should be continued through best response in order to maintain this response and then discontinued at the time of disease relapse/progression. Additionally, once the disease has failed to respond to an HMA, switching to another HMA likely has no utility. This again is extrapolated from the MDS population, in which patients previously treated with azacitidine were found to be unlikely to benefit from decitabine.[30] During administration of these agents, patients must be monitored closely for the emergence of cytopenias that may necessitate transfusional support and prophylactic antimicrobials. Therapy should not be modified for the emergence of anemia or thrombocytopenia, and a 4-week schedule should be maintained. Response to HMA therapy often requires several cycles of administration, and the duration of response is variable.

Ruxolitinib

Overactivation of the JAK-STAT signaling pathway is a hallmark of MPNs and therapeutic targeting of this pathway with the JAK1/2 inhibitor ruxolitinib (Jakafi, Incyte) has proven effective in the treatment of MF as well as PV.[31,32] Ruxolitinib as a single agent, however, has not shown significant clinical benefit in MPN-BP. In a phase 2 study of ruxolitinib in refractory leukemias, only 3 out of 18 patients with MPN-BP showed significant response: 2 with a complete remission and 1 with a complete remission with insufficient recovery of blood counts.[33] Although the 3 responders were *JAK2*V617F-positive, not all the *JAK2*V617F-positive patients responded. A phase 1/2 trial evaluating the use of ruxolitinib at high doses (50-200 mg twice a day) in relapsed or refractory AML resulted in no objective clinical response in any of the patients with MPN but instead was associated with a high incidence of infectious complications.[34] Therefore, single-agent ruxolitinib is not an appropriate therapy for MPN-AP/BP disease and remains best used earlier in the disease course.

Preclinical studies suggested a synergistic role of ruxolitinib in combination with an HMA, and published case reports have shown clinical activity of this combination in MPN-AP/BP.[35,36] A phase 1 trial assessing the combination of ruxolitinib and decitabine in 21 patients with MPN-AP/BP confirmed tolerability of the combination therapy approach and showed a signal of clinical efficacy, with an overall response rate of 53% and median overall survival of 7.9 months.[37] Unexpectedly, overall survival was better in the MPN-BP group (7.6 months) than in the MPN-AP group (5.8 months).[38] A maximum tolerated dose was not achieved, even at 50 mg twice daily. The recommended phase 2 dose of ruxolitinib was determined to be 25 mg twice daily in the first cycle and then 10 mg twice daily for subsequent cycles, with decitabine at 20 mg/m^2 given over 5 days every 4 weeks. An additional phase 1/2 trial is evaluating this combination in relapsed/refractory AML and MPN-BP, but patients with MPN-AP are not included (NCT02257138).

Supportive Therapy

Supportive therapy alone for MPN-BP results in a median survival of 2.5 months.[3,4] This option should be considered only in the setting of significant comorbidities or frailty that preclude the option of clinical trial enrollment or HMA therapy. Also, it is important to consider that this option is equivalent in outcome to induction chemotherapy that is not followed by HSCT. Given these realities, eligible patients with MPN-AP should be considered for a more aggressive treatment approach that begins before they progress to BP disease. Management of cytopenias, transfusion requirements, and symptom burden is a core component of a supportive care–only approach. It is crucial to have an open dialogue with the patient and his or her family regarding the option of hospice care as the disease progresses.

Future Directions

With the recent approval of several molecularly targeted agents for the treatment of AML, the potential utility of these agents in MPN-AP is of great interest. Although approximately one-third of patients with AML harbor a *FLT3* mutation, only 3% of patients with MPN-AP/BP have a *FLT3* mutation.[9] Therefore, the FLT3 inhibitor midostaurin (Rydapt, Novartis), which received US Food and Drug Administration (FDA) approval in 2017 for frontline treatment and consolidation of AML, is of limited clinical utility in MPN-AP/BP. *IDH1* and *IDH2* mutations are more common in MPN-AP/BP, with each reported to be present in 13% of patients with either condition.[9] Both the *IDH1* inhibitor ivosidenib (Tibsovo, Agios) and the *IDH2* inhibitor enasidenib (Idhifa, Celgene) have been approved as monotherapy for relapsed/refractory AML. These agents are currently

Table. Therapies in Ongoing Studies Enrolling Patients With MPN-AP

Agent	Phase	Study Name (Identifier)
Enasidenib or ivosidenib	1	Safety Study of AG-120 or AG-221 in Combination With Induction and Consolidation Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia With an *IDH1* and/or *IDH2* Mutation (NCT02632708)
Ivosidenib	3	Study of AG-120 (Ivosidenib) vs. Placebo in Combination With Azacitidine in Patients With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation (AGILE) (NCT03173248)
Venetoclax + ivosidenib	1b/2	Study of Venetoclax With the mIDH1 Inhibitor Ivosidenib (AG120) in IDH1-Mutated Hematologic Malignancies (NCT03471260)
Selumetinib	1	Study of MEK Inhibitor Selumetinib in Combination With Azacitidine in Patients With Higher Risk Chronic Myeloid Neoplasia (NCT03326310)
Pembrolizumab	1	PD-1 Inhibition in Advanced Myeloproliferative Neoplasms (NCT03065400)

MPN-AP, myeloproliferative neoplasm in accelerated phase; PD-1, programmed death 1.

being evaluated in combination with chemotherapy and HMA therapy in newly diagnosed AML, with most trials including MPN-BP (NCT02632708 and NCT03173248; Table). A phase 1 trial of combination enasidenib and ruxolitinib in patients with MPN, including compound mutant MPN-AP/BP, will soon open through the Myeloproliferative Neoplasm Research Consortium (MPN-RC). Preclinical studies reveal therapeutic cooperativity between ruxolitinib and enasidenib.

The BCL-2 inhibitor venetoclax (Venclexta, AbbVie/Genentech) was recently approved in combination with an HMA or low-dose cytarabine for patients with newly diagnosed AML who are older than 75 years or have comorbidities that preclude the use of intensive induction chemotherapy. The combination of venetoclax and an HMA resulted in a 67% overall response rate and median overall survival of 17.5 months in treatment-naive elderly patients with AML, and was generally well tolerated.[39] A phase 1/2 single-institution trial evaluating combination venetoclax and ivosidenib in advanced hematologic malignancies, including MPN-AP/BP, is currently under way (NCT03471260).

Approximately 6% of patients with MPN harbor activating mutations in the *RAS* signaling pathway that are associated with a proliferative disease state; these mutations are more prevalent in MPN-AP/BP than chronic MPNs.[40] MEK inhibitors target the Ras/Raf/MEK/ERK intracellular signaling cascade and are actively being tested in combination with azacitidine in advanced myeloid neoplasms, including MPN-AP (NCT03326310).

Dysregulation of the immune system in MPNs is evident, with many patients experiencing autoimmune phenomena.[41] Recent evidence implicates *JAK2*V617F-mediated STAT pathway induction of programmed death ligand 1 (PD-L1) expression in *JAK2*V617F-mutant monocytes, platelets, and megakaryocytes.[42] Immune checkpoint blockade using PD-L1 and programmed death 1 (PD-1) inhibitors activates the host immune system to target cancer cells and has shown efficacy in an array of solid tumors and hematologic malignancies. Pembrolizumab (Keytruda, Merck), a humanized antibody that blocks the receptor expressed on lymphocytes, is currently under investigation in a dual-institution phase 2 study in advanced MPNs, including MPN-AP/BP, that did not respond to HMA therapy (NCT03065400).

Conclusion

MPN-AP is a disease state that requires prompt recognition and therapeutic intervention, given the associated poor overall survival and eventual progression to MPN-BP. It is believed that sequential acquisition of both genetic and epigenetic alterations contributes to the progression of patients with MPN from chronic phase to AP and then ultimately to BP. Enhanced understanding of the molecular underpinnings of this process has led to the development of integrated clinical and molecular-driven prognostication tools and the evaluation of mechanism-based therapeutics. At this time, HSCT remains the only potential curative treatment option for a limited subset of eligible patients with advanced-phase MPNs. Cytotoxic chemotherapy improves outcome only when consolidative HSCT is available, and therefore should not be used alone as first-line therapy. HMA therapy is a less intensive ambulatory treatment option for patients with MPN-AP that can decrease morbidity and prolong survival in a subset of patients. Combination JAK inhibitor and HMA therapy is feasible but not clearly superior to HMA therapy alone. Given the poor outcome of MPN-AP/BP and the lack of a commercially approved disease course–modifying therapy, patients should be considered for enrollment in a clinical trial when available.

Disclosures

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