Prevention and treatment of transformation of myeloproliferative neoplasms to acute myeloid leukemia

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Abstract

Philadelphia-chromosome negative myeloproliferative neoplasms (MPN) are hematopoietic stem disorders with a risk of progression to an accelerated phase (AP) or blast phase (BP) that is influenced by clinical, pathological, cytogenetic, and molecular variables. Overall survival of patients with MPN-AP/BP is limited with current treatment approaches, particularly in those patients who cannot receive an allogeneic hematopoietic stem cell transplant (allo-HCT). In addition, long-term survival with allo-HCT is predominantly seen in chronic-phase MPN, which suggests that the ideal time for intervention may be before the MPN evolves to AP/BP. In this review we focus on the risk factors for progression to MPN-AP/BP, identification of high-risk chronic-phase MPN, potential early-intervention strategies, and considerations around the timing of allo-HCT. We also summarize current survival outcomes of patients with MPN-AP/BP, discuss the uncertainty around how to best gauge response to therapy, and outline clinical trial considerations for this population of patients. Lastly, we highlight future directions in the management of high-risk MPN.

Introduction

Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) are clonal hematopoietic stem cell disorders characterized by JAK/STAT pathway activation which carry a variable risk of progression to an accelerated (10-19% blasts) or blast phase (≥20% blasts) of disease (MPN-AP/BP).[1,2] This risk is affected by a number of factors, including disease phenotype, clinical features, cytogenetics, and the presence of somatic mutations.[3,4] The median overall survival is less than 6 months in MPN-BP with durable remissions typically only seen in patients who undergo allogeneic hematopoietic stem cell transplantation (allo-HCT).[5] Of note, the presence of ≥5% blasts in the bone marrow or peripheral blood is associated with limited overall survival and may be indicative of a disease in evolution to MPN-AP and therefore treated similarly.[6,7]

Historical outcomes with intensive chemotherapy in MPN-BP have been quite poor with median overall survival ranging from 4-9 months.[8-10] While there have been therapeutic advances in the treatment of acute myeloid leukemia (AML) over the last several years, these have not translated into the same sort of advancement for MPN-AP/BP. A retrospective analysis of outcomes of patients with MPN-AP/BP who were diagnosed in 2017 or later demonstrated a median overall survival of less than 12 months even with increased use of AML-directed therapies that have been approved.[11] Furthermore, MPN-AP/BP is a molecularly and morphologically distinct disease from *de novo* AML.[12-16] Treatment with venetoclax-based regimens has produced a median overall survival of 4-8 months in MPN-AP/BP;[17-20] this may be in part due to the dependence on BCL-XL rather than BCL-2 noted in this disease and the prevalence of *TP53* alterations (which are associated with inferior outcomes in *de novo* AML as well).[21-24] Given the role of JAK inhibitors in chronic-phase MPN, prospective studies of ruxolitinib-containing regimens have been pursued but there have been similarly limited survival outcomes.[25-27] One promising approach may be IDH inhibition, given the relative enrichment of *IDH1* and *IDH2* mutations in MPN-AP/BP; retrospective studies demonstrated durable remissions with IDH inhibitors although median overall survival still ranged from 10-15 months.[28-30] Table 1 summarizes the outcomes of patients treated with these strategies.

While improving the therapeutic armamentarium for MPN-AP/BP is a critical part of advancing care, there are a number of considerations in the management of high-risk MPN that need to be addressed, ranging from the time of intervention to the development of well-validated response

criteria. In this review article we aim to review the following: current prognostic tools available to identify patients at high risk of progression of MPN-AP/BP, the rationale for early intervention in patients with chronic-phase MPN in an effort to reduce risk of progression, timing of allo-HCT in eligible candidates, development of response criteria that better capture the benefit of treatment in MPN-AP/BP, and considerations around trial design to investigate novel therapeutics in this space.

Progression of disease to accelerated/blast phase myeloproliferative neoplasm

While a number of prognostic tools have been developed for primary myelofibrosis (PMF), currently there is no global risk stratification for chronic-phase MPN that captures the risk of progression to MPN-AP/BP. Acquisition of high-risk mutations in the chronic phase of disease is a key event

Table 1. Outcomes of patients with accelerated/blast-phase myeloproliferative neoplasms treated with select novel regimens.

First author (year), reference	Study	Treatment	Response rate	Overall survival
Venetoclax-containing regimens				
Tremblay *et al.* (2020)[17]	Retrospective analysis of 9 patients with MPN-AP/BP (frontline and R/R treatment)	HMA-venetoclax	CR/CRi rate: 33%	mOS: 4 months
Gangat *et al.* (2021)[19]	Retrospective analysis of 32 patients with MPN-BP (frontline and R/R treatment)	HMA-venetoclax	CR/CRi rate: 44%	mOS: 8 months
Masarova *et al.* (2021)[20]	Retrospective analysis of 31 patients with MPN-BP (frontline and R/R treatment)	Venetoclax-including regimens	CR/CRi rate: 23%	mOS: 4 months
King *et al.* (2021)[18]	Retrospective analysis of 27 patients with MPN-AP/BP (frontline and R/R treatment)	Venetoclax-including regimens	ALR-C/CCR rate: 37%	MPN-BP mOS:: 6 months MPN-AP mOS: 3.6 months
Systchenko *et al.* (2023)[85]	Retrospective analysis of 5 patients with MPN-BP (frontline)	Azacitidine + venetoclax + ruxolitinib	CR/CRi rate: 40%	mOS: 13.4 months
JAK inhibitor-including regimens				
Drummond *et al.* (2020)[25]	Phase Ib study of 34 patients with MPN-AP (N=19) and MPN-BP (N=15)	Ruxolitinib + azacitidine	MPN-AP CR/mCR rate: 26% MPN-BP ALR-P rate: 27%	1-year OS: 42%
Bose *et al.* (2020)[26]	Phase I/II study of 29 patients with MPN-BP (prior ruxolitinib exposure allowed)	Ruxolitinib + decitabine	ORR: 45%	mOS: 6.9 months
Mascarenhas *et al.* (2020)[27]	Phase II study of 25 patients with MPN-AP/BP (prior ruxolitinib exposure allowed)	Ruxolitinib + decitabine	ORR: 44%	mOS: 9.5 months
IDH inhibitor-including regimens				
Patel *et al.* (2020)[28]	Retrospective analysis of 8 patients with *IDH2*-mutated MPN-AP/BP (frontline and R/R treatment)	Enasidenib-including regimens	ORR: 37.5%	NR (median follow-up 9 months)
Chifotides *et al.* (2020)[29]	Retrospective analysis of 12 patients with *IDH1*- or *IDH2*-mutated MPN-BP (frontline and R/R treatment)	IDH inhibitor-including regimens	CR rate: 25%	mOS: 10 months
Bar-Natan *et al.* (2022)[86]	Ongoing phase II study of 5 patients with *IDH2*-mutated MPN-AP/BP	Ruxolitinib + enasidenib	CR rate: 40%	NR
Gangat *et al.* (2023)[30]	Retrospective analysis of 14 patients with *IDH1*- or *IDH2*-mutated MPN-BP (frontline and R/R treatment)	Ivosidenib monotherapy for *IDH1*-mutated patients Enasidenib monotherapy for *IDH2*- mutated patients	CR/CRi rate: 36%	mOS: 14.9 months

MPN: myeloproliferative neoplasm; AP: accelerated phase; BP: blast phase; R/R: relapsed/refractory; HMA: hypomethylating agent; CR: complete remission; CRi: complete remission with incomplete hematologic recovery; mOS: median overall survival; ALR-C: acute leukemia response - complete; ALR-P: acute leukemia response - partial; CCR: complete cytogenetic response; ORR: overall response rate; NR: not reported.

in the progression of MPN, but which mutations have prognostic impact varies across polycythemia vera (PV), essential thrombocythemia (ET), and PMF.[31] Table 2 summarizes mutations associated with a prognostic impact on the development of MPN-BP.

In PMF, the predominant influencers of survival outcomes are age, peripheral blood count abnormalities, and cytogenetics. Specific components have greater prognostic value regarding the development of MPN-BP. For example, development of the Dynamic International Prognostic Scoring System (DIPSS)-plus score identified thrombocytopenia and unfavorable karyotype as predictors of 10-year risk of MPN-BP.[32] More recent scores have incorporated high-risk molecular mutations as well, which can aid in identification of high-risk patient populations. Individual mutations are also associated with inferior outcomes; these have been incorporated into the Mutation-Enhanced International Prognostic Scoring System (MIPSS)70-plus; patients with a very high risk score had a 23% incidence of progression to MPN-BP.[33] A more recent analysis by Loscocco *et al.* incorporated mutational status of *CBL*, *NRAS*, *KRAS*, *RUNX1*, and *TP53* in conjunction with MIPSS-based prognostic scores; multivariate analysis demonstrated significant contributions from *ASXL1*, *SRSF2*, *U2AF1 Q157*, and *EZH2* but not from *IDH1*, *IDH2*, *TP53*, *CBL*, *NRAS*, or *KRAS*.[34] This suggests that even with molecular scores that have been incorporated into clinical practice, we still have not fully identified the mutations that are truly high risk in the context of PMF. Considerations around the timing of allo-HCT in the context of high-risk PMF mutations are discussed in a later section.

Prevention of progression to MPN-AP/BP by way of risk-assessment of PMF patients and referral for allo-HCT remains a cornerstone of therapeutic strategy. However, while the potential role of allo-HCT is well-established in PMF, it is less clear how to intervene in patients with PV and ET for whom there is considerable concern about disease progression. Typically strategies for both entities in the chronic phase center around reduction in thrombotic risk[35] but with little emphasis on assessment (or treatment options) for disease evolution. In addition, the progression to MPN-AP/BP for PV and ET does not always have a fibrotic stage; an analysis by Paz *et al*. of 49 patients who developed MPN-BP from an underlying PV or ET noted that only 16% of those patients had secondary myelofibrosis prior to MPN-BP progression.[36] Time to MPN-BP development can be highly variable based on the mutational profile that is present; mutations in *IDH1*, *IDH2*, *RUNX1*, and *U2AF1* are associated with shorter latency while *TP53*, *NRAS*, and *BCORL1* mutations are associated with longer time to MPN-BP development.[36] Given the molecular heterogeneity seen in PV and ET that progresses to MPN-BP, therapeutic intervention that has an anti-clonal effect in the chronic phase may be a means of preventing disease progression. The MAJIC-PV trial was a randomized phase II trial of ruxolitinib compared to best available therapy in patients with hydroxyurea-treated PV; the primary endpoint of complete response was met in the ruxolitinib arm. The study also analyzed outcomes based on molecular response, which was defined as a >50% reduction in *JAK2* V617F variant allele frequency. Achievement of a molecular response in patients treated with ruxolitinib was significantly associated with improved event-free survival and overall survival.[37] Of note, those patients with concurrent *ASXL1* mutations who received ruxolitinib were unlikely to achieve a molecular response.[37] The depth of molecular response also appears to have an impact on outcomes. Guglielmelli *et al*. analyzed 75 *JAK2*-mutated patients with PV or ET who received treatment with ruxolitinib and characterized *JAK2* molecular response as complete (<0.01%), deep (<2%), or partial (50% reduction in variant allele frequency). In the 14 patients who achieved a complete or deep response, none had progression to MF or MPN-BP; on the other hand, all three patients who progressed to MPN-BP did not have a molecular response.[38] Previous studies investigating the use of interferon in PV and ET have demonstrated the potential for achieving sustained molecular responses as well.[39-42] As such, clinical trials in ET and PV patients which focus on preventing clonal evolution and progression-free survival remain an area in need of further investigation.[43]

In addition to the molecular drivers of disease progression, the inflammatory micro-environment present in chronic-phase MPN is a key component of disease progression.[44] For example, interleukin-8 has been implicated in the progression of PMF to MPN-BP.[45] In addition, single-cell multi-omic analyses of MPN identified the contribution of chronic inflammation to providing an advantage to *TP53*-mutated cells and allowing for subsequent development of *TP53*-mutated MPN-BP.[46] The role of inflammation in myeloid disease progression goes beyond MPN; inflammation in clonal hematopoiesis of indeterminate potential confers a selective advantage and clonal expansion, which ultimately gives rise to overt myeloid malignancy.[47] Studies are investigating the role of anti-inflammatory therapies such as canakinumab in a variety of chronic myeloid diseases from clonal hematopoiesis of indeterminate potential to lower-risk myelodysplastic syndromes and chronic myelomonocytic leukemia, as well as MPN (NCT05641831, NCT04239157, NCT05467800). Whether such strategies alter clonal progression remains to be determined.

Allogeneic hematopoietic stem cell transplantation in high-risk myeloproliferative neoplasms

When patients with chronic-phase MPN enter the fibrotic stage of disease, considerations toward allo-HCT are primarily

Table 2. Prognostic mutations in chronic-phase myeloproliferative neoplasms with a focus on leukemia-free survival.

Mutation	Notes	Frequencies in MPN, %	References
DNA methylation			
IDH1/2	*IDH1* associated with inferior LFS in PMF *IDH2* associated with inferior LFS in PV *IDH2* associated with inferior LFS in PMF	PV: 3 PMF: 6 ET: 9 MPN-AP/BP: 19-26	14-16, 54, 87-89
Chromatin modification			
ASXL1	Associated with inferior LFS in PMF	PV: 7 PMF: 30 ET: 2 MPN-AP/BP: 25-47	14-16, 87-90
EZH2	Associated with inferior LFS in PMF	PV: 2 PMF: 5-7 ET: 1 MPN-AP/BP: 7-15	14-16, 87, 89
Splicing			
SRSF2	Associated with inferior LFS in PV Associated with inferior LFS in PMF	PV: 3 PMF: 9-14 ET: 2 MPN-AP/BP: 13-22	14-16, 87-89
SF3B1	Associated with inferior LFS in ET	PV: 10 PMF: 9-14 ET: 5 MPN-AP/BP: 7	14-16, 88, 89
DNA repair			
TP53	Associated with inferior LFS in ET	PV: 5 PMF: 5 ET: 6 MPN-AP/BP: 16-36	14-16, 88, 89

MPN: myeloproliferative neoplasm; PMF: primary myelofibrosis; LFS: leukemia-free survival; PV: polycythemia vera; ET: essential thrombocytosis; AP/BP: accelerated phase/blast phase.

driven by the patient's characteristics and risk profile. In the absence of approved therapies that meaningfully reduce the rate of progression to MPN-BP in myelofibrosis,[48] allo-HCT is thought to be the only modality with a curative potential that can impact the natural progression of myelofibrosis. Retrospective studies have identified a benefit from allo-HCT in patients with intermediate-2 or high-risk disease by DIPSS score; the benefit of allo-HCT in low/intermediate-1 risk disease is not as clear.[49,50] It is even less clear how to incorporate high-risk mutations into the decision-making around allo-HCT in myelofibrosis. Several studies have investigated the impact of high-risk mutations on allo-HCT outcomes in myelofibrosis with conflicting results, as summarized in Table 3.[51-56] While *TP53* mutations are not represented in myelofibrosis prognostic scores, the impact of *TP53* status on allo-HCT outcomes in patients with myelofibrosis has been analyzed. In a cohort of 349 patients with myelofibrosis who underwent allo-HCT, 49 patients had a *TP53* mutation. The median overall survival was 1.5 years in the *TP53*-mutated patients compared to 13.5 years for the *TP53* wild-type patients; the worst outcomes were noted in those with multi-hit *TP53* aberrations while those with a single-hit *TP53* aberration had a similar outcome to *TP53* wild-type patients.[57] Overall, strong consideration of allo-HCT should be given to eligible patients with intermediate-2/high-risk disease according to DIPSS score; the situation in patients with high-risk disease based on mutational profile is less clear. We would also strongly consider allo-HCT in patients with a single-hit *TP53* mutation. Regardless, the timing of allo-HCT is a key consideration in preventing disease progression to MPN-AP/BP, and optimal decision-making regarding the timing of transplant remains a key unresolved issue in myelofibrosis.

In patients with progression of disease to MPN-AP/BP, allo-HCT is the only modality with curative potential. Historically, consideration has been given to reducing blast burden prior to allo-HCT; however, that may not be necessary in all patients with MPN-AP. Gagelmann *et al*. reported on 35 patients with accelerated-phase myelofibrosis at the time of allo-HCT; although rates of relapse were higher in these patients than in those with chronic-phase myelofibrosis at the time of allo-HCT, durable remissions were observed in this population, with a 5-year overall survival rate of 65%.[58] Unfortunately, allo-HCT outcomes in MPN-BP are not as robust as those seen in MPN-AP. An analysis by the European Society for Blood and Marrow Transplantation (EBMT) of 663 patients with MPN-BP who underwent allo-HCT reported a 3-year overall survival of 36%; smaller analyses have reported survival outcomes ranging from a 5-year overall survival

Table 3. Impact of mutations on outcomes of patients with myelofibrosis who undergo allogeneic hematopoietic stem cell transplantation.

First author (year), reference	Disease and N of patients	N of genes tested	Conditioning regimen, %	Survival data %	Notes
Kroger *et al.* (2017)[54]	169 MF patients who underwent allo-HCT	16	MAC: 2 RIC: 98	5-year PFS: 48 5-year OS: 52	*CALR* mutation associated with improved OS *IDH2* mutation associated with inferior RFS *ASXL1* mutation associated with inferior RFS
Gagelmann *et al.* (2019)[51]	361 MF patients who underwent allo-HCT (201 in a training cohort, 156 in a validation cohort)	18	MAC: 36 RIC 64	5-year OS by MTSS risk group (validation cohort): Low: 83 Int: 64 High: 37 Very high: 22	*ASXL1* mutation associated with inferior OS Non-*CALR/MPL* driver mutation associated with inferior OS
Tamari *et al.* (2019)[52]	101 MF patients who underwent allo-HCT	585	MAC: 18 RIC: 82	5-year RFS: 51 5-year OS: 52	*U2AF1* mutation associated with inferior OS and RFS *DNMT3A* mutation associated with inferior RFS ≥3 somatic mutations not associated with worse OS compared to ≤2 somatic mutations MAC associated with improved OS High-risk MIPSS70 not associated with inferior OS compared to intermediate-risk MIPSS70
Ali *et al.* (2019)[53]	110 MF patients who underwent allo-HCT	72	RIC: 100	5-year PFS: 60 5-year OS: 65	*CBL* mutation associated with inferior OS and DFS *U2AF1* mutation associated with increased NRM MIPSS70 high-risk group with worse OS and DFS compared to int-risk group MIPSS70+ v2.0 very high-risk group with worse OS and DFS when compared to high-risk group.
Stevens *et al.* (2020)[56]	55 MF patients who underwent allo-HCT	54	MAC: 75 RIC: 25	10-year OS in DIPSS+ low/int-1 risk: 82 10-year OS in DIPSS+ int-2/high risk: 50 10-year PFS in DIPSS+ low/int-1 risk: 82 10-year PFS in DIPSS+ int-2/high risk: 46	≥3 somatic mutations in addition to *JAK2* or *CALR2* mutation associated with worse PFS in comparison to ≤2 mutations regardless of DIPSS+ score
Jain *et al.* (2022)[55]	42 MF patients who underwent allo-HCT with non-myeloablative conditioning and PTCy	63	RIC: 100	OS: 1-year 65 3-year 60 RFS: 1-year 65 3-year 31	*CALR* mutation associated with higher risk of relapse

Continued on following page.

First author (year), reference	Disease and N of patients	N of genes tested	Conditioning regimen, %	Survival data %	Notes
Gagelmann *et al.* (2023)[57]	349 MF patients who underwent allo-HCT including 30 patients with multi-hit *TP53* aberrations and 19 with single-hit *TP53* aberrations	Not reported	*TP53*^{wt} MAC: 13% RIC: 87% *TP53*^{SH} MAC: 53% RIC: 47% *TP53*^{MH} MAC: 50% RIC: 50%	6-year OS: *TP53*^{wt}: 64 *TP53*^{SH}: 56 *TP53*^{MH}: 25	*TP53*^{MH} status associated with inferior OS and RFS on multivariate analysis

MF: myelofibrosis; allo-HCT: allogeneic hematopoietic stem cell transplant; MAC: myeloablative conditioning; RIC: reduced-intensity conditioning; PFS: progression-free survival; OS: overall survival; RFS: relapse-free survival; MTSS: Myelofibrosis Transplant Scoring System; MIPSS: Mutation-Enhanced International Prognostic Score System; DFS: disease-free survival; NRM: non-relapse mortality; DIPSS+: Dynamic International Prognostic Scoring System-plus; PTCy: post-transplant cyclophosphamide; int: intermediate; wt: wild-type; SH: single-hit; MH: multi-hit.

of 18% to a 4-year overall survival of 38%.[59,60] Of note, blast reduction below 5% was not associated with improved outcomes related to allo-HCT.[59] Strong consideration of allo-HCT should be given to eligible patients with MPN-BP; however, the depth of response necessary prior to moving forward with allo-HCT is unclear. These data suggest that the time to intervene with allo-HCT is during the chronic phase or accelerated phase of the disease; while long-term survival can be seen in a proportion of patients with MPN-BP who undergo allo-HCT, the likelihood of this is considerably lower in patients with chronic-phase or accelerated-phase MPN.

Gauging response to therapy

There is heterogeneity in the assessment of response to therapy for patients with MPN-AP/BP. While well-established and recently revised response criteria exist for AML and higher-risk myelodysplastic syndrome,[61,62] the most recent MPN-AP/BP specific criteria come from 2012.[63] These criteria were developed to account for two aspects of disease: the AP/BP component and the chronic-phase MPN. For example, marrow fibrosis, leukoerythroblastosis, and eradication of molecular markers associated with the MPN clone are part of the 2012 response criteria. In addition, AML-specific response criteria do not have the same correlation with survival outcomes in MPN-AP/BP as they do in *de novo* AML. Blast reduction had no prognostic impact in patients with MPN-BP who received allo-HCT and outcomes of patients with MPN-BP and <5% blasts at the time of allo-HCT are considerably worse than those with AML and <5% blasts at the time of allo-HCT.[59,60,64] Potential reasons for discordance between AML-specific response criteria and MPN-BP criteria include the discrepancy between peripheral blood and bone marrow blasts seen in MPN, the spleen serving as a site of extramedullary transformation, and clonally distinct hematopoietic stem cell populations found in the spleen compared to the blood.[65,66] Furthermore, there can be considerable variance between serial peripheral blast counts in patients with MPN-AP/BP that can confound assessment. Table 4 compares assessment of response between the 2022 European LeukemiaNet (ELN) AML criteria, 2012 MPN-BP criteria, and modified Cheson criteria.

Large analyses to confirm which response criteria best predict survival in the absence of allo-HCT have not been conducted. This leads to considerable variance in response assessment even when specifically evaluating prospective trials for MPN-AP/BP. As an example, in the three trials of DNMT inhibitors + JAK inhibitors summarized in Table 1,[25-27] responses were assessed with myelodysplastic syndrome-based criteria, 2012 MPN-BP criteria, standard AML-based criteria, and modified AML-based criteria.[67,68] As novel therapeutics continue to be investigated specifically in MPN-AP/BP, harmonization of response criteria is vital to characterize benefit. Given the similar nature of disease once blast percentage is ≥10% in MPN, utilizing the traditional cutoff of 20% to determine what sort of response criteria should be used is unlikely to be helpful. Ultimately, response criteria that capture reduction in blast percentage and improvement in peripheral blood counts may be the most helpful; the addition of cytogenetic and molecular response may offer insight into the depth of remission and how that impacts long-term survival. The utility of incorporating chronic-phase MPN features such as bone marrow fibrosis is less clear given no strong correlation with efficacy outcomes in myelofibrosis.[69] Analysis of existing response criteria is needed in order to identify clinically meaningful criteria with which to assess novel therapeutics for MPN-AP/BP. In Table 5 we propose the endpoints that may be most meaningful when evaluating novel therapies in MPN-AP/BP, recognizing that each endpoint has both advantages and disadvantages. In addition, validated MPN patient-reported outcome tools should be routinely incorporated into MPN-AP/BP trials to capture impact beyond response and survival outcomes.[70]

Table 4. Comparison of 2022 European LeukemiaNet Acute Myeloid Leukemia response criteria, 2012 Myeloproliferative Neoplasm-Blast Phase response criteria, and modified Cheson criteria.

2022 ELN AML criteria[61]	2012 MPN-BP response criteria[63]	Modified Cheson criteria from MPN-RC 109 trial[27]
CR: Bone marrow blasts <5%; absence of circulating blasts; absence of extramedullary disease; ANC ≥1.0x10^9/L; platelet count ≥100x10^9/L	CMR: 0% peripheral blasts; ANC ≥4.0x10^9/L, hemoglobin ≥10 g/dL, platelet count ≥100x10^9/L; ≤5% bone marrow blasts with resolution of abnormal morphology, appropriate cellularity, and grade ≤1 fibrosis; non-palpable spleen; normal karyotype and no detectable molecular abnormalities associated with leukemic or MPN clone CCR: all criteria of CMR except molecular markers of MPN clone persist	CR: 0% peripheral blood blasts, WBC ≥4.0x10^9/L, hemoglobin ≥10 g/dL, and platelet count ≥100x10^9/L
CRh: ANC ≥0.5x10^9/L and platelet count ≥ 50 x10^9/L with all other CR criteria met CRi: all CR criteria except for residual neutropenia or thrombocytopenia	ALR-C: absence of peripheral blasts; ≤5% bone marrow blasts; <25% increase in spleen size by palpation or imaging if baseline spleen <10 cm or <50% if baseline spleen ≥10 cm; loss of cytogenetic or molecular markers associated with leukemic clone (markers associated with chronic-phase MPN can persist)	CRi: fulfilling criteria of CR except for ANC ≤1.0x10^9/L; or platelet count ≤100x10^9/L
PR: all hematologic criteria of CR, decrease of bone marrow blast percentage to 5% to 25%, and decrease of pre-treatment bone marrow blast percentage by at least 50%	ALR-P: >50% reduction in peripheral and bone marrow blasts; <25% increase in spleen size by palpation or imaging if baseline spleen <10 cm or <50% if baseline spleen ≥10 cm; no new cytogenetic or molecular abnormalities	PR: ≥50% decrease in peripheral blood blasts irrespective of blood counts
MLFS: Bone marrow blasts, 5%; absence of circulating blasts; absence of extramedullary disease; no hematologic recovery required; at least 200 cells should be numerated in aspirate or cellularity ≥10%	-	-

ELN: European LeukemiaNet; MPN: myeloproliferative neoplasm; BP: blast phase; MPN-RC: MPN Research Consortium; CR: complete remission; ANC: absolute neutrophil count; CMR: complete molecular remission; CCR: complete cytogenetic remission; CRh: CR with partial hematologic recovery; CRi: CR with incomplete hematologic recovery; ALR-C: acute leukemia response-complete; PR: partial remission; ALR-P: acute leukemia response-partial; MLFS: morphological leukemia-free state.

Prospective trial considerations in accelerated/blastic phase myeloproliferative neoplasms

Inclusion of patients with MPN-AP/BP into prospective trials is a uniquely vexing problem; chronic-phase MPN studies will often have a blast cutoff and trials focused upon myelodysplastic syndromes and AML will exclude patients with an antecedent MPN. This ultimately leads to treatment data being generated by real-world analyses given the paucity of prospective data available. As an example, CPX-351 was specifically investigated in patients with secondary AML, but patients with an antecedent MPN were excluded.[71] The currently available data for CPX-351 in MPN-AP/BP stem from a real-world analysis of 12 patients.[72] Furthermore targeted-therapy myeloid disease initiatives such as BEAT AML and MyeloMATCH do not currently have trials specifically designed for MPN-AP/BP.[73,74] In an effort to identify novel therapeutics with potential efficacy, we propose the inclusion of MPN-AP/BP cohorts in early-phase studies focused on chronic-phase MPN. In addition, the inclusion of MPN-AP/BP with the appropriate molecular marker should be strongly considered in targeted therapy protocols.

Conclusion and future directions

Despite the expansion of therapies in the management of myeloid malignancies, the treatment of MPN-AP/BP remains challenging. Figure 1 outlines current management approaches in the prevention and management of MPN-AP/BP while also considering novel strategies under investigation. In our estimation, the strategies to meaningfully impact how we approach these disease are as follows: identification of those patients with chronic-phase MPN at highest risk of progression to MPN-AP/BP, development of strategies with the potential to halt or delay progression, considerations around the timing of allo-HCT, harmonization of MPN-AP/BP response criteria, and inclusion of MPN-AP/

BP in early-phase studies focused on myeloid malignancies to identify therapeutics that merit further development in this space. Studies focused on PV and ET are investigating not just the primary endpoints of hematologic control, but also generating data on molecular response and how that may impact disease progression. Similar efforts are underway in myelofibrosis with a call to move beyond spleen response and symptom assessment in an effort to better

Table 5. Proposed endpoints in clinical trials of patients with accelerated/blast-phase myeloproliferative neoplasms.

Endpoint	Definition	Advantages	Disadvantages	Ideal type of trial for incorporation
Overall survival	Time from randomization (or enrollment) until death from any cause	Most robust clinical endpoint High event rate due to current limited OS in MPN-AP/BP	May be impacted by post-protocol interventions/ therapies (e.g., allo-HCT) Difficult to utilize in early-phase MPN studies that include but are not restricted to MPN-AP/BP	Primary endpoint in randomized phase III study or single-arm phase II study with historical control
Complete molecular response	Resolution of somatic mutations that developed at time of progression to MPN-AP/BP	Molecular response has been associated with EFS and OS in chronic-phase MPN[37] May provide best measure of the depth of response	Heterogeneity in sensitivity of molecular testing May not be feasible in patients who do not have comprehensive molecular data at the time of chronic-phase MPN	Correlative/exploratory endpoint in studies but not a primary endpoint
Complete cytogenetic response	Resolution of cytogenetic abnormalities that developed at time of progression to MPN-AP/BP	Cytogenetic response has been incorporated into both myelofibrosis and MPN-BP response criteria[63,91]	May not be feasible in patients who do not have cytogenetic studies performed at the time of chronic-phase MPN	Correlative/exploratory endpoint in studies but not a primary endpoint
Complete blast response*	Blast percentage <5% in peripheral blood and bone marrow	Has been prospectively studied in MPN-AP/BP[27] Accounts for underlying chronic-phase MPN and persistence of peripheral blasts (i.e., reversion of chronic-phase disease)	Blast reduction may not be an appropriate indicator of disease control[59]	Primary endpoint in phase II studies to determine efficacy
Partial blast response*	≥50% decrease in blast percentage in peripheral blood and bone marrow	Has been prospectively studied in MPN-AP/BP[27] May capture efficacy even if blasts not completely eradicated	Partial blast response may not correlate as well with long-term outcomes such as OS	Incorporated into an overall response primary endpoint in phase II studies to determine efficacy
Hematologic improvement	Erythroid response (pretreatment, <11 g/dL): Hb increase by ≥1.5 g/dL and 50% reduction of RBC transfusions Platelet response (pretreatment, <100x10^9/L): absolute increase of ≥30x10^9/L for patients starting with >20x10^9/L platelets or increase from <20x10^9/L to >20x10^9/L and by at least 100% Neutrophil response (pretreatment, <1.0x10^9/L): at least 100% increase and an absolute increase >0.5x10^9/L	Utilized in MDS criteria to assess improvement of hematologic parameters independent of blast control[62] May capture clinical benefit of therapies that address the AP/BP component of disease while also improving the underlying chronic-phase MPN	There are few data confirming the benefit of hematologic improvement in MPN-AP/BP	Secondary/exploratory endpoint incorporated into studies

*Blast response criteria are applicable to peripheral blood and/or bone marrow if there are ≥10% blasts. OS: overall survival; MPN: myeloproliferative neoplasm; AP/BP: accelerated phase/blast phase; allo-HCT: allogeneic hematopoietic stem cell transplant; EFS: event-free survival; Hb; hemoglobin; RBC: red blood cell; MDS: myelodysplastic syndrome.

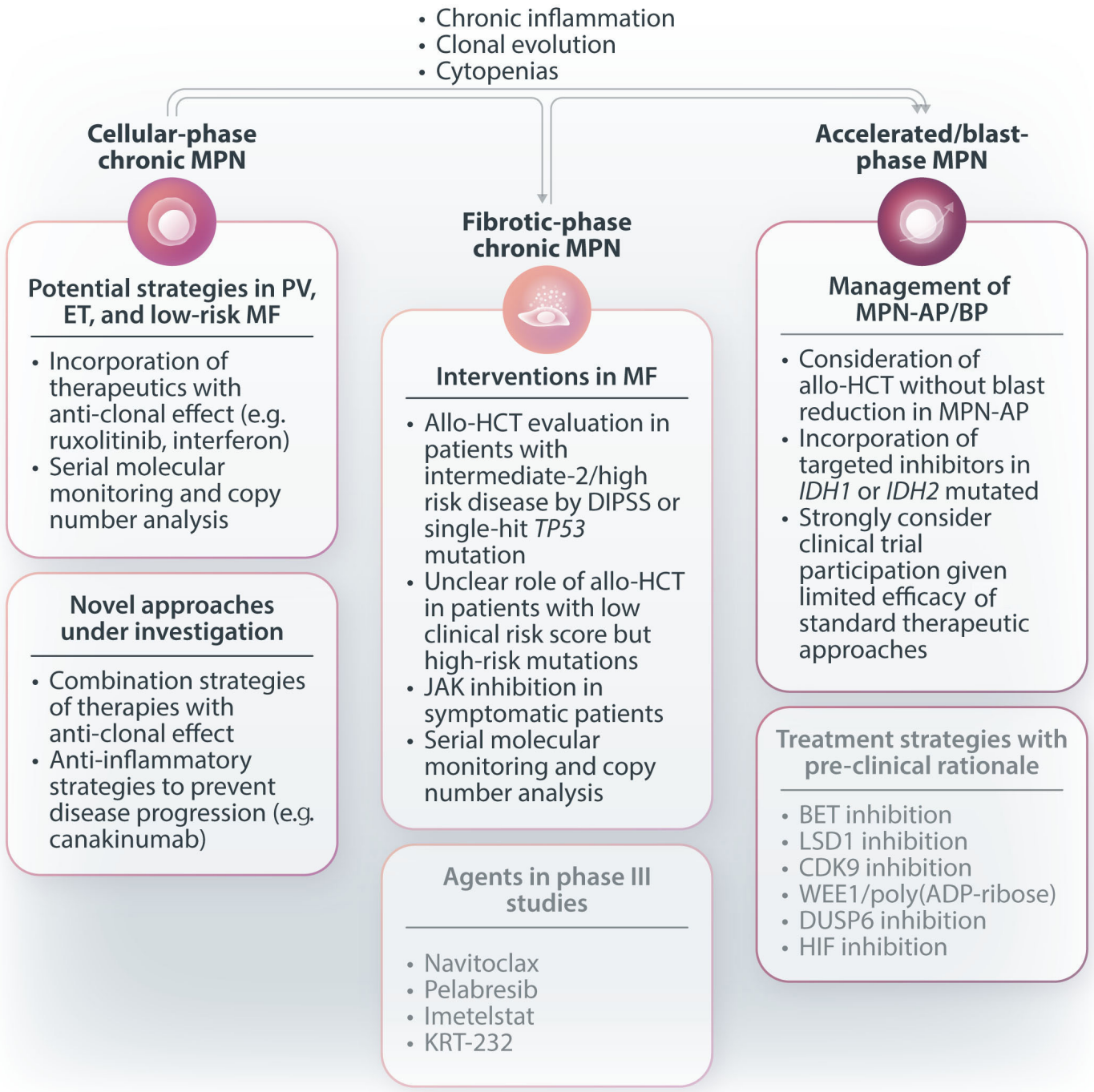

Figure 1. Evolution of accelerated/blast-phase myeloproliferative neoplasms with opportunities for intervention. MPN: myeloproliferative neoplasm; PV: polycythemia vera; ET: essential thrombocythemia; MF: myelofibrosis; allo-HCT: allogeneic hematopoietic stem cell transplantation; DIPSS: Dynamic International Prognostic Scoring System; AP: accelerated phase.

understand what disease modification means and if it can be achieved without allo-HCT.[75] Several combination strategies in myelofibrosis are under investigation, including phase III studies looking at the combinations of ruxolitinib + navitoclax and ruxolitinib + pelabresib that met their primary endpoints; longer-term follow-up may help to identify the impact of these approaches on the natural history of disease.[76-78] There are also encouraging preclinical data to elucidate progression pathways in MPN-AP/BP that could be targeted, such as loss of LKB1/STK11 and aberrant expression of DUSP6.[79,80] In addition, novel strategies such as BET inhibition, LSD1 inhibition, CDK9 inhibition, and combination WEE1/poly(ADP-ribose) polymerase inhibition have provided preclinical data supporting the investigation of these targets in prospective clinical trials.[81-84]

Disclosures

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Contributions

Both authors contributed to the conceptualization, design, and writing of this review article.

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