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Research paper

Outcomes and predictors of survival in blast phase myeloproliferative neoplasms

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ABSTRACT

We retrospectively reviewed treatment outcomes for 57 patients with myeloproliferative neoplasms in blast phase (MPN-BP). The median overall survival (OS) of the entire cohort was 5.8 months. For patients receiving induction therapy, 67% achieved a complete response (CR) and 75% received stem cell transplantation (SCT). Median OS for all transplanted patients (n = 19) was not reached after a median follow-up of 19.2 months compared with 3.8 months in non-transplanted patients ($p < 0.0001$); patients who did not receive SCT after induction chemotherapy survived a median of 4.9 months. OS was not improved in patients transplanted after CR (OS not reached after median follow-up of 26.7 months) compared with those transplanted upfront or after suboptimal response to initial therapy (9.0 months; $p = .097$). Those who were transfusion-dependent during their MPN course and received SCT had a median OS of 4.4 months, with all patients dying from SCT complications. Patients receiving hypomethylating agents (HMA) survived 6.7 months, while those receiving supportive care survived 1.1 months. Although outcomes for MPN-BP remain poor, long-term survival can be achieved in appropriately selected patients utilizing SCT, optimally after attaining a complete response with induction therapy. For patients ineligible for SCT, HMAs can offer similar survival to induction chemotherapy with less toxicity.

1. Introduction

The Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF) [1]. Mortality in patients with MPNs is most commonly due to thrombotic events but less frequently is due to transformation to blast phase, and/or infectious complications [2]. The frequency of evolution to acute leukemia, often termed MPN blast phase (MPN-BP), varies according to MPN subtype, with 10–20% of patients with MF developing BP within 10 years of diagnosis, compared to 2.3% of those with PV and only 0.7% with ET [3–5]. Risk factors for MPN-BP vary by MPN subtype but generally include advanced age [6–8], leukocytosis [4,9,10], exposure to myelosuppressivetherapy, [11] karyotypic abnormalities, as well as increased numbers of mutations in genes associated with myeloid neoplasms [4,12].

The prognosis of patients with MPN-BP is dismal, with a median overall survival (OS) ranging from 2.6-7.0 months [13–16]. Conventional induction chemotherapy for acute myeloid leukemia (AML) has limited efficacy, possibly due to the consequences of the different genomic landscape of MPN-BP or the advanced age of many of the patients [17]. Other therapies, such as hypomethylating agents (HMA), have also been reported to have some clinical activity and their use has been associated with a median survival of 8–9 months [18,19]. Currently, there is no standard of care for managing MPN-BP and no treatment to date has consistently led to prolonged survival and/or hematological remission apart from allogeneic hematopoietic stem cell transplantation (SCT). The risks of transplantation in this patient population, however, are not insignificant [20–22]. SCT may not be a viable option for all patients, and there is little guidance for optimal patient selection.

In this report, we studied patients who developed MPN-BP in order to better characterize the outcomes and to delineate the effects of therapeutic strategies frequently utilized.

2. Methods

This study was approved by the Institutional Review Boards of the Icahn School of Medicine at Mount Sinai (ISMMS) and the Massachusetts General Hospital (MGH). Patients were identified by searching the electronic health record database of each institution from

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Table 1
Schedule and dosing of hypomethylating agents (HMA).

HMA	n	Dose	Schedule	Cycles	Additional Agent
Decitabine	21	20 mg/m2 daily	Days 1–5 per 28 day cycle	Median 2.5 (range 1–32)	Ruxolitinib (n = 5), SGN-CD33a (n = 1)
	3	20 mg/m2 daily	Days 1–10 per 28 day cycle	Median 1 (range1-2)	Bortezomib (n = 2)
	1	10 mg/m2 daily	Days 1–10 per 28 day cycle	1	
	1	15 mg/m2 q8h	Days 1–3 per 28 day cycle	2	
Azacitidine	1	100 mg/m2 daily	Days 1–7 per 28 day cycle	4	

Table 2
Baseline characteristics of the overall study population.

Overall population	N = 57
Type of MPN	
MF	13 (23%)
PV	14 (25%)
ET	25 (44%)
Unclassified	5 (9%)
Sex.	
Male	33 (58%)
Female	24 (42%)
Median age at MPN diagnosis (y)	58 (range 25–85)
Median age at MPN-BP diagnosis (y)	68 (range 40–92)
Median time from MPN to MPN-BP (y)	8.7 (range 0.3–36)
Prior treatment for MPN	
Hydroxyurea	38
Ruxolitinib	11
Anagrelide	9
HMA	8
Lenalidomide	4
SCT	2
RBC transfusion dependent	17/55 (31%)
Constitutional symptoms present	16/54 (30%)
Karyotype	
Favorable	0
Intermediate	17/46 (37%)
Adverse	29/46 (63%)
Mutations at MPN diagnosis	
JAK2	25/40 (62.5%)
Mutations at MPN-BP diagnosis by frequency	
JAK2	28/44 (64%)
ASXL1	3/16 (19%)
NRAS	3/16 (19%)
SRSF2	3/16 (19%)
TET2	3/16 (19%)
TP53	3/16 (19%)
KRAS	2/16 (13%)
RUNX1	2/16 (13%)
NPM1	2/30 (7%)
FLT3-ITD	2/33 (6%)
BCOR	1/16 (6%)
DNMT3A	1/16 (6%)
IDH1	1/16 (6%)
PTPN11	1/16 (6%)
SETBP1	1/16 (6%)
CEBPA	1/31 (3%)

Table 3
Characteristics of patients receiving allogeneic stem cell transplantation (SCT).

Characteristic	SCT population (n = 19)	No SCT (n = 38)	P-value
MPN			
MF	1 (5%)	11 (29%)	P = .045
PV	6 (32%)	8 (21%)	NS
ET	11 (58%)	15 (39%)	NS
Unclassified	1 (5%)	4 (11%)	NS
Sex.			
Male	12 (63%)	22 (58%)	NS
Female	7 (37%)	16 (42%)	
Median age at MPN diagnosis (y)	46 (range 25–63)	64.5 (range 35–85)	P < 0.0001
Median age at MPN-BP diagnosis (y)	61 (range, 40–73)	71.5 (range 44–92)	P < 0.0001
RBC transfusion dependent	4/18 (22%)	13/37 (35%)	NS
Constitutional symptoms	3/17 (18%)	13/36 (36%)	NS
Time from MPN-BP diagnosis to SCT (d)	78 (range 8–183)		
Intensity			
RIC	15 (79%)		
MAC	4 (21%)		
Donor			
Matched sibling	6 (32%)		
Matched donor	12 (63%)		
Haplo-sibling	1 (5%)		
Clinical status at SCT			
In CR	9 (47%)		
Not in CR	10 (53%)		
Disease relapse after SCT	4/19 (21%)		
Early mortality after SCT (within 120 days)	4/19 (21%)		
Median OS	Not reached	3.8 months	P < 0.0001

RIC = reduced-intensity conditioning, MAC = myeloablative conditioning, NS = not significant.

2006 to 2016 for any combination of an MPN (PV, ET, MF) and acute leukemia. Appropriate patients were identified and included if they had a history of an MPN and were subsequently diagnosed with MPN-BP based on having a peripheral blood or bone marrow blast count greater than or equal to 20%, or if they had a myeloid sarcoma (1 patient). Relevant data regarding baseline characteristics, karyotype, clinical mutational profile, prior therapies, and patient outcomes were extracted from the medical charts.

2.1. Treatments and response

The treatments received for MPN-BP were categorized based on therapeutic intensity. Induction therapy included patients treated with "7 + 3" cytarabine plus an anthracycline, including one patient treated on a protocol utilizing a "7 + 3" backbone with alisertib. HMA included decitabine or azacitidine with or without additional therapies, as detailed in Table 1. Supportive therapy included antibiotics and transfusional support, without any leukemia directed therapy. "Other" agents included single-agent therapies outside of those mentioned: clofarabine, panobinostat, low-dose cytarabine, hydroxyurea, brentuximab vedotin, and busulfan.

In the absence of validated response criteria for MPN-BP [23], we classified responses based on AML criteria, consistent with prior MPN-BP studies. Complete response (CR) with or without count recovery was defined as bone marrow (BM) blasts < 5% and absence of peripheral blood (PB) blasts; while relapse was defined as reappearance of PB blasts or BM blasts > 5% after achieving a CR [24] Changes in the underlying BM features of the MPN were not considered in response assessment.

2.2. Cytogenetics and mutational analysis

Karyotypic analyses were performed using standard techniques at ISMMS's Tumor Cytogenomics Laboratory and the Cytogenetics Laboratory at MGH. Cytogenetics were classified as intermediate or adverse risk based on established criteria [25]. Somatic mutational data were collected as a part of clinical care both during the MPN course,