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5-Azacitidine has limited therapeutic activity in myelofibrosis

RA Mesa[1], **S Verstovsek**[2], **C Rivera**[3], **A Pardanani**[1], **K Hussein**[1], **T Lasho**[1], **W Wu**[1], **A Tefferi**[1]

[1]Division of Hematology, Mayo Clinic, Rochester, MN, USA;

[2]Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA and

[3]Division of Leukemia, Mayo Clinic Jacksonville, Jacksonville, FL, USA

Patients with primary and post-essential thrombocythemia—polycythemia vera myelofibrosis (PMF and post-ET/PV MF)—have a progressive decline marked by progressive cytopenias, extramedullary hematopoiesis (manifesting as splenomegaly and/or hepatomegaly), significant constitutional symptoms, potential for blastic transformation and premature death with current therapies rarely offering more than palliative benefit.[1] We have explored many therapeutic targets in these patients including farnesyl-transferase inhibition,[2] proteosome inhibition[3] and immunomodulation with lenalidomide.[4,5]

The use of DNA hypomethylation therapy has been found to be efficacious in patients with myelodysplastic syndrome (MDS) leading to the improvement in disease-associated cytopenias, delay in transformation to acute myeloid leukemia and improved survival.[6,7] Additionally, these agents have demonstrated activity in the myeloproliferative disorder (MPD)–MDS overlap syndrome of chronic myelomonocytic leukemia, which shares both the intrinsic proliferative phenotype of PMF and the ineffective hematopoiesis shared by MDS and PMF.[8] There are currently two federal drug administration (FDA)-approved agents in the United States of America including both 5-AZA and Decitabine (Dacogen, MGI Pharma, Bloomington, MN, USA).

Quintas-Cardama *et al*.[9] recently reported in Leukemia the results of a phase II trial of the DNA hypomethylation agent 5-Azacitidine (5-AZA) (Vidaza; Pharmion Boulder, CO, USA) in patients with PMF and post-ET/PV MF. This latter trial utilized the currently FDA-approved dose and schedules in patients with MDS (75mg/m^2 subcutaneously for 7 days every 4 weeks). With this latter regimen, the authors reported limited therapeutic benefit with one patient experiencing a partial response (3%) and 21% with a clinical improvement (mainly splenomegaly) by the International Working Group for Myelofibrosis Research and Treatment criteria. Responses were generally of modest duration with a median of 4 months (range: 2–22 months) in duration.

Although 5-AZA has traditionally been administered in a 7day (total 525mg/m^2/cycle) regimen, interest has remained high for a 5 day (total 375mg/m^2/cycle) alternative regimen to facilitate ease of administration (no weekend dosing) and hopefully less toxicity.[10] Recent results in MDS demonstrated comparable efficacy with 5-day 5-AZA in MDS. We designed

mesa.ruben@mayo.edu .

and initiated a 5-day 5-AZA trial in PMF (post-PV/ET MF) to compliment the results of the trial published by Quintas-Cardama *et al.*[9] to address whether the activity observed in that latter trial would be maintained in an abbreviated dosing trial in patients with symptomatic PMF (and post-ET/PV MF).

A total of 10 patients were enrolled in this alternate dose/ schedule trial of 5-AZA in PMF (n=8) or (post-ET/PV MF (one each)). Demographic features were typical for the disorder (outlined in Table 1) and are very similar to those patients enrolled in the 7-day trial published by Quintas-Cardama *et al.*[9] Therapy with the abbreviated 5-day 5-AZA was clinically ineffective for the patients with myelofibrosis, a decreased benefit as to what had been observed with the 7-day regimen. Utilizing the International Working Group for Myelofibrosis Research and Treatment response criteria,[11] no patient achieved even a clinical improvement (the minimal response recognized) in eligible categories (neutropenia as not present at baseline based on entry criteria) including splenomegaly or anemia (see Table 2).

A median of three cycles was given per patient (range: 1–8), and only two patients received over three cycles of therapy. Although the goal of therapy was to administer a minimum of six cycles of treatment (based on the published need for multiple cycles to achieve response in MDS patients) early discontinuation was due to death (n=1), progression, patient choice or toxicity (see Table 2). The latter death was an unexpected central nervous system hemorrhage after the second cycle of 5-AZA. The platelets were normal at the time of the event, and it was felt the event occurred from a probable previously undiagnosed brain aneurysm and therefore unlikely related to the ongoing therapy with 5-AZA.

Our current description of outcomes with the 5-day 5-AZA therapy in MF reaffirms the limited benefit of this agent in this disease reported by Quintas-Cardama *et al.*[9] However, unlike the latter communication, we had no responses with the 5-day 5-AZA regimen in PMF (and post-ET/PV MF). These results, with the modest numbers, are contrary to MDS patients whom had similar responses with three different analyzed schedules (5 days alone; 5 days–2 days off and another 5 days; or 5 days–2 days off and then 2 more days).[10] The obvious major difference is that the median number of cycles for the MDS trials was six, as was the median number for the trial by Quintas-Cardama *et al.*[9](median: 5.5 cycles, range: 2–18). Although it had been our intention to administer six or more cycle per patient in the 50-day regimen, toxicity and progression precluded that goal. Given the modest responses in the 7-day trial by Quintas-Cardama *et al.*[9], we would speculate that this benefit may well be dose and schedule-dependent.

The urgent need for improved therapeutic options for myelofibrosis patients has led to the recently described mutations in the activation of the JAK-STAT pathway by either the $JAK2^{V617F}$ and/or the $MPL^{W515L/K}$ mutations, which lead to downstream activation of cellular proliferation.[12] In aggregate, these mutations are present in about 50–65% of patients with PMF and post-ET -MF, and the majority are (V617F only) in post-PV -MF. Therapeutic targeting of these latter mutations are currently undergoing initial clinical testing with intriguing results,[13] with many new agents in preclinical development, which appear to be highly selective inhibitors of JAK2.[14,15] Results of these targeted therapeutic

approaches are awaited with great expectation to assess the validity of JAK2 inhibition as a therapeutic target, which will hopefully improve upon the efficacy of currently available therapies.

References

1. Cervantes F, Mesa R, Barosi G. New and old treatment modalities in primary myelofibrosis. Cancer J 2007; 13: 377–383. [PubMed: 18032975]
2. Mesa RA, Camoriano JK, Geyer SM, Wu W, Kaufmann SH, Rivera CE et al. A phase II trial of tipifarnib in myelofibrosis: primary, post-polycythemia vera and post-essential thrombocythemia. Leukemia 2007; 21: 1964–1970. [PubMed: 17581608]
3. Mesa RA, Verstovsek S, Rivera C, Pardanani A, Hussein K, Lasho T et al. Bortezomib therapy in myelofibrosis: a phase II clinical trial. Leukemia 2008; e-pub ahead of print 28 February 2008.
4. Tefferi A, Cortes J, Verstovsek S, Mesa RA, Thomas D, Lasho TL et al. Lenalidomide therapy in myelofibrosis with myeloid metaplasia. Blood 2006; 108: 1158–1164. [PubMed: 16609064]
5. Tefferi A, Lasho TL, Mesa RA, Pardanani A, Ketterling RP, Hanson CA. Lenalidomide therapy in del(5)(q31)-associated myelofibrosis: cytogenetic and JAK2V617F molecular remissions. Leukemia 2007; 21: 1827–1828. [PubMed: 17460705]
6. Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol 2002; 20: 2429–2440. [PubMed: 12011120]
7. Fenaux P, Mufti GJ, Santini V, Finelli C, Giagounidis A, Schoch R et al. Azacitidine (AZA) Treatment Prolongs Overall Survival (OS) in Higher-Risk MDS Patients Compared with Conventional Care Regimens (CCR): Results of the AZA-001 Phase III Study. ASH Annual Meeting Abstracts. Blood 2007; 110: 817.
8. Aribi A, Borthakur G, Ravandi F, Shan J, Davisson J, Cortes J et al. Activity of decitabine, a hypomethylating agent, in chronic myelomonocytic leukemia. Cancer 2007; 109: 713–717. [PubMed: 17219444]
9. Quintás-Cardama A, Tong W, Kantarjian H, Deborah T, Ravandi F, Kornblau S et al. A Phase II Study of 5-Azacitidine for Patients with Primary and Post Essential Thrombocythemia/ Polcythemia Vera Myelofibrosis. Leukemia 2008; 22: 965–970. [PubMed: 18385750]
10. Lyons RM, Cosgriff T, Modi S, McIntyre H, Fernando I, Backstrom J et al. Results of the Initial Treatment Phase of a Study of Three Alternative Dosing Schedules of Azacitidine (Vidaza(R)) in Patients with Myelodysplastic Syndromes (MDS). ASH Annual Meeting Abstracts. Blood 2007; 110: 819.
11. Tefferi A, Barosi G, Mesa RA, Cervantes F, Deeg HJ, Reilly JT et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). Blood 2006; 108: 1497–1503. [PubMed: 16675707]
12. Levine RL, Pardanani A, Tefferi A, Gilliland DG. Role of JAK2 in the pathogenesis and therapy of myeloproliferative disorders. Nat Rev Cancer 2007; 7: 673–683. [PubMed: 17721432]
13. Pardanani A. JAK2 inhibitor therapy in myeloproliferative disorders: rationale, preclinical studies and ongoing clinical trials. Leukemia 2008; 22: 23–30. [PubMed: 17882282]
14. Lasho TL, Tefferi A, Hood JD, Verstovsek S, Gilliland DG, Pardanani A. TG101348, a JAK2-selective antagonist, inhibits primary hematopoietic cells derived from myeloproliferative disorder patients with JAK2V617F, MPLW515K or JAK2 exon 12 mutations as well as mutation negative patients. Leukemia 2008, e-pub 20 March 2008.
15. Pardanani A, Hood J, Lasho T, Levine RL, Martin MB, Noronha G et al. TG101209, a small molecule JAK2-selective kinase inhibitor potently inhibits myeloproliferative disorder-associated JAK2V617F and MPLW515L/K mutations. Leukemia 2007; 21: 1658–1668. [PubMed: 17541402]

Table 1

Demographic and treatment Information for patients with myelofibrosis treated with 5-day regimen of 5-Azacitidine

Characteristics	
Disease	
Myelofibrosis	*N* = 10
Primary	*N* = 8 (80%)
Post-polycythemia vera	*N* = 1 (10%)
Post-essential thrombocythemia	*N* = 1 (10%)
Age	Median 69.2 years (range: 57–76 years)
Sex	Male (*n* = 8; 80%) Female (*n* = 2; 20%)
Lille score at diagnosis (myelofibrosis only)	
0	2 (20%)
1	5 (50%)
2	3 (30%)
Red cell transfusion-dependent	7 (70%)
Prior thrombosis or hemorrhage	*N* = 0
Prior therapy for myelofibrosis	7 (70%)

Table 2

Efficacy and treatment information for patients with myelofibrosis treated with 5-day regimen of 5-Azacitidine

Characteristics	
Treatment given Cycles given	Median three cycles (range 1–8)
>3 cycles	*N* = 2 (20%)
Reason for the discontinuation of therapy	*N* = 8
Progression	2 (20%)
Toxicity	4 (40%)
Patient choice	1 (10%)
Death (not related to progression)	1 (10%)
Toxicity	
Hematologic	
Grade 1–2	*N* = 1 event (Thrombocytopenia (*n* = 1))
Grade 3–4	*N* = 8 events (Leukopenia (*n* = 1), Thrombocytopenia (*n* = 2), neutropenia (*n* = 5))
Non-hematologic	
Grade 1–2	*N* = 23 events (edema (*n* = 1), pruritus (*n* = 5), nausea (*n* = 6), vomiting (*n* = 5), diarrhea (*n* = 1), dyspnea (*n* = 1), cough (*n* = 1), fatigue (*n* = 3))
Grade 3–4	*N* = 0
Response (IWG-MRT criteria)	CR: 0/10
	PR: 0/10
	CI: Splenomegaly: 0 of 9 eligible for response Anemia: 0 of 8 eligible for response Thrombocytopenia: 0 of 4 eligible for response

Abbreviations: CI, clinical improvement; CR, complete remission; PR, partial remission; IWG-MRT, International Working Group for Myelofibrosis Research and Treatment.