Published in final edited form as:

Cancer. 2015 February 15; 121(4): 556–561. doi:10.1002/cncr.29085.

Results of Phase II Randomized Study of Low-Dose Decitabine with or without Valproic Acid in Patients with Myelodysplastic Syndrome and Acute Myelogenous Leukemia

Jean Pierre Issa, MD¹, Guillermo Garcia-Manero, MD², Xuelin Huang, PhD², Jorge Cortes, MD², Farhad Ravandi, MD², Elias Jabbour, MD², Gautam Borthakur, MD², Mark Brandt², Sherry Pierce², and Hagop Kantarjian, MD²

¹Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine, Philadelphia, Pennsylvania

²Department of Leukemia, Division of Cancer Medicine, University of Texas M.D. Anderson Cancer Center, Houston, Texas, 77030

Abstract

Background—Hypomethylating agents have shown activity in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Pre-clinical and single-arm trials have suggested that adding histone deacetylase (HDAC) inhibitors may synergize the epigenetic modulation of hypomethylating agents and improve treatment results.

Study Aim—To evaluate the possible benefit of adding valproic acid, an HDAC inhibitor, to decitabine, in the treatment of MDS and AML.

Methods—Patients with higher risk MDS or with AML and age 60 years or older were eligible. Patients were randomized in a Bayesian response-adaptive design to decitabine 20mg/m² intravenously (IV) daily for 5 days or to decitabine with valproic acid 50mg/kg orally daily for 7 days. Courses were repeated every 4 to 6 weeks. A maximum of 150 patients were to be treated.

Results—A total of 149 patients were treated on study, including 87 patients with MDS and 62 patients with AML. The median age was 69 years (range 20 to 89 years; 42% 70 years). Overall, 34% of patients achieved CR and 55% had an objective response. The median survival was 11.9 months and the estimated 2-year survival rate was 27%. Outcome was not different with the addition of valproic acid to decitabine versus decitabine alone in relation to CR, overall response, or survival. Subset analyses did not demonstrate a benefit within the MDS or AML categories. Toxicities were higher with the combination, in particular neurotoxicity.

Address Correspondence: Hagop Kantarjian, MD, Department of Leukemia, Unit 0428, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030; Telephone: 713-792-7026, hkantarjian@mdanderson.org.

All authors have read and approved the manuscript.

This manuscript is not under consideration elsewhere.

Conflicts of interest: None

Conclusions—Adding valproic acid to decitabine was not associated with improved outcome in the treatment of MDS or elderly AML. Future therapies may consider combining hypomethylating agents with better HDAC inhibitors and using different schedules.

Introduction

Myelodysplastic syndrome (MDS) is a group of heterogeneous hematopoietic stem cell disorders characterized by dysplastic changes in myeloid, erythroid, and megakaryocytic progenitors. It is associated with cytopenias affecting one or more of the three lineages. Patients may present with complications related to anemia, including fatigue, neutropenia with infections, and thrombocytopenia and bleeding. In addition, variable expansions in blasts and, less commonly, leukocytosis are observed. Myelodysplastic syndrome may evolve into acute myeloid leukemia (AML) in about 50% of patients. (1-3)

Several risk classifications in MDS, based on morphology and percent of marrow blasts, karyotype, degree and number of cytopenias, and other features, predict prognosis in MDS. In general, prognosis is poor with a median survival of 2-3 years from diagnosis. Patients with higher risk MDS usually have a higher percent of marrow blasts, poor prognosis cytogenetics, and significant cytopenias (4-6). Standard therapy in MDS consists of hypomethylating agent therapy, with azacitidine or decitabine. These therapies improve the median survival in higher risk MDS from a median of 12-18 months to a median of 24-26 months (7-12).

Acute myeloid leukemia remains a highly fatal disease. With intensive modern chemotherapy regimens about 60% of patients achieve complete remission (CR) and 30-40% are cured. Prognosis is dependent on several factors including patient age, comorbid conditions, performance status, organ functions, leukemic cell karyotype, and molecular abnormalities. The backbone of AML therapy are regimens including cytarabine and anthracyclines (13,14).

Histone deacetylase (HDAC) inhibitors modulate epigenetics of cancer cells favorably to promote differentiation and apoptosis (15). Clinical experience with HDAC inhibitors suggest modest response rates to such therapy in both MDS and AML, with overall response rates ranges of 10-30% (16-18). Pre-clinical and clinical experience indicates synergy between hypomethylating agents and HDAC inhibitors. In vitro models using HL-60 and MOLT4 leukemic cells suggested that valproic acid, an antiepileptic agent with HDAC inhibitory capacity, synergizes with decitabine in affecting growth inhibition, and induction of apoptosis. These results led to Phase I-II studies of the combination which demonstrated safe administration of azacitidine and decitabine with valproic acid at doses up to 50 mg/kg orally daily for ten days. This combination had significant activity in patients with advanced relapsed-refractory AML and MDS (19,20). Similar safety profiles were reported by German investigators using a combination of valproic acid and all trans-retinoic acid (16).

Herein we report our results with a randomized study, using a Bayesian responseadaptive design, of decitabine therapy versus decitabine plus valproic acid in patients with MDS and AML.

Study Group and Therapy

Patients with MDS and > 5% blasts or international prognostic scoring system (IPSS) intermediate or high-risk disease and patients with AML age 60 years or older were eligible. Patients were required not to have received prior intensive chemotherapy or high-dose cytarabine (more than 1g/m²), or prior azacitidine for 3 cycles or more or prior decitabine for 2 cycles or more. Prior biologic therapies, targeted therapies or single-agent chemotherapy were allowed. Patients must have been off chemotherapy for at least two weeks before entering the study and recovered from prior side effects, unless there is evidence rapidly progressive disease. Hydroxyurea was permitted to control counts prior to study treatment. Growth factors including erythropoietin and granulocyte colony-stimulating factor were allowed before and on study, per institutional guidelines. Hydroxyurea was allowed in the first 2 weeks of study treatment for rapidly progressive disease. Patients were required to have a good Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and adequate liver (bilirubin of <2mg/dL), renal (creatinine <2 mg/dL), and cardiac functions (New York Heart Association cardiac III-IV excluded). Nursing and pregnant females were excluded. Patients of childbearing potential were required to practice effective methods of contraception. Other exclusions were: active and uncontrolled infection; uncontrolled intercurrent illnesses; and patients requiring valproic acid treatment continuously for seizure disorders control. All patients signed informed consent according to institutional guidelines and in accordance with the Declaration of Helsinki. The protocol was approved by our Institutional Review Board.

Therapy

Patients were assigned, in a Bayesian response-adaptive design, to one of the two treatment arms: arm A-decitabine 20 mg/m² intravenously (IV) over 1 hour daily for 5 days; arm B-decitabine at the same dose schedule with valproic acid 50mg/kg orally daily for 7 days (Days 1-7; simultaneous therapy with decitabine). Patients received courses every 4-6 weeks depending on persistence of disease, recovery of counts, and recovery from toxicities of the prior course. Dose modifications (reductions) for grade 3-4 toxicities were allowed for decitabine (to 15, 10, 7.5, and 5 mg/m² daily) and valproic acid (to 40, 30, 20, and 10 mg/kg orally daily). Responding patients were allowed to continue therapy for up to 3 years.

Statistical Considerations

Criteria for response were standard and as previously reported by the International Working Group for MDS and AML (21).

An adaptive randomization design was employed to assign patients to treatment based on outcome. Patients were also stratified by IPSS score. At first, 20 patients were assigned to each arm with equal assignment probability. As efficacy data accumulated, patient assignment to the two treatment arms became unbalanced in favor of the treatment that elicited the higher mean of the outcome scores, as described below. For a patient who dies, the score will be the actual number of weeks survived since the beginning of treatment. For a patient who is still alive, the score will be the number of weeks survived since the beginning of treatment plus an additional number which depends on the patient's current

status. Based on the median survival in weeks in the historical data, the numbers will be 40 for patients who go off study for resistance, 60 for patients without response but who remain on study, 75 for patients with complete response without platelet recovery (CRp) or with partial response (PR), and 110 for patients who have achieved CR. A maximum of 150 patients were to be accrued on study (22).

Results

A total of 149 patients have been treated. These included 87 patients with MDS and 62 patients with AML. The median age was 69 years (range 20 to 89 years); 42% were over the age of 70 years. Fifty-seven patients (38%) were female. The characteristics of the study group are detailed in Table 1.

Response to therapy and outcome in the total study group are shown in Table 2. Overall, 51 patients (34%) achieved CR, 22 patients (15%) had marrow CR without full recovery of counts, 1 partial response with full count recovery, and 8 patients (5%) had hematologic improvement. Death in the first two months of therapy was low (7 patients, 5%). Overall, the median survival was 11.9 months and the estimated 2-year survival rate 27%.

Outcomes were not significantly different with the addition of valproic acid to decitabine versus decitabine alone. Among all patients treated, the CR rates with decitabine versus decitabine + valproic acid were 31% versus 37% ($p=0.497$), and the overall response rates were 51% versus 58% ($p=0.407$). The estimated median survivals were 11.2 versus 11.9 months ($p=0.92$); the estimated 2 year survival rates were 30% versus 24%. Response and outcome within the subsets of MDS and AML are shown in Figure 1 A-C. Among patients treated for MDS, the respective CR rates were 29% versus 48% ($p=0.082$), the overall response rates 52% versus 68% ($p=0.136$), the estimated median survivals 16.9 versus 14.9 months, and the estimated 2-year survival rates 39% versus 25% (Figure 1 B). Among patients treated for AML, the CR rates were 33% versus 9% ($p=0.029$), the overall response rates 51% versus 35% ($p=0.208$), the estimated median survivals were 9.6 versus 7.9 months ($p=0.729$), and the estimated 2-year survival rates 23% versus 22% (Figure 1 C).

Toxicity profiles with decitabine versus decitabine + valproic acid are detailed in Table 3. As expected, neurotoxicity was slightly more common in the combination arm. However other side effects were similar in the two treatment arms.

The median number of courses was 4 (range 1-49) overall, 4 (range 1-49) in the decitabine arm, and 4 (range 1-30) in the decitabine + VPA combination arm. In the combination arm, VPA was discontinued in 8 patients and reduced in 25 patients. Decitabine alone was continued when VPA was discontinued in the combination arm.

Decitabine was held in 2 patients on the decitabine arm and the dose reduced in 1. In the combination arm, the decitabine dose was reduced in 5 patients.

Valproic acid levels were measured in 56 patients. Outcome of patients receiving valproic acid was not different by valproic acid levels (data not shown).

A total of 13 patients underwent allogeneic SCT following this program, 2 in the decitabine arm and 11 in the combination arm.

Discussion

Pre-clinical and pilot clinical experiences suggested the potential benefit of adding HDAC inhibitors to hypomethylating agents as combination epigenetic therapy in myeloid malignancies. This led to our current trial evaluating decitabine versus decitabine + valproic acid in patients with AML and MDS. Our results suggest no significant benefit of adding valproic acid to decitabine in the setting of MDS or AML. In MDS, the addition of valproic acid to decitabine resulted in an overall response rate of 68% versus 52% with decitabine alone ($p=0.136$). The median survivals were 14.9 months versus 16.9 months ($p=0.57$; Figure 1B).

While several single-arm trials suggested a potential benefit from adding HDAC inhibitors, the particular addition of valproic acid to decitabine in this study did not show encouraging results. Our results are similar to those reported by the US Leukemia Intergroup Trial E1905. In their phase II study of 149 patients with MDS ($n=97$) or AML ($n=52$) randomized to azacitidine for 10 days with or without entinostat (HDAC inhibitor), the addition of entinostat did not improve overall response rate (44-46%) and was associated with a trend for shorter median survival (13 versus 18 months) (23).

The negative experiences maybe due to the fact that in the context of MDS, HDAC inhibitors do not enhance epigenetic therapy favorably enough to improve outcome. Another possibility is the use of a particularly weak HDAC inhibitor. In this context, several new generation HDAC inhibitors may be more effective. Quintas-Cardama, et al. reported that the use of pracinostat in combination with azacitidine in nine patients with MDS and failure on azacitidine therapy resulted in eight responses, including seven marrow CRs and five complete cytogenetic responses (24). A third possibility is the scheduling of the hypomethylating agent and the HDAC inhibitor. The study by Prebet and colleagues also used simultaneous combination of azacitidine and entinostat and demonstrated less hypomethylation with the combination (23). The optimal schedule of the combination of hypomethylating agents with HDAC inhibitors has not been fully explored, and additional ongoing studies are exploring the potential benefit of different sequences of the combination (NCT01305499). Thus, in our particular study, the suboptimal results with the addition of valproic acid may have been the result of an inferior scheduling regimen.

In summary our experience with the addition of valproic acid to decitabine did not show improved outcome over decitabine alone in patients with MDS and AML. Future investigations will evaluate potentially better (new generation) hypomethylating agents like SGI-110, better HDAC inhibitors, different scheduling regimens of epigenetic therapies, combining hypomethylating agents with other active agents in AML and MDS such as sapacitabine, clofarabine, omacetaxine, onconova 1910, and growth factors (eltrombopag, romiplostim).

Acknowledgments

This study was in part supported by a grant from the National Institute of Health through MD Anderson's Cancer Center Support Grant CA016672 and by MD Anderson Cancer Center Leukemia SPORE CA100632.

References

1. Faderl, S.; Kantarjian, H. Myelodysplastic Syndromes. In: DeVita, V.; Lawrence, T.; Rosenberg, S., editors. *Cancer Principles and Practice of Oncology*. 9th. Lippincott Williams and Wilkins; Philadelphia, PA: 2011. p. 1988-96.
2. Silverman, L. The Myelodysplastic Syndrome. In: Hong, WK.; Blast, RC.; Hait, WN., et al., editors. *Cancer Medicine*. 8th. Shelton, CT: People's Medical Publishing House-USA; 2010. p. 1544-58.
3. Foran, JM.; Sekeres, MA. Myelodysplastic Syndromes. In: Aberloff, M.; Armitage, J.; Niederhuber, J.; Kastan, M.; McKenna, W., editors. *Aberloff's Clinical Oncology*. 4th. Churchill Livingstone Elsevier; Philadelphia, PA: 2008. p. 2235-2259.
4. Greenberg P, Cox C, LeBeau MM, et al. International Scoring System for evaluating prognosis in myelodysplastic syndromes. *Blood*. 1997; 89:2079-2088.
5. Greenberg P, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012; 120:2454-65. [PubMed: 22740453]
6. Kantarjian H, O'Brien S, Ravandi F, Cortes J, Shan J, Bennett JM, List A, Fenaux P, Sanz G, Issa JP, Freireich EJ, Garcia-Manero G. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. *Cancer*. 2008; 113(6):1351-61. [PubMed: 18618511]
7. Silverman LR, Demakos EP, Peterson BL, 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]
8. Fenaux P, Mufti G, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, Schoch R, et al. Efficacy of azacitidine (AZA) compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. *Lancet Oncology*. 2009; 10:223-32.
9. Kantarjian H, Issa JP, Rosenfeld C, Bennett J, Albitar M, dePersio J, et al. Decitabine improves patient outcomes in myelodysplastic syndromes. *Cancer*. 2006; 106:1780-1794.
10. Kantarjian H, Oki Y, Garcia-Manero G, Huang X, O'Brien S, Cortes J, et al. Results of a randomized study of 3 schedules of low-dose decitabine in high-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood*. 2007; 109:52-570. [PubMed: 16882708]
11. Kantarjian H, O'Brien S, Huang X, Garcia-Manero G, Ravandi F, Cortes J, et al. Survival advantage with decitabine versus intensive chemotherapy in patients with higher risk myelodysplastic syndrome. *Cancer*. 2007; 109:1133-1137. [PubMed: 17315156]
12. Steensma D, Baer M, Slack J, Buckstein R, Godley L, Larsen J, Arora S, Cullen M, Kantarjian H. A multicenter phase II trial of the decitabine alternative 5-day dosing regimen: Analysis of efficacy in various subgroups of patients with myelodysplastic syndromes (MDS). *Journal of Clinical Oncology*. 2008; 26:7032.
13. Kebriaei, P.; Champlin, R.; de Lima, M.; Estey, E. Management of Acute Leukemias. In: DeVita, V.; Lawrence, T.; Rosenberg, S., editors. *Cancer Principles and Practice of Oncology*. 9th. Lippincott Williams and Wilkins; Philadelphia, PA: 2011. p. 1928-1954.
14. Schiffer, CA.; Stone, RM. Acute Myeloid Leukemia in Adults: Mast Cell Leukemia and Other Mast Cell Neoplasms. In: Hong, WK.; Blast, RC.; Hait, WN., et al., editors. *Cancer Medicine*. 8th. Shelton, CT: People's Medical Publishing House-USA; 2010. p. 1559-81.
15. Gottlicher M, Minucci S, Zhu P, et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *Embo J*. 2001; 20:6969-78. [PubMed: 11742974]
16. Kuendgen A, Strupp C, Aivado M, et al. Treatment of myelodysplastic syndromes with valproic acid alone or in combination with all-trans retinoic acid. *Blood*. 2004; 104:1266-9. [PubMed: 15155466]

17. Garcia-Manero G, Assouline S, Cortes J, Estrov Z, Kantarjian H, Yang H, et al. Phase I study of the oral isotype specific histone deacetylase inhibitor MGCD0103 in leukemia. *Blood*. 2008; 112:981–9. [PubMed: 18495956]
18. Garcia-Manero G, Yang H, Bueso-Ramos C, Ferrajoli A, Cortes J, Wierda WG, et al. Phase I study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid [SA HA]) in patients with advanced leukemias and myelodysplastic syndromes. *Blood*. 2008; 111:1060–6. [PubMed: 17962510]
19. Soriano AO, Yang H, Faderl S, Estrov Z, Giles F, Ravandi F, et al. Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome. *Blood*. 2007; 110:2302–8. [PubMed: 17596541]
20. Garcia-Manero G, Kantarjian HM, Sanchez-Gonzalez B, Yang H, Rosner G, Verstovsek S, et al. Phase I/2 study of the combination of 5-aza-2'-deoxycytidine with valproic acid in patients with leukemia. *Blood*. 2006; 108:3271, 9. [PubMed: 16882711]
21. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003; 21:4642–49. [PubMed: 14673054]
22. Berry DA. Bayesian clinical trials. *Nat Rev Drug Discovery*. 2006; 5:27–36.
23. Prebet T, Sun Z, Figueroa M, Ketterling R, et al. Prolonged Administration of Azacitidine With or Without Entinostat for Myelodysplastic Syndrome and Acute Myeloid Leukemia with Myelodysplasia-Related Changes: Results of the US Leukemia Intergroup Trial E1905. *J Clin Onc*. 03/2014 (In Press).
24. Quintas-Cardama A, Kantarjian H, Ravandi F, Foudray C, Pemmaraju N, Kadia T, et al. Very High Rates of Clinical and Cytogenetic Response with the Combination of the Histone Deacetylase Inhibitor Pracinostat (SB939) and 5-Azacitidine in High-Risk Myelodysplastic Syndrome. *Blood*. 2012; 120 abstr 3821.

Figure 1. Survival by treatment with decitabine (DAC) $\pm$ valproic acid (VPA), overall (A), in MDS (B), and AML (C).

Table 1
Characteristics of the Study Group

		<u>No (%); or median [range]</u>		
Characteristic	Category	AML	MDS	Total
Total Treated		62	87	149
Age (years)	60	58 (94)	63 (72)	121 (81)
	Median [range]	70 [38-83]	66 [20-89]	69 [20-89]
Hemoglobin (g/dl)	10	48 (77)	66 (76)	114 (77)
	Median [range]	9.3 [6.1-14.6]	9.3 [6.4-13.4]	9.3 [6.1-14.6]
Platelets ($\times 10^9/L$)	< 50	23 (37)	46 (53)	69 (46)
	Median [range]	58 [4-454]	46 [9-576]	53 [4-576]
Karyotype	Diploid	23 (37)	32 (37)	55 (37)
	5 or 7 abnormality	21 (34)	38 (44)	59 (40)
	Complex abnormality	5 (8)	5 (6)	10 (7)
	< 3 abnormality	10 (16)	5 (6)	15 (10)
	Other	3 (5)	7 (8)	10 (7)
Secondary disease	yes	20 (32)	34 (39)	54 (36)

AML = acute myeloid leukemia; MDS=myelodysplastic syndrome

Table 2
Response and Outcome

Outcome	Decitabine (n = 70)	Decitabine + Valproic acid (n = 79)	Total (n = 149)	p-value
No. of CR (%)	22 (31)	29 (37)	51 (34)	0.497
No. of marrow CR+hematologic improvements+PR (%)	14 (20)	17 (22)	31 (21)	0.818
No. of overall response (%)	36 (51)	46 (58)	82 (55)	0.407
No. of deaths within 8 weeks (%)	4 (6)	3 (4)	7 (5)	0.582

Table 3

Side Effects

	No (%)			
	DAC (n=70)		DAC+VA (n=79)	
	1 - 2	3 - 4	1 - 2	3 - 4
Fatigue	6 (9)	0	8 (10)	1 (1)
Dizziness	0	0	5 (6)	0
Memory Impairment/somnolence/confusion	0	1 (1)	10 (13)	2 (3)
Neuropathy	1 (1)	2 (3)	4 (5)	1 (1)
Nausea	3 (4)	0	12 (15)	0
Diarrhea	3 (4)	1 (1)	4 (5)	0
Dermatology/rash	1 (1)	0	5 (6)	0
Renal	1 (1)	3 (4)	1 (1)	1 (1)
Edema	1 (1)	0	3 (4)	0
Cardiac	1 (1)	2 (3)	1 (1)	2 (3)
Infections/febrile neutropenia	0	10 (14)	0	9 (11)

Adverse events related to the central nervous renal and pulmonary systems which occurred in 2 patients at grades 1-2 or in 1 patients at grades 3-4, are not listed.