Blood Abstracts: 54th ASH Annual Meeting Abstracts; Vol. 120, Issue 21, 16 Nov 2012

Abstract 2622 Safety and Efficacy of Bendamustine and Idarubicin in Combination Therapy for Patients Age ≥50 with Untreated Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome – Results From a Phase I/II Adaptive Design Study

Mazyar Shadman, MD, MPH[1,2,3*], Jack M. Lionberger, MD, PhD[4*], Raya Mawad, MD[1,2,3], Ravinder K Sandhu, MD[2*], Carol Dean, RN[2*], Kathleen Shannon-Dorcy, RN[2*], Kyle Wathen, PhD[5*], Bart L Scott, MD, MS[2,3], Roland B. Walter, MD, PhD[2,3], Pamela S. Becker, MD, PhD[3], Frederick R. Appelbaum, MD[1,2], Elihu H. Estey, MD[2,3] and John M. Pagel, MD, PhD[1,2]

[1]Medical Oncology, University of Washington, Seattle, WA
[2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA
[3]Hematology, University of Washington, Seattle, WA
[4]Cancer Center, Saint Louis University, Saint Louis, MO
[5]Biostatistics, University of Texas MD Anderson Cancer Center, Houston, TX

Background: Acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS with 10-19% blasts) are associated with higher mortality in the elderly population. This poor outcome is in part attributed to therapy resistance and therefore, using combinations of agents with different mechanisms of action may improve outcomes. The nitrogen mustard Bendamustine combines unique alkylating characteristics with putative anti-metabolite activity while Idarubicin inhibits DNA and RNA synthesis by intercalation between DNA base pairs. In this single-arm adaptive phase I/II dose-escalation trial, we assessed increasing doses of Bendamustine in combination with a uniform dose of Idarubicin. We used a Bayesian approach to determine whether there was a dose of Bendamustine which, together with Idarubicin can provide a complete response (CR) rate of at least 40%, with minimal (<30%) grade 3-4 extramedullary toxicity in untreated AML or high-risk MDS patients age > 50.

Methods: Eligible patients were age ³50 with untreated AML or high-risk MDS, had an ECOG performance status <3 and creatinine and bilirubin each less <2.0. Patients received 1 of 3 doses of Bendamustine (45, 60 or 75 mg/m^2 daily days 1-5) together with Idarubicin (12 mg/m^2 days 1-2). Response was assessed according to the International Working Group (IWG) criteria (Cheson *et. al*., JCO, 2003) and non-hematologic toxicities according to the NCI CTCAE v.3. After each cohort of 3 patients at a given dose had been evaluated for toxicity and response, Bayesian posterior probabilities based on the data and non-

informative prior probabilities were computed. If no Bendamustine dose was associated with a >95% posterior probability of both grade 3-4 extramedullary toxicity <30% (between the 1/6 and 2/6 of the conventional 3+3) and CR rate >40%, the study stopped. Otherwise, the study would continue at the highest dose that met the above criteria until 45 patients had been treated. Treatments were administered in the outpatient setting and patients were admitted to the hospital only if medically indicated.

Results: Between October 2010 and May 2012, 39 patients were treated per protocol. The median age was 73 (range, 56-82). Patients had ECOG performance status of 1 (92%), or 2 (7%). AML patients comprised majority of the cases (34/39; 87%). Among AML patients, 35% (12/34) had primary AML, 47% (16/34) had AHD (antecedent hematologic disorders) and 18% (6/34) had secondary AML with a prior history of chemotherapy or radiation. None of the patients had favorable-risk cytogenetic (CG) and 19 (49%) had poor-risk CG including 9 patients (23%) with monosomal karyotype. None of the patients with normal CG had favorable molecular markers. Treatment was given in 1, 2, and 3 cycles in 25 (64%), 7 (18%) and 7(18%) patients, respectively. The number of patients in each cohort and the treatment efficacy and toxicity is reported in the table below. The MTD (maximum tolerated dose) was established at 60 mg/m^2 of Bendamustine as two grade 3 toxicities were seen at the dose of 75 mg/m^2 (congestive heart failure and mucositis in one patient each). Patients were treated as outpatients but hospitalization was required in 90% of the patients (35/39; 90%). The leading cause of admission was febrile neutropenia (26/35; 74%) followed by fungal infections (4/35; 11%).

Conclusion: The combination of Bendamustine (60 mg/m^2 (for 5 days) with Idarubicin (12 mg/m^2 for 2 days) can be delivered in the outpatient setting and had a <95% posterior probability of >30% toxicity. However, the posterior probability of a CR rate >40% was also <95%, suggesting that continued exploration of new therapeutic combinations is warranted in elderly patients with AML or high-grade MDS.

Dose level for Bendamustine	# Patients Treated	Toxicity	Efficacy		
			CR	CRi	CR + CRi
45 mg/m^2	3	0/3 (0%)	0	0	0/3 (0%)
60 mg/m^2	33	0/33 (0%)	6	4	10/33 (30%)
75 mg/m^2	3	2/3 (66%)	0	1	1/3 (33%)

Table-1: Toxicity and Efficacy in each dose group.

Disclosures: Off Label Use: Bendamustine is indicated for the treatment of CLL and indolent non-Hodgkin's lymphoma. In our study we are using Bendamustine to treat AML.

*signifies non-member of ASH

- Author name in bold denotes the presenting author
- Asterisk * with author name denotes a Non-ASH member
- denotes an abstract that is clinically relevant
-
- Cover image credits: "Blood cells cruising down a vein" (istockphoto)