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

Abstract 437 Fludarabine, Bendamustine, and Rituximab (FBR) Chemoimmunotherapy Is a Safe and Active Regimen for Relapsed/Refractory CLL with in Vivo Mechanism of Action for Combination Chemotherapy

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Chemoimmunotherapy (such as fludarabine, cyclophosphamide, and rituximab) is highly effective CLL therapy; adding novel agents or replacing standard with more effective agents could improve outcomes. Bendamustine (B) is a potent alkylating agent that induces DNA damage and repair response. Marked DNA damage response (H2AX phosphorylation) was seen with activation of p53 protein and PUMA, and cell death when fludarabine was combined with bendamustine *in vitro*. Base on this, we are conducting a phase I/II trial of escalating doses of bendamustine at 20 (n=6), 30 (n=17), 40 (n=6), or 50 (n=6) mg/m^2 on D1, 2, 3 with fludarabine 20 mg/m^2 administered prior to bendamustine on D2 & 3. Rituximab 375-500 mg/m^2 was given D3. Courses were repeated each 28 days for 6 planned courses to assess the safety and tolerability, clinical efficacy, and pharmacodynamics (PD) in previously treated CLL. Response assessment (IWCLL 2008 criteria) was after 3 courses and end of treatment; bone marrow residual disease was assessed by 4-color flow. We previously reported (ASH 2011) that no MTD was identified in phase I and identified bendamustine 30 mg/m^2 as safe for phase II expansion. We now report on efficacy of this FBR regimen in 35 pts treated in phase I & II who have response data available. The median age was 62 yrs; number of prior treatments was 3 (1-6); and

number of FBR courses was 3 (1-6). Dose-reduction after course 1 occurred in 10/35 pts. Responses are shown (Table) and were seen across all dose levels. Time-to-event endpoints will be presented. Pts had high-risk features: median b-2 microglobulin was 4.1 (1.8-10.4); 18/35 were Rai stage III-IV; 23/29 were $ZAP70^{+}$; 23/29 had unmutated IGHV; and FISH identified 3 pts with del17p and 13 with del11q. Myelosuppression was the most common treatment-related toxicity considering all courses given (n=106). Grade(G) 3&G4 neutropenia occurred in 26&29% of courses, respectively; thrombocytopenia G3&G4 occurred in 14&9% of courses, respectively; and anemia G3&G4 occurred in 15&2% of courses, respectively. There were no treatment-related deaths.

To test fludarabine triphosphate-mediated mitigation of DNA repair response induced by bendamustine, on D1 bendamustine was infused alone and on D2, fludarabine was administered 2 hours prior to second bendamustine infusion; circulating CLL cells from 11 pts at different bendamustine doses (3 at 20, 3 at 30, 3 at 40, and 2 at 50 mg/m^2) were evaluated. Phosphorylation of histone 2A variant X (H2AX) was used as damage response marker. There was heterogeneity in extent of DNA damage response elicited after first bendamustine infusion. Considering basal phosphorylation level in the pretreatment sample on D1 as 1.0, the H2AX phosphorylation at D1-6hr (bendamustine alone) ranged between 0.2-8 (n=11). Median intracellular fludarabine triphosphate level at the start of bendamustine infusion was 12 µM (range 5-21 µM). This was sufficient to increase H2AX phosphorylation in all 11 pts tested. At the end of D2-4hr (bendamustine combined with fludarabine) the range was between 0.9-22 and remained the same on D2-6hr. In 1 pt sample, the phosphorylation persisted at 26 until D3-pretreatement, while in others it ranged between 3-12. Consistent with H2AX data, molecular markers of DNA damage response showed activation of ATM measured in 5 pt samples as ser1981 phosphorylation and phosphorylation of p53 at ser15. In parallel, there was a decrease in anti-apoptotic proteins Mcl-1 and Bcl-2 at the end of D2-6hr; however protein levels were retained on D3.

In conclusion, this FBR regimen was tolerated up to the highest evaluated bendamustine dose; efficacy was demonstrated in previously treated pts with CLL. DNA damage and repair response biomarkers validated the hypothesis that fludarabine triphosphate inhibited bendamustine-induced DNA repair resulting in increased or sustained DNA damage. We continue to extend the clinical and PD investigations in phase II.

Table

Characteristic		**n**	**% CR/CRi**	**% OR**	**%MRD Neg**
All Pts		35	26	71	11
Rai Stage	III-IV	18	17	67	11
	0-II	17	35	76	12
No. Prior Rx	>2	19	16	58	5
	1-2	16	38	88	19

B2M	³4mg/l	19	11	53	11
	<4 mg/l	16	44	94	13
	FISH 17p del	3	33	100	0
	11q del	13	23	69	0
	+12	7	57	86	43
	None	3	0	33	33
	13q del	3	0	100	0
IGHV	Unmutated	23	26	70	9
	Mutated	6	33	100	33
ZAP70	Positive	23	22	70	13
	Negative	6	17	83	17
CD38 (>7%)	Positive	26	23	73	8
	Negative	8	38	75	25

CR, complete remission; CRi, CR with incomplete recovery of cytopenias; OR, overall response; MRD, minimal residual disease

Disclosures: No relevant conflicts of interest to declare.

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