Blood (ASH Annual Meeting Abstracts) 2010 116: Abstract **3286**

Poster Session

Acute Myeloid Leukemia - Therapy, excluding Transplantation: Poster III

Update of a Phase I/II Trial of 5-Azacytidine Prior to Gemtuzumab Ozogamicin (GO) for Patients with Relapsed Acute Myeloid Leukemia with Correlative Biomarker Studies

Edward D. Ball, MD[1], Bruno C. Medeiros, MD[*,2], Larissa Balaian, PhD[1], Tracy Roque[*,3], Sue Corringham[*,3], Richa Rajwanshi[*,4], Steven Coutre[*,4], Jason R Gotlib, MD, MS[*,2], Asad Bashey, MD, PhD[5] and Karen Messer[*,3]

[1] Moores UCSD Cancer Center, Univ. of California at San Diego, La Jolla, CA, USA,
[2] Stanford University School of Medicine, Stanford, CA, USA,
[3] Moores UCSD Cancer Center, Univ. of California at San Diego, La Jolla, CA,
[4] Stanford University School of Medicine, Stanford, CA,
[5] BMT Group of Georgia, Atlanta, GA, USA

Abstract 3286

Acute myeloid leukemia (AML) cells express the cell surface antigen CD33 that is a down-regulator of cell growth when ligated by a monoclonal antibody in a Syk-dependent manner. The response of AML cells to gemtuzumab ozogamicin (GO) also depends on Syk and SHP-1 expression (Leukemia 20:2093, 2006). The hypomethylating agent 5-azacytidine (5-aza) induced re-expression of Syk in some cases, therefore increasing the sensitivity of originally Syk-negative, non-responsive cells to CD33 ligation to levels of Syk-positive cells. We initiated a phase 1/2 clinical trial examining if treatment with 5-aza prior to GO is safe, efficacious, and whether in vivo responses to GO correlated with Syk expression and induction by 5-aza. Here we update the interim results of this trial (NCI registration number NCT00766116). In Phase I, 14 patients (9 males, 5 females), age range: 39–82 years [median: 66]) were treated with 75mg/m^2 5-aza daily and GO in a dose-escalation manner, 4 cohorts total. The first cohort (n=3) received 5-aza for 2 days followed by GO at 3 mg/m^2 on days 3 and 17; the second cohort (n=3) received 5-aza for 2 days followed by GO at 6 mg/m^2 on days 3 and 17; the third cohort (n=4) received 5-aza for 4 days followed by GO at 6 mg/m^2 on days 5 and 19; and the fourth cohort (n=4) at 5-aza for 6 days followed by GO at 6 mg/m^2 on days 7 and 21. There were no responses in the first 2 cohorts. One patient in cohort 3 achieved CR, and 2 in cohort 4 achieved CR and CRp. Adverse events (≥ Grade 3) included febrile neutropenia 36%, infection 14%, pancytopenia 7%, dyspnea 7%, and retinopathy 7%. Average length on study (n=14) was 45 days with a mortality rate of 14% (unrelated to treatment). No dose-limiting toxicities were encountered in phase I, therefore the MTD is the dose in cohort 4. The overall response rate in evaluable patients in phase I (n=11) is 27%. Average time to ANC recovery (n=6): 30 days (range 15–42, median 33 days). In Phase II, 10 patients (5 males, 5 females), age range: 29–64 years (median 60) were treated at the MTD:

5-aza for 6 days and GO at 6 mg/m^2 on days 7 and 21. 8 patients were in 1st relapse, 1 in 2nd and 1 in 3rd. There were 3 responders (2 CR, 1 CRp) in this phase, all in 1st relapse at baseline. Adverse events (≥ Grade 3) include febrile neutropenia 50%, infection 20%, increased LFTs 10%, thrombocytopenia 10%, dyspnea 10%, wheezing 10%, mucositis 10%, cough 10%, and hypoalbuminemia 10%. The average length on study (n=10) was 40 days with a mortality rate of 10% (not related to study treatment). Average time to ANC recovery in phase II (n=2): 15 days (range 12–17, median 15) with an overall response rate in evaluable patients (n=7) of 43%. The ORR for phase I/II (n=18) is 33%. 21 of the 24 patient sample pairs have been analyzed for Syk and SHP-1 expression (one patient did not have a baseline sample). Prior to therapy, Syk was expressed in 16 of 20 cases. After 5-aza treatment, Syk was re-expressed in all 4 negative cases, and increased over baseline in one case that was previously Syk +. SHP-1 was positive in 17 of the 20 cases and was re-expressed in all 3 negative cases. Leukemia cells from patients who achieved CR were Syk+ in 3 of 5 cases (the 6th hasn't been analyzed). Syk was re-expressed in the two negative cases after 5-aza. SHP-1 was expressed in 4 of 5 cases at baseline, and re-expressed in the one negative case after 5-aza. In vitro we analyzed inhibition of proliferation (for patients 1–6) or colony formation (for patients 7–24) induced by 5-aza and GO. 5-aza alone allowed 62.3+/–3.5 survival of leukemia cells and GO alone allowed survival of 59.5+/–1.7 leukemia cells. However, exposure to both agents resulted in a survival rate of 24.8+/–1.6 ($P<0.05$, Students t-test). We also compared pre- and post 5-aza samples from the same patients: in all cases 5-aza treatment increased the GO-mediated cytotoxicity from 39.4+/–3.1 to 66.8+/–2.4 (($P<0.05$, Students t-test). These data show that in vivo exposure to 5-aza can induce the expression of two biomarkers involved in the response to GO. This ongoing study indicates the combination of 5-aza and GO is well-tolerated, that Syk and SHP-1 are modulated by 5-aza in vivo, and that complete responses have been noted with this combination.

Disclosures: Ball: *Celgene:* Equity Ownership, Research Funding. **Off Label Use:** Will discuss use of 5-azacytidine (Vidaza) for treatment of relapsed AML in combination with Mylotarg (on label, but only as monotherapy). **Medeiros:** *Celgene:* Research Funding, Speakers Bureau; *Novartis:* Research Funding, Speakers Bureau; *Merck:* Research Funding; *Genentech:* Research Funding; *Alexion:* Speakers Bureau.

Footnotes

* Asterisk with author names denotes non-ASH members.