blood
Leading the world in reporting basic and applied hematology research
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Blood (ASH Annual Meeting Abstracts) 2008 112: Abstract 558

Oral Session

Advances in Treatment of Acute Myeloid Leukemia in Older Patients

Phase II Study of Single Agent Clofarabine in Previously Untreated Older Adult Patients with Acute Myelogenous Leukemia (AML) Unlikely to Benefit from Standard Induction Chemotherapy

Harry Paul Erba, MD, PhD[1], Hagop Kantarjian[2,*], David F. Claxton, MD[3,*], M. Arellano[4,*], Roger M Lyons, MD[5], Tibor J. Kovacsovics, MD[6], Janice Gabrilove, MD[7], Stephen Eckert, Ph.D[8,*], Rekha Abichandani, MD[9,*] and Stefan Faderl, MD[2]

[1] Univ. of Michigan Health System, Ann Arbor, MI, USA, [2] M.D. Anderson Cancer Center, Houston, TX, USA, [3] Hematology-Oncology, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA, [4] Emory University, Atlanta, GA, USA, [5] Cancer Care Centers South Texas/US Oncology, San Antonio, TX, USA, [6] Ctr. for Hematological Malignancies, OHSU, Portland, OR, USA, [7] Mount Sinai School of Medicine, New York, NY, USA, [8] BioMedical Data Sciences & Informatics, Genzyme Corporation, San Antonio, TX, USA, [9] Clinical Research, Genzyme Corporation, Cambridge, MA, USA

Abstract

Background: Older patients with AML have inferior treatment outcomes including high treatment related mortality rates, lower CR rates and short remission duration due to increase in both patient- and disease-related adverse risk factors. AML patients with unfavorable prognostic factors such as advanced age, poor performance status (PS), presence of an antecedent hematologic disorder (AHD), or an unfavorable risk karyotype have inadequate treatment outcomes with cytarabine and an anthracycline ("7+3") induction therapy.

Methods: This was a single arm, Phase II, open-label, 2-stage study with a planned enrollment of 109 patients. Eligible

patients included adults with untreated AML who were ≥60 years old with at least one adverse prognostic factor: age ≥70 years, AHD, PS=2, and/or intermediate/unfavorable risk karyotype. Clofarabine (CLO) was given on days 1–5 as a 1-hr IV infusion at dosages of 30 mg/m^2 during induction and 20 mg/m^2 during re-induction/consolidation. Patients could receive a maximum of 6 cycles. The primary endpoint was the overall remission rate (ORR = CR + CRp), confirmed by an Independent Response Review Panel (IRRP).

Results: 112 patients with AML confirmed by independent review enrolled between Oct 2006-Nov 2007 comprised the full analysis set. Median age was 71 years and 48% were classified as M1 or M2 by FAB classification. The % of patients with each baseline adverse prognostic factor was as follows: 62% with age ≥70 years, 36% with AHD, 96% with intermediate/ unfavorable risk karyotype (55% unfavorable, 41% intermediate and 4% unreported); 22% with PS 2, and 78% with 2 or more of these risk factors. As of database lock (27 June 2008), 11 patients were still receiving study drug. Seven (6%) patients discontinued treatment due to adverse events. The median number of cycles was 2. 66 patients initiated a second cycle of clofarabine (38 as re-induction; 28 as consolidation). The median time between cycles 1 and 2 was 41 days. The IRRP confirmed ORR was 46 % (51/112), including 42 (38%) CR and 9 (8%) CRp. The ORR was 42% in patients with unfavorable cytogenetics, 50% with AHD, 32% with ECOG PS 2, and 39% with age 70 years. ORR for patients with 1, 2 or 3 risk factors was 48%, 52% and 36%, respectively. ORR among patients with del 5, del 7 and complex karyotype (≥ 3 abnormalities) was 21% (3/14, 3 CR), 33% (6/18, 2 CR, 4 CRp) and 32% (8/25, 5 CR, 3 CRp) respectively. Median time to peripheral blood blast clearance was 5 days. The median duration of follow-up was 16.6 weeks. The median duration of remission has not yet been reached (95% CI, 33 weeks to not yet evaluable). Thirty day all-cause mortality was 9.8%. Drug-related adverse events occurring in >20% patients were nausea (62%), febrile neutropenia (39%), vomiting (38%), diarrhea (33%) and rash (30%). Most treatment-related events were Grades 1–2. Febrile neutropenia was reported in 63% patients (regardless of causality). Treatment-emergent Grade 4 neutropenia and thrombocytopenia were reported in 46% and 67% patients, respectively. Median time to ANC recovery for patients who achieved CR/CRp and platelet recovery for patients with CR was 30 and 26 days, respectively. Grade 3 or higher elevations of bilirubin occurred 12 patients (11%), AST 26 (23%), ALT 21 (19%), creatinine 7 (6%)

Summary/conclusions: These data indicate single-agent CLO is active and well-tolerated in treatment-naïve, older AML patients with 1 or more adverse prognostic factors, especially with unfavorable risk karyotype, age ≥70 years or AHD. The safety data are consistent with previously reported studies of CLO in older patients. The preliminary DOR and 30 day mortality data are encouraging. Patients remain in long term follow- up and updated data will be presented at the meeting.

Footnotes

Corresponding author

Disclosures: Erba: *Bristoll Myers-Squibb:* Speakers Bureau; *Celgene:* Speakers Bureau; *Cell Therapeutics:* Research Funding; *Cephalon:* Research Funding, Speakers Bureau; *Genzyme:* Consultancy, Research Funding; *Kanisa:* Research Funding; *MGI Pharma:* Speakers Bureau; *Novartis:* Research Funding, Speakers Bureau; *Pharmion:* Speakers Bureau; *Wyeth:* Research Funding; *Xanthus:* Research Funding. **Kantarjian:** *Genzyme:* Consultancy, Research Funding. **Claxton:** *Genzyme:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Bayer:* Consultancy, Honoraria; *Pfizer:* Equity Ownership; *GeminX:* Research Funding; *Cyclocel:* Research Funding. **Arellano:** *Genzyme:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Lyons:**

Amgen: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Celgene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *BMJ:* Consultancy, Research Funding; *Genzyme:* Research Funding. **Kovacsovics:** *Genzyme:* Research Funding. **Gabrilove:** *Genzyme:* Research Funding; *Roche:* Consultancy; *Lilly:* Equity Ownership; *J & J:* Equity Ownership; *GSK:* Equity Ownership; *Novartis:* Research Funding; *Aventis:* Consultancy, Research Funding; *Celgene:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Research Funding; *Memorial Sloan Kettering Cancer Center:* Royalties for patented discoveries. **Eckert:** *Genzyme:* Employment, Equity Ownership. **Abichandani:** *Genzyme:* Employment, Equity Ownership. **Faderl:** *Genzyme:* Consultancy, Research Funding. **Off Label Use:** clofarabine as initial therapy of AML.

 Online ISSN: 1528-0020