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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Significance of the Apoptotic Regulators BAX, BCL2, BCL- XL and MCL1 in Newly Diagnosed AML

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Introduction:
In acute myeloid leukemia (AML), cytogenetics and molecular mutations remain important prognostic tools for tailoring treatment after induction therapy. Abnormalities in multiple components of apoptotic pathways have been identified as potential drivers of AML. Identifying other biomarkers may help us further refine prognosis and identify other therapeutic strategies. B-cell lymphoma 2 (Bcl2), Bcl-xL and myeloid cell leukemia-1 (Mcl1) are commonly expressed prosurvival proteins in hematologic malignancies, whereas Bax acts as a promoter of apoptosis. We retrospectively evaluated the significance of Bax, Bcl2, Bcl-xL and Mcl1 expression in newly diagnosed AML patients using the Beat AML program [1].
Methods:
We analyzed RNA-expression data from The Beat AML study (672 tumor specimens collected from 562 patients) [1]. Data was extracted from the public database. Different expression levels of the above genes were compared using t-tests. Results were considered significant with p-value $< .05$. Kaplan-Meier curves were used to estimate survival.
Results:
For the correlative survival analyses, Bax, Bcl2, Bcl-xL and Mcl1 mRNA expression and clinical information were both obtained from the BeatAML cohort [1]. Patients were categorized into high expressers ($\geq$ median) and low expressers (<median). In total, 461 patients had available gene expression data. The mean age of diagnosis was 57 years, and 56.6% of patients were male. The most common specific diagnosis at inclusion was AML with mutated NPM1 (22%), followed by AML with myelodysplasia related changes (21%) and AML, NOS (11%). Complete response to induction was seen in more than half (56%) of the patients for which response was recorded (n=369). Others developed refractory AML (32%). No data was available for 12%. Standard chemotherapy (induction therapy with idarubicin and cytarabine (7+3) and consolidation therapy with high dose cytarabine) was used in 98.4% of these patients. Over half of the analyzed samples were peripheral blood (52%), and the remaining samples were either bone marrow aspirate (46%) or from leukapheresis (2%). Most of the specimens were collected at initial acute leukemia diagnosis (62.2%), others were collected with residual disease or post chemotherapy (25.1%).
The mean survival for this cohort was 13.7 months. Above median expression of Mcl1 was associated with longer survival (33 vs. 20 months; $p = 0.0262$). Above median expression of Bax was also associated with longer survival (32 vs. 18.2 months; $p = 0.0114$). In the Bax analysis, gene expression was further subdivided into 4 quartiles which showed correlation of expression levels with length of survival (Figure 1). The prognostic significance of the ratio Bax/ (Mcl1+Bcl2+Bcl-xL) was also analyzed given the mechanism of action of these various regulators. A higher ratio was associated with longer survival (40.7 vs. 18.7 months; $p = 0.0095$) (Figure 2)
Conclusions

Bcl-2, Bcl-xL and Mcl-1 are commonly expressed antiapoptotic proteins, whereas Bax is a promoter of apoptosis. The results with Bax are consistent with previous literature. Our results with Mcl1 expression differed from what we may have expected. This may be due to the sample size or methodology. However, it may also be due to the fact that a ratio of the actors is needed to help predict prognosis (as we analyzed in Figure 2). The overall survival between Bcl-2 and Bcl-xL was compared independently, however, they did not appear to have a significant difference in survival between high and low expression groups. We are currently working to see if this ratio can be validated in a prospective cohort of relapsed/ refractory AML patients treated on clinical trial and this data will be presented at the meeting.
The Bcl-2 inhibitor venetoclax has demonstrated promising results in treating AML. However, venetoclax appears to have limited activity as a single agent. Our study suggests that potentially a combination of agents targeting factors such as Bcl-2, Bcl-xL and Mcl-1 may be associated with improved survival in patients with AML. Further validation of these biomarkers is warranted, and Mcl-1 inhibitors are currently in clinical trials.

Disclosures Carraway: *AbbVie:* Other; *Novartis:* Consultancy, Other: Travel, Accommodations, Expenses , Speakers Bureau; *Genentech:* Consultancy; *Astex Pharmaceuticals:* Other; *Agios:* Consultancy, Speakers Bureau; *Stemline Therapeutics:* Consultancy, Speakers Bureau; *Daiichi:* Consultancy; *Celgene:* Research Funding; *Takeda:* Other; *Syndax:* Other: DSMB; *BMS:* Consultancy, Research Funding, Speakers Bureau; *Jazz Pharmaceuticals:* Consultancy, Other: Travel, Accommodations, Expenses , Speakers Bureau. **Gerds:** *AbbVie, Bristol Myers Squibb, Constellation Pharmaceuticals, GlaxoSmithKline, Kartos, Novartis, PharmaEssentia, Sierra Oncology:* Consultancy; *Accurate Pharmaceuticals, Constellation Pharmaceuticals, CTI BioPharma, Imago BioSciences, Incyte Corporation, Kratos Pharmaceuticals:* Research Funding. **Singh:** *Rigel:* Other: Advisor or review panel participant. **Mukherjee:** *Celgene (now BMS):* Consultancy; *BioPharm:* Consultancy; *EUSA:* Honoraria; *McGraw Hill Hematology Oncology Board Review:* Honoraria; *Bristol Myers Squibb:* Honoraria; *Celgene (now BMS):* Honoraria; *Aplastic Anemia and MDS International Foundation:* Honoraria; *EUSA:* Other: Advisory Board; *Genentech and AbbVie:* Other: Advisory Board; *Blueprint Medicines Corporation:* Other: Advisory Board; *Novartis:* Other: Advisory Board; *Bristol Myers Squibb:* Other: Advisory Board; *Celgene/Acceleron:* Other: Advisory Board; *Novartis:* Consultancy; *Bristol Myers Squibb:* Consultancy; *Celgene (now BMS):* Research Funding; *Novartis:* Research Funding; *Jazz Pharmaceuticals:* Research Funding. **Maciejewski:** *Regeneron:* Consultancy, Honoraria; *Alexion:* Membership on an entity's Board of Directors or advisory committees; *Omeros:* Consultancy; *Novartis:* Honoraria, Speakers Bureau. **Advani:** *Immunogen:* Research Funding; *Incyte:* Research Funding; *Kite:* Honoraria, Other: consulting, Research Funding; *Glycomimetics:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *OBI:* Research Funding; *Kura:* Honoraria; *Servier:* Research Funding; *Macrogenics:* Research Funding; *Seattle Genetics:* Research Funding; *Jazz:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Beam:* Honoraria; *Taiho:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Nkarta:* Honoraria; *Pfizer:* Honoraria, Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria, Other: advisory board, Research Funding.

Figure 1:

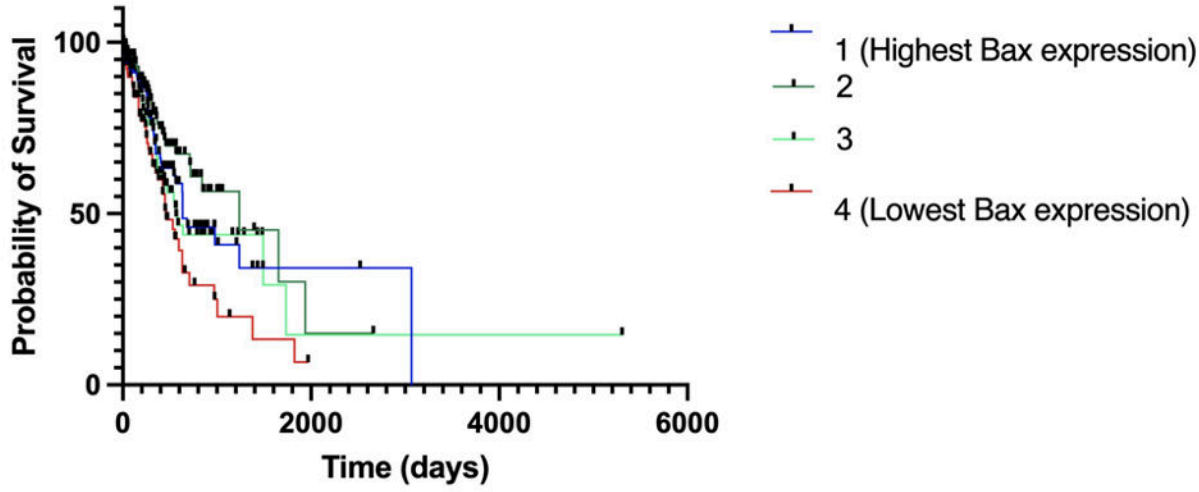

Figure 2:

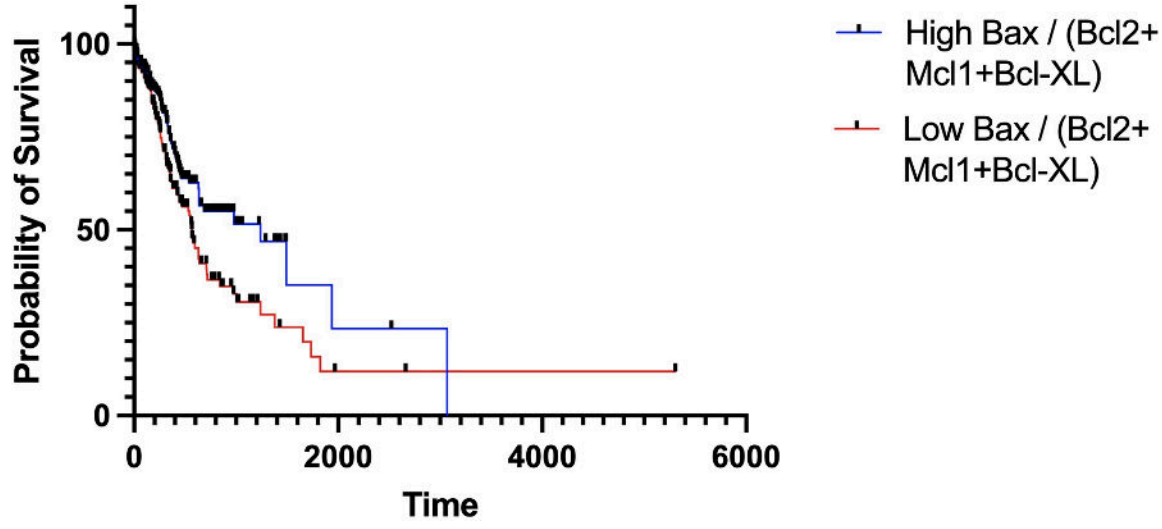

Figure 1

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