Crosstalk between metabolism and cancer: finding correlation between two branched chain aminotransferases and the survival of patients with lymphoma by using Kaplan Meier survival curves

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Abstract

Non-Hodgkin Lymphoma (NHL) accounts for 4% of annual cancer diagnosis and 3.4% of cancer deaths. This cancer commonly begins in the B lymphocytes and spreads throughout the lymphatic system. Though therapeutic strategies to combat NHL have advanced, this cancer continues to be resistant to current treatments. The metabolism of the branched chain amino acids plays an important role in cancer progression. Two genes, encoding the cytosolic and the mitochondrial branched chain aminotransferase, BCAT1 and BCAT2, respectively, are prognostic cancer markers for glioblastomas, colorectal, and hepatocellular cancers. To investigate the role BCAT1 and 2 may play in lymphoma, we undertook bioinformatic approach aiming at correlating the expression of the two metabolic genes with the survival of lymphoma patients. The genomic platform (R2) was used to access information about overall survival, disease survival, and treatment options for patients with diffuse large B-cell (DLBCL) and Mantle cell NHL. Kaplan Meier curves allowed to corelate the gene expressions with the patient survival. While higher expressions of BCAT1 and BCAT2 lead to lower overall cancer survival, we found that higher expression of BCAT1 correlated with a better probability for overall survival of DLBCL patients. In contrast, patients with Mantle cell NHL, who expressed higher levels of BCAT1 or BCAT2, had lower chances to survive. Lastly, treatment with the monoclonal antibody, rituximab, improved the overall survival for all patients regardless of their BCAT status. The results give insight into the variance in B-cell lymphomas and direct toward addressing the differences in patient survival on molecular level.

Objective

Bioinformatic data was used to correlate the gene expression of *BCAT1* and *BCAT2* with the overall survival of patients diagnosed with NHL.

The long-term goal is to identify whether those genes can be targeted for the treatment of NHL.

Methods

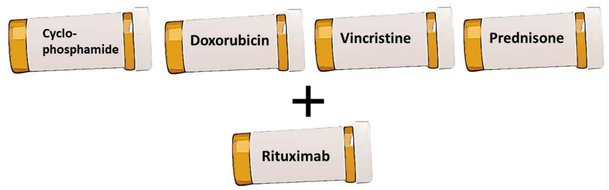
Bioinformatic analysis was completed utilizing the R2 genomics analysis and visualization platform. Several datasets of human B-cell NHL lymphomas were pulled and assessed for proper controls and research conditions. The genetic information was then correlated with the patient survival by using the Kaplan Meier function of the R2 platform. Three datasets were utilized for this presentation; two studies in DLBCL[2,3] and one Mantle Cell lymphoma[4].

Background

In DLBCL studies, analyzed during this research, patients were separated into two different categories of individuals based upon their treatment. The first category is patients who underwent a CHOP regimen, and the second category is patients who underwent a R-CHOP regimen. R-CHOP being the more preferred treatment amongst oncologists when dealing with harder to treat DLBCL cases[5].

CHOP regimen

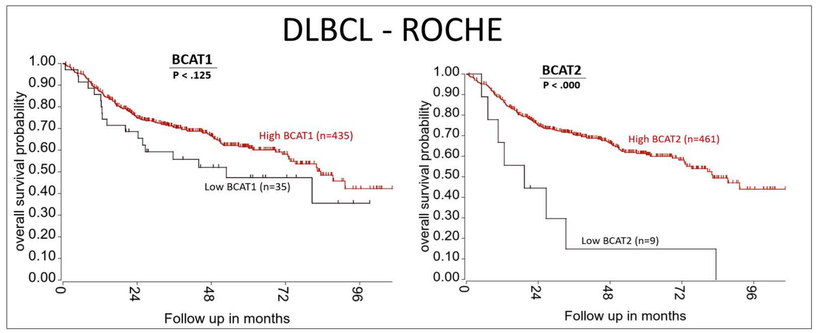
R-CHOP regimen

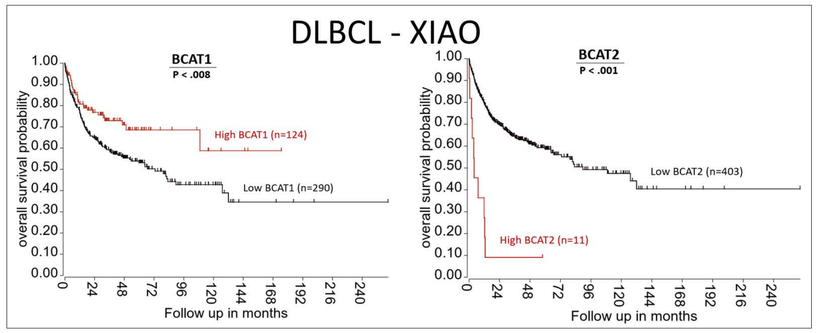


Rituximab, the key difference between these two treatments, is a monoclonal anti-CD20 molecule that is used to treat the relapsed or refractory CD20-positive NHL's[6]. It is known that rituximab can activate apoptotic signaling, complement activation, and cell-mediated cytotoxicity[6].

Results

Overall Disease Survival





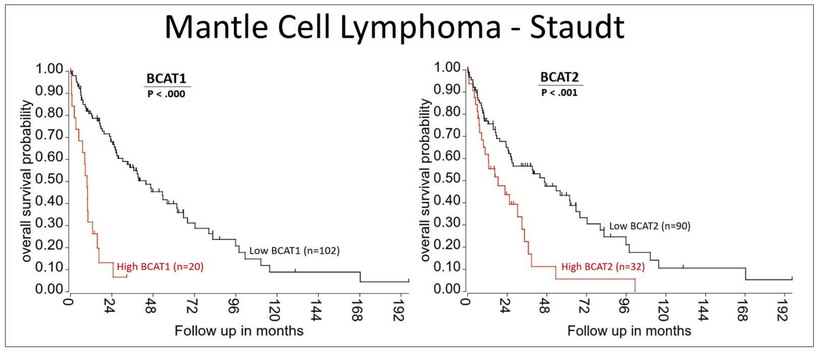


Figure 1 – Kaplan Meier survival curves comparing the overall survival of patients with high and low expression of *BCAT1* and *BCAT2 as* pulled from R2[1] and measured in Log2. DLBCL – Roche[2] had n (sample size) of 470 patients, DLBCL – Xiao[3] had n= 414 patients, and Mantle Cell Lymphoma –Staudt[4] had n= 122 patients.

Eventfree Survival – DLBCL only

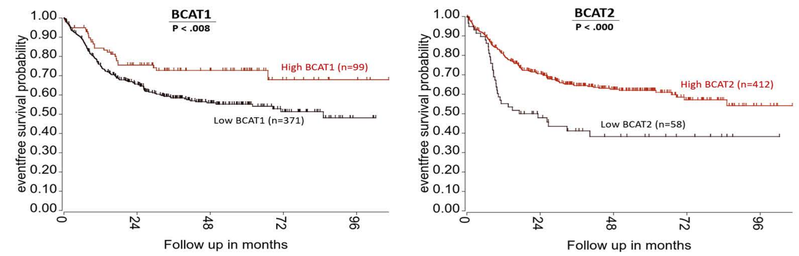


Figure 2 – Kaplan Meier curves compare event free survival in patients expressing high or low *BCAT1* and *BCAT2* expression, as measured in Log2. Data pulled from R2[1]; initial research completed by Roche[2].

CHOP Treatment vs. R-CHOP treatment - DLBCL

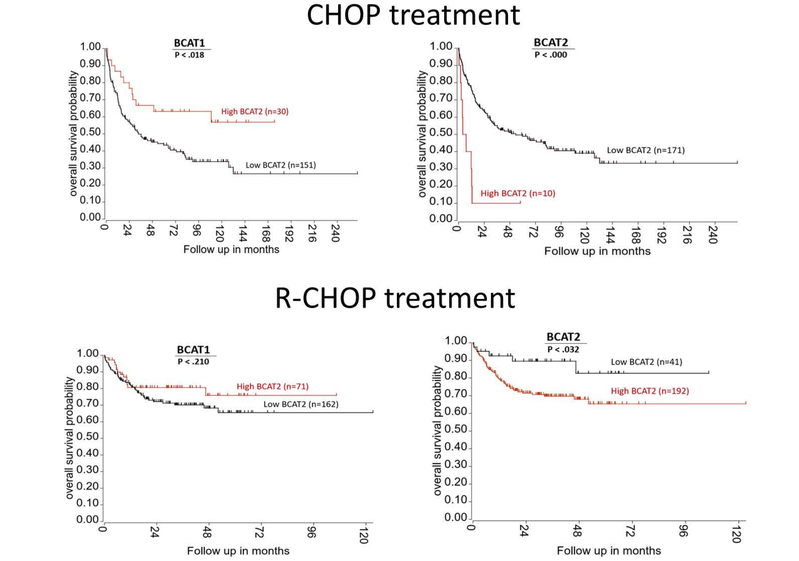


Figure 3 – Represents Kaplan Meier curves comparing overall survival between patients who have high or low expression of BCAT1 and BCAT2, additionally compared between patients treated with CHOP therapy and R-CHOP therapy. Data pulled from R2[1]; initial research conducted by Xiao[3].

Conclusions and Limitations

Conclusions

- In DLBCL patients higher *BCAT1* expression correlated with higher overall survival rate in patients, a result opposite of initial expectations as high *BCAT1* expression typically associates with poorer overall survival rates in other lymphomas or cancer types.
- Event free survival rates were also higher in DLBCL patients with higher expression of *BCAT1* and *BCAT2*.
- The addition of rituximab to CHOP therapy led to greater survival rates in all DLBCL patients regardless of their *BCAT* expression.
- In contrast, in patients with Mantle cell lymphoma, the high *BCAT1* and *BCAT2* expressions correlated with poorer overall patient survival.

Limitations

This data- was pulled from a source where researchers upload their own individual data, there may be a lot of information about the patients that is not know such as the progression of the DLBCL, length of treatment, etc. Additionally, further data sets are needed to conclude that these hold true for the population of DLBCL and not just the samples seen above.

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