Treatment Response Predictor Using ^{31}P MRS for CHOP and R-CHOP Therapy in Diffuse Large B-Cell Lymphoma

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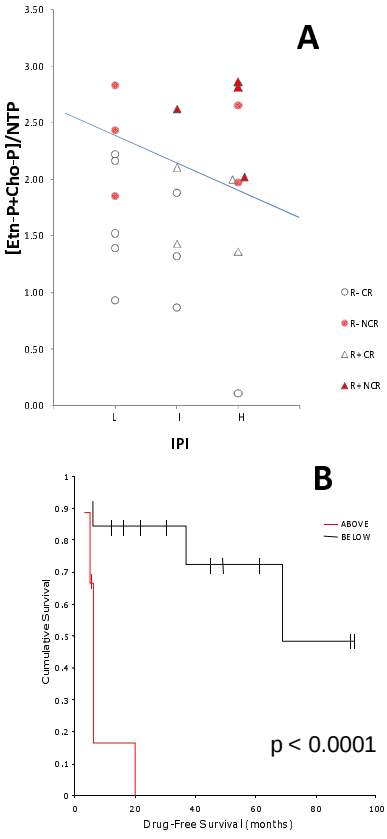
Introduction: Non-Hodgkin's lymphoma (NHL) which is the fifth most common cause of adult cancer in the US and has the fourth largest economic impact of all cancers is a heterogeneous group of malignancies with more than 20 histological varieties. Our ongoing international multi-institutional research program has demonstrated in over 102 NHL patients with various forms of this disease that the sum of the integrated resonance intensities of *phosphoethanolamine* plus *phosphocholine* [Etn-P + Cho-P] normalized by the total nucleotide triphosphates (NTP) in the tumor acquired prior to treatment initialization can predict treatment failure and drug-free survival. To make our results diagnosis- and treatment- specific, we selected patients with the most common form of this disease, diffuse large B-cell lymphoma (DLBCL) who were treated with the standard therapy of cyclophosphamide, hydroxydoxorubicin, oncovin and prednisone (CHOP) or similar treatments (CHOP-like). We divided these patients in two groups: those treated with CHOP-like therapy alone and those that have added rituximab (R-CHOP-like). We made this separation because we wanted to explicitly investigate the addition of rituximab to DLBCL therapy which has recently dramatically increased both response rates and drug-free survival. Considering that the last two are the clinical parameters that the pre-treatment [Etn-P + Cho-P]/NTP value can predict in standard treatment of all NHL patients, our goal was to explore if the addition of rituximab modified or negated the predictive benefit of [Etn-P + Cho-P]/NTP in DLBCL.

Procedures & Patients: The tumor areas of DLBCL patients were studied with 3D-localized, ^{1}H-decoupled, nuclear Overhauser affected, ^{31}P MR spectroscopy. Selection of patients based on clinical data completeness and adequate spectral quality gave a total of 22 patients with DLBCL; 14 of them treated with CHOP or CHOP-like therapy (R- patients) and eight with R-CHOP or R-CHOP-like therapy (R+ patients). In this research, we defined long-term response to therapy as the response assessed six-months after treatment ended using bidimensional radiological measurements in serial CT scans following WHO criteria. The patients were grouped as those with either a complete response (CR) and those without a complete response (NCR); the latter group included patients with partial responses, and stable or progressive disease. In addition, drug-free survival (DFS) was defined as the time in months between the end of treatment and initiation of a new treatment.



Results & Discussion: The pre-treatment [Etn-P + Cho-P]/NTP mean ± standard error(number of cases in parenthesis) for the CR and NCR cases for the R- group were1.38 ± 0.23 (9) and 2.35 ± 0.19 (5) respectively whereas for the R+ were 1.72 ± 0.19 (4) and 2.58 ± 0.19 (4) respectively. In both treatment groups a t-test showed significant differences between the CR and NCR values for the R- and R+ groups with $p < 0.007$ and $p < 0.02$, respectively.

The Fisher test of the R- group using a threshold of 1.78 by ROC analysis showed significance ($p < 0.03$, sensitivity = 0.67, specificity = 1.00). The R+ group showed a similar truth table but did not show significance due to the low number of cases. Considering the similar behavior of the CR and NCR groups for the R- and R+ treatments in t-tests, we also performed a Fisher test on the combined data. Here, the significance increased ($p < 0.004$) while the sensitivity and specificity remained basically unchanged (0.62 and 1.00, respectively).

We have previously shown that we can gain increased power by combining our measurements with the international prognostic index (IPI), a clinical prognosis parameter commonly utilized in DLBCL. The 22 patients were divided into low, intermediate and high risk groups using the IPI and their pre-treatment [Etn-P + Cho-P]/NTP values were plotted accordingly (Figure **A**). A threshold was generated by attempting to classify correctly as many cases as possible (slanted line in Figure **A**). In this way, only two cases were misclassified with a Fisher test significance of $p < 0.0002$ and a sensitivity and specificity of 0.92 and 0.89 respectively.

The two groups of patients generated by the IPI-dependent pre-treatment [Etn-P + Cho-P]/NTP threshold were analyzed for their drug-free survival using Kaplan-Meier tests and evaluating the test differences using the Tyrone-Ware procedure (Figure **B**). In these tests, a significant drug-free survival difference exists amongst the patients above and below the threshold ($p < 0.0001$).

Conclusion: Even though this study involves a fewer patients than previously reported, the results are stronger due to the tighter diagnosis- and treatment-specific selection of lymphoma cases (DLBCL treated with CHOP-like or R-CHOP-like therapy). As previously, these results show that the pre-treatment [Etn-P + Cho-P]/NTP ratio predicts long-term failure to treatment and drug-free survival in patients with DLBCL treated with CHOP-like or R-CHOP-like therapy.