The Addition of Rituximab to First-Line Chemotherapy for Newly-Diagnosed Diffuse Large B-Cell Lymphoma Does Not Modify the Prediction of Therapy Outcome by Phosphorus MR Spectroscopy

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Purpose: To assess in diffuse large B-cell lymphoma patients whether the correlation of the pretreatment tumor value of the phosphomonoesters, phosphoethanolamine and phosphocholine with treatment outcome differs between those patients treated with first-line standard of care alone and those treated with added rituximab.

Outline: The intracellular levels of phospholipid-related phosphomonoesters, phosphoethanolamine and phosphocholine have been associated with active tumor metabolism in animal and cell models of human cancer. To translate this basic science information into clinical relevance we have used *in vivo* phosphorus MR spectroscopy (^{31}P MRS) to measure phosphoethanolamine and phosphocholine in tumors of newly diagnosed diffuse large B-cell lymphoma (DLBCL) patients prior to the start of first-line chemotherapy. The pretreatment tumor value of phosphoethanolamine plus phosphocholine (PME) was normalized to nucleoside triphosphates (PME/NTP), which is a surrogate of cell viability and is also measureable by ^{31}P MRS.

For many years, first-line standard of care for newly diagnosed DLBCL patients has been CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or similar treatments (CHOP-like chemotherapy). However recently, rituximab, a chimeric monoclonal antibody against the protein CD20 has been added to first-line treatment of DLBCL significantly increasing relapse-free and overall survival. Because of the impact of rituximab on therapeutic response of DLBCL, we wanted to assess whether the correlation of the pretreatment tumor PME/NTP value with treatment outcome differs between those patients treated with CHOP-like therapy alone (**R$_{NEG}$**) and those treated with added rituximab (**R$_{POS}$**).
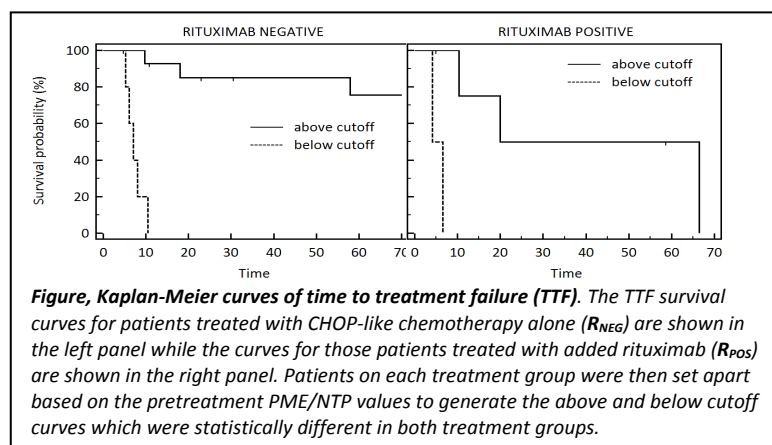
Figure, Kaplan-Meier curves of time to treatment failure (TTF). *The TTF survival curves for patients treated with CHOP-like chemotherapy alone (**R$_{NEG}$**) are shown in the left panel while the curves for those patients treated with added rituximab (**R$_{POS}$**) are shown in the right panel. Patients on each treatment group were then set apart based on the pretreatment PME/NTP values to generate the above and below cutoff curves which were statistically different in both treatment groups.*

Methods: Under ethical review board approval, twenty newly diagnosed DLBCL patients undergoing CHOP-like therapy alone (**R$_{NEG}$**) and seven with added rituximab (**R$_{POS}$**) were studied noninvasively using 3D localized, ^{1}H-decoupled, nuclear Overhauser-enhanced phosphorus MR spectroscopy at 1.5 T, prior to receiving therapy. Risk assignment determined by the clinically-obtained International Prognostic Index (IPI), and two endpoints of treatment outcome (therapy response at six months, and time to treatment failure, [TTF]) were also determined.

Results: 1. Therapy Response at six months. When the pretreatment tumor PME/NTP values were corrected for the risk assignment by IPI, their mean value in the **R$_{NEG}$** group, ($\pm$ SD, n) was significantly lower in those patients who achieved a complete response at six months (**CR**, 1.53 ± 0.48, 13), compared with those who did not achieve a complete response (**NCR**, 2.86 ± 0.56, 7; $p < 3\times10^{-5}$). Similarly, in the **R$_{POS}$** group the IPI-corrected pretreatment tumor PME/NTP was significantly lower when comparing **CR** *vs.* **NCR** (1.56 ± 0.61, 4 *vs.* 3.18 ± 0.41, 3; $p < 1\times10^{-2}$). In addition, there was no difference in response at six months between **R$_{NEG}$** and **R$_{POS}$** groups (t-test p=NS). *2. Time-to-Treatment Failure.* In the figure, the results of the Kaplan-Meier analysis of TTF in the **R$_{NEG}$** and **R$_{POS}$** groups, are shown. Patients in each treatment group were segregated into those with low (≤ 2.2) and those with high (> 2.2) pretreatment PME/NTP values. The differences in TTF in each treatment group segregated by the pretreatment PME/NTP values were statistically significant by the log-rank test ($p < 0.0001$ and $p < 0.01$ for **R$_{NEG}$** and **R$_{POS}$**, respectively).

Summary: The significant correlations of the pretreatment tumor PME/NTP parameter and two objective measures of therapy outcome in newly-diagnosed DLBCL patients receiving either CHOP-like chemotherapy alone or CHOP-like chemotherapy with added rituximab demonstrate the ability of the pretreatment tumor PME/NTP parameter to predict outcome in the absence or presence of rituximab.