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A Multicenter Phase 2 Study Incorporating High-Dose Rituximab into the CODOX-M/IVAC Regimen for Untreated Burkitt’s Lymphoma (BL): Examination of Correlative Serum and CSF Rituximab Levels

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Background: Two-year survival rates for adult BL remain <60-65%. Furthermore, there is a paucity of data adding Rituximab to CODOX-M/IVAC therapy and virtually no data regarding the significance of serum or cerebrospinal fluid (CSF) levels.

Methods: Twenty-five BL patients were enrolled. Patients had low-risk (LR) or high-risk (HR) disease; LR patients received 3 CODOX-M cycles, while HR had 4 alternating CODOX-M/IVAC cycles (Mead et al. Blood 2009). Rituximab (500mg/m2) was given x 2 doses each cycle. Correlative analyses of paired serum and CSF Rituximab levels were obtained for cycles 1+3 at 24+72 hours.

Results: There were 20 HR and 5 LR patients and median age was 44 years (range, 23-70). 3 HR and 1 LR patient were HIV+, while 15% of HR patients had CNS disease. Additionally, 35% of HR patients had bulk >10 cm and 40% had bone marrow involvement. Myelosuppression and mucositis appeared comparable with prior CODOX-M/IVAC data. The overall remission rate after 2 cycles was 100% with 67% complete remission. At 34-month median follow-up, 2-year PFS and OS rates for all patients were 86% and 86%, respectively (LR 2-year PFS and OS: both 100%; HR 2-year PFS and OS: both 82%). Further, the 2-year PFS and OS for HR, HIV-negative patients were 91% and 91%, respectively (disease-specific survival 100%). Two patients died from progressive disease (both HIV+ HR). The median serum and CSF rituximab levels for these patients were compared with patients without relapse (Table 1). Interestingly, cycle 1, 24-hour serum Rituximab levels were significantly higher among patients without relapse compared with the two patients who relapsed/died (P=0.042). Cycle 3, 24-hour Rituximab levels were of borderline significance (P=0.06).

Conclusions: The integration of Rituximab into CODOX-M/IVAC was associated with excellent survival rates, especially for HIV-negative BL. Further investigation of the predictive value of serum Rituximab levels is warranted.
Table 1. Rituximab Levels for Patients Without and With Disease Relapse.

<table>
<thead>
<tr>
<th>Chemotherapy cycle/hours after R infusion</th>
<th>Median serum R level (ng/ml) for pts without relapse</th>
<th>Serum R level for 2 pts with relapse</th>
<th>Median CSF R level (ng/ml) for pts without relapse</th>
<th>CSF R levels for 2 pts with relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pt #1</td>
<td>Pt #2</td>
<td>Pt #1</td>
<td>Pt #2</td>
</tr>
<tr>
<td>C1/24h</td>
<td>258,135</td>
<td>170,770</td>
<td>91,180</td>
<td>104</td>
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<tr>
<td>C1/72h</td>
<td>139,425</td>
<td>60,470</td>
<td>29,780</td>
<td>253</td>
</tr>
<tr>
<td>C3/24h</td>
<td>306,400</td>
<td>162,190</td>
<td>224,360</td>
<td>246</td>
</tr>
<tr>
<td>C3/72h</td>
<td>218,850</td>
<td>149,680</td>
<td>135,450</td>
<td>196</td>
</tr>
</tbody>
</table>

Abbreviations: C, cycle; h, hours; pt, patient; R, Rituximab.

Figure 1. Survival for High-Risk, HIV-Negative BL.