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# POSTER ABSTRACTS

## 627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

### Feasibility of a Dose-Intensive Regimen for Pediatric Burkitt Lymphoma in Malawi

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**Introduction:** Burkitt lymphoma (BL) is the commonest childhood cancer diagnosed in Sub-Saharan Africa (SSA). It is highly curable with survival rates >90% in resource-rich settings with dose-intensive regimens that contain the anti-CD20 monoclonal antibody, rituximab, high-dose methotrexate (HDMTX; ≥ 3000 mg/m $^2$) and high-dose cytarabine. In contrast, outcomes in SSA where patients typically receive less intense chemotherapy with lower-dose methotrexate (≤1000 mg/m $^2$) and without rituximab, remain poor. Major drawbacks to implementing HDMTX regimens in SSA include lack of adequate supportive care and inability to monitor drug levels. Improving long-term outcomes for BL in SSA requires graduated, stepwise, and cautious escalation of treatment tailored to available supportive care infrastructure. Based on the available evidence, we adopted a resource-adapted HDMTX-containing regimen as our standard of care for pediatric BL in Lilongwe, Malawi. We report preliminary data on patients treated with this regimen.

**Methods:** This is a prospective study of children (<18 years) with newly diagnosed BL, treated with our locally adapted regimen at Kamuzu Central Hospital in Malawi. This risk-stratified regimen incorporates HDMTX at doses of 1000-3000 mg/m $^2$ per cycle (Table 1) and is based on the Group B arm of the FAB/LMB backbone (standard of care in high-resource settings) with a 60% dose reduction of anthracycline-based on previously published data. Rituximab and two maintenance cycles were incorporated into the therapy for very high-risk patients (Table 1). Treatments were administered in 14-day cycles. Patients not in complete remission (CR) at the end of the first consolidation cycle received 4 cycles of DHAP (Dexamethasone, Cisplatin, HD-Cytarabine, Prednisone). To mitigate toxicity, we established locally appropriate best practices for supportive care and extended bicarbonate-containing fluid hydration for days with rate adjustments based on changes in daily creatinine levels in lieu of MTX levels-which were unavailable (Table 2). Adverse events (AE) were defined by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria. Using descriptive statistics, we report on the frequency of severe AEs in this cohort.

**Results:** Between June 2022 and July 2023, 40 consecutive patients with biopsy-proven BL were treated with this approach. They were mostly male (n=26, 65%) with a median age of 9 years (interquartile range, 6-12). The majority (n=22, 55%) had Murphy stage III disease, and 15 (38%) were stage IV at diagnosis. Five patients (13%) had central nervous system (CNS) disease, and 12 (31%) with bone marrow (BM) disease. All patients were stratified as high-risk or very high-risk. Nineteen (48%) have completed their planned first-line therapy, 7 (17%) are currently in therapy, 8 (20%) died before treatment completion, and 6 (15%) abandoned therapy. Treatment delays occurred in 12/107 (11%) HDMTX-containing cycles. For the non-rituximab HDMTX cycles (n=90), there have been 14 episodes (16%) of grade ≥3 febrile neutropenia, 1 episode (1%) of grade ≥3 mucositis, and 5 episodes (6%) of grade ≥3 anemia. One patient developed grade 3 acute kidney injury, which resolved with hydration. In patients who received rituximab (n=17) there have been 3 episodes (18%) of grade ≥3 febrile neutropenia, and 1 episode (6%) of grade ≥3 mucositis or anemia. In total, there were 12 (30%) deaths: 5 disease-related deaths, 4 early

deaths from sepsis, or tumor lysis before pre-HDMTX, 1 unknown cause, and 2 (6%) treatment-related deaths associated with HDMTX. Twenty-three patients had interim assessment at the end of the first consolidation and 18 (78%) were in CR. Of the patients with relapse or progressive disease (n=8), 4 (50%) had either CNS or BM disease.

**Conclusion:**

We demonstrate feasibility of administering dose-intensive intermediate dose MTX-containing treatment for pediatric BL in a very resource-limited setting with rigorous surveillance and supportive care. We will build on this by incorporating rituximab into all risk-groups, while evaluating its impact on efficacy and the immune reconstitution in a population with high prevalence of malnutrition, malaria, and tropical infections. Furthermore, given higher treatment-failure rates in patients with CNS or BM disease, strategies to intensify treatment in this cohort in the context of available support care resources will be needed.

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**TABLE 1: Treatment Schema for pediatric Burkitt Lymphoma at Kamuzu Central Hospital, Lilongwe, Malawi.**

| TREATMENT SCHEMA FOR PEDIATRIC BL AT KCH | | |
|---|---|---|
| **RISK STRATA** | **PHENOTYPE** | **CHEMOTHERAPY REGIMEN** |
| **STANDARD RISK** | Stage I/II with low LDH | COP Pre-phase followed by 2 cycles of COPADM and 2 cycles CYM<br>MTX dose=1,000mg/m$^2$ |
| **HIGH RISK** | Stage I/II with high LDH<br>Stage III regardless of serum LDH amount<br>Non-CNS Murphy Stage IV disease with Bone Marrow involvement of <25% | COP Pre-phase followed by 2 cycles of COPADM and 2 cycles CYM<br>MTX dose=3,000mg/m$^2$ |
| **VERY HIGH RISK** | Stage IV with Bone Marrow Involvement of >25%<br>Stage IV with CSF-positive disease | COP Pre-phase followed by 2 cycles of R-COPADM, 2 cycles R-CYM and 2 Cycles of Maintenance COPADM<br>MTX dose=3,000mg/m$^2$ |

**LEGEND**:
BL= Burkitt Lymphoma, LDH= Lactate Dehydrogenase

Low LDH= A level less than two times the upper limit of normal

High LDH= A level greater than or equal to two times the upper limit of normal

COP Pre-phase= Cyclophosphamide (300mg/m$^2$), Vincristine (1mg/m$^2$), Prednisone with Intrathecal Methotrexate, Cytarabine and Hydrocortisone

COPADM= Cyclophosphamide (1200mg/m$^2$), Vincristine (2mg/m$^2$), Prednisone (30mg/m$^2$), Doxorubicin/Adriamycin (25mg/m$^2$), Methotrexate (dose based on risk strata) with 2 Intrathecal Methotrexate, Cytarabine and Hydrocortisone

CYM= Cytarabine (100mg/m$^2$ daily for 5 days), Methotrexate (dose based on risk strata) with 2 Intrathecal Methotrexate, Cytarabine, and Hydrocortisone

R- COPADM= Rituximab (375mg/m$^2$), Cyclophosphamide (1200mg/m$^2$), Vincristine (2mg/m$^2$), Prednisone (30mg/m$^2$), Doxorubicin/Adriamycin (25mg/m$^2$), Methotrexate (dose based on risk strata) with 2 Intrathecal Methotrexate, Cytarabine and Hydrocortisone

R-CYM= Rituximab(375mg/m$^2$), Cytarabine (100mg/m$^2$ daily for 5 days), Methotrexate (dose based on risk strata) with 2 Intrathecal Methotrexate, Cytarabine, and Hydrocortisone

Maintenance COPADM= Cyclophosphamide (1000mg/m$^2$), Vincristine (2mg/m$^2$), Prednisone (30mg/m$^2$), Doxorubicin/Adriamycin (25mg/m$^2$), Methotrexate (3000mg/m$^2$) with 2 Intrathecal Methotrexate, Cytarabine and Hydrocortisone

**Table 2: Supportive care routines for patients on the pediatric Burkitt Lymphoma protocol at Kamuzu Central Hospital, Lilongwe, Malawi.**

| SUPPORTIVE CARE ROUTINES FOR PATIENTS ON THE PEDIATRIC BURKITT LYMPHOMA PROTOCOL AT KCH | |
|---|---|
| **ROUTINE MONITORING** | Fluid chart monitoring |
| **BLOOD COUNT MONITORING** | Start each cycle of therapy (exception pre-phase and 1st cycle): ANC ≥ 1,000/µl and platelets ≥100,000/µl. |
| | After cycle 1, routinely give GCSF 5mcg/kg daily to all patients from day 7 and continue until ANC >1000 post-nadir. |
| | Counts should be repeated at least 24 hours after the last dose of GCSF to confirm it's appropriate for chemotherapy. |
| | Chemo should be started no less than 48 hours after the last dose of GCSF. If delayed count recovery by day 18, give GCSF 5mcg/kg daily |
| **METHOTREXATE MONITORING** | IV Ringer's Lactate + 25mEq/L of $NaHCO_3$ for 12 hours pre-hydration prior to MTX then continued for 96 hours post-MTX infusion.<br>If urine pH < 7 after pre-hydration or anytime during MTX infusion increase sodium bicarbonate to 50mEq/L |
| | Urine dipstick at least once every day for Specific Gravity and pH and aim at urine pH of ≥7 and Specific Gravity ≤1.010. |
| | Folinic Acid: Start strictly 24 hours after MTX infusion start time, 15 mg/m$^2$/dose PO 6HRLY for 72hours; 12 Doses in total |
| | Nurses to Directly observe the start time of Folinic acid and every dose patient takes. |
| | If Serum creatinine rises by more than 25% of pre-MTX infusion level, increase IV fluids to 200 mL/m$^2$/hour and increase Folinic acid dose to 15 mg/m$^2$/dose PO 3HRLY if creatinine increase is >50%. Monitor creatinine levels daily until levels return to pre-MTX levels. |
| | Discuss with the Consultant the actual STOP time for fluids, Folinic Acid & $NaHCO_3$, it may be extended. |
| **LAB TESTS** | Creatinine, urea, sodium, and potassium on Day 0, 2, and Day 3 routinely and as needed if abnormal. |
| **PROPHYLAXIS** | Co-trimoxazole prophylaxis at discharge for 1 week. No co-trimoxazole prophylaxis 24 hours before and after Methotrexate |

**Figure 1**