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Successful Use of EPOCH-R in 2 Young Adult Patients With Burkitt Lymphoma and Acute Kidney Injury: A Case Report

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Summary: Pediatric Burkitt lymphoma has historically been treated with intensive methotrexate-based chemotherapy, which improves patient survival while causing severe toxicities. Young patients typically have better outcomes with intensive therapies, while adults and immunocompromised patients have higher toxicities and worse outcomes. Newer treatment regimens, including etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab (EPOCH-R), show promise for these patients. However, few studies exist to demonstrate efficacy and improved toxicity profile with EPOCH-R. We present 2 cases: a 25-year-old male with Down syndrome and an 18-year-old male with Burkitt lymphoma and significant renal injury who were successfully treated with EPOCH-R with minimal toxicities.

Key Words: EPOCH-R, Burkitt lymphoma, acute kidney injury, Down syndrome

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Burkitt lymphoma (BL) is an aggressive non-Hodgkin lymphoma that comprises 1% to 2% of lymphomas in the United States, but up to 30% to 50% of pediatric lymphomas.[1,2] Most cases present with a rapidly growing tumor and tumor lysis syndrome (TLS).[3] Typical therapeutic approaches for BL involve short, intensive chemotherapies including methotrexate, cytarabine, prednisone, and anthracycline.[4] These regimens are associated with severe grade 3-4 toxicities, including neutropenia, mucositis, sepsis, and nephrotoxicity.[5] In children, toxicities are usually manageable, allowing the necessary intensity.

Another treatment approach used in adults with BL is similar to that of acute lymphoblastic leukemia (ALL), with induction, consolidation, and maintenance chemotherapy, given over a prolonged period. An example of this approach is hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone (Hyper-CVAD), which causes significant myelosuppression.[6] Patients unable to tolerate toxicities have previously received less intensive regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). However, overall survival is substantially lower in patients who receive CHOP (38.8% vs. 82.8% with Hyper-CVAD).[7]

Recently, studies have looked at whether prolonged, less intense doses of chemotherapy are as effective in BL. Treatment with etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab (EPOCH-R) adjusted based on neutrophil count has been studied, mostly in acquired immunodeficiency syndrome–related BL. The rate of neutropenic fevers was 10% to 22%, which is substantially lower than that seen with more intensive regimens.[1] Patients treated with EPOCH-R showed an overall survival rate of 90% to 100% at 7 years.[1] More intensive regimens have survival rates of 80% to 90% at 2 years.[7] Therefore, EPOCH-R may be an effective alternative for patients who do not tolerate intensive therapies, as published in the adult literature. There is little data for this approach in the pediatric and adolescent young adult populations. This case report supports the successful use of this approach in 2 adolescent young adult patients, suggesting that treatment with lower intensity EPOCH-R can be considered in younger patients who are more medically fragile.

RESULTS

Case Description #1

A 25-year-old male with Down syndrome (DS) presented to an outside hospital (OSH) with 3 days of nausea, vomiting, and evidence of acute kidney injury (AKI) secondary to dehydration and prerenal injury (creatinine, 3.2 mg/dL). Computed tomographic (CT) scan of abdomen with contrast showed dilated loops of small bowel with transmural thickening and diffuse peritoneal caking, suspicious for lymphoma. There was no involvement of the kidneys on imaging.

He underwent exploratory laparoscopy with biopsy, and pathology was consistent with BL, stage II. Cytogenetics and fluorescence in situ hybridization revealed a MYC-IGH rearrangement. He had a significant intra-abdominal tumor burden that placed him at risk for TLS, with elevated uric acid requiring treatment with rasburicase initially. He was also treated with intravenous fluids for dehydration, after which creatinine improved to 2.1 mg/dL. A chest x-ray demonstrated right pleural effusion with possible infiltrate. He was started on antibiotics for suspected pneumonia, and underwent thoracentesis, which showed an exudative effusion.

He was started on prephase chemotherapy with steroids and cyclophosphamide, after which he developed worsening TLS and resulting renal injury requiring continuous venovenous hemofiltration, and pneumonia requiring intubation. As he was treated at an OSH, specific creatinine and electrolyte values were not available. He then received treatment with Hyper-CVAD 1A with pegfilgrastim for neutropenia. In addition to renal and pulmonary

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complications, he developed hypertension due to AKI, perianal herpes simplex virus dermatitis and diarrhea. There was no concern for posterior reversible encephalopathy syndrome despite his hypertension.

Because of his DS and concerns that he would not tolerate additional intensive chemotherapy, his parents decided to transfer to our institution, a pediatric hospital. He had a positron emission tomography (PET)-CT, bone marrow biopsy and lumbar puncture performed, which showed no evidence of metastasis. Although on presentation to our institution he had a normal potassium, phosphorus, and uric acid, these subsequently increased (potassium, 5.1 mmol/L; phosphorus, 5.5 mg/dL; and uric acid, 10 mg/dL) within a few days of arrival, requiring treatment with intravenous fluids and allopurinol with resolution of abnormalities. His creatinine also improved to 1.39 mg/dL after continuous venovenous hemofiltration at OSH and intravenous fluids. After review of his course, he was initiated on therapy with EPOCH-R per ANHL1131 in order to avoid further nephrotoxicity with methotrexate. He developed neutropenia, but responded well to pegfilgrastim. His course was notable for resolution of his AKI, TLS, perianal dermatitis, and pneumonia.

He was admitted 5 times thereafter for EPOCH-R and pegfilgrastim. His main side effects were nausea, AKI that improved with hydration, and hyperglycemia associated with steroids. He also experienced headaches associated with fluid overload. Between cycles, he only had grade 1-2 toxicities with headache, nausea, anorexia, mucositis, and peripheral neuropathy. He had no readmissions for fever and neutropenia.

Follow-up PET-CT after completion of 6 cycles of EPOCH-R demonstrated a small area of increased activity in the small bowel, with questionable bowel wall thickening, concerning for inflammatory or malignant process. Magnetic resonance imaging enterography showed no bowel wall thickening. Repeat imaging 3 months later demonstrated no evidence of recurrence. Of note, his creatinine remains persistently elevated around 1.5 mg/dL, although his electrolytes, fluid balance, and blood pressures remain normal. He is currently 3.5 years off therapy, and is clinically well without recurrence.

Case Description #2

An 18-year-old male presented to an OSH with abdominal pain, distention, and evidence of AKI. Kidney injury was initially thought to be due to dehydration and NSAID use for pain. A CT abdomen with contrast showed small bowel obstruction, diffuse edema, free fluid, bilateral pleural effusions, and hydroureteronephrosis. There were no masses within the kidney, though the kidneys had abnormal enhancement suggestive of pyelonephritis, for which he was started on antibiotics. Initially, an oncologic process was not identified.

His OSH course was complicated by worsening AKI (maximum creatinine, 9.1 mg/dL), obstructive uropathy requiring hemodialysis, hyperuricemia (maximum uric acid, 17.1 mg/dL; requiring treatment with rasburicase), small bowel obstruction, hepatobiliary obstruction, respiratory insufficiency, and hypertension. His obstructive uropathy and worsening AKI were thought to be due to lymphadenopathy causing obstruction. Because of concern for abdominal lymphadenopathy, with imaging showing multiple nodes of varying sizes, measuring up to 8 cm in circumference, he underwent paracentesis, which demonstrated multiple lymphocytes concerning for lymphoma. He was transferred to the intensive care unit at our hospital for further management.

Upon transfer, cytology from the ascites fluid was reviewed, which showed both C-MYC and MYC-IGH rearrangements, confirming the diagnosis of BL. Lumbar puncture and bone marrow biopsy showed clear cerebrospinal fluid and <1% bone marrow involvement. He was thus classified as stage IV. He was initially started on COP therapy (cyclophosphamide, vincristine, methylprednisolone) according to Children's Cancer Group 5961.

Moreover, upon transfer, he had significant TLS with uric acid of 14.4 mg/dL, potassium of 5.1 mmol/L, although phosphorus was normal. Creatinine improved to 1.76 mg/dL with hemodialysis at the OSH. However, given ongoing electrolyte abnormalities, he required initiation of continuous renal replacement therapy (CRRT) for 12 days, followed by intermittent hemodialysis for 1 month. He was started on CRRT in conjunction with initiation of chemotherapy to prevent further electrolyte abnormalities. After CRRT, electrolytes normalized and creatinine improved to 1.09 mg/dL. Following completion of intermittent hemodialysis, which was required due to recurrent moderate elevations in potassium, phosphorus, and uric acid, electrolytes stabilized and creatinine normalized to 0.49 mg/dL.

In addition to his kidney injury, he developed respiratory failure with bilateral pleural effusions requiring intubation. His AKI and pleural effusions were a contraindication to methotrexate administration, so he was given another cycle of COP with rituximab. Repeat imaging showed substantial reduction of tumor burden.

Because of multiple significant toxicities, and concern that he would not tolerate methotrexate, he was transitioned to treatment with dose-adjusted EPOCH-R with filgrastim. He tolerated this regimen well, and did not require further hemodialysis. His creatinine has remained normal. PET-CT after cycle 2 showed complete remission. He was admitted 4 times thereafter to complete 6 total cycles of chemotherapy. He experienced minimal toxicities, including hypertension related to fluid overload, neuropathic pain, and brief episodes of pancytopenia without associated infection. He did not require any dose reductions despite cytopenias. He is currently 3 years off therapy, and is doing well without evidence of disease recurrence.

DISCUSSION

Although treatment of pediatric BL is standardized, some pediatric patients and patients with underlying immunodeficiency may not tolerate the standard, more intensive regimens. Recent studies identified treatment with EPOCH-R as an alternative regimen. A few studies exist to indicate that this regimen is effective and less toxic, with similar overall survival rates and fewer hematologic and infectious toxicities.[1]

Our cases present further evidence of the utility of EPOCH-R, and expand upon the patient population that may benefit from this chemotherapy regimen. It should be considered in pediatric patients who will not tolerate toxicities from more intensive regimens, or who are presenting critically ill with evidence of significant end organ damage. Both of our patients presented with significant AKI, limiting use of the standard pediatric approach with regimens that include methotrexate. After transitioning to EPOCH-R, both patients had near resolution of their renal injury. Both

patients experienced little toxicity during subsequent cycles, most notably no serious infections related to neutropenia, demonstrating the safety of this regimen. Finally, both patients achieved remission after completing 6 cycles of EPOCH-R.

It has been well documented in children with DS and ALL that these patients have increased toxicities with methotrexate.[8,9] Rabin et al[10] showed that patients with DS had longer neutrophil nadirs, more frequent infections, and more severe mucositis. As such, it is important to consider less toxic, non–methotrexate-based therapies for these patients in order to minimize chemotherapy-associated morbidity and mortality.

Given that our patients achieved remission and had minimal severe toxicities from treatment with EPOCH-R, other patients with similar risk factors should be considered as candidates for this treatment regimen. Long-term outcomes must be monitored to ensure that recurrence rates and late effects are comparable with those regimens currently used.

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