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Prolonged low intensity EPOCH–rituximab has improved toxicity in Burkitt lymphoma compared with standard short, high intensity therapy

Shandiz Shahbazi, Cody J Peer, and William D Figg*
Clinical Pharmacology Program; Medical Oncology Branch; National Cancer Institute; Bethesda, MD USA

Burkitt lymphoma is an aggressive form of non-Hodgkin lymphoma that has a short doubling time, thus intense short-cycle chemotherapy has been thought to be essential. A recent NCI-sponsored clinical trial investigated DA-EPOCH-R given to 19 HIV-negative patients and a short course regimen (SC-EPOCH-RR) given to 11 HIV-positive patients in hopes of maintaining the efficacy of the regimen while decreasing the typical side effects from the intensive short-cycle chemotherapy. Low intensity EPOCH-R based therapy achieved excellent rates of efficacy despite a significant difference in the median cumulative dose between the DA-EPOCH-R and SC-EPOCH-RR cohorts. Furthermore, both cohorts experienced mainly grade 1 and grade 2 toxicities, with SC-EPOCH-RR cohort patients experiencing less adverse events than DA-EPOCH-R cohort patients. This recent clinical investigation suggests the most important therapeutic principle is not the intensity but rather the length of exposure time above an effective threshold concentration. Since short, intense bolus doses are the standard therapy for Burkitt lymphoma, these findings are clinically relevant and significant.

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*Correspondence to: William D Figg;
Email: wf13e@nih.gov

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Burkitt lymphoma, a relatively rare and aggressive form of non-Hodgkin lymphoma, has been recognized as the fastest growing human tumor.[1-4] Approximately 1200 people are diagnosed with Burkitt lymphoma in the United States each year.[5] The majority of Burkitt lymphoma cases occur in Africa, but due to a lack of cancer registries, an accurate worldwide incidence of the disease is unknown.[6] Burkitt lymphoma (BL) affects B lymphocytes, which are an integral part of the adaptive immune system and is associated with rapidly growing lymph node tumors in the chest and/or abdomen that are commonly spread to the central nervous system.[1] There are three subtypes of BL, endemic, sporadic, and immunodeficiency-associated, but all share a translocation between MYC and an immunoglobulin promoter, as well as a p53 mutation.[3,4] The endemic subtype, associated with the Epstein–Barr virus, is prevalent in tropical Africa and in African children between 4 and 7 years of age.[3] The majority of endemic BL cases present with jaw and facial bone involvement.[7] The sporadic subtype, found globally, is the most common subtype in the United States and is not associated with any infectious co-factors.[3,4] The immunodeficiency-associated subtype occurs primarily in HIV-positive patients, in addition to congenital immunodeficiency and organ-transplant patients.[1,3,4] Common sites of involvement for patients with the sporadic and immunodeficiency subtypes include the abdomen, liver, kidneys, spleen, bone marrow, ovaries, and testes.[3,7]

Since BL is a highly proliferative cancer with short doubling time, short intense multidrug bolus doses are commonly used. Typically, pediatric BL regimens have been altered for adult patients.[8] Investigators from the National Cancer Institute created the CODOX-M (cyclophosphamide, vincristine, doxorubicin, and high-dose methotrexate) with IVAC

(ifosfamide, etopside, high-dose cytarabine, and intrathecal therapy) regimen, where patients with high-risk disease were treated with 2 cycles of CODOX + methotrexate (M) that alternated with 2 cycles of IVAC, while low-risk patients received 3 cycles of CODOX-M.[9,10] Although these regimens were efficacious, this intense short-cycle chemotherapy had severe side effects including mucositis and severe neurotoxicity.[9,10] For example, all patients suffered from grade 3 or 4 neutropenia and 96% of patients suffered from thrombocytopenia.[8,10] EPOCH-R regimens, which include etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab, were tested as an alternative to CODOX-M/IVAC therapy to improve the toxicity profile while maintaining efficacy for the treatment of BL.[4,11]

Due to the severe side effects and inferior outcomes in immunodeficiency patients, a trial by Dunleavy et al. published in *The New England Journal of Medicine* investigated a standard dose-adjusted regimen of EPOCH with rituximab (DA-EPOCH-R) and a short course regimen with a double dose of rituximab (SC-EPOCH-RR) in untreated BL patients.[4] DA-EPOCH-R was previously used in diffuse large B-cell lymphoma with a progression free survival of 79%, and overall survival of 80% at 5 y.[12] Only 5% of cycles resulted in grade 3 gastrointestinal and neurotoxicity.[10] From November 2000 through December 2009, Dunleavy et al. enrolled 30 patients with BL who had not received prior systemic chemotherapy and had sufficient organ function apart from organ function affected by the disease. There were 19 HIV-negative patients in the DA-EPOCH-R cohort and 11 HIV-positive patients in the lower-dose SC-EPOCH-RR cohort. Patients ranged from 15 to 88 y old, with a median age of 33. Seventeen percent of patients had low-risk disease, 73% had intermediate-risk disease, and 10% had high-risk disease. All patients underwent standard laboratory tests, cytologic and flow cytometric analysis of the cerebrospinal fluid and imaging of the brain, tomographic scans of the whole body, and bone marrow aspirate and biopsy.

DA-EPOCH-R cohort patients received two cycles of chemotherapy after complete remission (a total of 6 to 8 cycles) and were dose-adjusted based on pharmacodynamic markers (concentration of neutrophil nadir). SC-EPOCH-RR cohort patients were not dose-adjusted and received one cycle of chemotherapy after complete remission (total of 3 to 6 cycles). DA-EPOCH-R patients without evidence of cerebrospinal-fluid involvement received eight 12-mg doses of prophylactic intrathecal methotrexate over nine weeks while SC-EPOCH-RR group patients received six 12-mg doses of prophylactic intrathecal methotrexate over 6 wk. However, patients with cerebrospinal-fluid involvement were actively treated with methotrexate.

Patients in both the DA-EPOCH-R and SC-EPOCH-RR cohorts had similar progression-free survival (PFS) rates. Ninety-five percent of patients in the DA-EPOCH-R cohort had PFS (95% CI: 75–99%) through median follow-up period (86 mo), while patients from the SC-EPOCH-RR cohort had PFS of 100% (95% CI: 72–100%) through follow-up of 73 mo. Overall survival (OS) rates for the DA-EPOCH-R cohort was 100% (95% CI: 82–100%), while the SC-EPOCH-RR demonstrated a 90% OS (95% CI:60–98). Furthermore, 92% of immunodeficiency-associated patients survived. No deaths were attributed to Burkitt lymphoma.

Patients in the SC-EPOCH-RR group had 47% and 57% lower median cumulative doses of doxorubicin–etoposide and cyclophosphamide, respectively, than patients in the DA-EPOCH-R group.[4] Although there was a significant difference in drug exposure between patients in these cohorts, PFS and OS was quite similar. This suggested that the most important therapeutic principle is not the peak concentration but rather the length of exposure time above an effective threshold concentration.

Adverse events related to DA-EPOCH-R and SC-EPOCH-RR therapy were mainly grade 1 or 2, with SC-EPOCH-RR patients experiencing less adverse effects.[4] Due to the severe side effects patients from previous trials were experiencing, the reduced toxicity for this trial is significant.[8,9] Nineteen percent of patients required hospital admission due to fever and neutropenia, compared with only 7% of patients 40 y old and higher. Since adult populations typically do not respond to treatment as effectively as adolescents, the small percentage of adult patient hospitalizations is promising. Moreover, neutropenia was reported in 31% of cycles of SC-EPOCH-RR compared with 52% of DA-EPOCH-R cycles. This was likely due to the lower treatment intensity of the SC-EPOCH-RR regimen. Additionally, non-hematopoietic toxic events with patients in both DA-EPOCH-R and SC-EPOCH-RR groups were similar to previous studies.[9] As the major limiting factor of current standard high intense therapy for BL is severe side effects, this prospective clinical study by Dunleavy et al. provides a much needed alternative therapy that is highly effective with much less toxicity.

Dunleavy et al. conclude that BL can be effectively treated with a low-intensity regimen in an outpatient setting. HIV-positive patients in the SC-EPOCH-RR group were given a regimen with significantly lower treatment intensity, and although they were immune-compromised and had more advanced disease than their counterparts in the DA-EPOCH-R group, all patients had complete remissions without additional therapy. BL patients in the SC-EPOCH-RR cohort were most vulnerable to the toxicity of standard regimens, and therefore the minimal occurrence of fever and neutropenia in these patients is notable.

The data from Dunleavy et al. suggest there is no longer a need for high-intensity treatment with high toxicity, as has been standard practice in BL.[11] Low intensity EPOCH-R based therapy has achieved excellent rates of efficacy despite a 57% difference in the median cumulative dose between the DA-EPOCH-R and SC-EPOCH-RR regimens. Given the severe toxicities with previous chemotherapy regimens for BL, the results from this uncontrolled prospective clinical trial is especially promising, and there are currently two confirmatory trials at the National Cancer Institute and Baylor College of Medicine using the EPOCH-R regimens.[13,14]

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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