ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Dose-Adjusted EPOCH-R for Burkitt Lymphoma

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H&O What is dose-adjusted EPOCH-R?

DH EPOCH-R refers to chemotherapy with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, plus the anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen Idec). The distinguishing feature of the dose-adjusted regimen is that it involves a longer exposure time above a certain threshold. Specifically, patients receive an infusion of doxorubicin, vincristine, and etoposide over 96 hours; cyclophosphamide and prednisone on a bolus schedule; and doxorubicin, etoposide, and cyclophosphamide that is pharmacodynamically dose-adjusted based on the neutrophil nadir. Dose-adjusted EPOCH-R (DA-EPOCH-R) is a treatment approach for hematologic malignancies that is based on the principle that intensity may not be as important as we once thought.

H&O What is the rationale behind the DA-EPOCH-R regimen?

DH Burkitt lymphoma is a highly proliferative tumor. The introduction of a short, dose-intensive treatment regimen—started in several childhood Burkitt lymphoma trials and later adapted similarly successfully to adults—has changed this disease from one with very poor outcome to one that is highly curable.

However, it was never explored whether prolonged exposure to a low concentration of chemotherapy could be equally effective in terms of response rate and overall survival (OS) compared with the short dose-intensive regimen. It is the merit of the EPOCH-R study to show that a prolonged continuous infusion of EPOCH-R with an improvement of drug concentration–response pharmacokinetic curve also may be sufficient.

H&O What was the preliminary evidence that this approach could be effective for Burkitt lymphoma?

DH Numerous studies have been conducted with DA-EPOCH-R. The initial data came from studies in diffuse large B-cell lymphoma (DLBCL). In 2002, Wilson and colleagues reported in *Blood* that in 50 patients with previously untreated DLBCL, 92% of tumors had a complete response to DA-EPOCH-R. Even tumors that were highly proliferative were sensitive to treatment, an outcome that had not been seen with treatments based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy.

In a phase 2 study of 72 patients with previously untreated DLBCL by Wilson and colleagues in the *Journal of Clinical Oncology* in 2008, the progression-free survival (PFS) and OS were 79% and 80%, respectively, with DA-EPOCH-R. The Cancer and Leukemia Group B (CALGB) conducted a similar study, which was published in *Haematologica* in 2012 with Wilson as the first author. Here, 69 patients with previously untreated DLBCL had a PFS of 81% and an OS of 84%, respectively, at 62 months with DA-EPOCH-R.

These studies, and in particular the evidence about the ability of DA-EPOCH-R to treat highly proliferative tumors, served as the basis for studying this regimen in Burkitt lymphoma.

H&O Could you describe the first studies of EPOCH-R in Burkitt lymphoma?

DH The initial study was conducted by Dunleavy and colleagues at the National Institutes of Health. In this study, patients with newly diagnosed Burkitt lymphoma—11 who were positive for human immunodeficiency virus (HIV) and 19 who were HIV-negative—were treated with EPOCH-R. The HIV-negative patients received 6 to 8 cycles of dose-adjusted treatment, and the HIV-positive patients received 3 to 6 cycles of a lower-dose, short-course regimen. Two different regimens were used: patients who were HIV-positive received an additional dose of rituximab per treatment cycle and also received a lower intensity treatment compared with patients who were HIV-negative.

H&O Could you please describe the results of this study?

DH Dunleavy and colleagues reported the study in the *New England Journal of Medicine* in 2013. At a median follow-up of 86 months, the OS rate among HIV-negative patients was 100%. For HIV-positive patients, the OS rate was 90% at 73 months. There were no treatment-related deaths. The most common toxicities were fever and neutropenia.

H&O How do these outcomes compare with dose-intensive chemotherapy for the treatment of Burkitt lymphoma?

DH The 2 regimens have not been directly compared in a randomized clinical trial. Ribera and colleagues reported a phase 2 study of dose-intensive chemotherapy with rituximab for Burkitt lymphoma in *Cancer* in 2013. In this study, 80 HIV-negative and 38 HIV-positive patients with Burkitt lymphoma or leukemia were treated with 4 or 6 cycles of intensive chemotherapy plus rituximab. The 4-year OS rate was 63% for HIV-positive patients and 78% for HIV-negative patients. Toxicities included grade 3/4 mucositis and severe infections, particularly among younger, HIV-positive patients.

In 2014, the PETHEMA (Programa para el Tratamiento de Hemopatias Malignas) Group and German HIV Lymphoma Cohort reported our findings from a study of 81 patients with Burkitt lymphoma or leukemia, all of whom were HIV-positive and all of whom received dose-intensive chemotherapy plus rituximab. These results were published online by Xicoy and colleagues in *Leukemia & Lymphoma* earlier this year. The 4-year OS rate was 72% in this study. However, adverse events were a problem, and the authors concluded that the approach was effective but toxic.

Another study, published in 2013 by Evens and colleagues in the *Annals of Oncology*, investigated the incorporation of high-dose rituximab and liposomal doxorubicin into the regimen of cyclophosphamide, vincristine, doxorubicin, and methotrexate with ifosfamide, etoposide, and cytarabine (CODOX-M/IVAC). Twenty-five patients with untreated Burkitt lymphoma—20 high-risk and 5 low-risk—were treated with liposomal doxorubicin, intravenous rituximab at 500 mg/m^2 twice per cycle, and the well-known CODOX-M/IVAC regimen. Here, the 2-year OS rate was 89%. The toxicities matched those seen with the CODOX-M/IVAC regimen alone except that several patients experienced grade 3 cardiac events.

In the United Kingdom, the Lymphoma Group LY06 study evaluated CODOX-M and CODOX-M/IVAC in patients with Burkitt lymphoma. In this study, published by Mead and colleagues in the *Annals of Oncology* in 2002, the overall treatment-related mortality was 6 out of 52 patients: a total of 12%. By contrast, the study by Dunleavy and colleagues mentioned earlier saw no treatment-related mortality.

The German Multicenter Study Group for Adult Lymphoblastic Leukemia initiated a short dose-intensive regimen with rituximab in 2002. Of 363 patients with Burkitt lymphoma, 88% achieved a complete response. The OS was 86% for patients aged 55 years or older, and 62% for those younger than 55 years. In this large study, prognostic factors such as age, International Prognostic Index score, age-adjusted International Prognostic Index score, and sex had a significant influence. Our results will be published soon in *Blood*.

H&O Is DA-EPOCH-R continuing to be studied for Burkitt lymphoma?

DH In 2012, a Dutch team began a phase 2 study of first-line treatment with risk-adapted DA-EPOCH-R for patients with Burkitt lymphoma. In this ongoing study, low-risk patients receive 2 doses of rituximab for 3 treatment cycles, whereas high-risk patients receive 1 dose of rituximab for 6 treatment cycles.

What we need now is a randomized trial that will compare EPOCH-R with dose-intensive chemotherapy as a treatment for Burkitt lymphoma. There are several reasons why such a randomized trial is unlikely right now. First, Burkitt lymphoma is a rare disease, so a randomized study would involve a long accrual period. Second, there are many promising new anti-CD20 antibodies and also other antibodies, so many researchers may be interested in studying these new agents in comparison with rituximab.

H&O Based on the data that do exist, do you think DA-EPOCH-R is an appropriate choice for the first-line treatment of Burkitt lymphoma?

DH Yes, but with a caveat. The evidence that DA-EPOCH-R leads to less toxicity and thereby a better quality of life, no disease-related deaths, and promising overall outcome is based on a small number of patients. The 30 patients in the study were accrued over a period of 9 years, and there were only 3 high-risk patients. In addition, the result was obtained in only 1 experienced center.

Thus, the ongoing DA-EPOCH-R study by the Dutch team, with more participating centers and hopefully the inclusion of more high-risk patients, will provide much-needed information about this highly interesting approach as a new first-line treatment for Burkitt lymphoma for a broader range of patients.

Suggested Reading

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