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LETTER TO THE EDITOR

# Burkitt lymphomas failing dose-adjusted R-EPOCH (DA-R-EPOCH)

**Igor Aurer · Sandra Bašić-Kinda · Ivo Radman · Ivana Ilić · Josip Joachim Grah**

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Dear Editor,

Adults with Burkitt lymphoma/leukemia (BL) are usually treated with high-dose methotrexate-based chemotherapy and rituximab (R-HD-MTX)-containing regimens. While exact drug combinations and schedules vary, all contain HD-MTX and all result in similar outcomes [1–7]. Survival (OS) ranges from 70 to 90 % and treatment-related mortality (TRM) is 10–20 %. Recently, excellent results with dose-adjusted R-EPOCH (DA-R-EPOCH) have been reported with 100 % OS and 0 % TRM [8]. We therefore tried DA-R-EPOCH in patients with BL and high risk of complications but were unable to obtain comparable results.

DA-R-EPOCH was administered in hospital in accordance with published guidelines [9]. HIV-infected patients were continued on highly active antiretroviral therapy (HAART).

Our first patient was a 39-year-old woman admitted to another hospital. After 1 month, a diagnosis of BL stage IVB was made and the patient transferred to us. She was in poor condition with massive intra-abdominal disease, bone marrow infiltration, hypercalcemia, and kidney failure. One cycle of DA-R-EPOCH resulted in tumor regression. Blood counts normalized after 2 weeks, but pulmonary and neurological dysfunction progressed and she died within a month from multiorgan failure.

The second patient was a 34-year-old man who presented with ophthalmoplegia. An epipharyngeal tumor and HIV infection were found. Diagnostic evaluation showed stage IVB BL with involvement of lymph nodes, epipharynx, liver, and bone marrow. He achieved complete remission (CR) after three DA-R-EPOCH cycles. Dose escalations were continued for five cycles, and a dose reduction was necessary in the sixth. The epipharynx was irradiated. Five months after the end of immunochemotherapy, he relapsed with a submandibular nodal mass. The patient received four cycles of our R-HD-MTX-based regimen [7], achieved CR, and was autografted. He is well and free of disease 3 months after transplantation and 18 months after diagnosis.

The third patient was a 37-year-old man with AIDS responding to HAART. He had stage IVB BL with a large intra-abdominal mass, abdominal wall, and small bowel involvement. CR was achieved after three cycles of DA-R-EPOCH. Dose escalations were continued for four cycles. Two weeks after the end of sixth cycle, he relapsed with a large intra-abdominal mass. He failed to respond to multiple lines of chemotherapy, including our standard regimen, and radiotherapy and died 1 year after diagnosis.

After this, we switched back to using R-HD-MTX in all patients with BL and did not have any failures since.

Our limited experience with DA-R-EPOCH is different from the originally reported [8]. DA-R-EPOCH is less toxic and easier to administer than R-HD-MTX but might not be without TRM and as effective as described. These discrepancies are probably caused by differences in referral patterns. The first patient, who was referred too late, serves to illustrate that in such instances, toxic deaths will occur

I. Aurer (✉) · S. Bašić-Kinda · I. Radman
Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, Kispaticeva 12, 10000, Zagreb, Croatia
e-mail: aurer@mef.hr

I. Aurer
Medical School, University of Zagreb, Zagreb, Croatia

I. Ilić
Department of Pathology, University Hospital Centre Zagreb, Zagreb, Croatia

J. J. Grah
Department of Oncology, University Hospital Centre Zagreb, Zagreb, Croatia

even with DA-R-EPOCH. The other two cases suggest that the anti-BL activity of R-HD-MTX-based therapy might be superior to DA-R-EPOCH.

We believe that prior to abandoning R-HD-MTX therapy in favor of DA-R-EPOCH, more experience in unselected patients is needed. The best way to decide on optimal chemotherapy for BL would be an international randomized trial.

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**Conflict of interest**The authors declare that they have no conflict of interest. Since this was not a clinical trial, patients were not requested to give formal informed consent but available treatment options were discussed with them.

## References

1. Thomas DA, Faderl S, O'Brien S, Bueso-Ramos C, Cortes J, Garcia-Manero G, Giles FJ, Verstovsek S, Wierda WG, Pierce SA, Shan J, Brandt M, Hagemeister FB, Keating MJ, Cabanillas F, Kantarjian H (2006) Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer 106:1569–1580
2. Oriol A, Ribera JM, Bergua J, Gimenez Mesa E, Grande C, Esteve J, Brunet S, Moreno MJ, Escoda L, Hernandez-Rivas JM, Hoelzer D (2008) High-dose chemotherapy and immunotherapy in adult Burkitt lymphoma: comparison of results in human immunodeficiency virus-infected and noninfected patients. Cancer 113:117–125
3. Hoelzer D (2008) Recent results in the treatment of Burkitt lymphomas. Ann Oncol 19(suppl4):83, abstr.8
4. Grisekvicius L, Stulpinas R, Saulyte-Trakymiene S, Mickys U, Pranys D, Kurtinaitis J, Jurgutis M (2009) Favorable outcome with chemo-immunotherapy in Burkitt lymphoma and leukemia. Leuk Res 33:587–588
5. Rizzieri DA, Johnson JL, Byrd JC, Lozanski G, Powell BL, Shea TC, Nattom S, Hoke E, Cheson BD, Larson R (2010) Efficacy and toxicity of rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or Burkitt-like leukemia/lymphoma: Cancer and Leukemia Group B (CALGB) study 10002. Blood 116:374, abstr.858
6. Barnes JA, LaCasce AS, Feng Y, Toomey CE, Neuberg D, Michaelson JS, Hochberg EP, Abramson JS (2011) Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis. Ann Oncol 22:1859–1864
7. Dujmovic D, Aurer I, Radman I, Serventi-Seiwerth R, Dotlic S, Stern-Padovan R, Dubravcic K, Santek F, Labar B (2012) Addition of rituximab to high-dose methotrexate-based chemotherapy improves survival of adults with Burkitt lymphoma/leukemia. Acta Haematol 127:115–117
8. Dunleavy K, Little RF, Pittaluga S, Grant N, Shovlin M, Steinberg S, Yarchoan R, Janik J, Jaffe ES, Wilson WH (2008) A prospective study of dose-adjusted (DA) EPOCH with rituximab in adults with newly diagnosed Burkitt lymphoma: a regimen with high efficacy and low toxicity. Ann Oncol 19(suppl4):83–84, abstr.9
9. Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, Steinberg SM, Little RF, Janik J, Gutierrez M, Raffeld M, Staudt L, Cheson BD, Longo DL, Harris N, Jaffe ES, Chabner BA, Wittes R, Balis F (2002) Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood 99:2685–2693