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For High-Grade and Aggressive Non-Hodgkin Lymphomas, Treat Adults Like Children

By Caroline Helwick
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Outcomes for adults with high-grade and aggressive non-Hodgkin lymphomas (NHLs) appear to be better when these patients are treated with pediatric-inspired protocols, according to **Mitchell S. Cairo, MD**, Chief of the Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Maria Fareri Children's Hospital; Professor of Pediatrics, Medicine, Pathology, Microbiology, and Immunology; and Professor of Cell Biology and Anatomy, New York Medical College, Valhalla, New York. At the 2016 Pan Pacific Lymphoma Conference in Koloa, Hawaii, Dr. Cairo supported his recommendation with abundant data showing that these more intensive regimens seem to pay off.[1]

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> *— Mitchell S. Cairo, MD*

"There may be biologic differences between children and adults with these diseases.... Burkitt lymphoma and diffuse large B-cell lymphoma may look different in adults than in children, but the two age groups respond identically to therapy that is designed to hit the rapidly proliferating B cells. The outcome in adults with high-grade NHL is significantly improved with pediatric-inspired treatments," Dr. Cairo emphasized.

Epidemiology Differs

Lymphoma subtypes differ in frequency between young patients and adults. In children and adolescents, there is a predominance of Burkitt lymphoma and lymphoblastic leukemia, which tend to be rare in adults. In adults, the predominant NHL subtypes are diffuse large B-cell lymphoma and the indolent lymphomas. The germinal center B subtype predominates in children, whereas non–germinal center B subtypes are more common in adults. This finding suggests prognosis may be better in pediatric diffuse large B-cell lymphoma, since the germinal center B subtype is more sensitive to chemoimmunotherapy than non–germinal center B subtypes, he proposed.

The question is whether these malignancies are the same disease or different ones in children vs adults. They do have different gene-expression signatures, according to age, but these differences may not matter therapeutically, Dr. Cairo noted.

Novel Protocols Improve Outcomes

The addition of rituximab (Rituxan) to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy clearly improved event-free survival in patients with aggressive lymphomas. However, 10-year overall survival still remains only 50% for adults with diffuse large B-cell lymphoma treated with R-CHOP.[2]

In 1996, Dr. Cairo and his colleagues developed a new protocol for mature B-cell lymphoma/leukemia and tested it in the first and largest prospective international trial of newly diagnosed patients: the French-American-British Mature B-Cell Lymphoma 96 (FAB LMB 96) study.[3] In brief, the FAB LMB 96 regimen was short and intensive therapy using fractionated high-dose cyclophosphamide, high-dose methotrexate, and high-dose cytarabine. The study tested the regimen in 1,111 children and adolescents stratified into 3 risk groups. It also included a fourth arm that evaluated reduced doses of cyclophosphamide and anthracycline.

Group A included completely resected stage I patients and patients with completely resected abdominal stage II lesions; group C included patients with any central nervous system (CNS) and/or bone marrow involvement with ≥ 25% blasts; group B included all patients who were not eligible for group A or C.

At 4.5 years, both the event-free and overall survival rates for the study population approached 90%, with a plateau observed out to 8 years. By risk group, 3-year event-free survival was 99% for group A, 89% for group B, and 79% for group C. The less intense regimen was effective in group B (intermediate-risk patients) and became the recommended approach. It was inferior to standard treatment in group C (high-risk patients).

Pediatric-Inspired Regimens in Aggressive NHL

- Intensive pediatric-inspired regimens have greatly improved outcomes in children, adolescents, and young adults with aggressive forms of NHL, with 3-year event-free survival rates as high as 95%.

The investigators further improved upon the regimen by adding rituximab to the FAB LMB 96 B4 and C1 regimens in the Children's Oncology Group (COG) ANHL01P1 trial.[4] The population included children, adolescents, and young adults with stage III/IV, CD20-positive, mature B-cell lymphoma.

- These regimens may improve outcomes in adults as well, with the RD-CODOX-M-IVAC regimen resulting in a 4-year progression-free survival rate of 78%.
- Researchers are evaluating ways to reduce the intensity of these regimens in both adults and children.

"In this study, we took only the most advanced patients—those with stages III and IV Burkitt lymphoma and diffuse large B-cell lymphoma and those with bone marrow and/or CNS involvement," he said. "We took the best treatments for group B (reduced-intensity regimen) and group C (standard regimen) from FAB LMB 96 and added dose-dense rituximab, for a total of six doses. We showed a nice improvement, compared to historical controls, by adding six doses of rituximab."

Patients with stage III/IV Burkitt lymphoma and diffuse large B-cell lymphoma had a 3-year event-free survival of 95%, compared with a 2-year event-free survival of 84% with the FAB LMB 96 regimen—the same chemotherapy without rituximab. The 3-year event-free/overall survival rate was 90% for the entire cohort and 93% in patients with CNS involvement—historically those with the worst prognosis—when treated with rituximab plus FAB LMB 96 standard therapy, without cranial irradiation.

"These are the best numbers we've seen to date," Dr. Cairo commented. "These outcomes are so much better than we got with CHOP.... But we didn't stop there. There were those who felt we needed a randomized controlled trial."

The COG ANHL1131 trial randomized children and adolescents with high-risk mature B-cell NHL to FAB LMB 96 chemotherapy with or without rituximab. The study was closed early, when interim results showed a 1-year event-free survival rate of 94.2% with rituximab vs 81.5% with chemotherapy alone (hazard ratio = 0.44; P = .006).[5]

Reduced Therapeutic Burden in Young Patients


Stanton Goldman, MD

The investigators have since developed a consortium to ask a different question: Can this relatively toxic chemotherapy regimen be further modified (within the ANHL01P1 FAB LMB 96 regimen) to reduce the risk of long-term complications in children? The initiative, called Reduced Burden of Oncologic Therapy in Advanced B-Cell Lymphoma (REBOOT ABLY), is led by Dr. Cairo and **Stanton Goldman, MD,** a pediatric hematologist-oncologist practicing in Dallas. "We use a lot of intrathecal therapies on our protocol. We want to reduce the number of lumbar punctures," Dr. Cairo explained.

The REBOOT ABLY protocol incorporates a liposomal form of cytarabine that has a long half-life in spinal fluid and therefore prolonged drug exposure, which may reduce the need for frequent lumbar punctures. The regimen also reduces the dose of doxorubicin by 60% in intermediate-risk patients, since patients also receive rituximab. The approach has yielded a 3-year event-free survival of 100% in the first 30 patients.[6]

"We have been able to reduce the burden of therapy and therefore toxicity. Hopefully down the road, this will lead to reduced morbidity and fewer late effects," said Dr. Cairo.

Testing Pediatric-Inspired Regimens in Adults

"In adults, we have incorporated the pediatric-inspired regimen by adding rituximab and liposomal [cytarabine] to CODOX-M-IVAC (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate; ifosfamide, etoposide, and high-dose cytarabine)," explained Dr. Cairo.

In 30 patients with high-risk Burkitt lymphoma or diffuse large B-cell lymphoma, treatment with RD-CODOX-M-IVAC resulted in a 4-year progression-free survival rate of 78%.[7] "With this regimen, we began to see outcomes like we had seen in children," Dr. Cairo revealed.

In the 2014 German GMALL-B-ALL-NHL-2002 trial of 363 patients with Burkitt lymphoma/leukemia, treatment with 6 chemotherapy cycles of high-dose methotrexate, high-dose cytosine arabinoside, cyclophosphamide, etoposide, ifosfamide, corticosteroids, and triple intrathecal therapy (reduced intensity in patients > 55 years) also resulted in 5-year progression-free survival (71%) and overall survival (80%) rates similar to those in pediatric patients.[8]

In adults with lymphoblastic lymphoma, a pediatric-like acute lymphoblastic leukemia (ALL) regimen also yielded good outcomes in the phase II GRAALL-LYSA LL03 study of 148 previously untreated patients.[9] This treatment was an adapted pediatric-like ALL protocol that included a corticosteroid prephase, a five-drug induction reinforced by sequential cyclophosphamide administration, dose-dense consolidation, late intensification, CNS prophylaxis, and a 2-year maintenance phase. In patients with T-lineage ALL, 3-year event-free survival was 63.3%, disease-free survival was 72.4%, and overall survival was 69.2%.

A new finding from the study was the independent prognostic value of a four-gene oncogenetic classifier (*NOTCH1/FBXW7/RAS/PTEN).* "The researchers showed the same mutations that play a role in pediatric patients are also unfavorable in adults. When you remove this subset, the outcomes are similar to what we see in children," Dr. Cairo noted.

Therefore, Dr. Cairo advocates pediatric-inspired protocols for adults with Burkitt lymphoma and diffuse large B-cell lymphoma. However, he appreciates that clinicians are hesitant to use such intensive regimens in their older patients. It may be possible, he added, to reduce the doses of some drugs without compromising outcomes in older patients, and he would like to see these approaches evaluated in clinical trials.

"This is our concept of reducing the burden of oncologic therapy," concluded Dr. Cairo. "I think it can be done in adults, but we need to look carefully at it first." ■

Disclosure: Dr. Cairo has served on advisory boards or as a consultant or speaker for Roche, Celgene, Gilead, Jazz, and Sanofi.

References

1. Armitage JO, Cairo MS: Management of patients with lymphoma across the age spectrum: What lessons can we teach each other? 2016 Pan Pacific Lymphoma Conference. Presented July 18, 2016. (https://www.eventscribe.com/2016/UNMC-PPLC/login.asp)

2. Coiffier B, Thieblemont C, Van Den Neste E, et al: Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: A study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 116:2040-2045, 2010. (http://www.bloodjournal.org/content/116/12/2040?sso-checked=true)

3. Cairo MS, Sposto R, Gerrard M, et al: Advanced stage, increased lactate dehydrogenase, and primary site, but not adolescent age (> 15 years), are associated with an increased risk of treatment failure in children and adolescents with mature B-cell non-Hodgkin's lymphoma: Results of the FAB LMB 96 study. J Clin Oncol 30:387-393, 2012. (http://jco.ascopubs.org/content/30/4/387)

4. Goldman S, Smith L, Anderson JR, et al: Rituximab and FAB/LMB 96 chemotherapy in children with stage III/IV B-cell non-Hodgkin lymphoma: A Children's Oncology Group Report. Leukemia 27:1174-1177, 2013. (http://www.nature.com/leu/journal/v27/n5/full/leu2012255a.html)

5. Minard-Colin V, Auperin A, Pillon M, et al: Results of the randomized Intergroup trial Inter-B-NHL Ritux 2010 for children and adolescents with high-risk B-cell non-Hodgkin lymphoma and mature acute leukemia: Evaluation of rituximab efficacy in addition to standard LMB chemotherapy regimen. 2016 ASCO Annual Meeting. Abstract 10507. Presented June 3, 2016. (http://meetinglibrary.asco.org/content/164975-176)

6. Goldman S, Barth MJ, Oesterheld JE, et al: Preliminary results of a reduced burden of therapy trial by incorporation of rituximab and intrathecal liposomal cytarabine in children, adolescents and young adults with intermediate (FAB Group B) and high risk (FAB Group C) mature B-cell lymphoma/leukemia. 2016 ASCO Annual Meeting. Abstract 10534. Presented June 6, 2016. (http://meetinglibrary.asco.org/content/166131-176)

7. Corazzelli G, Frigeri F, Russo F, et al: RD-CODOX-M/IVAC with rituximab and intrathecal liposomal cytarabine in adult Burkitt lymphoma and 'unclassifiable' highly aggressive B-cell lymphoma. Br J Haematol 156:234-244, 2012. (http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2011.08947.x/abstract;jsessionid=2E6B21A615FCB652759FD199D38D7886.f04t03)

8. Hoelzer D, Walewski J, Döhner H, et al: Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: Report of a large prospective multicenter trial. Blood 124:3870-3879, 2014. (http://www.bloodjournal.org/content/124/26/3870)

9. Lepretre S, Touzart A, Vermeulin T, et al: Pediatric-like acute lymphoblastic leukemia therapy in adults with lymphoblastic lymphoma: The GRAALL-LYSA LL03 Study. J Clin Oncol 34:572-580, 2016. (http://jco.ascopubs.org/content/34/6/572)