

ADVANCES IN LLM

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

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Update on Burkitt Lymphoma and Leukemia

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H&O Can you explain the different variants of Burkitt leukemia?

DH Burkitt lymphoma and Burkitt leukemia (also called mature B-cell acute lymphocytic leukemia [ALL]) have identical cytogenetic aberrations, surface markers, and molecular genetics. The clinical manifestations of Burkitt lymphoma resemble more of high grade malignant lymphomas, whereas B-cell ALL is similar to other subtypes of ALL. Additionally, there is a substantial difference in epidemiology. Burkitt lymphoma is endemic in Africa and a rare disease entity in western countries. In HIV-infected patients, Burkitt lymphoma is one of the most predominant malignancies as a secondary event.

The cytogenetic aberrations are identical in Burkitt lymphoma and mature B-cell ALL: the translocations t(8;14)(q24;q32), t(8;22)(q24;q11), the latter reflecting chromosome 8q24 juxtaposed to the immunoglobulin heavy chain gene locus on chromosome 14q32, and least frequently, the translocation t(2;8)(p12;q24) involving the immunoglobulin kappa gene locus on 2p12.

The surface immunoglobulin is present in both mature B-cell ALL and Burkitt lymphoma, whose cells are usually terminal deoxynucleotidyl transferase (TdT)-negative. The CD19 antigens, as well as the CD20 antigens, are expressed in more than 90% of cells in both disease entities, which are of potential interest for the development of specific antibody therapies.

H&O What is the standard of care for patients with Burkitt leukemia, and what success have we seen with it?

DH Two decades ago, adult patients with mature B-cell leukemia were treated with protocols designed for ALL.

The outcome was dismal, with a 5-year survival of less than 10% in nearly all reports in the literature.¹ However, the treatment strategies for B-cell ALL changed when successful approaches in Burkitt lymphoma emerged.

The first was the introduction of fractionated high-dose cyclophosphamide in Burkitt lymphoma. Since then, treatment protocols have been developed including high-dose fractionated alkylating agents, high-dose methotrexate (MTX), and high-dose cytosine arabinoside in combination with more “conventional” drugs such as steroids, vincristine, and anthracyclines. The cure rate in adult Burkitt lymphoma improved to 50%; results for mature B-cell ALL also improved, but to a lower extent.

The rational treatment for these regimens is the fast doubling time of malignant cells. The treatment cycles have a short length of approximately 5 days, and between the treatment cycles, there are only short intervals to avoid recovery of the malignant cell population.

H&O Are pediatric regimens considered beneficial in adult patients?

DH More or less all successful regimens applied in adult Burkitt leukemia/lymphoma are derived from pediatric protocols. These are mainly the CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate)/IVAC (ifosfamide, etoposide, and high-dose cytarabine) and hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone)-Ara-C/MTX regimens and those in the German-Berlin-Frankfurt-Munster (BFM) and the French LMB trials. With these protocols, the cure rate of pediatric Burkitt lymphoma/leukemia is high, with a cure rate of 80–90%.^{2,3} When the same regimens were applied to adults, the cure rates improved by 50% or more, which is a substantial improvement compared to the earlier survival rate of less than 10%, but still clearly inferior to the results obtained in children. In particular, elderly patients (>50 years old) with mature B-cell ALL showed only a modest improvement.

H&O What are some of the unresolved issues in the treatment of Burkitt leukemia?

DH When pediatric regimens with short, intensive, high-dose therapies were applied in adults, they caused, in

contrast to children, a substantially higher toxicity—neurotoxicity and mucositis in particular. These toxicities led to longer phases of recovery and thereby treatment delays, which are disadvantages in these disease entities. Thus, further intensification did not seem to be the only way to improve outcome in adult Burkitt lymphoma/leukemia.

A new treatment option for adults was the combination of established chemotherapies with an antibody therapy, rituximab (Rituxan, Genentech) in particular, because there is a high expression of CD20. In 2 adult Burkitt lymphoma/leukemia trials, the survival rate was substantially increased. One trial investigated a rituximab plus hyper-CVAD regimen.⁴ In this study, 44 patients with newly diagnosed non-HIV Burkitt leukemia, Burkitt-like leukemia/lymphoma, or B-cell ALL were treated (median age, 46 years; 23% ≥60 years). Rituximab at 375 mg/m² was given on days 1 and 11 of hyper-CVAD and on days 1 and 8 of methotrexate and cytarabine for a total of 8 doses. The overall complete response (CR) rate was 89%, with 2 patients achieving partial response (PR); all patients who were 60 years old or older achieved CR. The 3-year survival rates were superior compared to those in patients treated with hyper-CVAD alone.

The other trial is the B-NHL/ALL 90 regimen where rituximab was also combined with intensive chemotherapy.⁵ In this study, a protocol including rituximab at 375 mg/m² before each chemotherapy cycle and 2 maintenance cycles, with the addition of 2 cycles of high-dose Ara-C (2 g/m²) were given. Younger patients (<55 years old) received high-dose MTX of 1.5 g/m², and older patients (>55 years old) received a dose-reduced regimen of MTX at 500 mg/m² and without high-dose Ara-C; 227 patients with Burkitt leukemia/lymphoma, B-cell ALL, or primary mediastinal diffuse large B-cell lymphoma (DLBCL) were evaluable for response after the first 2 cycles. The CR rate was 90% in Burkitt leukemia/lymphoma patients, 83% in B-cell ALL patients, and 69% in primary mediastinal DLBCL patients. The overall survival rate was 89% for Burkitt lymphoma and 87% for the mature B-cell ALL in a patient population aged 15–55 years.

Therefore, we can see that whereas the chemotherapy strategies for Burkitt lymphoma/leukemia were explored in pediatric patients, the combination with antibody therapy is now pioneered in the adult patient population and may be transferred to pediatric protocols (eg, for high risk patients).

Since the outcome for adult Burkitt lymphoma/leukemia patients has substantially improved, there are now 2 major issues. One is the challenge to further improve results, which could be achieved by an earlier identification of poor responders. The laboratory and clinical parameters that are analyzed so far do not clearly define a poor risk population, possibly due to the small patient cohorts in dif-

ferent studies. New approaches may include fluorodeoxyglucose positron emission tomography analysis to detect early responders and non-responders. The latter would be candidates for an alternative treatment instead of continuing with a proposed schedule.

The other major issue is the reduction of toxicities associated with this intensive chemotherapy regimen. It is of interest that rituximab did not increase the pattern and extent of toxicities. Therefore, the next step would be to reduce the number of chemotherapy cycles (eg, in early responders). However, it is imperative that any reduction should not affect the excellent survival rates. This is a situation faced for the first time in the treatment of adult Burkitt lymphoma/leukemia; it was previously posed and experienced by our pediatric colleagues. We are currently faced with the reduction of a successful therapeutic approach, but hopefully it will lead to a more individualized therapy.

H&O What are some new modalities thought to produce promising results in the future?

DH From the present data available and from ongoing studies, there is no clear picture of how one should proceed. The current focus is to bring the promising chemotherapies and antibody therapies in Burkitt lymphoma/leukemia up to a standard, but also to extend these treatments to other patients, as it has been successful in HIV-positive Burkitt patients.⁶ New treatment options include additional antibody therapy, such as those directed against CD19; for example, blinatumomab (MT-103, Micromet) has been shown to eliminate target cells in particular.⁷ Other treatment options may be improved stem cell transplantation in better-defined early nonresponders or new classes and principles of therapy such as molecular targeting (eg, with various inhibitors).

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