ADVANCES IN LLM

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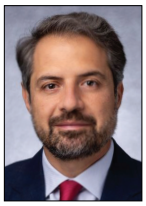
Hyper-CVAD–Based Regimens in Adult Patients With Acute Lymphoblastic Leukemia



Elias J. Jabbour, MD
Professor of Medicine
Department of Leukemia
The University of Texas
MD Anderson Cancer Center
Houston, Texas

H&O How was the hyper-CVAD regimen originally used?

EJ The hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimen was developed by Kantarjian and colleagues at MD Anderson Cancer Center in 1992. This regimen was inspired by a treatment for Burkitt lymphoma developed by the pediatric oncology group at St Jude Children's Research Hospital in the 1980s. Hyper-CVAD follows the basic therapeutic principles of the pediatric regimens, but with decreased reliance on asparaginase during the period of remission induction. The hyper-CVAD regimen was modified later in several iterations to incorporate BCR-ABL tyrosine kinase inhibitors (TKIs) for Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL), rituximab and ofatumumab for Burkitt and pre–B-cell ALL, lower-intensity chemotherapy with antibodies in older patients with ALL, and dose adjustments of methotrexate (MTX) and cytarabine in the intensive even-numbered courses.

H&O What are some of the modifications made to the hyper-CVAD regimen to treat adults?

EJ The hyper-CVAD regimen has undergone many modifications to make administration more palatable and user-friendly for patients and physicians in community and academic settings. The regimen was refined to avoid complications and adverse events. There are several examples of how the regimen has been improved.

A difference between the regimens is that for adults, the hyper-CVAD regimen does not incorporate early use of asparaginase. Asparaginase is reserved for late consolidation. For the pediatric population, the asparaginase-based regimen is used from the beginning of therapy.

The hyper-CVAD regimen is administered in conjunction with intrathecal chemotherapy. A modification to the original hyper-CVAD regimen was to reverse the order of intrathecal MTX and cytarabine during the even-numbered courses. In the even-numbered courses, the systemic chemotherapy includes high-dose MTX. With the modified regimen, cytarabine is given first and MTX is given later. This change was made to avoid an early peak of MTX systemically and in the central nervous system (CNS), and thereby decrease the rate of complications from the drug. Another modification was to hold azoles the day before, the day of, and the day after administration of the vincristine injection. Other changes were to administer prophylactic antibiotics and growth factor support. We monitor clearance of creatinine and MTX to avoid renal failure and CNS complications. Lastly, we modified the doses of cytarabine and MTX. We administer 2 g/m^2 of cytarabine and 750 mg/m^2 (not 1 g/m^2) of MTX. These doses are further reduced beyond those specified (2 g/m^2 and 750 mg/m^2) for older patients.

We have also modified the hyper-CVAD regimen by simplifying it. Historically, hyper-CVAD included 8 courses of intensive chemotherapy, with the hyper-CVAD alternating with MTX/cytarabine. This treatment is followed by 2 and a half years of maintenance therapy, as well as intrathecal chemotherapy. With the integration of immunotherapy, we are trying to shorten the consolidation and maintenance phases.

These are the primary modifications that were made to improve the efficacy and safety of hyper-CVAD. There are multiple benefits. For example, the changes have decreased the regimen's toxicity, enabling better treatment exposure by reducing treatment discontinuation for toxicity.

H&O Are there other modifications for certain subtypes of patients?

EJ There are now different versions of the hyper-CVAD regimen. My colleagues and I evaluated the addition of rituximab to hyper-CVAD among patients who were CD20-positive. The 4- to 5-year rate of overall survival was 40% to 50%. In a subsequent study, we added ofatumumab (Arzerra, Novartis) to hyper-CVAD. Ofatumumab is more effective than rituximab in patients with CD20 expression of 20% or higher. With this regimen, the 4-year rate of survival was approximately 60%. Among young adult patients (≤39 years), the 4-year rate of survival was approximately 70%, which is similar to the rates seen with the pediatric-inspired regimens.

Among patients with Ph-positive ALL, we added a TKI. We replaced 26 months of maintenance therapy with 6-mercaptopurine, MTX, vincristine, and prednisone (POMP) with vincristine, a corticosteroid, and a TKI, ideally ponatinib (Iclusig, Takeda), for 2 years, followed by a TKI indefinitely. In addition, we administered 12 cycles of intrathecal chemotherapy. This number was increased from a total of 8 cycles owing to late isolated CNS relapses observed with the long-term improvement of outcome among patients with Ph-positive ALL. No further CNS relapses were observed after this amendment.

Immunotherapy, such as bispecific T-cell engagers and antibody-drug conjugates, is effective in the relapsed ALL setting, as well as in patients with measurable residual disease (MRD). My colleagues and I investigated whether the addition of blinatumomab (Blincyto, Amgen) early in the treatment course could improve outcome by eradicating MRD. Instead of giving 8 courses of hyper-CVAD, we gave 4 courses, followed by 4 courses of blinatumomab. Then we shortened the maintenance from 30 months of POMP to 12 cycles of POMP, with 1 cycle of blinatumomab given after every 3 cycles of POMP. We administered this regimen to 38 patients. The survival rate was 85%, which is a breakthrough in ALL.

With the integration of immunotherapy, we are trying to shorten the consolidation and maintenance phases.

H&O Are there adjustments to the hyper-CVAD–based regimens for older patients with ALL?

EJ Patients who are older (≥60 years) often cannot tolerate hyper-CVAD. We treat these patients with a regimen known as "mini-CVD," which omits the anthracycline. The dose of chemotherapy is also significantly reduced. We lower the doses of vincristine to 1 mg, of dexamethasone to 20 mg, and of cyclophosphamide to 150 mg/m^2. We also added inotuzumab ozogamicin (Besponsa, Pfizer). This regimen was adopted for older patients and patients with relapsed/refractory ALL.

Mini-CVD in combination with inotuzumab ozogamicin has been evaluated in older patients. Their median age was 68 to 70 years. The 5-year survival was 55%. Historically, these older patients had a survival of approximately 18 months. We then added blinatumomab to this regimen for the older population to further optimize the results. In order to further reduce treatment morbidities and mortalities in patients ages 70 years and older, a new chemotherapy-free regimen is evaluating a combination of inotuzumab and blinatumomab only.

H&O What are the advantages and disadvantages of the hyper-CVAD regimens for children vs adults?

EJ For adults, the hyper-CVAD regimen is administered in the hospital throughout 4 to 5 days. This is a drawback. The other pediatric-inspired regimens are mainly administered on an outpatient basis. The hyper-CVAD regimen for adults is more flexible, and it is easier to combine this regimen with the immunotherapy that is currently being evaluated in the frontline setting.

H&O How do you use hyper-CVAD–based regimens in adult patients with ALL?

EJ The patient is admitted to the hospital, where he or she receives chemotherapy administered throughout 4 to 5 days. For the hyper-CVAD regimen, we administer

dexamethasone for 8 days (days 1-4 and days 11-14). Vincristine is given at a dose of 1.2 mg/m^2 up to 2 mg total on days 4 and 11. Cyclophosphamide is given at 300 mg/m^2 every 12 hours for 6 doses. Anthracycline at 50 mg/mg^2 is administered on day 4 throughout 24 hours. For patients who are CD20-positive, we add rituximab or ofatumumab. On day 5, we give granulocyte colony–stimulating factor (GCSF). We also administer an antibiotic and antifungal antiviral prophylaxis. We withhold the azoles around the time that vincristine is administered.

We perform bone marrow testing on days 14 and 21. An assessment of residual day 14 bone marrow blasts is highly predictive of the achievement of a complete response, as well as event-free survival and overall survival, with induction chemotherapy. However, the day 14 bone marrow blast assessment is less prognostic of long-term outcomes when an MRD assessment is also available. Once the blood count recovers, we start cycle 2. We use the bone marrow test to assess MRD. Among patients who are MRD-negative, we repeat MRD assessment once every 3 months. Cycle 2, which consists of MTX/cytarabine, is administered in the hospital. We give MTX in the first 24 hours. After we confirm clearance of MTX, we administer cytarabine. Currently, we give cytarabine at a dose of 2 g/m^2 on days 2 and 3. We administer GCSF on day 4. For patients who are CD20-positive, we administer rituximab or ofatumumab.

H&O Do you anticipate that the use of hyper-CVAD–based regimens in patients with ALL will evolve?

EJ I definitely believe that the use of these regimens will evolve. Compared with the pediatric regimen, the hyper-CVAD regimen for adults has several advantages. An important advantage is that the regimen is flexible and can be adjusted to incorporate immunotherapy. Future treatment of ALL will use less chemotherapy and a more targeted approach. As an example, when administering hyper-CVAD to patients with Ph-positive ALL, we evaluated the addition of a TKI, such as ponatinib. This regimen led to an overall survival rate of 75% at 5 years. In adult patients, we have used hyper-CVAD plus blinatumomab. We are now adding inotuzumab ozogamicin, as well. In older patients, we evaluated mini-CVD plus inotuzumab ozogamicin and blinatumomab. We are evaluating the combination of mini-CVD plus venetoclax (Venclexta, AbbVie/Genentech) and navitoclax, as well. Future regimens will use a backbone of hyper-CVAD or adjustable hyper-CVAD and will be combined with targeted therapies. Such a regimen is an important therapy for ALL that will likely lead to a cure in our lifetime.

Disclosure

Dr Jabbour has received research grants from and has consulted for Amgen, Adaptive Biotechnologies, Pfizer, Genentech, AbbVie, Ascentage, BMS, and Takeda.

Suggested Readings

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