

Beyond Hyper-CVAD in ALL: Highlights From SOHO 2021



Alexis C. Geppner, MLS, CTTS, PA-C, of The University of Texas MD Anderson Cancer Center, discusses key data from a session on hyper-CVAD and additional therapies for patients with acute lymphoblastic leukemia presented by Elias Jabbour, MD, also of MD Anderson Cancer Center, at the 2021 SOHO Annual Meeting.

Hyperfractionated cyclophosphamide, vincristine (VNC), doxorubicin, and dexamethasone (hyper-CVAD), developed in 1992, became the mainstay in the treatment of acute lymphoblastic leukemia (ALL). The combination included eight courses of intensive therapy with hyper-CVAD alternating with high-dose methotrexate (MTX) and cytarabine (Ara-C) followed by 2.5 to 3 years of maintenance therapy. Multiple modifications have been made to optimize outcomes and assist in reducing both short- and long-term adverse effects.

MODIFICATIONS TO HYPER-CVAD REGIMEN

Modifications to the hyper-CVAD regimen include:

- Dose adjustment for advanced age in even courses of MTX and Ara-C.
- Prevention of renal failure and cerebellar toxicity by holding Ara-C when creatinine > 1.4.
- VNC 2 mg flat dose. Omit VNC for neuropathy.

- Introduction of prophylactic antimicrobials.
- Avoidance of excess neurotoxicity by holding azole antifungals days 1, 0, and +1 of VNC
- Day 2 intrathecal (IT) MTX changed to Ara-C in even courses (with systemic MTX) to avoid excess neurotoxicity.

MONOCLONAL ANTIBODIES

The use of monoclonal antibodies (blinatumomab [Blincyto], rituximab [Rituxan], ofatumumab [Arzerra], and inotuzumab [Besponsa]), in place of hyper-CVAD as front-line therapy helped to improve responses and survival and reduce adverse effects and toxicities.

Hyper-CVAD + blinatumomab (a bispecific CD19 antibody), showed a complete response (CR) rate of 85% at 2 years and reduced the number of maintenance courses from 30 months to 15 months (Short et al., 2020).

Mini-hyper-CVD (lower intensity without anthracycline) + inotuzumab (CD19 antibody) +/- blinatumomab allowed for a treatment dose reduction in older patients and reduced the number of maintenance cycles from 3 years down to 1 year while still maintaining a 96% overall response (Jabbour et al., 2018a; Kantarjian et al., 2018). Inotuzumab was given in cycles 2 and 4 to deepen the minimal residual disease (MRD) response.

Hyper-CVAD + ofatumumab was found to be far superior to hyper-CVAD + rituximab with a 3-year overall survival (OS) rate of 98% (Jabbour et al., 2020).

Blinatumomab + dasatinib in newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) yielded a 60% molecular response (MR) with a 41% complete mo-

lecular response (CMR) and 88% OS at 24 months (Chiaretti et al., 2021). 50% proceeded to stem cell transplantation following blinatumomab.

Key Points

- The treatment of ALL has been altered to optimize patient outcomes and reduce long- and short-term side effects.
- Amount of IT chemo doses in Ph+ ALL changed from 8 to 12 and improved the 6-year CNS relapse-free survival from 87% to 100%.
- Hyper-CVAD with the addition of TKIs has become the standard of care in Ph+ ALL.
- Monoclonal antibodies are being used in place of hyper-CVAD as frontline therapy to improve survival, reduce toxicities, and allow for earlier completion of therapy.
- MRD testing by NGS is superior to flow cytometry and should be reevaluated after each course of therapy to ensure adequate response.

PONATINIB

Tyrosine kinase inhibitors (TKIs) are added based on the presence or absence of the Philadelphia chromosome (Ph+). With the addition of ponatinib (Iclusig), a third-generation pan-BCL-ABL inhibitor, 100% of patients with Ph+ ALL are achieving CMR, 99% MRD negativity by flow, and rarely proceed to allogeneic SCT (Jabbour et al., 2018b; Short et al., 2020). Ponatinib has more potent activity compared with other TKIs and overcomes *T315I* mutations (Sasaki et al., 2016). For this reason, hyper-CVAD + ponatinib has become standard of care in Ph+ ALL.

A phase II study evaluated the safety and efficacy of hyper-CVAD + ponatinib (76 patients) and compared it to ponatinib plus blinatumomab (28 patients) as front-line therapy. Dosing of ponatinib was amended due to the risk of vascular toxicity. While the addition of ponatinib to hyper-CVAD induced a higher rate of sustained remission, of the patients receiving combination therapy with ponatinib and blinatumomab, 84% of patients achieved a major molecular response (MMR) and 58% a CMR. Of patients with refractory Ph+ ALL, 75% achieved a CMR after 1 cycle (28 days) of therapy (Short et al., 2021). Estimated event-free survival and OS rates are 93% for newly diagnosed patients.

MINIMAL RESIDUAL DISEASE

Minimal residual disease negativity by next-generation sequencing (NGS) is far superior to MRD by flow cytometry and should be assessed as soon as possible and after each course of hyper-CVAD or alternative therapy. Acute lymphoblastic leukemia demonstrates a lower degree of clonal heterogeneity compared with acute myeloid leukemia (AML), and NGS helps clarify molecular subsets of ALL to augment disease classification and risk assessment previously driven by cytogenetics and clinical features (Aleem et al., 2021). ●

The Advanced Practitioner Perspective

Advanced practitioners (APs) will need to continue to stay abreast of changes in the treatment of ALL, particularly in the elderly and the salvage setting. Although intensive chemotherapy remains the mainstay of treatment, an attempt is being made to focus more on antibody-based therapy combinations with shorter durations of treatment. This change will hopefully reduce toxicities and time spent inpatient while optimizing outcomes and quality of life.

As APs, is it important to understand and be up to date on the ever-changing management of our patients with ALL. We need to be aware

of the updated monitoring parameters (e.g., NGS for MRD) and be able to properly guide our patients through their complex treatment course. We are often the first to evaluate patients and must be cognizant of the potential adverse effects (e.g., neurotoxicity with blinatumomab) and recognize the correct course of action. Future directions in the treatment of ALL include CAR T-cell therapy and the attempt to replace allogeneic SCT.

Disclosure

Ms. Geppner has served as a consultant and advisor for AbbVie.

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