Detection and outcome of occult leptomeningeal disease in diffuse large B-cell lymphoma and Burkitt lymphoma

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SUPPLEMENTARY METHODS

Systemic Therapy

Patients with DLBCL received CHOP-based regimens including Mega-CHOP, and contained rituximab following its approval, in the Spanish Group and at the Daniel den Hoed Caner Center[18]. Patients with DLBCL treated at the National Cancer Institute received DA-EPOCH ± rituximab, depending on the protocol[19]. Patients with Burkitt lymphoma treated by the Spanish Group and at the Daniel den Hoed Caner Center received dose-intense Burkitt regimens including Hyper-CVAD, CODOX-M/IVAC, and the "Hoelzer" schedule[20,21,22]. Patients with Burkitt lymphoma treated at the National Cancer Institute received DA-EPOCH-R based treatment.

Central Nervous System Therapy

At the Spanish Group for the Study of CNS Disease, patients with DLBCL considered at risk of CNS disease (bone marrow) and a negative CSF by FCM and/or cytology received prophylactic intrathecal therapy (Methotrexate 15 mg, Cytarabine 40 mg, Dexamethasone 20 mg) on every cycle. In 25% of centers, patients with bone marrow disease and increased LDH only received intrathecal therapy on the first cycle. BL patients with a negative CSF by FM and/or cytology received intrathecal therapy on every cycle except in 25% of centers where patients younger than 55 years only received intrathecal therapy on the first cycle. DLBCL or BL patients with a positive CSF by FCM and/or cytology received active intrathecal treatment 2-3 times per week until the CSF became negative followed by one intrathecal treatment per cycle.

At Daniel den Hoed Caner Center, patients with DLBCL at risk of CNS disease (extranodal sites involving the sinus, orbit, testis, ovary) and a negative CSF by FCM and/or cytology received prophylactic therapy with 6 intrathecal injections of methotrexate (12 mg) and dexamethasone. Patients with BL received the "Hoelzer" schedule, which includes prophylactic intrathecal triple therapy. DLBCL or BL patients with a positive CSF by FCM and/or cytology received active treatment with twice weekly intrathecal methotrexate and dexamethasone until the CSF normalized after which treatment was tapered (approximately 10-12 doses). Less commonly high-dose systemic methotrexate (range: 1-6.7 gm/m^2 per cycle) and/or cytarabine (range: 4-12 mg/m^2 per cycle) were administered. Patients with a positive CSF were followed with serial FCM and evaluated with computerized tomography (CT) scans or magnetic resonance imaging of the brain.

At the National Cancer Institute, patients at risk of CNS disease (DLBCL with > 1 extranodal sites and elevated lactate dehydrogenase or bone marrow involvement; HIV infection and/or BL) and a negative CSF by FCM and/or cytology received prophylactic intrathecal methotrexate (12 mg) on days 1 and 5 of cycles 3-6 of DA-EPOCH for a total of 8 doses. DLBCL or BL patients with a positive CSF by FCM and/or cytology received active treatment with twice weekly intrathecal methotrexate (12 mg) for 4 weeks, followed by weekly x 6 and monthly x 4 months if FCM negative. Patients with a positive CSF were followed with serial FCM and evaluated with computerized tomography (CT) scans or magnetic resonance imaging of the brain.

Statistical Methods

Comparisons of dichotomous parameters were made between groups of patients based on CSF involvement using the Fisher exact test, while ordered categorical parameters were evaluated for the statistical significance using the Cochran-Armitage trend test[23]. Continuously measured parameters were compared between groups using an exact Wilcoxon rank sum test. Logistic regression analysis was used to further evaluate whether any factors were jointly associated with a classification to positive or negative results. The association between various parameters and overall survival or freedom from CNS relapse was determined using Kaplan-Meier curves beginning at date primary treatment began with curves compared using the log-rank test. Patients with DLBCL who were positive by FCM, FCM with or without cytology, or had a negative CSF were divided into three tertiles based on the number of intrathecal chemotherapy treatments. These groupings were used to form an initial set of Kaplan-Meier curves. The differences among the three curves were tested by a global log-rank test. The McNemar test for paired categorical data was used to determine the degree to which there was concordance or discordance between FCM and cytology results on the same individual. All *P* values are two-tailed and have not been adjusted for multiple comparisons.

To determine if differences among the three institutions influenced the study results, we performed a stratified analysis by institution for all plots with adequate events and the results were unaffected (data not shown).