Original Study

A Retrospective Study of Double-hit Lymphomas in Elderly Patients (Aged > 70 Years): Overall Outcomes

Christie Hancock,[1] Phillip Knouse,[2] Imad Almanaseer,[3] Jacob Bitran[4]

Abstract

Double-hit lymphoma can be an aggressive disease that is difficult to treat in the elderly population. We evaluated patients aged > 70 years and their outcomes after treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), R-EPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), and other chemotherapy regimens. The results showed the outcomes were dependent on patient performance status and comorbidities. Intensive regimens should be considered for elderly patients who are medically fit.

Background: Double-hit lymphomas (DHLs) are high-grade diffuse large B-cell lymphomas with concurrent translocations involving myc and bcl-2 and/or bcl-6. A patient with DHL often has advanced disease at presentation and typically responds poorly to standard therapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). More intensive treatment regimens have been studied; however, few data are available on the outcomes in elderly patients (aged > 70 years) treated with these therapies. We retrospectively studied the efficacy and tolerability of chemotherapy regimens in elderly patients within the Advocate Healthcare System. **Materials and Methods:** A system-wide search of patients treated from 2012 to 2017 was completed to identify patients with c-myc with bcl-2 and/or bcl-6 translocations using fluorescence in situ hybridization. The patients were reviewed for the following: age at diagnosis, stage, lactate dehydrogenase, Eastern Cooperative Oncology Group performance status, chemotherapy details, grade 3/4 toxicities, and response to therapy. Overall survival (OS) and event-free survival (EFS) were calculated. **Results:** We identified 17 patients (9 men and 8 women) with a median age of 73 years (range, 70-89 years). Six patients received R-EPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), 5 received R-CHOP, 1 received bendamustine and rituximab, 1 received the MaGrath regimen, and 1 received cyclophosphamide and rituximab. Three patients were not treated and were referred to hospice care. For all patients, the median follow-up period was 25 months, the EFS and OS were 28% at 36 months, and the median survival was 7.5 months. For patients treated with R-EPOCH, the EFS was 33% at 24 months. For the R-CHOP group, the EFS was 40% at 24 months. Most common grade 3/4 toxicities were neutropenia, anemia, thrombocytopenia, and infections and were more common in the R-EPOCH group. Three patients each died in the R-EPOCH and R-CHOP groups. **Conclusion:** Although the numbers are small, elderly patients with DHL can achieve durable EFS and OS. Using the comprehensive geriatric assessment can aid in decision making in the treatment options for elderly patients. Our retrospective analysis, given a small sample size, suggests that intensive treatment regimens can be offered to elderly patients with DHL.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■ Published by Elsevier Inc.
Keywords: Chemotherapy, Comorbidities, Geriatric, Lymphoma, Treatment

[1]Department of Hematology/Oncology
[2]Department of Internal Medicine
[3]Department of Pathology
[4]Department of Hematology/Oncology, Advocate Lutheran General, Park Ridge, IL

Submitted: Dec 26, 2017; Revised: Jan 19, 2018; Accepted: Feb 10, 2018

Address for correspondence: Christie Hancock, MD, Department of Hematology/Oncology, Advocate Lutheran General, 1775 Dempster Street, Park Ridge, IL 60068
E-mail contact: Christie.hancock@advocatehealth.com

2152-2650/$ - see frontmatter Published by Elsevier Inc.
https://doi.org/10.1016/j.clml.2018.02.006

Introduction

The frequency of double-hit diffuse large B-cell lymphomas (DLBCLs), which represent ≥ 4% of all DLBCL cases, is increasing.[1] These double-hit lymphomas (DHLs) have been defined by the 2016 World Health Organization classification as high-grade DLBCLs with translocations involving c-myc in combination with translocations of bcl-2 and/or bcl-6.[2]

The c-myc oncogene is found on chromosome 8q24 and its protein is detected in 70% to 100% of the particularly aggressive Burkitt lymphoma. c-Myc plays an important role in cell cycle progression and proliferation, and its mutation leads to a more aggressive disease. Bcl-2 is located on chromosome 18q21 and was originally identified in the more indolent follicular lymphoma. Its protein is seen in > 50% of DLBCL. The normal function is to stimulate cell survival by inhibiting cell death.[1] The bcl-6 protein acts to suppress the functions of c-myc and bcl-2 in B-cell maturation and without its restrictions allows an uncontrolled, abnormal B cell to develop.[1] The deregulation in the c-myc and bcl-2 oncogenes leads to increased proliferation driven by c-myc and inhibition of apoptosis by bcl-2 ultimately often leading to a more aggressive phenotype.[1] Translocations of c-myc and bcl-6 are also described as DHL, but might result in less aggressive disease compared with DHL with translocations of c-myc and bcl-2.[1] The most common translocations involve c-myc and bcl-2 in 62% of cases while only 18% of cases will have translocation with c-myc and bcl-6.[3] Twenty percent of patients will have mutations of all 3 genes, referred to as triple-hit lymphoma (THL).[3]

A patient with DHL can have an aggressive presentation at diagnosis with an elevated lactate dehydrogenase, bone marrow and central nervous system (CNS) involvement, and a high International Prognostic Index (IPI) score. Reviews have also demonstrated that patients with DHLs have a poor prognosis and inferior outcomes when treated with standard chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). The 2-year overall survival reported in 1 study evaluating 31 DHL patients treated with R-CHOP was 35% compared with 61% for nonmutated DLBCL.[4] These outcomes have been consistent in multiple reports.[5-8] Despite the inferior outcomes with R-CHOP, no prospective, randomized clinical trials have investigated alternative chemotherapy regimens. Thus, no standard of care has been established for these patients. Instead, management of DHL has been based on retrospective studies that contain little data on outcomes for elderly patients (age > 70 years).[9-11] The studies that exist have suggested that more intensive regimens such as dose-adjusted R-EPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), hyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), and R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, high-dose cytarabine) lead to better responses.[12] Concerns exist that elderly patients with significant comorbidities might be unable to tolerate these therapies because of treatment-related toxicities.

It has been reported that patients aged > 80 years with the less aggressive DLBCL can tolerate treatment with anthracycline-based regimens and that these patients should be offered more intensive therapy for prolonged survival.[13] No studies have been reported of the efficacy and tolerability of chemoimmunotherapy for DHL specifically in the elderly. We retrospectively studied the outcomes of patients aged > 70 years with a diagnosis of DHL and THL within our health care system.

Materials and Methods

We performed a system-wide search of cases diagnosed from 2012 to 2017 to identify patients with a c-myc rearrangement concurrent with bcl-2 and/or bcl-6 translocations based on fluorescent in situ hybridization analysis. Patients were screened by reviewing aggressive lymphoma fluorescent in situ hybridization panels. Patients with a c-myc rearrangement were then evaluated for the presence of translocations involving bcl-2 or bcl-6. We did not include patients with double-expressor DLBCL if they did not have DHL or THL, because it is known that such patients might have a slightly better overall prognosis. Patients aged < 70 years were excluded. The institutional review board approved the study protocol (approval no., 6715), and we were allowed access to multiple hospitals in the Advocate Healthcare System.

The patients were reviewed for sex, age at diagnosis, stage, lactate dehydrogenase level, performance status, details of chemotherapy, grade 3 and 4 toxicities, and responses to therapy. The IPI was scored according to the guidelines. Overall survival (OS) was defined from the date of diagnosis to death from any cause. Event-free survival (EFS) was defined from the date of diagnosis to relapse, progression, or death from treatment or lymphoma. OS and EFS were calculated using Kaplan-Meier plots.[14]

Results

We identified 17 patients (9 men and 8 women) with a median age of 73 years (range, 70-89 years; Table 1). Of the 17 patients, 9 (53%) had stage IV and 1 had CNS disease at presentation. In addition, 3 other patients had CNS involvement at some point during their disease course (Table 2). The median IPI score was 4 (Table 1). Of the 17 patients, 7 (41%) had translocations involving c-myc and bcl-2, 6 patients (35%) had c-myc and bcl-6 partner translocations, and 4 patients (24%) had THL (Tables 1 and 3).

No patient had received previous therapy. Of the 17 patients, 6 received R-EPOCH (rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), 5 received R-CHOP, 1 received bendamustine and rituximab, 1 received the R-CODOX-M/IVAC regimen, 1 received cyclophosphamide and rituximab, and 3 were not treated and were referred to hospice care because of patient choice or significant comorbidities (Tables 1 and 3). Seven patients received either CNS prophylaxis or treatment with intrathecal or systemic methotrexate (Table 2).

For all patients, the median follow-up was 25 months, and the EFS and OS rate was 28% at 36 months (Figure 1). The median survival was 7.5 months. At the last follow-up examination, 5 patients (28%) were alive without progression and 11 patients had died. For patients treated with R-EPOCH, the EFS rate was 33% at 24 months. For those who received R-CHOP, the EFS rate was 40% at 24 months. No formal statistical analysis was performed owing to the small patient numbers; thus, these data should be interpreted with caution.