Original Study

Pegylated Liposomal Doxorubicin Replacing Conventional Doxorubicin in Standard R-CHOP Chemotherapy for Elderly Patients With Diffuse Large B-Cell Lymphoma: An Open Label, Single Arm, Phase II Trial

Yasuhiro Oki,[1] Michael S. Ewer,[2] Daniel J. Lenihan,[3] Michael J. Fisch,[4] Fredrick B. Hagemeister,[1] Michelle Fanale,[1] Jorge Romaguera,[1] Barbara Pro,[1] Nathan Fowler,[1] Anas Younes,[1] Alan B. Astrow,[5] Xuelin Huang,[6] Larry W. Kwak,[1] Felipe Samaniego,[1] Peter McLaughlin,[1] Sattva S. Neelapu,[1] Michael Wang,[1] Luis E. Fayad,[1] Jean-Bernard Durand,[2] M. Alma Rodriguez[1]

Abstract

This phase II trial evaluated pegylated liposomal doxorubicin instead of doxorubicin in standard R-CHOP therapy for elderly patients with diffuse large B-cell lymphoma. Of 79 eligible patients, the overall and complete response rates were 86% and 78%, respectively. Cardiac events greater than grade 3 were identified in 3 patients (4%). This regimen represents an effective strategy in this elderly population.

Background: The present multicenter phase II trial evaluated the safety and efficacy of pegylated liposomal doxorubicin (PLD) instead of conventional doxorubicin in standard R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine [Oncovin], and prednisone) therapy for elderly patients with diffuse large B-cell lymphoma. **Materials and Methods:** Patients aged > 60 years who had stage II to IV disease were included. Treatment consisted of rituximab 375 mg/m^2 intravenously (I.V.); cyclophosphamide 750 mg/m^2 IV; PLD 40 mg/m^2 (maximum, 90 mg) I.V. over 1 hour; and vincristine 2.0 mg I.V., all on day 1. Additionally prednisone, 40 mg/m^2, was given orally on days 1 to 1 to 5 (DRCOP [rituximab, cyclophosphamide, PLD, vincristine, and prednisone]). The cycles were repeated every 3 weeks for 6 to 8 cycles. **Results:** Eighty patients were enrolled and were evaluable for toxicity. The median age was 69 years. All except 1 had additional cardiac risk factors for anthracycline-induced cardiac toxicity beyond advanced age. From the intent-to-treat analysis of 79 eligible patients, the overall response rate was 86%, and the complete response rate was 78%. Cardiac events greater than grade 3 were identified in 3 patients (4%); grade 1 to 2 events, mostly asymptomatic declines in ejection fraction, were noted in another 16 patients. One death was attributed to cardiac failure. The estimated 5-year event-free and overall survival rate was 52% and 70%, respectively. **Conclusion:** DRCOP represents an effective strategy for potentially mitigating cardiotoxicity in elderly patients with aggressive B-cell lymphoma. Future studies incorporating baseline cardiac risk assessments, long-term follow-up data, and biospecimen collection for correlative science should be undertaken.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 3, 152-8
Keywords: Anthracycline, Cardiac toxicity, Diffuse large B-cell lymphoma, Elderly patients, Pegylated liposomal doxorubicin

Presented in part at the 2011 Annual Meeting of the American Society of Clinical Oncology (abstract no. 83967).

[1]Department of Lymphoma and Myeloma, University of Texas MD Anderson Cancer Center, Houston, TX
[2]Department of Cardiology, University of Texas MD Anderson Cancer Center, Houston, TX
[3]Division of Cardiovascular Medicine, Vanderbilt University, Nashville, TN
[4]Department of General Oncology, University of Texas MD Anderson Cancer Center, Houston, TX
[5]Division of Hematology/Oncology, Department of Medicine, Maimonides Medical Center, Brooklyn, NY
[6]Department of Biomathematics, University of Texas MD Anderson Cancer Center, Houston, TX

Submitted: Jun 6, 2014; Revised: Sep 11, 2014; Accepted: Sep 17, 2014; Epub: Sep 28, 2014

Address for correspondence: Yasuhiro Oki, MD, Department of Lymphoma and Myeloma, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 429, Houston, TX 77030
E-mail contact: yoki@mdanderson.org

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2014.09.001

Introduction

Anthracyclines are considered a crucial part of intent-to-cure regimens for patients with diffuse large B-cell lymphoma (DLBCL).[1] However, anthracyclines exhibit cumulative dose-related cardiotoxicity. Although myocyte destruction has been universally seen, the extent and expression of this injury varies and is dependent on the degree of previous myocyte compromise and the sensitivity of the heart.[2,3] Older patients and those with pre-existing cardiac disease are known to have a greater incidence of both overt heart failure and asymptomatic declines of cardiac parameters.[2-4] A less cardiotoxic approach is critically needed.[5]

Modern anticancer regimens have incorporated strategies to reduce the cardiotoxic burden of anthracyclines, such as reducing the cumulative dose of cardiotoxic agents, using the cardioprotective agent dexrazoxane, and incorporating continuous infusion administration schedules. Each presents a compromise in increased noncardiac adverse events, convenience, or concerns regarding reduced efficacy.

Pegylated liposomal doxorubicin (PLD) offers an additional strategy for limiting cardiotoxicity that allows localized penetration of the anthracycline molecule selectively through the impaired vasculature, thereby concentrating the delivery of the agent to the tumor. Additionally, the overall peak plasma concentration to which the heart is exposed is reduced with PLD.[6] To test the efficacy and safety of PLD in patients with DLBCL, we conducted a multicenter phase II trial of DRCOP (rituximab, cyclophosphamide, PLD, vincristine, and prednisone).

Materials and Methods

Patients

Our institutional review board approved the present study, which was registered at clinicaltrials.gov (NCT00101010). All patients provided written consent. The primary objectives of the present study were to determine the overall response rate and determine the extent of grade 3 or 4 overall and cardiac-specific toxicity. The secondary objectives were to determine the event-free survival (EFS) and overall survival (OS).

The inclusion criteria were age > 60 years, histologically confirmed untreated DLBCL, stage II or greater disease, measurable disease, Eastern Cooperative Oncology Group performance status 0 to 2, an adequate bone marrow reserve evidenced by an absolute neutrophil count > 1000/μL and a platelet count > 100,000/μL, and adequate kidney and liver function (serum creatinine concentration < 2 mg/dL; serum bilirubin concentration < 2 mg/dL). Additionally, a left ventricular ejection fraction (LVEF) of ≥ 50% by 2-dimensional echocardiography using the method of disks or multigated acquisition scan (MUGA) was required.[7] Those patients with known heart disease were eligible if their cardiac disease was stable and had been evaluated by a cardiologist to optimize their cardiovascular status. The exclusion criteria were primary central nervous system lymphoma, recent myocardial infarction (within 6 months of the inclusion evaluation), symptomatic heart failure, uncontrolled hypertension, uncontrolled ventricular arrhythmia, and unstable coronary ischemia.

Table 1 Patient and Disease Characteristics (n = 80)

Characteristic	No. of Patients (%)
Age at diagnosis (years)	
61-70	49 (61)
71-80	21 (26)
81-90	9 (11)
≥91	1 (1)
Performance status	
0 or 1	64 (80)
2	16 (20)
Serum lactate dehydrogenase level	
Normal	41 (51)
High	39 (49)
No. of extranodal disease sites	
0 or 1	55 (69)
≥2	25 (31)
Ann Arbor stage	
II	18 (23)
III	20 (25)
IV	42 (53)
International prognostic index	
1	9 (11)
2	24 (30)
3	29 (36)
4	12 (15)
5	6 (8)
Histologic type	
DLBCL	79 (99)
SLL (not eligible)	1 (1)
Cardiac risk factors	
Obesity (BMI ≥ 30 kg/m^2)	32 (40)
Diabetes mellitus	27 (34)
History of coronary artery disease	20 (25)
History of hypertension	73 (91)
History of hyperlipidemia	45 (56)
History of hypothyroidism	21 (26)
History of smoking tobacco	35 (44)
None of these 6 cardiac risk factors	2 (3)
Cardiac evaluation before treatment	
Nuclear cardiac scan	53 (66)
Echocardiography	67 (84)
LVEF < 50%	0 (0)

Abbreviations: BMI = body mass index; DLBCL = diffuse large B-cell lymphoma; LVEF = left ventricular ejection fraction; SLL = small lymphocytic lymphoma.

Treatment

The cancer treatment regimen of DRCOP consisted of rituximab 375 mg/m^2 intravenously (I.V.), cyclophosphamide 750 mg/m^2 I.V., PLD 40 mg/m^2 (maximum, 90 mg) I.V. over 1 hour, and vincristine 2.0 mg I.V., all on cycle day 1. Additionally patients received prednisone, 40 mg/m^2 orally, on days 1 to 5 of each cycle.