Original Study

Pegylated GCSF Can Be Used With First-Line da-EPOCH-R Without Compromising Dose Intensity, Safety, or Efficacy

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Abstract

Dose-adjusted EPOCH-R (etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab) remains a therapeutic option for high-risk, aggressive B-cell non-Hodgkin lymphoma subsets. Whether pegylated granulocyte colony-stimulating factor (peg-GCSF) affords similar efficacy compared with daily granulocyte colony-stimulating factor is unknown. In this study we found similar attained dose level and patient outcomes, supporting a role for peg-GCSF with dose-adjusted EPOCH-R.

Introduction: Infusional da-EPOCH-R (dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab) is a dose-intensified regimen with a potential role in treating high-risk subtypes of aggressive B-cell non-Hodgkin lymphoma (B-NHL). Studies of da-EPOCH-R use daily injections of granulocyte colony-stimulating factor (GCSF) to tailor chemotherapy dosing, and whether 1-time administration of pegylated GCSF (peg-GCSF) is as efficacious has not been addressed. **Patients and Methods:** We reviewed aggressive B-NHL patients treated at our center with first-line da-EPOCH-R for clinician choice of growth factor, and analyzed dose level achieved, rate of unplanned hospitalizations, and patient outcomes. **Results:** Among 73 patients, 44 received peg-GCSF. Overall, 11 patients (15%) patients achieved dose level 4. Baseline characteristics between peg-GCSF and GCSF groups were similar. The proportion of patients who achieved dose level 4 was comparable in the peg-GCSF group (5 of 44 [11%]) and daily GCSF (6 of 29 [21%]; $P = .24$). The rate of unplanned hospitalizations, and event-free and overall survival, were also similar between groups. **Conclusion:** We suggest routine use of peg-GCSF is an acceptable alternative to daily GCSF, for patients in whom da-EPOCH-R is selected as first-line treatment for aggressive B-NHL.

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Introduction

The regimen of infusional da-EPOCH-R (dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, and rituximab), recently shown equivalent to standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) in diffuse large b-cell lymphoma (DLBCL) in a large randomized trial, might retain a role in treatment of certain lymphoma subsets.[1] More than 90% with primary mediastinal B-cell lymphoma (PMBCL) achieved durable progression-free survival in a phase II trial of da-EPOCH-R, a result achieved without use of radiotherapy as consolidation.[2] Patients with aggressive B-cell lymphomas bearing *MYC* rearrangements fare poorly with standard R-CHOP, whereas improved outcomes with da-EPOCH-R have been reported in these diseases in observational studies and a meta-analysis.[3-7] However, da-EPOCH-R administration is considerably more complex than R-CHOP, requiring twice-weekly laboratory monitoring, universal administration of granulocyte colony-stimulating factor (GCSF), and dose adjustment on the basis of repeated complete blood count evaluations. Infectious

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complications with this intensified regimen are more frequent, with approximately one-third of patients experiencing neutropenic fever.[1,8] Nonetheless, dose intensification via reaching neutrophil nadir of < 500/μL is critical to the success of da-EPOCH-R; a historical (pre-rituximab) randomized trial reported that EPOCH (etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone) produced inferior survival to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), when no dose adjustment is performed.[9]

Because of the importance of dose adjustments on the basis of neutrophil count with da-EPOCH-R, the selection of growth factor might affect therapy. Daily GCSF, used in published prospective trials studies to date, affords a mean dose level of 2, with approximately 25% of patients reaching dose level 4.[10,11] In a study of younger patients primarily with PMBCL, more than half of patients attained dose level 4.[2] Pegylated GCSF (peg-GCSF), a long-acting formulation achieving comparable outcomes over daily GCSF in prophylaxis of febrile neutropenia,[12] has not been formally studied in conjunction with da-EPOCH-R. A report of 34 patients showed that use of peg-GCSF was associated with dose adjustment at a frequency similar to that expected with daily GCSF,[13] but whether peg-GCSF produces similar treatment and survival outcomes with da-EPOCH-R as GCSF is unknown.

We sought to characterize our institutional use of da-EPOCH-R for aggressive B-cell non-Hodgkin lymphoma (B-NHL), define the frequency of pegylated filgrastim (peg-GCSF) and daily GCSF use, and assess for an effect on patient outcomes. In particular, we assessed whether choice of GCSF or peg-GCSF affected da-EPOCH-R dose level achieved, rates of unplanned hospitalizations or febrile neutropenia, or event-free survival and overall survival.

Patients and Methods

Through pharmacy and clinic records, we identified all patients receiving da-EPOCH (dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine and prednisone) from 2005 to 2015 at the University of Washington and Seattle Cancer Care Alliance (UW/SCCA). Baseline features (age, sex, and international prognostic index [IPI] score), growth factor used (GCSF or peg-GCSF), maximum dose level attained, and outcomes were identified. Patients with DLBCL and variants (PMBCL, transformed lymphoma, DLBCL-posttransplant lymphoproliferative disorder [PTLD], and B-cell lymphoma, unclassifiable were analyzed with institutional review board approval, with further inclusion criteria as follows: received at least 4 cycles of da-EPOCH-R as first-line standard of care therapy and adequate data to identify growth factor choice and dose level achieved. Categorical variables are summarized and compared between groups using χ^2 testing. Event-free and overall survival, measured from diagnosis, are estimated via the Kaplan–Meier method (JMP version 12.2; SAS Institute Inc). Events included disease relapse or initiation of second-line therapy, or death from any cause.

Results

One hundred sixty-five patients receiving da-EPOCH were identified, representing an overall 5-fold increase in the use of this regimen over the 10-year study period. Of these, only 91 had received first-line da-EPOCH for aggressive B-NHL (54 were excluded on the basis of histology, including T-cell lymphoma or Burkitt lymphoma; 20 were excluded for receiving da-EPOCH as second-line or later therapy). An additional 17 were excluded for not receiving at least 4 cycles of therapy, in the context of complications or for elective reasons.

In total, 73 patients were eligible and had data for detailed review on the basis of the previously mentioned criteria. Diagnoses included 41 with DLBCL, 12 with B-cell lymphoma-unclassifiable bearing *MYC* rearrangement, 9 with PTLD with DLBCL morphology, and 6 with PMBCL.

Baseline characteristics, and comparisons between groups receiving GCSF and peg-GCSF, are reported in Table 1. The median age was 60 (range, 24-78) years, 23 (31%) were female, and 31 of 65 patients (47%) for whom IPI could be calculated had a score of 0 to 2. IPI risk distribution was similar between groups.

Most patients (44 of 73, or 60%) received peg-GCSF rather than daily GCSF with da-EPOCH-R. Event-free and overall survival were similar between growth factor groups (Figures 1 and 2).

Dose details of da-EPOCH-R are described in Table 2. Patients received a median of 6 cycles of da-EPOCH-R (range, 4-8); 75% of patients received 6 cycles of da-EPOCH-R. The median highest dose level was 2 without a difference in groups receiving peg-GCSF or daily GCSF. Overall, 45 of 73 (61%) of patients attained dose level of 2, 30 of 73 (41%) achieved level 3, and 11 of 73 (15%) achieved level 4. The proportion of patients who achieved dose level 4 was comparable in the peg-GCSF group (11%) and daily GCSF (21%; $P = .24$). Unplanned hospitalizations and febrile neutropenia occurred in 19 of 73 (26%) of our patients overall, including 9 of 44 (20%) in the peg-GCSF group.

Discussion

Infusional da-EPOCH-R was increasingly used at our institution from 2005 to 2015. When analyzing patients who underwent first-line treatment with da-EPOCH-R for aggressive B-cell lymphoma as a whole, 11 of 73 (15%) reached dose level 4, lower than has been observed in other studies. Preliminary results from the US cancer and leukemia group B 50303 study showed that 25% achieved dose level 4 or beyond.[11] In a study of patients with PMBCL, with a median age of 30 years, more than half of the patients exceeded dose level 4.[2] Because age predicts da-EPOCH dose

Table 1 Patient Characteristics

Parameter	All Patients (n = 73)	GCSF (n = 29)	Peg-GCSF (n = 44)	χ^2 P[a]
Median Age, y	60	56	61	NA
Age > Older Than 60 y	35	11 (38%)	24 (63%)	.04
HIV-Positive	5 (7%)	0 (0%)	5 (11%)	.06
Female Sex	23 (31%)	12 (41%)	11 (25%)	.15
R-IPI Group[b]				
Very Good (0)	—	1	3	—
Good (1-2)	—	10	17	—
Poor (3-5)	—	15	19	.7

Abbreviations: GCSF = granulocyte colony-stimulating factor; peg-GCSF = pegylated granulocyte colony-stimulating factor; R-IPI = Revised International Prognostic Index.
[a]Between GCSF and peg-GCSF groups.
[b]Among 65 with available data.