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Factors and Costs Associated With Delay in Treatment Initiation and Prolonged Length of Stay With Inpatient EPOCH Chemotherapy in Patients With Hematologic Malignancies

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Abstract

Reducing delays related to inpatient chemotherapy may reduce healthcare costs. Using a national database, we identified patients with lymphoma/leukemia with 1 etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) chemotherapy claim and evaluated chemotherapy initiation delay (ID), >1 day from admission. Standard tests/procedures prior to initiation were evaluated. Among 4453 inpatient cycles, 19.7% had ID, odds ratio 2.28 (95% confidence interval: 1.83–2.85) with cycle 1 compared to cycle 2, and mean costs were higher in patients with ID than without ID ($p < .0001$). Prior to cycle 1, patients were more likely to undergo routine diagnostic procedures compared to subsequent cycles. Efforts to perform routine procedures prior to admission may reduce hospital length of stay and costs.

Keywords

Chemotherapy; health sciences research; outcomes research

Introduction

Prolonged hospital length of stay (LOS) is associated with increased risk of hospital-acquired conditions (HACs), such as thromboembolic disease and iatrogenic infections (1–3). In addition, prolonged LOS is associated with higher direct costs of care (3). Hospitals

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may not be reimbursed for prolonged hospital stays and certain hospital-acquired conditions. For example, in 1983, the Centers for Medicare and Medicaid Services (CMS) initiated an inpatient prospective payment system which incentivized hospitals to reduce LOS by reimbursing a single flat rate per diagnosis (4, 5). In 2008, CMS discontinued additional payments for HACs that were deemed preventable, such as iatrogenic infections and thromboembolic disease (4, 6, 7). These policies pressure hospitals to reduce LOS to ensure their operating margins are met, and to prevent iatrogenic complications that could lead to non-reimbursement.

Delays in chemotherapy initiation following elective admission can lead to longer LOS, which can subsequently increase costs, consume hospital resources, and decrease patients' satisfaction (8–12). Previous research regarding the efficacy of chemotherapy delivery has focused on the outpatient setting, and is largely from small single institution studies (8, 9, 12, 13). These demonstrated that chemotherapy delays are highly prevalent in the outpatient setting and are associated with patient dissatisfaction (8, 9, 12, 13). To date, no prior research has evaluated delays in chemotherapy initiation in the inpatient setting.

Cancer patients typically receive chemotherapy in the outpatient setting. Certain circumstances, such as continuous multi-day infusions of vesicants, may require administration in the inpatient setting (14). Etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) chemotherapy is a regimen frequently used to treat non-Hodgkin lymphoma and other hematologic malignancies, and can be administered in the outpatient or inpatient setting (15–21). In this regimen, etoposide, vincristine, and doxorubicin are continuously infused through a central venous catheter over 96 h, then cyclophosphamide is administered on day 4 or 5 (15–25). The objectives of this study were to evaluate the proportion of patients who received inpatient EPOCH chemotherapy and determine factors associated with delays in EPOCH initiation and prolonged hospital LOS in patients with hematologic malignancies using a large national hospital database.

Methods

Data source

Data from the *Perspective* database (Premier, Charlotte, NC, USA), a voluntary, fee-supported database, were used. Perspective database contains a representative sample of more than 500 acute-care hospitals throughout the United States that contribute data on inpatient hospital admissions and outpatient procedures, including patient demographics, disease characteristics, and procedures performed; the database also collects information about all billed services rendered during a patient's hospital stay. Hospitals within this database are predominantly small to mid size (78% with <400 beds, 15% with 400–600 beds, and 7% with >600 beds), geographically diverse (13% are located in the Northeast, 25% in the Midwest, 42% in the South, and 20% in the West), nonteaching facilities (74% non-teaching) that serve a largely urban population (74% urban). Data in Perspective undergo a rigorous quality control process and have been used in several outcome studies (26–33).

EPOCH cycle selection

We analyzed patients 18 years of age with a diagnosis of lymphoma or leukemia (International Classification of Diseases, Ninth Revision [ICD-9] codes 200–202, 204–208) who received concurrent treatment for at least 4 days with etoposide, doxorubicin, and cyclophosphamide from 2006–2014. Since vincristine may be held in patients who develop neuropathy or have pre-existing neuropathy, receipt of vincristine was not required (92.7% of the cohort was treated with vincristine) (17, 18, 20, 21, 23). To capture patients who received EPOCH (a continuous 4–5-day infusion) versus a similar regimen, we only included patients who had a service bill for any of the EPOCH drugs, including rituximab and/or bortezomib on day 4–5 from the date of admission. Each EPOCH cycle was analyzed separately, so a single patient may have had multiple treatment cycles. The following exclusion criteria were used: Inpatient cycles with a delay of EPOCH initiation of >7 days from admission, which likely represented an admission for reasons other than EPOCH administration, and cycles in which patients were treated with additional chemotherapy agents, with the exception of rituximab and/or bortezomib, since these agents may be given with EPOCH (16, 17, 19, 22, 24, 25, 34–36). EPOCH cycles were classified on the basis of their setting (inpatient vs. outpatient).

Clinical and demographic covariates

Demographic covariates analyzed included age, race (White, Black, or others), marital status (married, single, unknown), insurance status (Medicare, Medicaid, commercial, uninsured, or unknown), and year of EPOCH administration (2006–2014). The hospitals at which patients were treated were characterized by location (urban, rural), teaching status (yes, no), size (<400 beds, 400–600 beds, >600 beds), and region of the country (Northeast, Midwest, South, and West). Clinical covariates included assessment of comorbid conditions performed, using the Elixhauser comorbidity score, and EPOCH cycle number (37, 38).

Inpatient EPOCH initiation time

The hospital day was recorded for each inpatient cycle using the billing file in Perspective database, which identifies the hospital day on which a particular procedure or service occurred. The LOS from admission to EPOCH initiation was categorized as the same day (hospital day 1), 2 days, or >2 days. Patients were considered to have a delay in EPOCH initiation if the time from admission to treatment initiation of any of the EPOCH drugs, including rituximab and/or bortezomib, was >1 day, since this analysis was limited to patients with elective admissions for EPOCH.

Length of stay

Length of stay was obtained from the billing file in Perspective database. The expected LOS for EPOCH is 4–5 days (17, 18, 20, 21, 23). LOS was categorized as 5 days or >5 days. Patients were considered to have a prolonged LOS if the LOS was greater than 5 days.

Pre-treatment tests and procedures prior to inpatient chemotherapy initiation

Hospital resources utilized from the time of admission until the time of EPOCH initiation were identified using ICD-9 procedure codes, hospital billing text, and Perspective database-

generated standard billing text codes. Specific pre-treatment tests and procedures evaluated were: laboratory test(s), imaging test(s), cardiology test(s) (echocardiogram or multiple-gated acquisition scan (MUGA)), blood product transfusion, antibiotics, hydration, lumbar puncture, bone marrow biopsy, and central intravenous (IV) access.

Direct costs of hospital admissions

Direct costs of hospital admissions for each episode were identified using the cost variable in the billing file. This variable includes both fixed (overhead) and variable (direct) costs to treat a patient for that particular admission (comprises cost for supplies, labor, depreciation of equipment, etc.).

Statistical analysis

Frequency distributions between categorical variables were compared using the χ^2 test. We used multivariable generalized estimating equation regression models to determine the factors associated with the setting of EPOCH infusion (inpatient vs. outpatient), delays in EPOCH initiation, prolonged LOS, and hospital resource utilization prior to EPOCH initiation. Patient and hospital characteristics were modeled as independent variables. All models included a random intercept for each hospital to account for hospital-level clustering. Patient and hospital characteristics were modeled as independent variables. Covariates were included if these were clinically meaningful or were significantly associated with the outcome in an unadjusted analysis. Covariates included age, race, marital status, insurance status, hospital location, hospital teaching status, hospital size, hospital region, patient comorbidity score, EPOCH cycle number, receipt of central IV access during hospitalization, and delay in EPOCH initiation (for LOS model only). Resource utilization was evaluated prior to patients initiating EPOCH cycle 1, and subsequent cycles.

Direct hospital admission costs were compared by delay in EPOCH initiation for each episode. We used ANOVA to compare the mean costs and the non-parametric median scores to compare the median costs by delay in EPOCH initiation. All analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and $p < .05$ was considered to be significant.

Results

We identified 1710 eligible patients. This resulted in 4863 unique EPOCH treatment cycles. Of these, 4453 (91.6%) were inpatient EPOCH cycles and 410 (8.4%) were outpatient EPOCH cycles. The majority of the population who received inpatient EPOCH comprised males (60.4%), White (68.4%), and treated at urban hospitals (95.1%). Clinical and demographic characteristics are displayed in Table 1. In a multivariable model (Table A1 in Appendix), compared with outpatient EPOCH cycles, inpatient EPOCH cycles were more likely to occur in patients with comorbidities (Elixhauser comorbidity score of 1: odd's ratio (OR) 2.38, 95% confidence interval (CI): 1.67–3.39; score of 2: OR 5.11, 95% CI: 3.05–8.57; score of 3: OR 14.18 95% CI: 7.17–28.07, compared to a score of 0), and those treated at teaching hospitals (OR 3.86, 95% CI: 1.28–11.65) compared to those treated at non-teaching hospitals.

Of the 4453 inpatient EPOCH episodes, 3578 (80.4%) initiated EPOCH on hospital day 1, 612 (13.7%) on hospital day 2, and 263 (5.9%) between hospital days 3 and 7. In a multivariable model (Table 1), compared with patients who initiated EPOCH on hospital day 1, a delay of 2 days were more likely to occur in patients who were single (OR 1.40, 95% CI: 1.05–1.88) compared to married; patients with higher Elixhauser comorbidity scores, i.e., score 2 (OR 1.36, 95% CI: 1.02–1.82) and score >3 (OR 2.02, 95% CI: 1.44–2.82) compared to patients with a score of 0; patients treated during cycle 1 of EPOCH (OR 2.28, 95% CI: 1.83–2.85) compared to patients treated during cycle 2; and patients who received central IV access during their hospitalization (OR 2.65, 95% CI: 2.08–3.38). Results were similar in a multivariable model comparing episodes with a delay of 3 to 7 days with those who began treatment on hospital day 1 (data not shown).

The mean LOS was 5.9 days, median 5.0, and 1099 (24.7%) had a prolonged LOS (>5 days). In a multivariable model (Table 2), compared to patients with a LOS of ≤5 days, prolonged LOS was more likely to occur in patients with Medicare (OR 2.17, 95% CI: 1.55–3.05) or Medicaid insurance (OR 1.50, 95% CI: 1.09–2.07) compared to those with commercial insurance; patients with comorbidities, Elixhauser score of 1 (OR 1.43, 95% CI: 1.07–1.91), Elixhauser score of 2 (OR 1.79, 95% CI: 1.35–2.38), Elixhauser score of 3 or higher (OR 3.45, 95% CI: 2.50–4.75) compared to those with a score of 0; patients treated during EPOCH cycle 1 (OR 1.29, 95% CI: 1.06–1.56) compared to those treated during EPOCH cycle 2, and patients who had a delay in EPOCH initiation (OR 10.43, 95% CI: 8.03–13.55). Older patients, ≥75 years (OR 0.49, 95% CI: 0.31–0.79) compared to patients aged 44 or younger; patients who were treated during subsequent EPOCH cycles, i.e., EPOCH cycle 3 (OR 0.72, 95% CI: 0.58–0.90), EPOCH cycle 4 or greater (OR 0.55, 95% CI: 0.45–0.67) compared to those treated during EPOCH cycle 2 were less likely to have a prolonged LOS.

There were 1154 hospitalizations for cycle 1 of EPOCH and 3299 hospitalizations for subsequent EPOCH cycles. Compared to subsequent inpatient EPOCH cycles, patients receiving their first EPOCH cycle were more likely to utilize hospital resources prior to EPOCH initiation; including transfusions (OR 1.45, 95% CI: 1.12–1.87), imaging tests (OR 2.36, 95% CI: 1.95–2.86), cardiology tests (OR 4.73, 95% CI: 3.51–6.37), bone marrow biopsies (OR 9.89, 95% CI: 4.90–19.99), and central IV access placement (OR 2.76, 95% CI: 2.15–3.53) (Figure 1).

Direct hospital costs were higher in patients with delayed chemotherapy initiation (Figure 2). Mean costs were US\$12,857 (SD \$13,089), \$16,863 (SD \$20,707), and \$34,221 (SD \$41,282), respectively, for patients who initiated treatment on hospital day 1, 2, or ≥3 ($p < .0001$). Median costs were US\$10,515, \$13,064, and \$19,870 ($p < .0001$) respectively.

Discussion

We found that the vast majority of EPOCH treatment cycles for leukemia/lymphoma are administered in the inpatient setting. Of inpatient EPOCH admissions, approximately 20% have delays in treatment initiation beyond 1 day, and almost one-quarter have a prolonged LOS. Delays in chemotherapy initiation and increased LOS were more likely to occur during

the first cycle of EPOCH compared to subsequent cycles. Prior to cycle 1, inpatients were more likely to undergo routine procedures, including cardiology tests and bone marrow biopsies. Finally, hospital costs were approximately 20% higher in patients who had a delay in chemotherapy initiation of 1 day, and 50% higher in patients with a delay in chemotherapy initiation of >2 days.

Health care costs are rising at an unsustainable rate, while costs of cancer care, in particular, are projected to rise at a faster rate than overall medical expenditures (39). Inpatient hospital expenditures account for more than one-third of the total cancer-related costs (40). Hospitals are incentivized to reduce LOS, since they are reimbursed a single flat rate based on the discharge diagnosis (4, 5). In addition, prolonged LOS is associated with an increased risk of iatrogenic conditions; development of which may affect the hospital's ability to be reimbursed (1–4, 6, 7). As a result, hospitals are interested in reducing LOS.

Jiang et al. (41) demonstrated significant cost savings associated with reduced LOS for induction therapy in patients with acute promyelocytic leukemia with the oral formulation of arsenic compared to the IV formulation of arsenic trioxide (ATO), with treatment costs of US\$7233 in the oral group compared to US\$9090 in the IV group ($p < .001$). Patients who require intensive salvage or induction therapy with acute myeloid leukemia or myelodysplastic syndrome often have prolonged LOS; a nonrandomized phase II trial of early discharge versus continued inpatient care was conducted in this population at the Fred Hutchinson Cancer Center between 2011 and 2014 ($n = 178$), which showed a significant reduction in median daily charges (US\$3840 vs. \$5852, $p < .001$) with no difference in early mortality ($p = .6$) in patients who received early discharge. This study demonstrated, in select patients, care delivery could be shifted from the inpatient setting to the outpatient setting safely to reduce LOS (42). A smaller study showed that a shift in radiotherapy delivery from the inpatient setting to the outpatient setting also could lead to substantial reductions in LOS (43). The literature suggests that a reasonable strategy to reduce LOS and associated costs is to shift care delivery from the inpatient to the outpatient setting as much as possible.

A cross-sectional analysis of outpatients treated at comprehensive cancer centers across Ontario in 2004 found that, of 1044 patients who received chemotherapy, patients with a delay in chemotherapy initiation had a worse perception of the quality of care they received compared to patients without a delay in chemotherapy initiation (10). Another study found that excessive wait period for outpatient chemotherapy was a significant source of patient dissatisfaction; (8) in addition, 78% of first-time patients reported that they would be dissatisfied if they had to wait for more than 60 min for their treatment. On average, outpatient chemotherapy wait period exceeded 60 min (8, 9, 12, 13). Patients with higher satisfaction related to their care experience may have better outcomes than less satisfied patients; a previous cohort study of 986 patients with lung cancer found, in a multivariable analysis, that patients who were completely satisfied with their care had significantly lower mortality (HR 0.71, 95% CI: 0.60–0.85) compared to patients who were not completely satisfied with their care (44). Recently, there has been increasing attention toward providing patient-centered care (45). Reducing delays in inpatient EPOCH initiation may be an

opportunity to improve patients' care experience, and potentially lead to improved outcomes while reducing costs from prolonged LOS.

After a new diagnosis of lymphoma or leukemia, additional tests and procedures prior to initiating chemotherapy are necessary. National Comprehensive Cancer Network (NCCN) guidelines (46) recommend a bone marrow biopsy for staging, evaluating left ventricular function with either a MUGA scan or echocardiogram, and a lumbar puncture in selected cases. It is also necessary to obtain central IV access due to the 96-h continuous infusion (15–25). In our analysis, we found that a high proportion of patients with first cycle delays in EPOCH initiation underwent these procedures while hospitalized. Completing these procedures in the ambulatory setting prior to admission may be an opportunity to reduce LOS and subsequent costs.

Although our study benefits from the inclusion of a large national sample, we recognize several important limitations. The Perspective database contains a relatively high proportion of patients treated at small to mid-size, nonteaching, urban, and Southern facilities. As a result, our findings may not be generalizable to the entire US population. Using administrative data, we lack information on the reason for first admission to EPOCH. It is possible that some patients had aggressive disease, rapid progression of disease, poor performance status, or lived far from their medical centers, all of which could require patients to receive their necessary post-diagnosis testing as an inpatient to avoid treatment delays. The Perspective database does not include data regarding household income, education level, cancer stage, and distance from household to the hospital, which may influence the ability to undergo ambulatory procedures. Data from Perspective is provided by participating hospitals; however, hospitals included in our analysis may not have been included in the Perspective database continuously throughout our analysis, and thus we may not have accurately accounted for EPOCH cycles. However, we expect the impact of this to be small. Perspective database also reports dates of service in a month/year format without the specific date of service, and as a result we may have misclassified patients as having an initiation delay if they were admitted late in the day and initiated chemotherapy after midnight (next calendar day); however, we believe the impact of this to be small, since most chemotherapy is not initiated overnight (after midnight) due to the complexity of chemotherapy order entry and administration. In addition, to accurately capture patients who received EPOCH (a continuous 4–5 days infusion) versus a similar regimen, we only included patients who had a service bill on day 4–5 from the date of admission. It is possible, we excluded episodes where individuals received outpatient EPOCH; however, we performed a sensitivity analysis, including all outpatient cycles ($n = 523$ vs. $n = 410$) with receipts of etoposide, doxorubicin, and cyclophosphamide, and the results were not different.

In conclusion, we found that approximately 20% of inpatient EPOCH episodes had a significant delay in chemotherapy initiation, which led to prolonged LOS and higher hospital costs. Many necessary pretreatment procedures, including central IV access placement, occurred in the inpatient setting prior to the first cycle of EPOCH, which can lead to treatment delays. In an effort to curb unnecessary spending and improve patient satisfaction, efforts should be made to perform routine procedures necessary for

chemotherapy delivery in the outpatient setting to reduce delays in chemotherapy initiation, reduce LOS, and reduce costs of care.

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Declaration of interest

Dr. Neugut has consulted for Pfizer, Teva Pharmaceuticals, Otsuka Pharmaceuticals, and United Biosource Corporation, and is on the Medical Advisory Board of EHE Intl. Dr. Accordino is a recipient of Dr. Charles A. Coltman Jr. Fellowship from the Hope Foundation. Drs Hershman (NCI R01 CA186084) and Wright (NCI R01CA169121) are recipients of grants from the National Cancer Institute. Dr. Hershman is a recipient of a grant from The American Society of Clinical Oncology/Breast Cancer Research Foundation.

References

1. Thromboembolic Risk Factors (THRIFT) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *Brit Med J (BMJ)*. 1992; 305(6853):567–574. [PubMed: 1298229]
2. Broderick A, Mori M, Nettleman MD, Streed SA, Wenzel RP. Nosocomial infections: validation of surveillance and computer modeling to identify patients at risk. *Am J Epidemiol*. 1990; 131(4):734–742. [PubMed: 2180283]
3. Clarke A. Why are we trying to reduce length of stay? Evaluation of the costs and benefits of reducing time in hospital must start from the objectives that govern change. *Qual Health Care (QHC)*. 1996; 5(3):172–179. [PubMed: 10161532]
4. Ginsburg PB, Rivlin AM. Challenges for Medicare at 50. *N Engl J Med*. 2015; 373(21):1993–1995. [PubMed: 26422645]
5. Guterman S, Dobson A. Impact of the medicare prospective payment system for hospitals. *Health Care Fin Rev*. 1986; 7(3):97–114.
6. Lee GM, Kleinman K, Soumerai SB, Tse A, Cole D, Fridkin SK, et al. Effect of nonpayment for preventable infections in US hospitals. *N Engl J Med*. 2012; 367(15):1428–1437. [PubMed: 23050526]
7. Hospital-Acquired Conditions. [[Accessed 2016 Jun 21]] Available from: https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/HospitalAcqCond/Hospital-Acquired_Conditions.html
8. Kallen MA, Terrell JA, Lewis-Patterson P, Hwang JP. Improving wait time for chemotherapy in an outpatient clinic at a comprehensive cancer center. *J Oncol Pract/Am Soc Clin Oncol*. 2012; 8(1):e1–e7.
9. Aboumatar HJ, Winner LE, Davis RO, et al. No time to waste: decreasing patient wait times for chemotherapy administration using automated prioritization in an oncology pharmacy system. *Am J ManagCare*. 2008; 14(5):309–316.
10. Sandoval GA, Brown AD, Sullivan T, Green E. Factors that influence cancer patients' overall perceptions of the quality of care. *Int J Qual Health Care (ISQua)*. 2006; 18(4):266–274.
11. Rupp LB, Doyle TJ. A successful physician-led multidisciplinary approach to process improvement for inpatient chemotherapy. *J Soc Health Syst*. 1993; 4(1):18–33. [PubMed: 8268466]
12. Soh TI, Tan YS, Hairom Z, Ibrahim M, Yao Y, Wong YP, et al. Improving wait times for elective chemotherapy through Pre-preparation: a quality-improvement project at the national university cancer institute of singapore. *J OncolPract*. 2015; 11(1):e89–94.
13. Lingaratnam S, Murray D, Carle A, Kirsas SW, Paterson R, Rischin D. Developing a performance data suite to facilitate lean improvement in a chemotherapy day unit. *J Oncol-Pract*. 2013; 9(4):e115–e121. [PubMed: 23942927]
14. Dollinger M. Guidelines for hospitalization for chemotherapy. *Oncologist*. 1996; 1(1 & 2):107–111. [PubMed: 10387975]

15. Wilson WH, Bryant G, Bates S, Fojo A, Wittes RE, Steinberg SM, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. *J Clin Oncol*. 1993; 11(8):1573–1582. [PubMed: 7687667]
16. Wilson WH, Jung SH, Porcu P, Hurd D, Johnson J, Martin SE, et al. A cancer and leukemia group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. *Haematologica*. 2012; 97(5):758–765. [PubMed: 22133772]
17. Sparano JA, Lee JY, Kaplan LD, Levine AM, Ramos JC, Ambinder RF, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood*. 2010; 115(15):3008–3016. [PubMed: 20023215]
18. Khaled HM, Zekri ZK, Mokhtar N, Ali NM, Darwish T, Elattar I, et al. A randomized EPOCH vs. CHOP front-line therapy for aggressive non-Hodgkin's lymphoma patients: long-term results. *Ann Oncol: Off J Eur Soc Med Oncol (ESMO)*. 1999; 10(12):1489–1492.
19. Purroy N, Bergua J, Gallur L, Prieto J, Lopez LA, Sancho JM, et al. Long-term follow-up of dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor prognosis large B-cell lymphoma. A phase II study conducted by the Spanish PETHEMA group. *Brit J Haematol*. 2015; 169(2):188–198. [PubMed: 25521006]
20. Stokoe CT, Ogden J, Jain VK. Activity of infusional etoposide, vincristine, and doxorubicin with bolus cyclophosphamide (EPOCH) in relapsed Hodgkin's disease. *Oncologist*. 2001; 6(5):428–434. [PubMed: 11675520]
21. Wilder DD, Ogden JL, Jain VK. A multicenter trial of infusional etoposide, doxorubicin, and vincristine with cyclophosphamide and prednisone (EPOCH) in patients with relapsed non-Hodgkin's lymphoma. *Clin Lymphoma*. 2001; 1(4):285–292. [PubMed: 11707843]
22. Wilson WH, Dunleavy K, Pittaluga S, Hegde U, Grant N, Steinberg SM, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. *J Clin Oncol*. 2008; 26(16):2717–2724. [PubMed: 18378569]
23. Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood*. 2002; 99(8):2685–2693. [PubMed: 11929754]
24. Dunleavy K, Pittaluga S, Maeda LS, Advani R, Chen CC, Hessler J, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. *N Engl J Med*. 2013; 368(15):1408–1416. [PubMed: 23574119]
25. Jeremann M, Jost LM, Taverna C, Jacky E, Honegger HP, Betticher DC, et al. Rituximab-EPOCH, an effective salvage therapy for relapsed, refractory or transformed B-cell lymphomas: results of a phase II study. *Ann Oncol Off J Eur Soc Med Oncol (ESMO)*. 2004; 15(3):511–516.
26. Lagu T, Rothberg MB, Nathanson BH, Pekow PS, Steingrub JS, Lindenauer PK. The relationship between hospital spending and mortality in patients with sepsis. *Arch Intern Med*. 2011; 171(4):292–299. [PubMed: 21357803]
27. Lindenauer PK, Pekow PS, Lahti MC, Lee Y, Benjamin EM, Rothberg MB. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. *J Am Med Assoc (JAMA)*. 2010; 303(23):2359–2367.
28. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med*. 2005; 353(4):349–361. [PubMed: 16049209]
29. Rothberg MB, Pekow PS, Lahti M, Brody O, Skiest DJ, Lindenauer PK. Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *J Am Med Assoc (JAMA)*. 2010; 303(20):2035–2042.
30. Logan AC, Yank V, Stafford RS. Off-label use of recombinant factor VIIa in US hospitals: analysis of hospital records. *Ann Intern Med*. 2011; 154(8):516–522. [PubMed: 21502649]
31. Wright JD, Neugut AI, Ananth CV, Lewin SN, Wilde ET, Lu YS, et al. Deviations from guideline-based therapy for febrile neutropenia in cancer patients and their effect on outcomes. *JAMA Intern Med*. 2013; 173(7):559–568. [PubMed: 23460379]

32. Hershman DL, Richards CA, Kalinsky K, Wilde ET, Lu YS, Ascherman JA, et al. Influence of health insurance, hospital factors and physician volume on receipt of immediate post-mastectomy reconstruction in women with invasive and non-invasive breast cancer. *Breast Cancer Res Treat*. 2012; 136(2):535–545. [PubMed: 23053659]
33. Accordino MK, Wright JD, Buono D, Neugut AI, Hershman DL. Trends in use and safety of image-guided transthoracic needle biopsies in patients with cancer. *J Oncol Pract (Am Soc Clin Oncol)*. 2015; 11(3):e351–e359.
34. Castillo JJ, Reagan JL, Sikov WM, Winer ES. Bortezomib in combination with infusional dose-adjusted EPOCH for the treatment of plasmablastic lymphoma. *Brit J Haematol*. 2015; 169(3):352–355. [PubMed: 25612847]
35. Fedele PL, Gregory GP, Gilbertson M, Shortt J, Kumar B, Opat S, et al. Infusional dose-adjusted epoch plus bortezomib for the treatment of plasmablastic lymphoma. *Ann Hematol*. 2016; 95(4):667–668. [PubMed: 26801792]
36. Ratner L, Rauch D, Abel H, Caruso B, Noy A, Barta SK, et al. Dose-adjusted EPOCH chemotherapy with bortezomib and raltegravir for human T-cell leukemia virus-associated adult T-cell leukemia lymphoma. *Blood Cancer J*. 2016; 6:e408. [PubMed: 27015285]
37. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998; 36(1):8–27. [PubMed: 9431328]
38. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care*. 2009; 47(6):626–633. [PubMed: 19433995]
39. Centers for Medicare and Medicaid Services. [[Accessed 2015 Jun 26]] National health expenditure projections 2011–2021. Available from: <http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/Proj2011PDF.pdf>
40. Soni, A. Statistical Brief #443. Agency for Healthcare Research and Quality; Trends in Use and Expenditures for Cancer Treatment Among Adults 18 and Older, US Civilian Noninstitutionalized Population, 2001 and 2011. Available from: http://www.meps.ahrq.gov/mepsweb/data_files/publications/st443/stat443.pdf [[Accessed 2016 Jun 21]]
41. Jiang H, Liang GW, Huang XJ, Jiang Q, Han S, Shi LW, et al. Reduced medical costs and hospital days when using oral arsenic plus ATRA as the first-line treatment of acute promyelocytic leukemia. *Leuk Res*. 2015; 39(12):1319–1324. [PubMed: 26403986]
42. Vaughn JE, Othus M, Powell MA, Gardner KM, Rizzuto DL, Hendrie PC, et al. Resource utilization and safety of outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia or myelodysplastic syndrome: a nonrandomized clinical comparative analysis. *JAMA Oncol*. 2015; 1(8):1120–1127. [PubMed: 26355382]
43. Pintova S, Holcombe RF, Blacksburn S, Friedlander P. Impact of inpatient radiation on length of stay and health care costs. *J Comm Support Oncol*. 2015; 13(11):399–404.
44. Gupta D, Rodeghier M, Lis CG. Patient satisfaction with service quality in an oncology setting: implications for prognosis in non-small cell lung cancer. *Int J Qual Health Care J Int Soc Qual Health Care (ISQua)*. 2013; 25(6):696–703.
45. Epstein, RM., Street, RL, Jr. Patient-Centered Communication in Cancer Care: Promoting Healing and Reducing Suffering. Bethesda, MD: National Cancer Institute; 2007. NIH publication No. 07–6225
46. NCCN Guidelines. [[Accessed 2016 Jun 28]] NCCN Clinical Practice Guidelines in Oncology. Non-Hodgkin's Lymphomas Version 3. 2016. Available from: https://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf

Appendix

Table A1

Characteristics associated with inpatient versus outpatient EPOCH chemotherapy administration from 2006 to 2014.

	Total EPOCH		Inpatient EPOCH		Outpatient EPOCH		Adjusted OR (95% CI)* OR	p value
	N 4863	% 100	N 4453	% 91.6	N 410	% 8.4		
Age (years)								
44	1209	24.9	1039	23.3	170	41.5	Reference	
45–54	959	19.7	879	19.8	80	19.5	1.29 (0.77–2.16)	.34
55–64	1052	21.6	958	21.5	94	22.9	1.34 (0.88–2.04)	.17
65–74	1062	21.8	1020	22.9	42	10.2	1.39 (0.86–2.27)	.18
75	581	12.0	557	12.5	24	5.9	1.07 (0.61–1.88)	.80
Gender								
Males	2944	60.5	2690	60.4	254	61.9	Reference	
Females	1919	39.5	1763	39.6	156	38.1	1.06 (0.75–1.51)	.74
Year of EPOCH							1.02 (0.91–1.14)	.73
2006	189	3.9	182	4.1	7	1.7		
2007	166	3.4	141	3.2	25	6.1		
2008	263	5.4	230	5.2	33	8.0		
2009	334	6.9	297	6.7	37	9.0		
2010	456	9.4	425	9.5	31	7.6		
2011	538	11.1	476	10.7	62	15.1		
2012	745	15.3	673	15.1	72	17.6		
2013	978	20.1	912	20.5	66	16.1		
2014	1194	24.5	1117	25.0	77	18.8		
Race								
White	3342	68.7	3047	68.4	295	72.0	Reference	
Black	467	9.6	439	9.9	28	6.8	1.11 (0.59–2.10)	.75
Others	1054	21.7	967	21.7	87	21.2	0.99 (0.64–1.52)	.95
Marital status								
Married	2292	47.1	2089	46.9	203	49.5	Reference	
Single	1892	38.9	1716	38.5	176	42.9	0.78 (0.54–1.14)	.20
Unknown	679	14.0	648	14.6	31	7.6	1.74 (0.68–4.42)	.25
Insurance status								
Medicare	1811	37.2	1734	38.9	77	18.8	1.57 (0.99–2.50)	.05
Medicaid	669	13.8	614	13.8	55	13.4	1.06 (0.65–1.73)	.81
Commercial	2112	43.4	1860	41.8	252	61.5	Reference	
Uninsured	175	3.6	152	3.4	23	5.6	0.81 (0.54–1.20)	.29
Unknown	96	2.0	93	2.1	3	0.7	1.10 (0.55–2.19)	.78
Hospital location								
Urban	4542	93.4	4237	95.1	305	74.4	Reference	

	Total EPOCH		Inpatient EPOCH		Outpatient EPOCH		Adjusted OR (95% CI) [*] OR	p value
	N 4863	% 100	N 4453	% 91.6	N 410	% 8.4		
Rural	321	6.6	216	4.9	105	25.6	0.23 (0.09–0.60)	.003
Elixhauser comorbidity score								
0	1189	24.4	921	20.7	268	75.4	Reference	
1	1297	26.7	1198	26.9	99	20.2	2.38 (1.67–3.39)	<.0001
2	1097	22.6	1064	23.9	33	8.0	5.11 (3.05–8.57)	<.0001
3	1280	26.3	1270	28.5	10	2.4	14.18 (7.17–28.07)	<.0001
Teaching hospital								
No	2313	47.6	2051	46.1	262	63.9	Reference	
Yes	2550	52.4	2402	53.9	148	36.1	3.86 (1.28–11.65)	.02
Bed size								
<400	2069	42.5	1830	41.1	239	58.3	Reference	
400–600	1218	25.1	1149	25.8	69	16.8	0.43 (0.17–1.07)	.07
>600	1576	32.4	1474	33.1	102	24.9	0.63 (0.17–2.29)	.48
Region								
Northeast	1072	22.0	1045	23.5	27	6.6	Reference	
Midwest	567	11.7	510	11.5	57	13.9	0.82 (0.17–3.88)	.80
South	2062	42.4	1872	42.0	190	46.3	1.25 (0.38–4.08)	.71
West	1162	23.9	1026	23.0	136	33.2	1.59 (0.43–5.91)	.49
EPOCH cycle								
1	1276	26.2	1154	25.9	122	29.8	0.92 (0.76–1.11)	.37
2	1150	23.7	1040	23.4	110	26.8	Reference	
3	871	17.9	792	17.8	79	19.3	1.03 (0.88–1.20)	.75
4+	1566	32.2	1467	32.9	99	24.1	1.22 (1.00–1.48)	.05

* Adjusted for other variables listed in the table and clustering at the hospital/facility level.

Bolded values indicate statistical significance at $p < .05$.

Figure 1. Multivariable analysis of hospital resource utilization prior to initiation of cycle 1 of EPOCH chemotherapy compared to subsequent cycles from 2006–2014 ($n = 4453$). Adjusted for covariates listed in Table 2 with the exception of central IV access placement.

Figure 2. Direct costs of hospital admissions for EPOCH chemotherapy from 2006–2014 ($n=4451$). Bars display one standard deviation (SD) from the mean, and are truncated at US\$0. Two patients without costs data were omitted from the analysis.

Characteristics associated with delay of initiation until hospital day 2 of EPOCH chemotherapy from 2006–2014.*

Table 1

	Total EPOCH		EPOCH initiation hospital day 1		EPOCH initiation hospital day 2		OR* (95% CI)		p value
	N	%	N	%	N	%	OR		
Age (years)	4453	100	3578	80.4	612	13.7			
<44	1039	23.3	798	22.3	173	28.3	Reference		
45–54	879	19.8	666	18.6	155	25.3	0.98 (0.67–1.44)		.92
55–64	958	21.5	784	21.9	126	20.6	0.73 (0.51–1.04)		.08
65–74	1020	22.9	857	24.0	108	17.6	0.83 (0.52–1.33)		.45
75	557	12.5	473	13.2	50	8.2	0.77 (0.48–1.25)		.29
Gender									
Males	2690	60.4	2166	60.5	365	59.6	Reference		
Females	1763	39.6	1412	39.5	247	40.4	1.11 (0.87–1.42)		.43
Year of EPOCH							0.98 (0.93–1.04)		.54
2006	182	4.1	149	4.2	24	3.9			
2007	141	3.2	111	3.1	20	3.3			
2008	230	5.2	182	5.1	28	4.6			
2009	297	6.7	254	7.1	23	3.7			
2010	425	9.5	359	10.0	30	4.7			
2011	476	10.7	397	11.1	55	9.0			
2012	673	15.1	511	14.3	121	19.8			
2013	912	20.5	726	20.3	142	23.2			
2014	1117	25.0	889	24.8	170	27.8			
Race									
White	3047	68.4	2521	70.5	384	62.7	Reference		
Black	439	9.9	322	9.0	83	13.6	0.86(0.61–1.22)		.40
Others	967	21.7	735	20.5	145	23.7	1.20 (0.82–1.77)		.35
Marital status									
Married	2089	46.9	1773	49.6	228	37.3	Reference		
Single	1716	38.5	1303	36.4	289	47.2	1.40 (1.05–1.88)		.02

	Total EPOCH		EPOCH initiation hospital day 1		EPOCH initiation hospital day 2		OR* (95% CI)		p value	
	N	%	N	%	N	%	OR			
Insurance status	Unknown	648	14.6		502	14.0	95	15.5	1.42 (0.72–2.83)	.26
	Commercial	1860	41.8		1513	42.3	261	42.7	Reference	
	Medicare	1734	38.9		1444	40.3	188	30.7	0.90(0.61–1.31)	.58
	Medicaid	614	13.8		428	12.0	130	21.2	1.39 (0.93–2.08)	.10
	Uninsured	152	3.4		110	3.1	24	3.9	1.10 (0.71–1.70)	.68
Hospital location	Unknown	93	2.1		83	2.3	9	1.5	0.65 (0.22–1.89)	.43
	Urban	4237	95.1		3396	94.9	594	97.1	Reference	
Elixhauser comorbidity score	Rural	216	4.9		182	5.1	18	2.9	0.99(0.53–1.85)	.96
	0	921	20.7		809	22.6	85	13.9	Reference	
	1	1198	26.9		989	27.6	168	27.4	1.33 (1.00–1.79)	.05
	2	1064	23.9		865	24.2	143	23.4	1.36 (1.02–1.82)	.04
	3	1270	28.5		915	25.6	216	35.3	2.02 (1.4492013;2.82)	<.0001
Teaching hospital	No	2051	46.1		1731	48.4	205	33.5	Reference	
	Yes	2402	53.9		1847	51.6	407	66.5	1.32 (0.76–2.31)	.33
Bed size	<400	1830	41.1		1506	42.1	210	34.3	Reference	
	400–600	1149	25.8		972	27.2	128	20.9	1.14(0.66–1.96)	.64
	>600	1474	33.1		1100	30.7	274	44.8	0.88 (0.44–1.74)	.71
Region	Northeast	1045	23.5		735	20.5	220	35.9	Reference	
	Midwest	510	11.5		448	12.5	45	7.4	0.68 (0.32–1.47)	.33
	South	1872	42.0		1506	42.1	247	40.4	1.11 (0.56–2.21)	.76
	West	1026	23.0		889	24.9	100	16.3	0.80 (0.38–1.69)	.55
EPOCH cycle	1	1154	25.9		743	20.8	237	38.7	2.28 (1.83–2.85)	<.0001
	2	1040	23.4		871	24.3	128	20.9	Reference	

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	Total EPOCH		EPOCH initiation hospital day 1		EPOCH initiation hospital day 2		OR* (95% CI)	p value
	N	%	N	%	N	%		
3	792	17.8	682	19.1	88	14.4	0.87 (0.68–1.10)	.25
4+	1467	32.9	1282	35.8	159	26.0	0.74 (0.55–1.00)	.05
Central IV access obtained during hospitalization								
No	3531	79.2	2979	83.3	417	68.1	Reference	
Yes	922	20.7	599	16.7	195	31.9	2.65 (2.08–3.38)	<.0001

* Adjusted for clustering at the hospital/facility level.

** Row percentages may not add up to 100%.

Bolded values indicate statistical significance at $p < .05$.

Table 2
Characteristics associated with prolonged LOS after inpatient EPOCH chemotherapy administration from 2006–2014.

	Total inpatient admissions			LOS 5 days			LOS > 5 days			p value
	N	%		N	%		N	%	OR* (95% CI)	
Age (years)	4453	100.0		3354	75.3		1099	24.7		
44	1039	23.3		775	23.1		264	24.0	Reference	
45–54	879	19.8		625	18.6		254	23.1	0.94 (0.65–1.37)	.75
55–64	958	21.5		732	21.8		226	20.6	0.89 (0.63–1.27)	.53
65–74	1020	22.9		785	23.4		235	21.4	0.56 (0.32–1.00)	.05
75	557	12.5		437	13.1		120	10.9	0.49 (0.31–0.79)	.003
Gender										
Males	2690	60.4		2020	60.2		670	61.0	Reference	
Females	1763	39.6		1334	39.8		429	39.0	1.11 (0.89–1.40)	.36
Year of EPOCH									0.96 (0.91–1.01)	.13
2006	182	4.1		132	3.9		50	4.4		
2007	141	3.2		95	2.8		46	4.2		
2008	230	5.2		171	5.1		59	5.4		
2009	297	6.7		241	7.2		56	5.1		
2010	425	9.5		347	10.4		78	7.1		
2011	476	10.7		360	10.7		116	10.6		
2012	673	15.1		493	14.7		180	16.4		
2013	912	20.5		697	20.8		215	19.6		
2014	1117	25.0		818	24.4		299	27.2		
Race										
White	3047	68.4		2337	69.7		710	64.6	Reference	
Black	439	9.9		290	8.6		149	13.6	1.31 (0.92–1.88)	.15
Others	967	21.7		727	21.7		240	21.8	1.04 (0.74–1.47)	.82
Marital status										
Married	2089	46.9		1655	49.3		434	39.5	Reference	
Single	1716	38.5		1184	35.3		532	48.4	1.25 (0.96–1.63)	.10
Unknown	648	14.6		515	15.4		133	12.1	0.85 (0.59–1.43)	.53

	Age (years)	Total inpatient admissions			LOS		5 days		LOS > 5 days		OR* (95% CI) OR	p value
		N 4453	%	100.0	N 3354	%	75.3	N 1099	%	24.7		
Insurance status												
	Medicare	1734	38.9		1284	38.3		450	40.9		2.17 (1.55–3.05)	<.0001
	Medicaid	614	13.8		402	12.0		212	19.3		1.50 (1.09–2.07)	.01
	Commercial	1860	41.8		1483	44.2		377	34.3		Reference	
	Uninsured	152	3.4		107	3.2		45	4.1		1.11 (0.59–2.08)	.75
	Unknown	93	2.1		78	2.3		15	1.4		1.08 (0.34–3.40)	.90
Hospital location												
	Urban	4237	95.1		3185	95.0		1052	95.7		Reference	
	Rural	216	4.9		169	5.0		47	4.3		0.85 (0.46–1.54)	.58
Elixhauser comorbidity score												
	0	921	20.7		811	24.2		110	10.0		Reference	
	1	1198	26.9		969	28.9		229	20.9		1.43 (1.07–1.91)	.02
	2	1064	23.9		812	24.2		252	22.9		1.79 (1.35–2.38)	<.0001
	3	1270	28.5		762	22.7		508	46.2		3.45 (2.50–4.75)	<.0001
Teaching hospital												
	No	2051	46.1		1615	48.2		435	39.6		Reference	
	Yes	2402	53.9		1738	51.8		664	60.4		1.12 (0.71–1.78)	.62
Bed size												
	<400	1830	41.1		1418	42.3		412	37.5		Reference	
	400–600	1149	25.8		918	27.4		231	21.0		0.99 (0.63–1.56)	.96
	>600	1474	33.1		1018	30.3		456	41.5		1.34 (0.79–2.27)	.27
Region												
	Northeast	1045	23.5		745	22.2		300	27.3		Reference	
	Midwest	510	11.5		425	12.7		85	7.7		1.11 (0.62–1.97)	.73
	South	1872	42.0		1372	40.9		500	45.5		1.54 (0.97–2.43)	.07
	West	1026	23.0		812	24.2		214	19.5		1.54 (0.90–2.64)	.12
EPOCH cycle												
	1	1154	25.9		683	20.4		471	42.8		1.29 (1.06–1.56)	.01
	2	1040	23.4		785	23.4		255	23.2		Reference	

	Total inpatient admissions			LOS		LOS > 5 days		OR* (95% CI) OR	p value
	N	%		N	%	N	%		
Age (years)	4453	100.0		3354	75.3	1099	24.7		
3	792	17.8		644	19.2	148	13.5	0.72 (0.58-0.90)	.004
4+	1467	32.9		1242	37.0	225	20.5	0.55 (0.45-0.67)	<.0001
Hospital day of EPOCH initiation									
Day 1	3578	80.3		3121	93.0	457	41.6	Reference	
Day 2	875	19.7		233	7.0	642	58.4	10.43 (8.03-13.55)	<.0001
Central IV access obtained prior to EPOCH initiation									
No	3531	79.2		2800	83.5	731	66.5	Reference	
Yes	922	20.7		554	16.5	368	33.5	1.22 (0.96-1.55)	.11

* Adjusted for other variables listed in the table and clustering at the hospital/facility level.

Bolded values indicate statistical significance at $p < .05$.