



Frane Mlinar. *Rest*. Oil on canvas, 30" × 30". Courtesy of The Weatherburn Gallery, Naples, Florida.

The association of premature termination of CHOP with survival among chemosensitive patients with non-Hodgkin's lymphoma differs according to age.

Factors Associated With Early Termination of CHOP Therapy and the Impact on Survival Among Patients With Chemosensitive Intermediate-Grade Non-Hodgkin's Lymphoma

Elizabeth A. Chrischilles, PhD, Brian K. Link, MD, Shane D. Scott, PharmD, David J. Delgado, PhD, and Moshe Fridman, PhD

Background: Six to eight cycles of CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) is standard for intermediate-grade non-Hodgkin's lymphoma (NHL) but is associated with toxicity that may cause premature termination of therapy.

Methods: We studied factors associated with premature termination of CHOP therapy (receiving <6 cycles) and the relationship of premature termination with survival. Subjects consisted of a population-based sample of Iowa residents with intermediate-grade NHL who were planned to receive ≥6 cycles of CHOP and who were chemosensitive (ie, achieved a documented partial or complete response to CHOP).

Results: In a comparison with patients 18-59 years of age, the odds of premature termination of CHOP therapy was 2.6 (95% CI, 0.7-9.2) for those aged 60-74 and 6.2 (95% CI, 1.7-23.3) for those aged ≥75. Patients with cycle 1 febrile neutropenia hospitalization (FNH) were 4.4 times (95% CI, 1.4-13.8) more likely to terminate CHOP prematurely than those without cycle 1 FNH. Among patients aged 60-74, but not those aged ≥75, premature termination appeared to be associated with decreased 5-year survival (hazard ratio [HR] = 6.0; 95% CI, 2.4-15.2) compared with those completing CHOP therapy (HR = 2.1; 95% CI, 1.0-4.2). Findings for overall survival were similar.

Conclusions: First-cycle FNH and age ≥60 years were associated with premature termination of CHOP therapy. The association of premature termination with survival among chemosensitive patients differed by age.

From the University of Iowa, Iowa City, Iowa (EAC, BKL, SDS), Amgen Inc, Thousand Oaks, California (DJD), and AMF Consulting, Los Angeles, California (MF).

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Address reprint requests to Elizabeth Chrischilles, PhD, Department of Epidemiology, College of Public Health, University of Iowa,

200 Hawkins Dr, C21-J-GH, Iowa City, IA 52242. E-mail: chrischilles@uiowa.edu

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Introduction

Intermediate-grade non-Hodgkin's lymphoma (NHL), as classified by the Working Formulation with diffuse large-cell lymphoma as the prototype, represents a group of potentially curable diseases.¹ Anthracycline-based multi-agent chemotherapy has been the mainstay of curative treatment strategies for NHL.² The impact of dose intensity (DI; the amount of chemotherapy delivered per unit of time) on cure rates in NHL has been a subject of widespread interest. Retrospective data suggest that diminished DI, with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as a standard,³ may be associated with lower response rates.^{4,5} Less is known about the importance of duration of chemotherapy in patients with chemosensitive disease. Debate concerning the duration of chemotherapy in advanced NHL centers on whether 6 or 8 cycles of CHOP should be considered standard for patients with advanced-stage disease. For patients with limited-stage disease, 3 or 4 cycles of chemotherapy followed by involved-field radiation therapy comprise an acceptable alternative to more-prolonged chemotherapy.⁶

Emerging data suggest that delivery of planned chemotherapy is often incomplete, especially in the elderly, due to toxicities encountered early in the chemotherapy course.^{7,9} In a previous analysis of this study population, the incidence of febrile neutropenia among those 65 years of age and older was 34% compared with 21% among patients under age 65.¹⁰ Febrile neutropenic hospitalization rates were 28% (95% confidence interval [CI], 26% to 30%) among patients ≥ 65 years of age and 16% (95% CI, 14% to 18%) among patients < 65 years of age.

The survival advantage or disadvantage of completing a full 6 cycles of chemotherapy is unknown in patients who respond to chemotherapy but experience significant toxicity that prompts consideration of discontinuation. Our retrospective, historical study links observed practice patterns with survival data, describes risk factors associated with receiving < 6 cycles of CHOP chemotherapy among those planned to receive at least 6 cycles, and assesses the relationship of administering < 6 cycles of CHOP chemotherapy with survival.

Methods

Study Design and Patient Selection

This retrospective study analyzed chart-abstracted data from a subset of patients in the Oncology Practice Pattern Study (OPPS) database described by Morrison

et al.¹⁰ The purpose of the OPPS was to study the current clinical practice use of chemotherapy and the clinical management of chemotherapy-related neutropenia in aggressive NHL. The present study reports on the population-based stratified random sample of cases contributed by University of Iowa investigators. Patients were Iowa residents aged 18 and over who were diagnosed with histologically confirmed (any microscopic confirmation) aggressive NHL as their first invasive cancer from January 1, 1993, through December 31, 1996, and received chemotherapy as part of the first course of therapy. Patients were excluded if they were on clinical trial treatment protocols during the first course of therapy or had HIV disease or HIV-positive status. The three strata for sampling were (1) eligible patients receiving chemotherapy from the University of Iowa Hospitals and Clinics (UIHC), (2) eligible Iowa residents receiving chemotherapy in large community treatment centers but not from UIHC, and (3) eligible Iowa residents receiving chemotherapy in smaller community treatment centers but not from UIHC or a large treatment center. The achievement of this population-based study was made feasible by the participation of the Iowa Surveillance, Epidemiology, and End Results (SEER) program. A random number was assigned to each case that met the study selection criteria. The last two digits of the random number were compared to the last two digits of the sampling fraction for the stratum. If the last two digits of the random number were less than the last two digits of the sampling fraction, the case was eligible for the study. The sampling fractions were designed to approximately equalize the number of cases within the strata and achieve a total sample size of 300. The final sampling fractions were 1.0 for UIHC, 0.32 for large treatment centers, and 1.0 for smaller treatment centers. The distribution of eligible and completed cases was as follows: UIHC 86, large treatment centers 138, and smaller treatment centers 71 ($n = 295$ total).

Long-term follow-up data for our study population were obtained from the Iowa SEER registry. Survival data were captured from the Iowa Department of Public Health death certificate files. For the OPPS, a SEER abstractor extracted information from medical records onto study forms. The study forms contained a study identification number, which was linked to a SEER identification number in a separate confidential file. The Iowa SEER registry maintains a link of SEER identification numbers to vital status data from the state's Department of Public Health, thus enabling the capture of survival data.

Patients were eligible for our study if they were at least 18 years of age, had intermediate-grade NHL (lymphoma histology was categorized according to the

Working Formulation,¹ which was in use by pathologists during the study period), were scheduled to receive at least 6 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, and had at least 4 months of follow-up data after chemotherapy was initiated. This ensured availability of the minimal follow-up time required to capture 6 cycles of CHOP. All included patients received at least 1 cycle of CHOP chemotherapy and had documented chemosensitive disease defined as chart documentation of a partial or complete response any time after initiation of CHOP therapy but before beginning a subsequent treatment strategy. Patients who did not have a documented partial or complete response were excluded. Patients also were excluded if they were on a clinical trial treatment protocol, had HIV infection, or received concurrent radiation therapy.

The project was approved by the University of Iowa institutional review board. Individual informed consent was not obtained in this database-only study.

Study Independent Variables and Operational Definitions

Patient characteristics that were extracted from medical records included patient age, sex, comorbid conditions, cancer disease stage, number of extranodal sites involved, B symptoms (ie, recurrent fever, night sweats, or the loss of >10% of body weight), lymphoma histology, bone marrow involvement, and response data. Patient age was stratified a priori as 18 to 59 years, 60 to 74 years, or ≥ 75 years based on the trend analysis data from Morrison et al.¹⁰ Because few clinical trials include patients ≥ 75 years of age, little is known about this subgroup. Comorbid conditions were classified as either 0 or ≥ 1 , based on a modified Charlson Comorbidity Index (CCI) with a scale of 0 to 12.¹¹⁻¹³ Additionally, the comorbid conditions of heart disease and renal disease were classified as present (ICD9-CM codes 410, 411, 412, 414, 427, and 428 for heart disease; ICD9-CM codes 403, 404, 580 to 586, and 588 for renal disease) or absent. NHL disease stage was categorized as limited (Ann Arbor stages I or II) or advanced (Ann Arbor stages III or IV).¹⁴ The number of extranodal sites involved was classified as 0 to 1, ≥ 2 , or unknown. B symptoms and bone marrow involvement were categorized as present, absent, or unknown. Response data were classified as either complete or partial. Disease status was abstracted from the medical record upon completion of the current chemotherapy course. Abstractors could indicate complete response, partial/response/stable, no response/progression, not evaluated, or unknown. Lymphoma histology was categorized according to the Working Formulation,¹ which was in use by pathologists during the study period.

Treatment Characteristics and Outcomes

Agent-specific relative dose intensity (RDI) for each patient was calculated to determine how closely the patient's dose of chemotherapy compared with the standard-dose regimen of CHOP. Planned RDI was calculated as a ratio of the planned first cycle DI divided by the corresponding standard CHOP dose in mg/m² per week. The average planned relative dose intensity (ARDI)¹⁵ for each patient was obtained by averaging the planned RDIs for cyclophosphamide and doxorubicin. Planned ARDI was classified as either >80% or $\leq 80\%$. Delivered ARDI was calculated in a similar manner.

Febrile neutropenia was defined as a body temperature of >100.6° F and an ANC of $<1.0 \times 10^9/L$. Febrile neutropenic hospitalization was documented from the patient's medical record. Early use of colony-stimulating factors (CSFs) was defined as any administration of CSFs during the first 5 days of the first cycle of chemotherapy.

Statistical Methods

Patient characteristics are reported overall and by early termination status (delivery of <6 cycles of CHOP chemotherapy). Chi-square tests, *t* tests, and Wilcoxon rank-sum tests were used for bivariate comparisons. Individual factors significantly associated with early termination were evaluated with multivariate logistic regression. The survival time was summarized with Kaplan-Meier plots,¹⁶ and the significance of early termination of CHOP chemotherapy on survival was tested by the Wilcoxon rank test, stratifying data by cancer stage and age groups. In addition, the adjusted effect of covariates on survival was modeled using proportional hazards multiple regression. Stepwise selection methods to select factors were employed to generate the final models. Only second-order interactions were tested for significance. All reported *P* values are two-tailed.

Results

Description of Study Population

A total of 124 patients met the study entry criteria. Of this group, 41% were 60 to 74 years of age and 23% were 75 years or older (Table 1). Forty-four percent (44%) of the study patients had advanced-stage disease, and 66% had diffuse large-cell histology. Twenty percent (20%) of the study population received <6 cycles of CHOP chemotherapy. Of the 8 patients receiving early CSE, 7 (88%) received G-CSE. The median patient follow-up was 72 months (range 5 to 87 months). Sixty-two percent (62%) of the patients died during the follow-up period.

Table 1. — Characteristics of 124 Patients With Chemosensitive Intermediate-Grade Non-Hodgkin's Lymphoma and Risk Factors Associated With Early Termination of CHOP Therapy

Patient Characteristics	No. of Patients Receiving ≥ 6 Cycles of CHOP Therapy (n = 99) (%)	No. of Patients Receiving < 6 Cycles of CHOP Therapy (n = 25) (%)	P Value
Age:			
18-59	41 (41.4)	4 (16)	.007
60-74	41 (41.4)	10 (40)	
≥ 75	17 (17.2)	11 (44)	
Sex:			
Male	50 (50.5)	9 (36)	.283
Female	49 (49.5)	16 (64)	
Charlson Comorbidity Index:			
0	65 (65.7)	17 (68)	$> .99$
≥ 1	34 (34.3)	8 (32)	
Renal disease:			
Present	3 (3.3)	1 (4)	$> .99$
Absent	96 (96.7)	24 (96)	
Heart disease:			
Present	12 (12.1)	5 (20)	.485
Absent	87 (87.9)	20 (80)	
Ann Arbor stage:			
Limited (I-II)	53 (53.5)	16 (64)	.474
Advanced (III-IV)	46 (46.5)	9 (36)	
Extranodal sites:*			
0-1	73 (74.5)	23 (100)	.015
≥ 2	25 (25.5)	0 (0)	
B symptoms:			
Present	23 (23.2)	2 (8)	.156
Absent	76 (76.8)	23 (92)	
Bone marrow involvement:*			
Present	13 (13.1)	3 (13)	.941
Absent	76 (86.9)	20 (87)	
Histology Working Formulation:*			
D	9 (9.2)	1 (4)	.793
E	6 (6.1)	1 (4)	
F	11 (11.2)	2 (8)	
G	65 (66.3)	18 (72)	
H	7 (7.1)	3 (12)	
Planned ARDI:			
$\leq 80\%$	23 (23.2)	5 (20)	.938
$> 80\%$	76 (76.8)	20 (80)	
Delivered ARDI:			
$\leq 80\%$	32 (32.3)	10 (40)	.625
$> 80\%$	67 (67.7)	15 (60)	
Early CSF use:**			
Yes	7 (7.1)	1 (4)	.918
No	92 (92.9)	24 (96)	
Cycle 1 FNH:			
Present	9 (9.1)	8 (32)	.008
Absent	90 (90.9)	17 (68)	
Response:			
Partial	33 (33.3)	9 (36)	.988
Complete	66 (66.7)	16 (64)	

* "Unknown" category has been omitted from calculations.
** Defined as CSF use within the first 5 days of cycle 1.
ARDI = average relative dose intensity
CSF = colony-stimulating factor
FNH = febrile neutropenia hospitalization

Risk Factors Associated With Early Termination

Risk factors significantly associated with premature discontinuation of CHOP therapy included age ≥ 60 years ($P=.007$), 0 to 1 extranodal sites ($P=.015$), and cycle 1 febrile neutropenic hospitalization ($P=.008$). In a multivariate analysis of predictors of receiving < 6 cycles of CHOP chemotherapy, patients 60 to 74 years of age and those ≥ 75 years old had 2.6 (95% CI, 0.7 to 9.2) and 6.2 times (95% CI, 1.7 to 23.3), respectively, the odds of terminating CHOP chemotherapy prematurely compared with patients aged 18 to 59 (Table 2). Patients with first-cycle febrile neutropenic hospitalization were 4.4 times (95% CI, 1.4 to 13.8) more likely to receive < 6 cycles of CHOP chemotherapy after controlling for age compared with patients who did not experience febrile neutropenia in cycle 1.

Description of Overall and 5-Year Survival

Kaplan-Meier plots of overall survival for patients with limited- and advanced-stage NHL, stratified by age

Table 2. — Impact of Patient Characteristics on Early Termination of CHOP Therapy Among Patients With Chemosensitive Intermediate-Grade Non-Hodgkin's Lymphoma

Patient Characteristics	Odds of Receiving < 6 Cycles of CHOP Therapy (Multivariate)	95% Confidence Interval
Age 60-74*	2.6	0.7-9.2
Age ≥ 75 *	6.2	1.7-23.3
Cycle 1 FNH	4.4	1.4-13.8

* Reference group included all patients aged 18 to 59.
FNH = febrile neutropenia hospitalization

and delivery of < 6 cycles of CHOP chemotherapy, are presented in Figs 1-2. The reference group used in all Kaplan-Meier plots included patients who were 18 to 59 years of age. None of the patients with advanced stage NHL in this age group discontinued CHOP chemotherapy early, and only 4 of the patients with limited-stage NHL in this age group received < 6 cycles of CHOP therapy.

Overall and 5-year survival rates were significantly better among patients aged 60 to 74 years who received ≥ 6 cycles of CHOP chemotherapy compared with patients in this same age group who received < 6

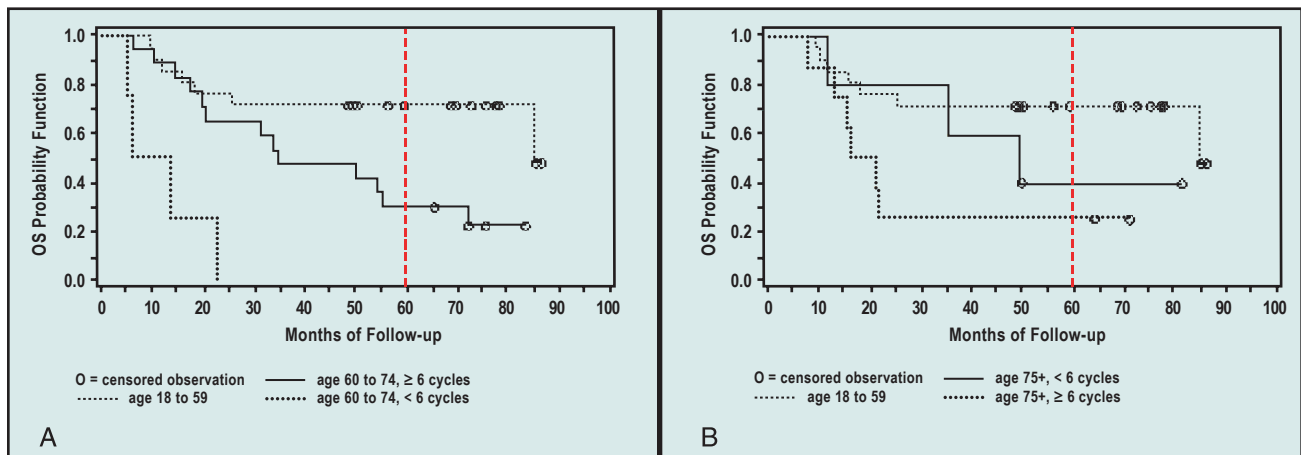


Fig 1A-B. — Stratified Kaplan-Meier plot of overall survival for advanced-stage patients (OS = overall survival).

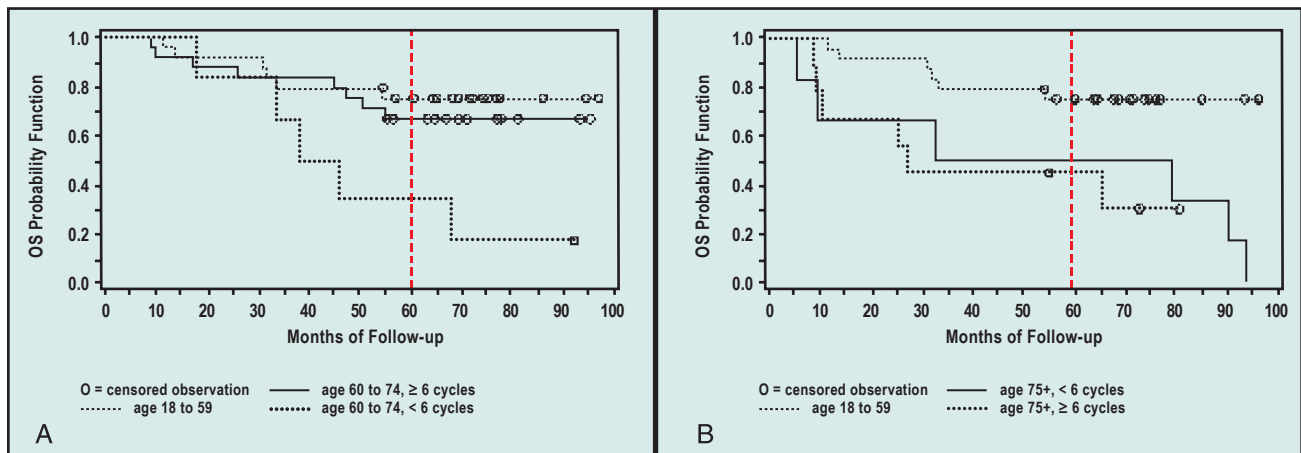


Fig 2A-B. — Stratified Kaplan-Meier plot of overall survival for limited-stage patients (OS = overall survival).

Table 3. — Univariate Cox Proportional Hazard Model Estimates of Overall and 5-Year Hazard Ratio of Death for 124 Patients With Chemosensitive Intermediate-Grade Non-Hodgkin's Lymphoma

Patient Characteristics	Overall Risk of Death (Univariate)		5-Yr Risk of Death (Univariate)	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Age: 60 to 74*	2.3	1.2-4.4	2.3	1.2-4.6
≥75*	3.6	1.8-7.1	3.2	1.5-6.7
Sex: male	0.7	0.4-1.2	0.7	0.4-1.1
Charlson Comorbidity Index ≥1	1.3	0.8-2.1	1.5	0.9-2.5
Presence of renal disease	1.2	0.3-5.0	1.3	0.3-5.4
Presence of heart disease	2.0	1.1-3.9	2.2	1.1-4.1
Advanced-stage disease (III-IV)	1.8	1.1-3.0	1.8	1.1-3.1
≥2 Extranodal sites	1.1	0.9-1.4	1.1	0.9-1.4
Presence of B symptoms	1.2	0.7-2.2	1.4	0.7-2.6
Bone marrow involvement	2.2	1.1-4.4	2.3	1.2-4.6
Planned ARDI ≤80%	1.4	0.8-2.4	1.4	0.8-2.5
Early CSF use**	1.1	0.4-3.0	1.2	0.4-3.3
Presence of cycle 1 FNH	1.7	0.9-3.3	1.5	0.7-3.0
Received <6 cycles CHOP	1.6	0.9-2.8	1.5	0.8-2.7
Partial response	1.8	1.1-2.9	1.7	1.0-2.9

* Reference group included all patients aged 18-59.
 ** Defined as CSF use within the first 5 days of cycle 1.
 CI = confidence interval
 ARDI = average relative dose intensity
 CSF = colony-stimulating factor
 FNH = febrile neutropenia hospitalization

cycles of chemotherapy ($P=.0004$ and $.0017$ for overall and 5-year survival, respectively.) While the ≥ 75 age group was underpowered to draw meaningful conclusions, no significant improvement in survival was observed among patients ≥ 75 years old who received ≥ 6 cycles of CHOP chemotherapy compared with patients aged ≥ 75 years who received < 6 cycles of chemotherapy ($P=.3705$ and $.4150$ for overall and 5-year survival, respectively). Analyses were adjusted by stratifying on age and stage. No other measured risk factors were associated with early termination of therapy (Tables 1 and 2).

Risk Factors Associated With Overall and 5-Year Survival

Univariate proportional hazard regressions (Table 3) indicate that advanced age (≥ 60 years), advanced cancer stage, bone marrow involvement, and heart disease were significantly associated with reduced overall and 5-year survival. Additionally, partial response to chemotherapy was significantly associated with reduced overall survival relative to complete response. Patients aged 60 to 74 years and those ≥ 75 years had an

overall hazard ratio of death of 2.3 (95% CI, 1.2 to 4.4) and 3.6 (95% CI, 1.8 to 7.1), respectively, compared with patients aged 18 to 59. Patients with heart disease, advanced-stage NHL, bone marrow involvement, or partial response had approximately twice the risk of death compared with patients with no heart disease, limited stage disease, no bone marrow involvement, or complete response, respectively.

The investigation of possible effects of early termination by specific age group was continued. Age was cross-classified by completion (≥ 6 cycles) or early termination (< 6 cycles) of CHOP chemotherapy (Table 4), and the stage-adjusted effects of these variables were examined using multivariate analysis. The reference category for the three age groups by two cycle-completion groups in this analysis was the age group 18 to 59 years (only 4 of 45 of these younger patients

were terminated early). As expected, the youngest age group (18 to 59 years) had significantly better survival than older patients (≥ 60 years old) in most cases. Advanced age was also significantly associated with lower body surface area, higher prevalence of comorbidity (Charlson Comorbidity Index ≥ 1), higher prevalence of heart disease, and higher prevalence of B symptoms ($P<.05$). The oldest patients were also more likely to have large cleaved or non-cleaved cell/diffuse histology (Working Formulation class G) ($P<.05$). Adjusted for stage, poorer 5-year survival among patients aged 60 to 74 appeared to be associated with early cessation of CHOP chemotherapy compared with completing 6 cycles of CHOP chemotherapy (hazard ratio [HR] = 6.0 vs 2.1, respectively). Although results from the ≥ 75 -year

Table 4. — Impact of Patient Characteristics on Overall and 5-Year Hazard Ratio of Death Among Patients With Chemosensitive Intermediate-Grade Non-Hodgkin's Lymphoma

Patient Characteristics	Overall Risk of Death (Multivariate)		5-Yr Risk of Death (Multivariate)	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Ann Arbor stage: advanced	2.1	1.3-3.6	2.1	1.2-3.7
Age ≥ 75 , received ≥ 6 cycles*	4.2	1.9-9.3	3.8	1.7-8.7
Age ≥ 75 , received < 6 cycles*	3.1	1.3-7.3	2.4	0.9-6.5
Age 60-74, received ≥ 6 cycles*	2.0	1.0-4.1	2.1	1.0-4.2
Age 60-74, received < 6 cycles*	6.4	2.6-15.4	6.0	2.4-15.2

* Reference group included all patients 18-59 years of age.
 CI = confidence interval

age group are difficult to interpret because of the small sample size, early cessation of CHOP chemotherapy in this subgroup did not appear to be associated with poorer 5-year survival rates compared with those completing 6 cycles of CHOP chemotherapy (HR = 2.4 vs 3.8, respectively).

Discussion

The disparity between optimal planned strategies for treatment of potentially curable NHL, which are relatively well defined, and actual delivered therapy in non-protocol settings is increasingly evident in recent literature.¹⁰ Much of this disparity appears related to toxicity of chemotherapy in early cycles.^{7,9} Strategies to decrease the incidence of such toxicity based on models identifying patients at risk are under development.⁸ Little is known, however, about optimal strategies for subsequent treatments following significant toxicity early in the treatment course. Specifically, when chemotherapy results in a clinical antitumor effect with concurrent significant toxicity, options to consider include the following: (1) continue chemotherapy without attenuation and accept the risk of more substantial toxicity, (2) continue chemotherapy at full dose and duration with supportive CSF therapy, (3) continue chemotherapy at a diminished DI, (4) proceed with alternative chemotherapy, or (5) abbreviate the planned initial course of therapy. This retrospective historical review of a population-based sample of patients with chemosensitive intermediate-grade NHL explored observations related to abbreviating the planned initial course of therapy. Specifically examined factors were pretreatment or treatment-related characteristics and their association with early termination. Similarly, the association of early termination with survival was examined.

In this sample of individuals with aggressive NHL planned by their treating oncologist to receive at least 6 cycles of CHOP chemotherapy and documented to achieve partial or complete response to CHOP chemotherapy, first-cycle febrile neutropenic hospitalization and age ≥ 60 years were associated with early termination of CHOP chemotherapy. Patients ≥ 75 years of age had a higher likelihood of early termination compared with patients 60 to 74 years old. Most prospective studies of chemotherapy for lymphoma contend that the elderly tolerate chemotherapy well and that special considerations for dosing are not required a priori, yet most of these studies have populations weighted toward patients aged 60 to 74.^{17,18} This retrospective study demonstrates that in practice, patients over age 60 are less likely to receive the initial planned course of chemotherapy despite the documentation of chemo-

sensitive disease. Febrile neutropenic hospitalization in cycle 1 is associated with risk of premature termination of chemotherapy across all age groups. This observation supports the development of strategies to reduce risk of early neutropenic complications.

The survival observations compare patients who received at least 6 cycles of chemotherapy relative to the cohort receiving an abbreviated number of cycles. On univariate analysis among patients aged 60 to 74, completing at least 6 cycles was associated with statistically better overall survival. Striving for delivery of at least 6 cycles of chemotherapy in responding patients despite toxicity may be beneficial in this age group. Among patients aged 75 and older, completing at least 6 cycles was associated with a trend toward a higher hazard ratio of death (5-year and overall) compared with the cohort receiving less than the planned number of cycles. This trend, however, did not reach statistical significance. Such an observation has not been previously described but should be explored in other datasets and with other study methods, including prospective clinical trials. The potential that a subset of patients exists for whom early termination of chemotherapy is reasonable and perhaps even beneficial increases the need for tools that allow earlier assessment of long-term prognosis. Further studies of functional imaging such as fluorodeoxyglucose positron emission tomography (FDG-PET) early in the course of chemotherapy will potentially lead to strategies to identify good candidates for abbreviated courses of chemotherapy.

Speculative explanations for these apparent differences among age groups include a real difference in CHOP effectiveness by age group or confounding by unmeasured characteristics such as performance status and evolving comorbidities, which were not reliably assessed in this retrospective study and not included in any analyses. In addition, determination of partial and complete response relied on medical records, including radiology reports, but there was no central validation of response assessments. Furthermore, the imperfections of the Working Formulation classification used by the pathologists during much of the treatment period studied could affect some of these observations. The distribution of mantle cell lymphoma, representing less than 10% of all lymphomas and strongly associated with high hazard ratio of death at 5 years, cannot be accounted for among the patients in this study and may be more likely to be distributed among the elderly patients. The peripheral T-cell lymphomas, another modestly small subset with a high hazard ratio of death at 5 years, also are unaccounted for although by chance would likely be evenly distributed among the age-specific subsets.

Conclusions

We found that first-cycle febrile neutropenic hospitalization and age ≥ 60 years were associated with premature termination of CHOP therapy and that the association between completing a full course of therapy and survival differed by age group. Larger retrospective studies or prospective, controlled trials are needed to further explore and confirm these findings.

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