VOLUME 36 · NUMBER 16 · JUNE 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Diagnosis-to-Treatment Interval Is an Important Clinical Factor in Newly Diagnosed Diffuse Large B-Cell Lymphoma and Has Implication for Bias in Clinical Trials

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Published at jco.org on April 19, 2018.

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0732-183X/18/3616w-1603w/$20.00

ABSTRACT

Purpose

Selection bias in clinical trials has consequences for scientific validity and applicability of study results to the general population. There is concern that patients with clinically aggressive disease may not have enrolled in recent diffuse large B-cell lymphoma (DLBCL) trials due to the consent process and the inability to delay therapy for eligibility evaluation. We have examined the diagnosis-to-treatment interval (DTI) and its association with clinical factors and outcome in a clinic-based observational cohort of patients with DLBCL from the United States. Validation of results was performed in an independent, clinical trial-based cohort from Europe.

Patients and Methods

Patients were prospectively enrolled in the University of Iowa and Mayo Clinic Specialized Programs of Research Excellence Molecular Epidemiology Resource (MER; N = 986) or the Lymphoma Study Association (LYSA) LNH-2003 clinical trials program (N = 1,444). All patients received anthracycline-based immunochemotherapy at initial diagnosis. Associations of DTI with clinical factors and outcome were examined. Outcome was assessed using event-free survival at 24 months from diagnosis (EFS24).

Results

Median (range) DTI was 15 days (0 to 155 days in the MER and 23 days (0 to 215 days) in LYSA. Shorter DTI was strongly associated with adverse clinical factors, including elevated lactate dehydrogenase levels, poor performance status, B symptoms, and higher International Prognostic Index in both cohorts (all $P < .001$). Longer DTI was associated with improved EFS24 in both the MER (per-week odds ratio, 0.80; 95% CI, 0.74 to .0.87) and LYSA (per-week odds ratio, 0.90; 95% CI, 0.86 to 0.94); association with EFS24 remained significant after adjustment for International Prognostic Index.

Conclusion

DTI is strongly associated with prognostic clinical factors and outcome in newly diagnosed DLBCL. DTI should be reported in all clinical trials of newly diagnosed DLBCL and future trials should take steps to avoid selection bias due to treatment delay.

J Clin Oncol 36:1603-1610. © 2018 by American Society of Clinical Oncology

INTRODUCTION

The selection bias of patients participating in cancer clinical trials has been long postulated to limit the generalizability of clinical trials to the general population.[1] Although selection bias is widely acknowledged as a product of trial inclusion and exclusion criteria,[2] other factors, such as patient preference, provider preference, socioeconomic status, and access to medical care, may inadvertently play a role in patient selection. The latter factors typically do not reflect different disease biology. However, in an aggressive malignancy, real or perceived urgency for initiation of therapy has to be weighed against the time required for trial screening, the consent process, and any relevant pathology and biomarker assessment. The resulting exclusion of patients with rapidly progressive or symptomatic

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.76.5198

DOI: https://doi.org/10.1200/JCO.2017.76.5198

disease may lead to selection of patients with less aggressive disease to participate in clinical trials. This bias may not be captured by study eligibility criteria and standard prognostic factors.

The phenomenon of time-dependent selection bias in clinical trials may be particularly evident in the treatment of diffuse large B-cell lymphoma (DLBCL). DLBCL is an aggressive malignancy and most patients are cured using anthracycline-based immunochemotherapy regimens, typically given as a combination of rituximab, cyclophosphamide, doxorubicin hydrochloride (aka, hydroxydaunorubicin), vincristine sulfate, and prednisone (R-CHOP)[3-6] or similar combinations. Gene expression profiling has identified molecular phenotypes of DLBCL, grouping most patients into one of two molecular classifications: germinal center B cell (GCB) and activated B cell,[7,8] and recent trial designs in DLBCL have included molecular phenotyping as part of eligibility criteria or subset analyses. These studies have typically required central pathology review before enrollment or treatment, with some trials requiring additional research biopsy procedures before enrollment. Several therapy combinations showing promise in nonrandomized studies largely failed to demonstrate improvement over the control arm in randomized studies.[9-12] Moreover, better-than-expected outcomes on the control (standard therapy) arm were observed despite attempts to limit inclusion to patients with high-risk disease as defined by available clinical and biologic prognostic factors.[10,13]

To evaluate the potential influence of the timing of initiation of therapy on outcome, we have examined the effect of diagnosis-to-treatment interval (DTI) in DLBCL in two large, independent, prospectively enrolled cohorts of patients: (1) the University of Iowa/Mayo Clinic Specialized Program of Research Excellence (SPORE) Molecular Epidemiology Resource (MER), and (2) patients enrolled in the LNH-2003 clinical trials program from the Lymphoma Study Association (LYSA) group.

PATIENTS AND METHODS

Discovery Cohort

This study was reviewed and approved by the human subjects institutional review boards at the Mayo Clinic and the University of Iowa, and written informed consent was obtained from all participants. Details on the cohort have been previously reported.[6,14,15] Briefly, adult patients with newly diagnosed DLBCL without prior lymphoma history were prospectively enrolled in the MER from 2002 to 2013. All patients were within 9 months of initial diagnosis at the time of enrollment. All diagnoses were confirmed by a study hematopathologist. Cell-of-origin (COO) determination (GCB *v* non-GCB) was performed in accordance with Hans algorithm.[16] All patients in this analysis received anthracycline-based immunochemotherapy (IC); patients with primary CNS lymphoma, posttransplant lymphoproliferative disorders, and primary mediastinal B-cell lymphoma were excluded. Baseline clinical, laboratory, and treatment data were abstracted from medical records by using a standard protocol. Patients were systematically contacted every 6 months for the first 3 years and annually after 3 years; treatments, progression, and deaths were validated by medical record review. The date of diagnosis was defined as the biopsy date from the first biopsy specimen containing lymphoma; this includes biopsy specimens in which the subtype was unable to be determined and later biopsy specimens were needed to determine the subtype, as well as biopsies performed at an outside institution.

Validation Cohort

A validation cohort was assembled from patients enrolled in the LYSA LNH03 clinical trial series.[17-21] The LNH2003B program of the LYSA consisted of six prospective, multicenter studies of patients with DLBCL who were older than 18 years. Patients were stratified by age and age-adjusted International Prognosis Index (IPI) for treatment allocation in four randomized phase III and two phase II studies. All patients were included in initial intent-to-treat analysis; sensitivity analysis was performed on data from patients with central pathology–confirmed DLBCL. During the first 2 years after treatment, assessment consisted of physical examination and laboratory tests every 3 months and computed tomography scans of the chest, abdomen, and pelvis every 6 months. Thereafter, physical examination and laboratory tests were done every 6 months and computed tomography scans every year for 5 years.

DTI was defined as the number of days from date of diagnosis to the initiation of IC therapy. Event-free survival (EFS) was defined as time from the start of IC therapy to progression or relapse; initiation of new, unplanned lymphoma therapy for efficacy purposes; or death (any cause). The primary outcome analysis used the DLBCL-specific end point of event-free survival at 24 months (EFS24), which was defined using the EFS status at 24 months from initiation of treatment.[6,22] Loess curves were used to identify the nature of the association between DTI and EFS24. Strength of associations between clinical outcomes and DTI were assessed using χ^2 and Wilcoxon rank-sum tests. Associations with EFS24 were assessed using logistic regression, with case weights for patients censored for EFS before 24 months. Two-sided *P* values were used for all tests. Additional details on the statistical analysis approach can be found in the Appendix, Statistical Methods.

RESULTS

MER Cohort (Discovery)

A total of 986 patients with DLBCL treated with IC and available DTI were enrolled in the MER from 2002 to 2012. Median age at diagnosis was 63 years (range, 18 to 92 years) and 57% were men. Most patients (65%) had advanced-stage disease. Full patient characteristics are listed in Table 1. At a median follow-up of 84 months (by reverse Kaplan-Meier analysis), 451 patients (46%) had an event and 340 patients (34%) had died; the EFS24 failure rate by Kaplan-Meier analysis was 31%(95% CI, 28% to 34%). The median (range) time from diagnosis to treatment initiation was 15 days (range, 0 to 155 days; Fig 1A).

Shorter DTI was strongly associated with adverse prognostic factors at initial diagnosis (Table 2; Appendix Table A1, online only). Compared with patients who initiated treatment ≥ 15 days after diagnosis, patients initiating treatment within 14 days had higher lactate dehydrogenase (LDH) levels (elevated LDH levels, 68% *v* 42%; $P < .001$), advanced-stage disease (stage III-IV, 74% *v* 56%; $P < .001$), worse Eastern Cooperative Oncology Group performance status (ECOG PS ≥ 2, 28% *v* 10%; $P < .001$), more frequent B symptoms(33% *v* 18%; $P < .001$), more bulky (ie, ≥ 10 cm) disease (14% *v* 8%; $P = .0030$), and worse age-adjusted IPI (aaIPI 2-3, 58% *v* 33%; $P < .001$). Associations were weaker between DTI and sex (Wilcoxon $P = .026$) and age (Wilcoxon $P = .077$; Table 2; Appendix Table A1).

Examining the functional form showed an approximately linear association of increasing DTI and achieving EFS24 (Fig 2), and DTI was thus analyzed as a linear variable in models for EFS24. DTI was strongly associated with EFS24 in unadjusted (per-week odds ratio [OR], 0.77 [95% CI, 0.71 to 0.84]; $P < .001$) and

Table 1. Patient Characteristics

Characteristic	MER (n = 986) No. (%)	LYSA (n = 1,444) No. (%)	All (N = 2,430) No. (%)
Age > 60 years	564 (57)	740 (51)	1,304 (54)
Male sex	560 (57)	784 (54)	1,344 (55)
LDH > ULN	483 (54)	871 (60)	1,354 (58)
Stage III/IV *v* I/II	636 (65)	1,050 (73)	1,686 (69)
ECOG PS ≥ 2	176 (18)	247 (17)	423 (17)
At least two extranodal sites	208 (21)	571 (40)	779 (32)
IPI			
0-2	610 (62)	765 (53)	1,375 (57)
3-5	376 (38)	678 (47)	1,054 (43)
aaIPI			
0-1	551 (56)	756 (52)	1,307 (54)
2-3	435 (44)	687 (48)	1,122 (46)
B symptoms	245 (25)	505 (35)	750 (31)
Bulky disease (≥ 10 cm)	106 (11)	300 (21)	406 (17)
GCB (Hans algorithm)	372 (64)	132 (47)	504 (58)
Treated while in clinical trial	89 (9)	1,446 (100)	1,535 (63)
ALC < 1,000	272 (35)	557 (39)	829 (38)
Distance (miles) from MER center			
0-50	239 (24)	NA	NA
50-100	300 (30)		
100-250	246 (25)		
> 250	201 (20)		

Abbreviations: aaIPI, age-adjusted International Prognostic Index; ALC, absolute lymphocytic count; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LYSA, Lymphoma Study Association; MER, Molecular Epidemiology Resource; NA, not applicable; ULN, upper limit of normal.

IPI-adjusted models (per-week OR, 0.83 [95% CI, 0.76 to 0.91; $P < .001$; Table 3). Kaplan-Meier EFS curves grouped by week of DTI are shown in Figure 3 and results from Cox models examining the association between continuous DTI and continuous EFS are shown in the Appendix Table A5.

We closely examined the MER data to assess if referral bias may explain MER results. There was no evidence of a strong association between the distance from a patient's residence to their enrolling MER location with either DTI (Spearman correlation = 0.053; $P = .093$) or EFS24 ($P = .61$). Primary results were also consistent when stratified by patients who enrolled in MER before initiating therapy (56%) versus patients who enrolled after initiation of therapy (44%; results not shown).

LYSA Cohort (Validation)

A total of 1,446 patients were enrolled in the LYSA 2003 program from 2003 to 2009; DTI data were available for 1,444. Median age at diagnosis was 61 years (range, 17 to 95 years) and 54%

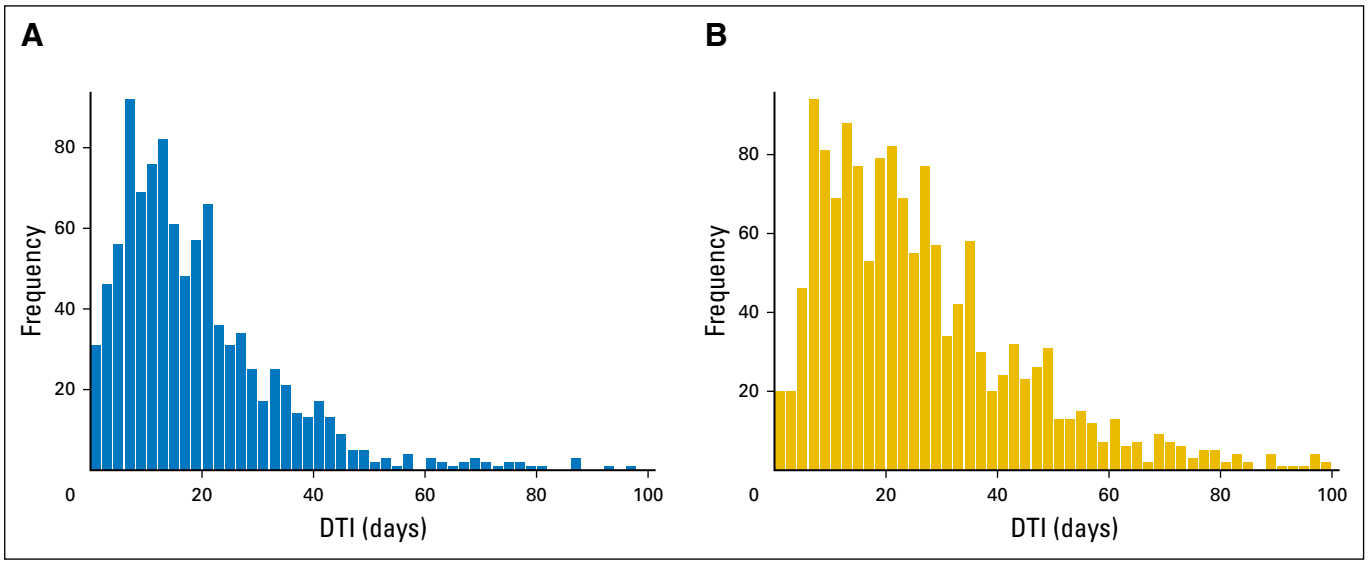

Fig 1. Distributions of DTI by cohort. (A) Data for three patients with DTI > 100 days not shown. (B) Data for 13 patients with DTI not shown. DTI, diagnosis-to-treatment interval.

Table 2. Patient Characteristics by Diagnosis-to-Treatment Interval ≤ 14 days

	MER (n = 986)			LYSA (n = 1,444)		
Variable	Initiated Therapy 0-14 Days From Diagnosis (n = 452) No. (%)	Initiated Therapy ≥ 15 Days From Diagnosis (n = 534) No. (%)	*P*	Initiated Therapy 0-14 Days From Diagnosis (n = 418) No. (%)	Initiated Therapy ≥ 15 Days From Diagnosis (n = 1,026) No. (%)	*P*
Age > 60 years	242 (54)	322 (60)	.033	207 (50)	533 (52)	.40
Male sex	267 (59)	293 (55)	.11	210 (50)	574 (56)	.048
LDH > ULN	279 (69)	204 (42)	< .0001	329 (79)	542 (53)	< .0001
Stage III/IV *v* I/II	335 (74)	301 (56)	< .0001	319 (76)	731 (71)	.050
ECOG PS ≥ 2	125 (28)	51 (10)	< .0001	113 (27)	134 (13)	< .0001
≥ 2 Extranodal sites	123 (27)	85 (16)	.0001	196 (47)	375 (37)	.0003
IPI						
0-2	228 (50)	382 (72)	< .0001	174 (42)	591 (58)	< .0001
3-5	224 (50)	152 (28)		243 (58)	435 (42)	
aaIPI						
0-1	191 (42)	360 (67)	< .0001	153 (37)	603 (59)	< .0001
2-3	263 (58)	174 (33)		264 (63)	423 (41)	
B symptoms	147 (33)	98 (18)	< .0001	198 (47)	307 (30)	< .0001
Bulky disease (≥ 10 cm)	63 (14)	43 (8)	.0030	124 (30)	176 (17)	< .0001
GCB (Hans algorithm)	149 (58)	223 (68)	.013	31 (45)	101 (47)	.74
Treated while in clinical trial	48 (11)	41 (8)	.11	420 (100)	1026 (100)	1
ALC < 1,000	152 (42)	120 (29)	.0002	206 (50)	351 (35)	< .0001
Patient residence distance (miles) from MER center			.99	NA	NA	
0-50	111 (25)	128 (24)				
50-100	139 (31)	161 (30)				
100-250	111 (25)	135 (25)				
> 250	91 (20)	110 (21)				

Abbreviations: aaIPI, age-adjusted International Prognostic Index; ALC, absolute lymphocytic count; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LYSA, Lymphoma Study Association; MER, Molecular Epidemiology Resource; NA, not applicable; ULN, upper limit of normal.

were men. Most patients (73%) had advanced-stage disease. Full patient characteristics are listed in Table 1. At a median follow-up of 41 months (by reverse Kaplan-Meier analysis), 551 patients (38%) had an event and 352 patients (24%) had died; the EFS24 failure rate by Kaplan-Meier analysis was 34% (95% CI, 31% to 36%). The median (range) time from diagnosis to treatment was 23 days (range, 0 to 215 days), and 418 patients (29%) initiated treatment within 14 days of diagnosis (Fig 1B).

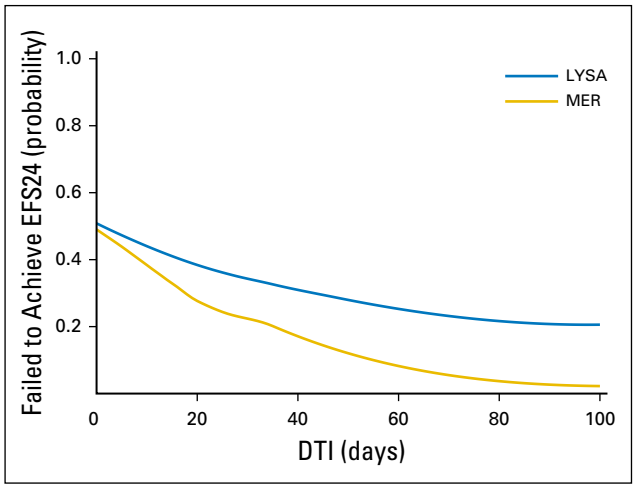

Fig 2. Functional form of DTI versus EFS24. DTI, diagnosis-to-treatment interval; EFS24, event-free survival at 24 months; LYSA, Lymphoma Study Association; MER, Molecular Epidemiology Resource.

Similar to the MER, shorter DTI was associated with poor prognostic factors (Table 2; Appendix Table A1). Patients initiating treatment within 14 days had higher LDH levels (elevated LDH levels, 79% *v* 53%; $P < .001$), worse ECOG PS (ECOG PS≥ 2, 27% *v* 13%; $P < .001$), more frequent B symptoms(47% *v* 30%; $P < .001$), more bulky disease (30% *v* 17%; $P < .001$), and worse aaIPI (aaIPI 2-3, 63% *v* 47%; $P < .001$). The association was weaker between DTI and advanced-stage disease (stage III-IV, 76% *v* 71%; $P = .050$) and between DTI and sex (Wilcoxon $P = .089$); there was no evidence of significant association between DTI and age (Wilcoxon $P = .14$). Results were consistent in the subset of patients with central pathology confirmed DLBCL (Appendix Table A4).

DTI was also strongly associated with outcome in the LYSA cohort. The functional form analysis confirmed a linear association of improving EFS24 with longer DTI (Fig 2). Longer DTI was associated with improved EFS24 in unadjusted (per-week OR, 0.88 [95% CI, 0.84 to 0.92]; $P < .001$) and IPI-adjusted models (per-week OR, 0.93 [95% CI, 0.88 to 0.98]; $P = .0050$). The association was slightly stronger in the subset of patients (n = 1,222) with central pathology–confirmed DLBCL (IPI-adjusted OR, 0.92 [95% CI, 0.86 to 0.987], $P = .0023$; Appendix Table A2). Kaplan-Meier EFS curves grouped by per-week DTI are shown in Figure 3 and results from Cox models examining association between continuous DTI and continuous EFS are reported in Appendix Table A5.

Table 3. Logistic Regression Models of Continuous Diagnosis-to-Treatment Interval for Event-Free Survival at 24 Months

Model	Cohort	Subset	No.	Adjustment	DTI OR	95% CI	*P*
1	MER	All	986	None	0.77	0.71 to 0.84	< .0001
2	MER	All	986	IPI	0.83	0.76 to 0.91	< .0001
3	LYSA	All	1,444	None	0.88	0.84 to 0.92	< .0001
4	LYSA	All	1,443	IPI	0.93	0.88 to 0.98	.0050
5	Combined	IPI 0-2	1,375	Cohort	0.88	0.82 to 0.93	< .0001
6	Combined	IPI 3-5	1,054	Cohort	0.89	0.84 to 0.95	.0003
7	GCB	GCB (Hans algorithm)	504	Cohort	0.79	0.71 to 0.86	< .0001
8	Non-GCB	non-GCB (Hans algorithm)	362	Cohort	0.82	0.73 to 0.92	.0009

NOTE. Continuous diagnosis-to-time interval modeled using time scale of 1 week (diagnosis-to-time interval in days); OR represents per-week change (reduction) in risk of failure to achieve event-free survival at 24 months.
Abbreviations: DTI, diagnosis-to-time interval; GCB, germinal center B cell; IPI, International Prognostic Index; LYSA, Lymphoma Study Association; MER, Molecular Epidemiology Resource; OR, odds ratio.

Subset and Sensitivity Analyses in Combined Cohort

To increase the sample size to assess DTI in specific patient subsets, we combined the MER and LYSA cohorts with analysis adjusted by cohort (MER *v* LYSA). The association between longer DTI and improved EFS24 was consistent in GCB (OR, 079 [95% CI, 0.71 to 0.86]; $P < .001$) and non-GCB (OR, 0.82 [95% CI, 0.73 to 0.92]; $P < .001$) COO subsets and remained significant when examined in low-risk (IPI 0-2: OR,0.88 [95% CI, 0.82 to 0.93]; $P < .001$), and high-risk (IPI 3-5: OR, 0.89 [95% CI, 0.84 to 0.95]; $P < .001$) patient subsets (Table 3), as well as when adjusting for individual IPI components in a multivariable model (OR, 0.93 [95% CI, 0.88 to 0.97], $P = .0014$; Appendix Tables A3 and A6).

DISCUSSION

In this study, we identified that the simple measure of the number of days between diagnosis and treatment initiation identifies patients with vastly different outcomes in newly diagnosed DLBCL. Patients who initiate therapy sooner have significantly worse outcomes compared with patients with longer time from diagnosis to initiation of treatment. This effect appears to be a function of disease aggressiveness: Shorter DTI was strongly associated with adverse disease–related prognostic factors, including elevated LDH level, poor performance status, symptomatic disease, and bulky disease. Importantly, however, the prognostic value of DTI was independent of the IPI. The effect between DTI and outcome appears to be continuous, which is important for translation to other datasets, because a typical DTI will likely vary based on regional clinical and pathology practices. This observation has important implications in any research efforts that may restrict patient participation based on time from diagnosis to treatment.

Strengths of the study include demonstration of these findings in two large, prospective cohorts, including a US clinic–based cohort and a European clinical trials cohort. Limitations include the lack of COO classification on the complete cohorts, though results were consistent in the subset with available data. Clinical parameters in the MER were captured as performed clinically under routine care; when multiple assessments were performed before the beginning treatment, the assessment closest to diagnosis was used. Thus, there may be changes in these clinical variables before the initiation of therapy; however, assessment of the effect of this variation is beyond the scope of the current study.

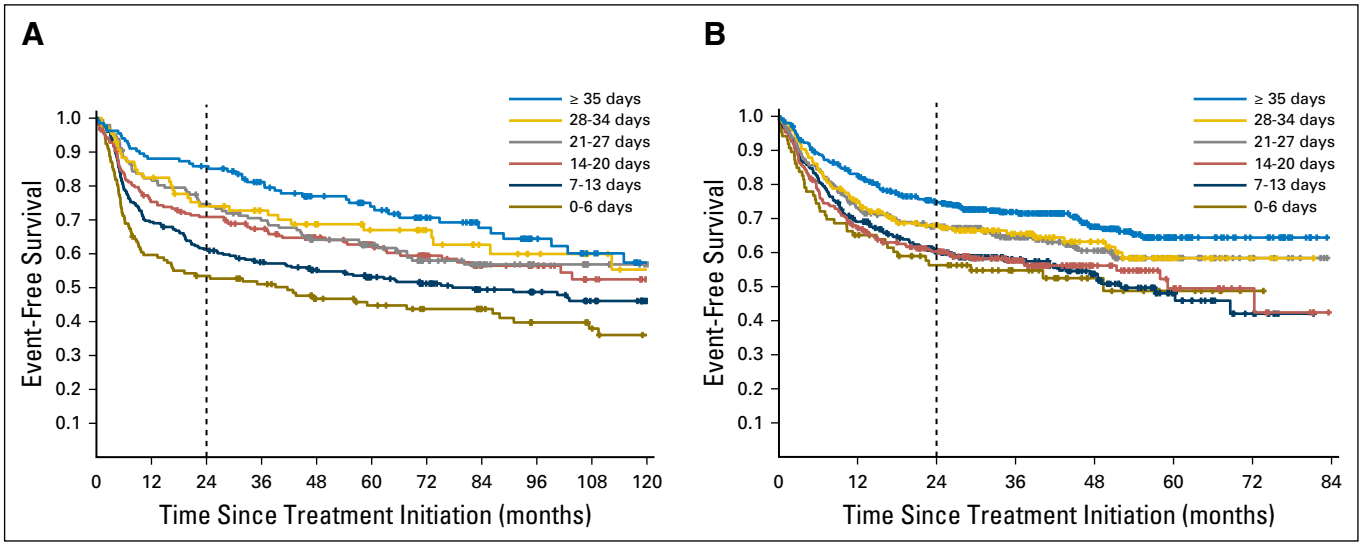

Fig 3. (A and B) Kaplan-Meier Curves of event-free survival by diagnosis-to-treatment interval grouped by week.

Patients enrolled in the MER are from two tertiary care centers in the upper midwestern United States.[15] All MER patients were seen at either the Mayo Clinic or University of Iowa within 9 months of initial diagnosis and some may have initiated treatment locally in the community. We did not see any association between the distance from a patient's residence to their enrolling MER center with either DTI or outcome; other demographic factors such as age and sex were not strongly associated with DTI. Results were also consistent in patients with pretherapy versus posttherapy MER consent. Two recent Canadian studies examined the timing of treatment in DLBCL, focusing on delay in therapy and potential detrimental effect.[23,24] Neither study found an association between socioeconomic status, income, or distance to treatment center with timing of therapy, but both identified variables related to more aggressive disease such as IPI, bone marrow involvement, and inpatient chemotherapy initiation, to be related to prevention of a treatment delay. In addition, patients with none to 1 week of treatment delay had the worst overall survival in the Toronto series,[23] whereas outcome was inferior for patients with DTI of no longer than 4 weeks in a series from the British Columbia Cancer Agency.[24] These findings further support DTI being a function of disease aggressiveness and not because of referral bias.

The association of DTI with clinical factors and outcomes were validated in an independent cohort of European patients. Patients in the LYSA cohort initiated therapy (median DTI, 23 days) later than the MER cohort (median DTI, 15 days), with only 29% of the LYSA cohort initiating therapy within 14 days. Associations between EFS24 and DTI in the LYSA cohort were also slightly weaker than in the MER, though they remained statistically significant and independent of the IPI. These differences are not unexpected, because all the LYSA patients were enrolled in the trial (ν 9% in MER), so presumably some patient selection was present and the LYSA cohort may underrepresent patients with clinically aggressive disease who needed urgent therapy. Validation of the association of DTI with outcome in such a cohort provides strong evidence that the observed associations in the MER are not a spurious finding. Furthermore, similar associations among DTI and prognostic factors and outcome have recently been reported[25] from the GOYA (GA101 for diffuse large B-cell lymphoma) trial.[9]

These findings have important consequences for design and interpretation of clinical trials in DLBCL. DTI must be taken into account when analyzing results of clinical trials or other efforts to compare otherwise similar cohorts. This is especially of concern in single-arm studies where success rules are predicated on the basis of historical data; these data suggest the improvement in outcomes may be strictly due to a lengthier process to enroll the patient in the trial. DTI should be used to evaluate single-arm clinical trials to gauge potential selection bias and help inform validity of results when compared with historical data or other trials in the setting of newly diagnosed DLBCL. DTI can similarly be used to evaluate the control arm for randomized trials and provide inference when outcomes are better than expected. The observation that DTI has an independent association with outcome beyond established clinical and biologic prognostic factors suggests that current trial inclusion criteria are not sufficient for nonbiased patient selection. Efforts to include patients with clinically aggressive disease in need of urgent therapy are critically important to ensure a representative group of patients enrolled in the trial. Strategies for this may include streamlined enrollment procedures, rapid review of pathological material, or allowing bridging therapy before starting the trial.[26,27] Single-arm trials can consider determination of biomarker-based eligibility while patients are undergoing the first cycle of experimental treatment, with ineligible patients receiving subsequent therapy off trial if determined ineligible.[28] Multiarm trials could consider beginning all patients on standard-of-care therapy (eg, R-CHOP) while phenotyping is ongoing, and assigning study therapies after cycle 1. Researchers may also want to consider an upper limit on time from diagnosis as part of entry criteria.

Prognostic scores such as the IPI are designed to help stratify patients, with the goal of lessening bias in clinical trials and assisting clinicians in identifying the most appropriate treatment of a given patient based on results of prior studies. Our observation that DTI is a prognostic factor independent of IPI suggests clinicians can identify patient factors that lead them to accelerate initiation of therapy that are, indeed, associated with a worse prognosis yet are not accounted for in standard prognostic tools. This supports ongoing efforts to continue to refine prognostic scales such as the IPI and demonstrates clinical judgement remains a vital factor in determining the right treatment of the right patient even in this era of personalized molecular medicine.

Our observations regarding importance of DTI in the newly diagnosed setting may also have importance in relapsed and refractory DLBCL, where the same principles may apply. The effect of the ability to delay therapy on response rate and outcome is unknown in the relapsed setting, but recent data from the MER[29] and the SCHOLAR-1 study[30] suggest significant diversity in clinical outcomes in the relapsed setting. The observed associations among DTI, clinically aggressive disease, and outcomes at diagnosis are especially concerning for patient selection bias and, subsequently, optimistic response rates and outcomes in single-arm studies of novel agents that require therapy delays because of specimen testing and/or preparation of individualized therapy, as well as potential delays while patients await slots in the trial to open at their treatment location.

Our results for DLBCL are, in fact, broadly relevant in all malignancies as the regulatory, pathologic, and/or genetic requirements to enroll in a trial have become stricter, and more laborious and time consuming. The danger lies in patients who enroll in the trial who do not accurately represent the target patient population for the therapy. Many precision medicine trials are not randomized and there is concern of being too optimistic about single-arm trial results, because of patient selection for known and unknown factors. There is concern that exceptional outcomes in small, uncontrolled studies of targeted agents with biomarker-based testing are influenced by selection of patients healthy enough to remain in a holding pattern while waiting for trial testing; our results suggest that this selection may bias toward a more favorable clinical disease as well.

In conclusion we have identified that the time from diagnosis to treatment is an important factor in newly diagnosed DLBCL and is strongly associated with adverse clinical factors and poor outcome. DTI should be reported in all clinical trials of newly diagnosed DLBCL. Steps must be taken in clinical trials in newly diagnosed DLBCL to avoid selection bias due to treatment delay (Appendix Tables A4-A6.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported in part by National Cancer Institute Specialized Programs of Research Excellence in Human Cancer (Grants No. P50 CA97274 and U01 CA195568), and the Henry J. Predolin Foundation.

Prior Presentation

Presented in part at the 58th American Society of Hematology Annual Meeting, San Diego, CA, December 4, 2016; 59th American Society of Hematology Annual Meeting, Atlanta, GA, December 11, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Diagnosis-to-Treatment Interval Is an Important Clinical Factor in Newly Diagnosed Diffuse Large B-cell Lymphoma and Has Implication for Bias in Clinical Trials

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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No relationship to disclose

Brian K. Link
Consulting or Advisory Role: Roche, AbbVie, Gilead Sciences, Celgene
Research Funding: Roche (Inst)
Travel, Accommodations, Expenses: Roche, Celgene

Jean-Philippe Jais
No relationship to disclose

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Research Funding: Kite Pharma

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Patents, Royalties, Other Intellectual Property: Inventor of technology for which Mayo Clinic holds an unlicensed patent or has submitted a patent application (Inst)

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Consulting or Advisory Role: Sandoz, Checkmate Pharmaceuticals
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Research Funding: Bristol-Myers Squibb (Inst), Celldex (Inst), Seattle Genetics (Inst), Merck (Inst), Affimed Therapeutics (Inst), Trillium Therapeutics (Inst)

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Appendix

Statistical Methods

Diagnosis-to-treatment interval (DTI) was defined as the number of days from date of first lymphoma-containing biopsy specimen to the initiation of immunochemotherapy. Patient's residence distance from Molecular Epidemiology Resource location was defined using the zip code of patient residence and the enrolling center (Rochester, MN, or Iowa City, IA). Event-free survival (EFS) was defined as time from initiation of therapy to progression or relapse; initiation of new, unplanned lymphoma therapy; or death (any cause). The primary outcome analysis used the diffuse large B-cell lymphoma–specific end point of event-free survival at 24 months (EFS24), which was defined using the EFS status at 24 months from initiation of therapy.[6,22] Patients with $<$ 24 months of follow-up were included, using case weights based on probability of achieving EFS24, as previously described (Maurer MJ, et al: Am J Hematol 91:179-184, 2016). Association of continuous DTI with clinical factors was assessed using Wilcoxon rank-sum and Spearman correlation; clinical factors were also assessed using the median split (0 to 14 days) of DTI from the discovery dataset via χ^2 and Wilcoxon rank-sum tests. Associations between DTI and EFS24 were assessed using logistic regression models with case weights for patients censored for EFS before 24 months. The functional form of association between continuous DTI with EFS24 was assessed using loess curves (Cleveland: J Am Stat Assoc 74:829-836) and a linear fit through 60 days from diagnosis was used for modeling DTI with EFS24. DTI was grouped by week from enrollment for Kaplan-Meier analyses of continuous EFS and Cox proportional hazards models were used to assess associations between DTI and continuous EFS. Validation of Molecular Epidemiology Resource results was performed in the Lymphoma Study Association (LYSA) cohort using all patients enrolled on the LYSA trials as an intent-to-treat approach. Sensitivity analyses were performed on the data from the subset of patients in the LYSA cohort who had diffuse large B-cell lymphoma on central pathology review. Two-sided *P* values were used for all tests. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC) and R, version 3.3.1 (https://www.r-project.org/).

Table A1. Association of Patient Characteristics With Continuous DTI

Group	Patient Characteristic	No. of Patients	DTI Median	DTI IQR	Wilcoxon *P*
MER	Stage I-II	349	20	12-23	< .0001
MER	Stage III-IV	636	14	8-23	
LYSA	Stage I-II	394	25	14-40	.0028
LYSA	Stage III-IV	1,050	22	13-35	
MER	No B symptoms	741	17	11-28	< .0001
MER	B symptoms	245	12	7-20	
LYSA	No B symptoms	939	27	15-42	< .0001
LYSA	B symptoms	505	18	11-27	
MER	No bulky disease	880	17	9-27	< .0001
MER	Bulky disease	106	12	7-17	
LYSA	No bulky disease	1,114	25	14-38	< .0001
LYSA	Bulky disease	300	17	10-27	
MER	ECOG PS 0-1	808	18	11-28	< .0001
MER	ECOG PS 2-4	176	10	6-16	
LYSA	ECOG PS 0-1	1,196	25	14-38	< .0001
LYSA	ECOG PS 2-4	247	15	9-25	
MER	LDH < ULN	410	20	13-31	< .0001
MER	LDH > ULN	483	12	7-21	
LYSA	LDH < ULN	573	30	20-46	< .0001
LYSA	LDH > ULN	871	19	11-29	
MER	Female	426	17	9-26	.026
MER	Male	560	15	9-25	
LYSA	Female	660	22	13-35	.089
LYSA	Male	784	24	14-37	
MER	0-1 Extranodal sites	778	17	10-27	.0009
MER	> 1 Extranodal sites	208	13	8-21	
LYSA	0-1 Extranodal sites	873	25	14-39	< .0001
LYSA	> 1 Extranodal sites	571	21	11-32	
MER	Age, years	986	0.056*		0.077
LYSA	Age, years	1,444	0.038*		0.14
MER	ALC	782	0.19*		< .0001
LYSA	ALC	1,427	0.24*		< .0001
MER	Normalized LDH	893	−0.35*		< .0001
LYSA	Normalized LDH	1,443	−0.37*		< .0001
MER	Distance (miles) from MER center	986	0.053*		0.093

Abbreviations: ALC, absolute lymphocytic count; DTI, diagnosis-to-treatment interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; LDH, lactate dehydrogenase; LYSA, Lymphoma Study Association; MER, Molecular Epidemiology Resource; ULN, upper limit of normal.
*Spearman Correlation with DTI.

Table A2. LYSA Sensitivity Analysis of DTI With Event-Free Survival at 24 Months in Patients With Central Pathology–Confirmed DLBCL

Adjustment	Subset	No. of Patients	OR	95% CI	*P*
None	LYSA ITT	1,444	0.88	0.84 to 0.92	<.0001
None	LYSA (DLBCL)	1,222	0.87	0.82 to 0.92	<.0001
IPI	LYSA ITT	1,443	0.93	0.88 to 0.98	.0050
IPI	LYSA (DLBCL)	1,222	0.92	0.86 to 0.97	.0023

Abbreviations: DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; ITT, intent to treat; LYSA, Lymphoma Study Association; OR, odds ratio.

Table A3. Multivariable Logistic Regression Model of DTI With Event-Free Survival at 24 Months Adjusted by Individual IPI Components

Variable	OR	95% CI	*P*
MER	0.81	0.66 to 0.99	.037
DTI (per week)	0.93	0.88 to 0.97	.0014
Stage III/IV	1.86	1.47 to 2.36	< .0001
ECOG PS ≥ 2	2.10	1.66 to 2.65	< .0001
At least two extranodal sites	1.06	0.86 to 1.31	.61
LDH > ULN	1.90	1.55 to 2.33	< .0001
Age > 60 years	1.45	1.20 to 1.75	.0001

Abbreviations: DTI, diagnosis-to-treatment interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MER, Molecular Epidemiology Resource; OR, odds ratio; ULN, upper limit of normal.

Table A4. LYSA Sensitivity Analysis of DTI With Clinical Characteristics in Patients With Central Pathology–Confirmed DLBCL

	Initiated Therapy 0-14 Days From Diagnosis (n = 420)	Initiated Therapy ≥ 15 Days From Diagnosis (n = 1,026)	
Variable	No. (%)	No. (%)	*P*
Age > 60 years	176 (49)	454 (52)	.34
Male sex	182 (51)	476 (55)	.22
LDH > ULN	287 (81)	466 (54)	< .0001
Stage III/IV *v* I/II	267 (75)	613 (71)	.13
ECOG PS ≥ 2	96 (27)	122 (14)	< .0001
At least two extranodal sites	160 (45)	322 (37)	.012
IPI			
0-2	147 (41)	491 (57)	< .0001
3-5	209 (59)	375 (43)	
aaIPI			
0-1	129 (36)	499 (58)	< .0001
2-3	227 (64)	367 (42)	
B symptoms	166 (47)	257 (30)	< .0001
Bulky disease (≥ 10 cm)	105 (29)	144 (17)	< .0001
GCB (Hans algorithm)	31 (45)	101 (47)	.74
ALC < 1,000	174 (49)	298 (35)	< .0001

Abbreviations: aaIPI, age-adjusted International Prognostic Index; ALC, absolute lymphocytic count; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase; LYSA, Lymphoma Study Association; ULN, upper limit of normal.

Table A5. Cox Models of Continuous DTI with Event-Free Survival

Adjustment	Cohort	Subset	No. of Patients	HR	95% CI	*P*
None	MER	All	986	0.88	0.84 to 0.93	< .0001
IPI	MER	All	986	0.94	0.89 to 0.99	.017
None	LYSA	All	1,444	0.90	0.87 to 0.94	< .0001
IPI	LYSA	All	1,443	0.94	0.91 to 0.98	.0039
Cohort	Combined	IPI 0-2	1,375	0.92	0.88 to 0.94	.0004
Cohort	Combined	IPI 3-5	1,054	0.93	0.89 to 0.67	.0006
Cohort	GCB	GCB (Hans algorithm)	504	0.87	0.80 to 0.94	.0006
Cohort	Non-GCB	non-GCB (Hans algorithm)	362	0.89	0.82 to 0.97	.0063

Abbreviations: GCB, germinal center B cell; HR, hazard ratio; IPI, International Prognostic Index; LYSA, Lymphoma Study Association; MER, Molecular Epidemiology Resource; OR, odds ratio.

Table A6. Multivariable Cox Proportional Hazards Regression Model of DTI With Event-Free Survival at 24 Months from Treatment Initiation, Adjusted by Individual IPI Components

Variable	HR	95% CI	*P*
MER	Strata		
DTI (per week)	0.95	0.92 to 0.99	.0072
Stage III/IV	1.52	1.28 to 1.80	< .0001
ECOG PS ≥ 2	1.72	1.49 to 2.03	< .0001
At least two extranodal sites	1.08	0.93 to 1.24	.32
LDH > ULN	1.49	1.29 to 1.73	< .0001
Age > 60 years	1.49	1.30 to 1.71	< .0001

Abbreviations: DTI, diagnosis-to-treatment interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; MER, Molecular Epidemiology Resource; OR, odds ratio; ULN, upper limit of normal.