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ORIGINAL ARTICLE

Progression-free survival at 24 months (PFS24) and subsequent outcome for patients with diffuse large B-cell lymphoma (DLBCL) enrolled on randomized clinical trials

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Background: Patients with diffuse large B-cell lymphoma treated with first-line anthracycline-based immunochemotherapy and remaining in remission at 2 years have excellent outcomes. This study assessed overall survival (OS) stratified by progression-free survival (PFS) at 24 months (PFS24) using individual patient data from patients with DLBCL enrolled in multicenter, international randomized clinical trials as part of the Surrogate Endpoint for Aggressive Lymphoma (SEAL) Collaboration.

Patients and methods: PFS24 was defined as being alive and PFS24 after study entry. OS from PFS24 was defined as time from identified PFS24 status until death due to any cause. OS was compared with each patient's age-, sex-, and country-matched general population using expected survival and standardized mortality ratios (SMRs).

Results: A total of 5853 patients enrolled in trials in the SEAL database received rituximab as part of induction therapy and were included in this analysis. The median age was 62 years (range 18–92), and 56% were greater than 60 years of age. At a median follow-up of 4.4 years, 1337 patients (23%) had disease progression, 1489 (25%) had died, and 5101 had sufficient follow-up to evaluate PFS24. A total of 1423 assessable patients failed to achieve PFS24 with a median OS of 7.2 months (95% CI 6.8–8.1) after progression; 5-year OS after progression was 19% and SMR was 32.1 (95% CI 30.0–34.4). A total of 3678 patients achieved PFS24; SMR after achieving PFS24 was 1.22 (95% CI 1.09–1.37). The observed OS versus expected OS at 3, 5, and 7 years after achieving PFS24 was 93.1% versus 94.4%, 87.6% versus 89.5%, and 80.0% versus 83.7%, respectively.

Conclusion: Patients treated with rituximab containing anthracycline-based immunochemotherapy on clinical trials who are alive without progression at 24 months from the onset of initial therapy have excellent outcomes with survival that is marginally lower but clinically indistinguishable from the age-, sex-, and country-matched background population for 7 years after achieving PFS24.

Key words: DLBCL, prognosis, survival, PFS24

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma in the USA [1] and Europe [2]. Outcomes have improved with the introduction of immunochemotherapy for DLBCL [3–5] with the majority of patients being cured by front-line therapy. Patients with DLBCL who receive first-line anthracycline-based immunochemotherapy who have not had an event (relapse, re-treatment, or death), at 24 months from diagnosis (EFS24) have excellent outcomes with an overall survival (OS) that is similar to the age- and sex-matched general populations in patient cohorts from observational studies from the USA, France, and Denmark [6, 7].

There is a need for early end points to assess approaches from randomized clinical trials that would not necessitate waiting for OS results in newly diagnosed DLBCL. The Surrogate Endpoint for Aggressive Lymphoma (SEAL) group was assembled to compile a large meta-database as previously described [8]. Progression-free survival (PFS) in patients who had defined evaluation and scan point may offer a more accurate assessment of the time of relapse compared with registry or population-based cohorts. To evaluate the robustness and generalizability of a 24-month end point in the clinical trial setting, this study assessed OS stratified by PFS at 24 months (PFS24) using individual patient data from patients with newly diagnosed DLBCL enrolled in 14 different multi-center, international randomized clinical trials.

Patients and methods

SEAL is an international collaboration of hematologists, oncologists, hematopathologists, statisticians, and scientists. Clinical trials and data in the SEAL database as of 15 July 2016 were utilized for the study [3–5, 9–18]. Individual patient data were pooled as previously described [8]. Central data alignment was carried out by the SEAL statistics and data center at Mayo Clinic Rochester. All patients who were treated with rituximab-containing, anthracycline-based immunochemotherapy as part of initial induction therapy on the trial were included in this analysis. This study was approved by the Institutional Review Board at the Mayo Clinic; research was conducted in accordance with the Declaration of Helsinki.

PFS was defined as the time from study entry to the earliest occurrence of progressive disease, relapse, or death. PFS24 was a binary end point defined as being alive and progression free 24 months (731 days) after initiation of therapy. In patients with progression within 24 months from initiation of therapy (fail to achieve PFS24), OS from PFS24 was defined as time from progression to death from any causes. In patients who were alive and progression free 24 months after initiation of therapy (achieve PFS24), OS from PFS24 was defined as time from achieving PFS24 to death from any cause. Living patients were censored on the date when they were last documented as alive. The OS and PFS24 were derived according to consistent calculation rules across studies. Standardized mortality ratio (SMR) was defined as the ratio of observed deaths to expected deaths in the general population. OS was compared with the age-, sex-, and country-matched general population via SMR and expected survival using a conditional approach [19] via the survexp function in R (package survival), modified to allow country of origin as an additional matching feature in a multinational dataset. Population rate tables for countries were obtained via www.mortality.org where available. A per-study average rate table was used when an individual patient's country of residence was unavailable. OS beyond 9 years from treatment initiation was only available at the time of analysis for two trials (13% of the cohort); therefore, follow-up from PFS24 was restricted to the first 7 years after PFS24. Analyses were carried out by using SAS version 9.4 (SAS Institute, Inc.) and Rv3.3.1.

Results

From 7975 patients, 5835 (73%) in the SEAL database received rituximab and anthracycline-based immunochemotherapy as part of induction therapy on the trial and were included in this analysis (Table 1). The median age was 62 years (range 18–92), 56% were greater than 60 years of age, 57% were male, 57% had an elevated LDH, 63% had stage III/IV disease, and 13% had an Eastern Cooperative Oncology Group performance status of 2–4. The International Prognostic Index (IPI) was 0–1 in 36%, 2 in 25%, 3 in 23%, and 4–5 in 16%.

At a median follow-up of 4.4 years, 1337 (23%) of patients had disease progression, 1489 patients died; the Kaplan–Meier estimate for achieving PFS24 for the entire cohort of 5835 patient was 73% (95% CI 72% to 74%) and the SMR from diagnosis was 2.42 (95% CI 2.30–2.55). Totally, 5101 patients had sufficient follow-up to be assessable for PFS24; 1423 of assessable patients (28%) did not achieve PFS24 (Figure 1A) with a median OS of 7.2 months (95% CI 6.8–8.1) after progression. The 5-year OS from progression was 19% and the SMR comparing outcomes to expected survival for the age-, sex-, and country-matched general population was 32.1 (95% CI 30.0–34.4). A total of 3678 patients were progression-free at 24 months (achieved PFS24). The subsequent OS after achieving PFS24 approached the age- and sex-matched general population (Figure 1B) with observed versus expected OS at 3, 5, and 7 years of 93.1% versus 94.4%, 87.6% versus 89.5%, and 80.0% versus 83.7%, respectively (Table 2). The SMR after achieving PFS24 was 1.22 (95% CI 1.09–1.37). Higher IPI at diagnosis was associated with greater discrepancies between observed and expected survival (Table 2).

Discussion

In this large series of patients on randomized clinical trials, the PFS24 from the start of initial induction therapy stratifies DLBCL patients treated with the international standard of care, rituximab-containing anthracycline-based immunochemotherapy into populations with distinct outcomes. DLBCL patients who are alive without progression at 24 months from the onset of initial therapy have excellent survival. The OS for this group was marginally lower than, but clinically indistinguishable from the age-, sex-, and country-matched background population for at least 5 to 7 years after achieving PFS24. Survival without an event at this timepoint provides clinicians, patients, and caregivers with a clear benchmark for evaluating the success of initial treatment in the modern era.

The strengths of this study include the large numbers of patients treated prospectively on protocol who were followed at protocol defined time intervals and evaluation criteria to prospectively document progression. This is the largest series of patients with DLBCL studied in the immunochemotherapy era world-wide with prospectively collected data of treatment and outcomes at prespecified follow-up intervals and should have excellent generalizability. Combining data from multiple randomized controlled clinical trials added substantial increases in

Table 1. Patient's characteristics

Variable	N	%
Sex		
Male	3148	46
Female	2705	54
Age (years)		
≤60	2587	44
>60	3256	56
ECOG Performance Status		
0–1	5079	87
2–4	763	13
Ann Arbor Stage		
I–II	2164	37
III–IV	3656	63
Number of extranodal sites		
≤1	3660	72
≥2	1395	28
LDH		
Not elevated	2490	43
Elevated	3303	57
IPI		
0–1	1788	36
2	1280	25
3	1149	23
4–5	809	16
Clinical trial		
ANZINTER3	224	4
ECOG 4494	318	5
LNH031B	110	2
LNH032B	380	6
LNH036B	602	10
LNH985	202	3
MAIN	787	13
MEGACHOEP	262	4
MINT	413	7
NHL13	741	13
PIX203	124	2
RICOVER60	610	10
UCL	1080	18
Country of residence		
Austria	207	4
Belgium	157	3
Czech Republic	74	1
France	1144	20
Germany	861	15
Italy	235	4
UK	1080	18
United States	391	7
Other	504	9
Unknown	1200	21

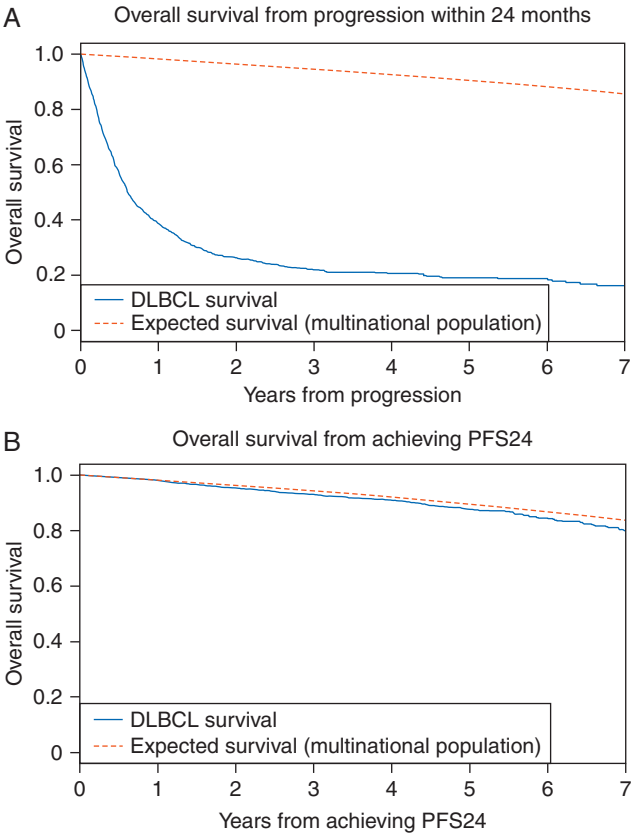

Figure 1. (A) OS from progression of the 1423 patients who failed to achieve PFS24 versus the expected survival from age-, sex-, and country-matched general population data. (B) OS from PFS24 of the 3678 SEAL patients who were progression free at 24 months after initiating treatment versus expected survival from age-, sex-, and country-matched general population data.

sample size and statistical power. The limitations of this analysis include the following. There is an under-representation of patients older than 85 years of age. Outcomes for older individuals with DLBCL have been previously assessed using registry data linked to a claims database [20]. In this analysis, there was a lack of long-term follow-up >10 years and only two trials, 13% of the cohort, had OS data beyond 9 years. The patients included in these studies may not reflect the general population of DLBCL since they needed to qualify for the study and there may have been a time to treatment bias [21]. Patients with significant end-organ disease, central nervous system disease, HIV, and other contraindications to clinical trials would not have been included in this analysis. The impact of management was not assessed after relapse, which is beyond the scope of this dataset, and such information is not routinely collected in clinical trials. Finally, analysis was carried out using the PFS definition from the individual clinical trials. EFS, where change in therapy was considered an event, was only available on a small subset of trials in the SEAL database at the time of this study. The evaluation of EFS24 versus PFS24 for patients being treated on trials may be explored in a future study as more EFS data becomes available in the SEAL database.

These data confirm other recently published data in newly diagnosed DLBCL. In a cohort of 767 patients from the USA with a median follow-up of 60 months, the SMR after achieving EFS24 (freedom from progression, second therapy, or death) was 1.18 (0.89–1.57) [6]. In the same publication, a Lyon/Groupe d'Etude des Lymphomes de l'Adulte (GELA) cohort of 820 patients with a median follow-up of 42 months had an SMR after achieving EFS24 of 1.09 (0.69–1.74). In a Danish population-based cohort of 1621 patients with a median follow-up of 85 months, those

Table 2. Observed versus expected survival in at 3, 5, and 7 years after achieving PFS24

Subset	*N*	3 years from PFS24			5 years from PFS24			7 years from PFS24		
		N at risk	% alive	% expected per population	*N* at risk	% alive	% expected per population	*N* at risk	% alive	% expected per population
All	3678	1617	93.1	94.4	753	87.6	89.5	269	80.0	83.7
Age <60	1597	492	97.7	98.5	195	96.7	97.5	46	96.7	95.9
Age ≥60	2080	1125	90.3	91.9	558	83.4	85.9	223	74.4	79.1
Male	1948	836	92.8	93.4	387	86.1	87.7	123	77.8	81.2
Female	1730	780	93.4	95.5	366	89.3	91.5	146	82.2	86.3
Stage I/II	1528	678	94.3	94.8	309	88.8	90.1	94	83.1	84.5
Stage III/IV	2137	935	92.2	94.1	443	86.7	89.1	175	78.1	83.1
LDH<ULN	1723	771	94.2	94.3	362	89.6	89.2	123	81.5	83.1
LDH>ULN	1934	846	92.1	94.5	391	85.9	89.8	146	78.6	84.2
ECOG PS 0–1	3309	1432	93.4	94.5	662	88.4	89.8	235	81.3	84.1
ECOG PS 2–4	367	185	90.7	93.2	91	81.4	87.6	34	71.1	80.4
IPI 0–1	1297	533	96.5	96.3	228	93.9	92.7	53	89.5	88.3
IPI 2–3	1653	848	92.3	93.6	413	85.7	88.3	164	77.8	82.1
IPI 4–5	427	232	87.5	92.5	111	80.4	86.8	52	71.2	80.2

who achieved EFS24 from the completion of frontline immunochemotherapy had a subsequent SMR of 1.27 (1.12–1.44) [7]. Combined with our study, these results support a small but clinically insignificant reduction in survival for DLBCL survivors in the first 5–7 years after achieving EFS24 or PFS24. Additional follow-up is needed on these and other cohorts to evaluate longer outcomes and assess for impact of late relapses, quality of life and other factors that may negatively affect survivorship beyond the time periods that have been studied.

Our results and the findings of these corroborating studies have significant implications for lymphoma survivorship. Given that the vast majority of DLBCL events occur in the first 24 months, individuals treated with R-CHOP who survive to this time point without relapse are highly likely to experience a near normal life expectancy. Surveillance imaging with computed tomography has been demonstrated to be of limited value [22, 23]. Novel approach for surveillance assessment utilizing circulating tumor DNA are in development [22–25]. Our data suggest that studies evaluating novel surveillance strategies for disease relapse are likely to be of greatest benefit in the first 2 years following immunochemotherapy. Following achievement of PFS24, the critical research questions for DLBCL survivors should focus on quality of life, secondary malignancies, and other outcomes.

It is important to caution that extension of these results in the settings of relapsed DLBCL or maintenance after immunochemotherapy in DLBCL is not supported at this time. A number of randomized clinical trials have failed to show either a PFS or OS benefit for maintenance therapy after immunochemotherapy [5, 18, 26, 27] in DLBCL while a recent trial showing a benefit of PFS for maintenance after completion of immunochemotherapy failed to show an OS benefit [28]. It is important to note that both the pattern of treatment failure and overall prognosis in the maintenance setting are distinct from diagnosis. The rate of progression or relapse for newly diagnosed DLBCL is highest in the first 6 months after diagnosis, reduces slightly between 6 and 12 months, and then shows further decreases between 12 and 24 months and beyond 24 months [6]. In regard to prognosis, the SMR of patients in CR or CRu after immunochemotherapy was 1.75 in a recent Danish study [7] that was markedly lower than the SMR at diagnosis of 2.42 from our study and SMRs of 2.88 and 4.99 reported in USA and French patients at diagnosis [6]. In addition, there are limited data on the validity of PFS24 in the current relapsed and refractory setting in DLBCL. A recent study evaluated 1617 patients with relapsed DLBCL or Hodgkin lymphoma who were 2-year survivors after autologous hematopoietic transplant [29]. At a median follow-up of 10.6 years of the cohort, the 5-year OS was 89% and the SMR for relapsed DLBCL was 3.4 (95%: 2.9–4.1) compared with the age- and sex-matched general population. However, the marked clinical heterogeneity of outcomes in patients with relapsed DLBCL [30] make adaptation of PFS24 challenging in the broader relapsed setting. Further evaluation is needed before utilization of the PFS24 end point can be extended to the relapsed setting.

In summary, patients treated with rituximab containing anthracycline-based immunochemotherapy who are alive without progression at 24 months from the onset of initial therapy on clinical trials have excellent outcomes with survival that is marginally lower but clinically indistinguishable from the age-, sex-, and country-matched background population for 7 years after achieving PFS24. Further follow-up will be needed to assess any long-term impact of late relapse and survivorship issues in this population.

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