Systematic Review and Meta-Analysis

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Model-based meta-analysis of progression-free survival in non-Hodgkin lymphoma patients

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Abstract

Background: Non-Hodgkin lymphoma (NHL) is a group of lymphoproliferative malignancies with varying treatment responses and progression-free survival (PFS) times. The objective of this study was to quantify the effect of treatment and patient–population characteristics on PFS in patients with NHL.

Methods: A database was developed from 513 NHL clinical trials reported from 1993 to 2015. Summary-level PFS was obtained from 112 of these trials, which included 155 cohorts and 11,824 patients. Characteristics evaluated for their impact on PFS included cohort treatment, percentage of patients with each NHL subtype, percentage of patients with different numbers of prior treatments, percentage of subjects previously administered rituximab, performance status, disease stage, median age, and sex distribution.

Results: Rituximab, bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone combination)/CHOP-like, and other nonchemotherapy drugs, aside from bortezomib, prolonged median PFS time 2 to 4-fold. Follicular lymphoma patients had 60% longer median PFS time than mantle cell lymphoma (MCL) patients, while diffuse large B-cell lymphoma patients had a median PFS time that was 25% of MCL patients. Patients who received $\leq$1 prior treatment had median PFS times $>$ 10-fold longer than patients who received $\geq$2 prior treatments. The final model predicted the hazard ratio in 75% of the studies within 25% of the observed value and the observed median PFS time of 92% of the studies fell within the predicted 90% confidence intervals.

Conclusions: The developed PFS model predicts the median PFS time and hazard ratio for specific populations and treatment combinations quantitatively and can potentially be extended to link short-term and long-term clinical outcomes.

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone combination, CR = complete response, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, HR = hazard ratio, KM = Kaplan–Meier, MCL = mantle cell lymphoma, NHL = non-Hodgkin lymphoma, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PR = partial response, SD = stable disease, TTP = time to progression.

Keywords: meta-analysis, model based drug development, non-Hodgkin lymphoma, progression-free survival

1. Introduction

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies that include all lymphomas except Hodgkin lymphoma. There are 3 main subtypes of NHL. Diffuse large B-cell lymphoma (DLBCL), an aggressive subtype, is the most common type of NHL, constituting about one-third of all NHLs in the US. Follicular lymphoma (FL) is a slow-growing and the second most common type of NHL in the US. Mantle cell lymphoma (MCL) can be aggressive or indolent and constitutes about 7% of all lymphomas. Other NHL subtypes include peripheral T-cell lymphoma and marginal zone lymphoma.[1,2]

Overall survival (OS) is the universally accepted primary endpoint for cancer therapies. However, measurement of OS requires long-term follow-up and may be affected by crossover and sequential therapies. In the case of the more indolent and treatable subtypes of NHL, measuring OS as the primary endpoint becomes impractical due to the long survival time. On the contrary, progression-free survival (PFS), defined as the time from randomization until objective tumor progression or death, requires a smaller sample size and shorter follow-up time, and is not affected by crossover or subsequent therapies. It is also accepted by the FDA, which has recently approved several new drugs for various cancers, with PFS as the primary endpoint.[3,4] In case of NHL, PFS has been used as a primary endpoint for the approval of many therapies, including rituximab as a combination therapy in 2006 and ibritumomab as a first-line therapy in 2009.[4] We have recently evaluated the relationship between response rates and median PFS in NHL[5] and median OS in acute myeloid leukemia.[6] However, the impact of various trial-specific and patient-specific covariates on PFS needs to be determined to better design clinical studies and predict clinical outcomes in NHL using PFS as the primary endpoint.[7] Therefore, the objective of the study was to quantify the effect of treatment and patient–population characteristics on PFS in patients with NHL.

Editor: Laszlo Geza Boros.

ND, AHS, and KJF are employees of AbbVie and may hold AbbVie stock or stock options. ML is a former intern of AbbVie. AbbVie provided financial support for the studies and participated in the design, study conduct, analysis and interpretation of data as well as the writing, review, and approval of the manuscript.

The authors disclose no conflicts of interest.

Supplemental Digital Content is available for this article.

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Medicine (2017) 96:35(e7988)

Received: 24 May 2017 / Received in final form: 31 July 2017 / Accepted: 14 August 2017

http://dx.doi.org/10.1097/MD.0000000000007988

2. Methods

2.1. Trial selection

Relevant trials between 1993 and 2015 were systematically identified, screened, and assessed to develop a database according to the steps described in the Cochrane Handbook for Systematic Review of Interventions[8] and reporting items in the PRISMA statement.[9] The trials were mainly identified in PubMed, using patient-type subfilters "diffuse large B-cell lymphoma" or "follicular lymphoma" or "mantle cell lymphoma" and study design and publication-type subfilters "clinical trial, phase II' or 'clinical trial, phase III." In addition, regulatory reviews from FDA websites, including clinical trial registries on clinicaltrials.gov and abstracts published in the scientific proceedings of the annual meetings for the American Society of Clinical Oncology and American Society of Hematology, were also examined. Electronic copies of study reports were obtained from internet or local libraries. The search results were exported to an excel spreadsheet for further analyses.

Only trials that had at least 1 cohort using a drug treatment and with at least 1 primary or secondary outcome such as complete response (CR), partial response (PR), objective response rate (ORR), stable disease (SD), OS, PFS, and time-to-progression (TTP) were included in the dataset. In addition, details of trial design, sample size, treatment, percentage of patients with prior treatment, percentage of males, percentage of patients with subtype of NHL, and percentage of patients with disease at advanced stage III or IV were also included in the database. If indication, treatment, clinical outcome, comparison between treatments, study type (phase I study, reviews, meta-analysis, case report, cost-analysis), clinical outcome, or comparison between treatments were not relevant, or if the sample size was less than 25, the trial was eliminated from the database. Only trials within the established database that reported PFS Kaplan–Meier (KM) curves in at least 1 cohort of the study were included in the meta-analysis.

2.2. Data analysis

A nonlinear mixed-effects modeling approach was utilized (NONMEM 7.2.0). The model is described in detail in the Supplemental Content - Model Description, http://links.lww.com/MD/B853. The following characteristics were evaluated for their impact on the PFS curves: cohort (i.e., strata or arm) treatment, percentage of patients with each NHL subtype, percentage of patients with different numbers of prior treatments (naive, 1, and 2+ prior treatments), percentage of subjects previously administered rituximab, percentage of patients with performance status greater than or equal to 2, percentage of patients with disease stage greater than or equal to 3, median age, and sex distribution. In addition, subanalyses were conducted to separate relapsed or refractory patients by the number of prior treatments. For percentage of subjects previously administered rituximab, median age, and sex distribution covariates, the missing values were imputed as medians. Drug treatments were classified as rituximab, CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone) or CHOP-like (3 out of 4 drugs the same as CHOP regimen), bendamustine, bortezomib, other chemotherapies, and other drugs. Other chemotherapy treatment regimens include vorinostat, fludarabine, MCP (mitoxantrone, chlorambucil, and prednisone), DHAP (dexamethasone, cytarabine, and cisplatin), ICE (ifosfamide, carboplatin, and etoposide), BEAM (carmustine, etoposide, cytarabine, and melphalan), pentostatin, GemOx (gemcitabine and oxaliplatin), NIMP (vinorelbine, ifosfamide, mitoxantrone, and prednisone), THP (pirarubicin), gemcitabine, CMD (chlorambucil, mitoxantrone, dexamethasone), FM (fludarabine and mitoxantrone), FC (fludarabine and chlorambucil), pirarubicin, PEPC (prednisone, etoposide, procarbazine and cyclophosphamide), IFE (ifosfamide and etoposide), AD+C (doxorubicin, dexamethasone and chlorambucil), cytarabine, mitoxantrone, FMD (fludarabine, mitoxantrone, and dexamethasone), and COP-X (cyclophosphamide, vincristine, prednisone, and daunorubicin). Other drugs included temsirolimus, GM-CSF (granulocyte-macrophage-colony-stimulating factor), enzastaurin, celecoxib, tositumomab, alisertib, lenalidomide, pidilizumab, idelalisib, flavopiridol, cladribine, ibrutinib, everolimus, SAM486A, dacetuzumab, bevacizumab, galiximab, obinutuzumab, inotuzumab, thalidomide, epratuzumab, dexamethasone, ofatumumab. Exponential model centered by median covariate value was utilized to assess covariate effects, and a stepwise forward inclusion ($P < .01$) and backward elimination ($P < .001$) procedure was applied to select the statistically significant covariates.

On the basis of 1000 simulated trials, in order to test the performance of the model, an internal validation was carried out for median PFS time and hazard ratio (HR) using 1000 simulated trials. For median PFS time, the database included 80 studies, 107 cohorts, and 17 randomized studies, while for the HR, the database included 11 randomized studies including 24 cohorts.

Limited imputation of covariates was conducted due to missing values in a subset of studies. Therefore, a sensitivity analysis was conducted that included only the studies with complete covariate information to determine the impact of imputation.

3. Results

The database consisted of 179 trials that met the pre-defined inclusion and exclusion criteria (Fig. 1). Further, 17 trials were removed due to duplication. Fifty of these 162 trials were excluded, as they did not report PFS KM curves. The final dataset used for meta-analysis included 112 studies (of which 22 were randomized studies), 155 cohorts (arm/strata), 11,824 patients, 22 randomized studies, and 3098 observations (Fig. 1). A detailed description of characteristics of cohorts studies included in the analysis is presented in Table 1. In brief, the median age was 63 years and the median % male patients was 59%. Rituximab was used in the majority (63.2%) of the cohorts, with other drugs being the second most commonly used treatment option (38.7% of cohorts). About 33.5% and 51.6% cohorts received 1 and 2 therapies, respectively, whereas 14.8% cohorts received 3 therapies.

The visual predictive check of the final model for PFS versus time showed that the model adequately described the natural tendency of the observed data (Fig. 2). Goodness of fit plots demonstrated that the model adequately described the data with limited bias (Additional file - Figure S1, http://links.lww.com/MD/B853). The final model parameters estimated are summarized in the Supplemental Content - Table S1, http://links.lww.com/MD/B853. The relative effect of treatment type on median PFS showed that rituximab, bendamustine, CHOP/CHOP-like, and other drugs prolonged median PFS time by 2- to 4-fold, while bortezomib and other chemotherapy drugs did not affect median PFS time (Fig. 3A). In the case of tumor subtypes, the FL patient population had a 60% longer median PFS time than the MCL

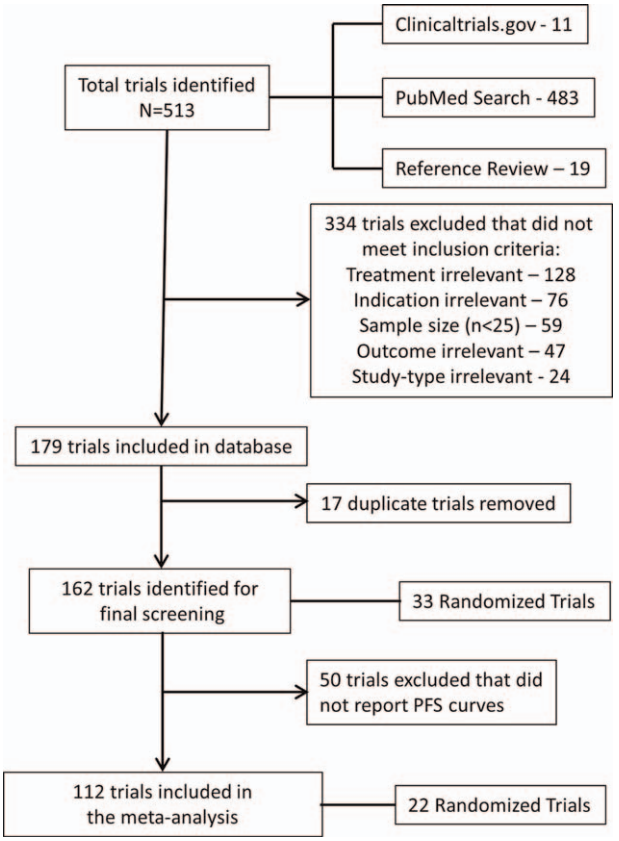

Figure 1. Flowchart of database development and selection of trials included in the meta-analysis.

Table 1

Summary of the characteristics of the included cohorts.

Characteristic	Value
Total number of cohorts [no. (%)]	155 (100)
Age, y [median (range)]	63 (47–83)
Not reported [No. of cohorts (%)]	8 (5.1)
Sex (% male patients) [median (range)]	59 (29–91)
Not reported [No. of cohorts (%)]	14 (9)
Type of treatment [No. of cohorts (%)]	
Rituximab	98 (63.2)
CHOP/CHOP-like	41 (26.4)
Bendamustine	11 (7)
Other chemotherapy	36 (23.2)
Bortezomib	22 (14.2)
Other drugs	60 (38.7)
Number of treatments [No. of cohorts (%)]	
1	52 (33.5)
2	80 (51.6)
3	23 (14.8)
NHL subtype [No. of cohorts (%)]	
FL	44 (28.4)
MCL	33 (21.3)
DLBCL	49 (31.6)
Other	4 (2.5)
Mixed	25 (16.1)
Percentage patients with performance status ≥2 [Median (range)]	0.08 (0–0.6)
Not reported [No. of cohorts (%)]	40 (25.8)
Percentage patients with Stage ≥III [Median (range)]	0.86 (0–1)
Not reported [No. of cohorts (%)]	33 (21.3)

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone combination, DLBCL = diffuse large B-cell lymphoma, FL = follicular lymphoma, MCL = mantle cell lymphoma, NHL = non-Hodgkin lymphoma.

patient population, while the DLBCL patient population had a median PFS time of only 25% of that in the MCL patient population. The median PFS time in other NHL subtypes, in general, was similar to the MCL patient population (Fig. 3B). The subanalysis conducted to further evaluate the impact of the number of prior therapies demonstrated that median PFS time in treatment-naive patient population and patients with 1 prior line treatment were not statistically different ($P > .01$), while the patient population with 2 or more prior therapies had significantly smaller λ ($P < .001$), resulting in less than one-tenth the median PFS time than patient populations with ≤1 prior therapies (Fig. 3C). Median age, sex distribution, prior rituximab treatment, performance status, and stage of disease did not have a statistically significant ($P > .01$) impact on PFS.

Similarly, the internal validation demonstrated that the observed median PFS time in 92% cohorts was covered in 90% confidence interval (95% CI) of predictions. The internal validation of HR demonstrated that the model predicted 100% of cohorts within 0.5- to 2-fold of the observed HR and 75% cohorts within 25% of observed HR.

For the sensitivity analysis, 21 studies were removed (12 studies were missing percentage of subjects previously administered rituximab, 6 studies were missing median age, and 7 studies were missing sex distribution covariates). The sensitivity analysis identified the same covariates as the main analysis in addition to treatment and tumor subtype that were shown to affect k. The sensitivity analysis had a minimal effect (<15%) on the primary parameter estimates of k and lambda (Supplemental Content - Table S1, http://links.lww.com/MD/B853), demonstrating the analysis was insensitive to the limited covariate imputation conducted.

4. Discussion

The impact of treatment and patient-specific covariates on PFS was quantified in NHL using a database of 112 trials involving 155 cohorts of patients with FL, DLBCL, MCL, and other subtypes. To our knowledge, this is the first meta-analysis of covariates on PFS in a large NHL dataset. The resulting PFS model can quantitatively predict the PFS curve, the median PFS time, and the HR for a specific population and treatment in patients with NHL. In addition, the model is able to identify the most effective treatment and most responsive patient populations across studies, allowing for better clinical trial design.

The use of PFS as a surrogate marker for OS has been established in various cancers such as colorectal cancer,[10,11] gastrointestinal stromal tumors,[12] and metastatic prostate cancer.[13] Similarly, Beauchemin et al[14] found that the median PFS or TTP can be used as surrogate for OS in chronic lymphocytic leukemia, as it was highly correlated with median OS (Spearman correlation coefficient: 0.813, $P < .001$). In multiple myeloma, Cartier et al[15] found a positive correlation [correlation coefficient (r) = 0.82, $P < .0001$) between HR of PFS and OS indicating that the PFS can be a valid surrogate for OS. Lee et al found the Spearman rank correlation coefficient (r_s) to be 0.90 (95% CI: 0.73–0.96) between PFS and OS in aggressive NHL, although they could not establish the same correlation between PFS and OS in indolent NHL.[16] None of these above-mentioned studies evaluated the impact of covariates on PFS. In

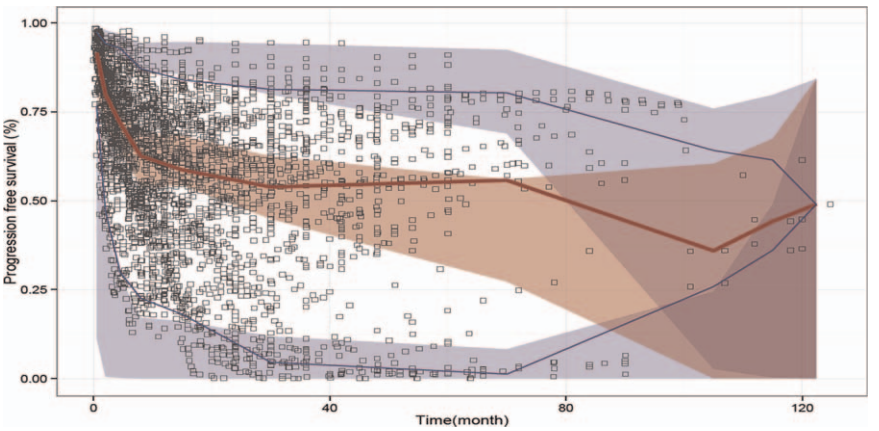

Figure 2. Visual predictive check of the final PFS model. The solid red line represents the median observed % PFS, and the semitransparent red field represents a simulation-based 90% confidence interval for the median. The observed 10% and 90% percentiles are presented with blue lines, and the 90% confidence intervals for the corresponding model predicted percentiles are shown as semitransparent blue fields. The observed %PFS for each cohort are represented by the black squares.

order to establish use of PFS as a surrogate endpoint and better design clinical studies, it is important to determine the impact of patient population covariates as well as the different treatment options on PFS by meta-analysis of available clinical trial data.

Treatment-naive patients typically demonstrate a higher sensitivity to a new NHL treatment when compared with relapsed or refractory patients. This is primarily due to the absence of prior treatment-related cross-resistance, which leads to much higher median PFS for treatment-naive patients for a given NHL treatment. Rituximab-based chemotherapies have become standard frontline treatment for various types of NHL. Several studies suggested that reuse of rituximab-based treatment in relapsed setting is also effective.[17–20] In our analysis, prior rituximab treatment was not found to be a statistically significant covariate. Consistent with these results, Johnston et al[21] have also reported no difference in PFS between rituximab-naive and rituximab-retreated patients in a single-center retrospective cohort study in 178 patients with relapsed and refractory B-cell lymphomas. Also, the FL patient population was estimated in the current study to have 60% longer median PFS time than patients with MCL, which is in concordance with the fact that FL is the most indolent (slow progressing) form of NHL. Hence, a better clinical outcome is usually expected for these patients when compared with DLBCL or other subtypes of NHL. Impact of age and sex was not found to be significant.

Despite the large number of clinical studies included in this meta-analysis, the dataset had some limitations. For several cohorts, the missing values for the covariates of median age, sex distribution, and percentage of subjects previously administered rituximab were imputed as medians. However, the sensitivity analysis on only the studies with complete covariates information showed a minimal change (<15%) in the primary parameter estimates of k and lambda, demonstrating that the analysis was insensitive to the limited covariate imputation conducted.

Pharmacodynamic drug interactions or other treatment details, such as duration of treatment, drug potency, and dose, were not considered in the model development, as there were not sufficient details available for many of the trials. Similarly, some patient prognostic factors, such as international prognostic index and bone marrow involvement, were not considered in model development, again due to the large amount of missing values.

In summary, the effect of treatment and patient population characteristics on PFS over time in patients with NHL was quantified. As expected, trials enrolling treatment-naive patients and patients with FL had a higher median PFS. Median age, sex distribution, prior rituximab treatment, performance status, and stage did not demonstrate a statistically significant influence on PFS. The determined quantitative relationships can be used to predict the PFS over time, the median PFS time, and the HR for specific patient populations and treatments.

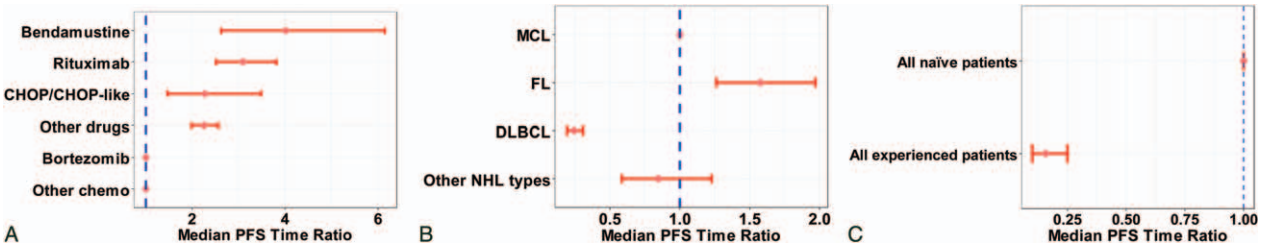

Figure 3. Model predictions for various covariates effects on relative median PFS time. (A) Effect of treatment on relative median PFS time, (B) effect of tumor subtype on relative median PFS time, (C) effect of treatment-naive versus experienced patients on relative median PFS. Dashed blue lines represent median PFS time for reference population (median PFS ratio = 1.0). Dots and bars represent model-estimated median PFS time (relative to reference population, referred as "median PFS time ratio") and 90% confidence interval, respectively.

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