Use of External Data to Guide Long-Term Survival Extrapolations of Trial Data for Chronic Lymphocytic Leukemia

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Introduction

• Prediction of survival outcomes beyond the period of clinical trial follow-up is often necessary for economic evaluation.
• Extrapolation of survival data has typically been performed by fitting parametric survival functions to trial data and extending them beyond the observed trial period.
• Long-term extrapolation is problematic:
  - The use of long-term follow-up data from other studies, external to the clinical trial, to validate the parametric function is often not available.
  - In most cases, the observed outcome in the trial is the most relevant long-term outcome to directly apply to the economic model populated with trial data.
  - Differences in patient population characteristics.
  - Differences in treatment regimens.
  - Improvements in outcomes in recent years due to general improvements in disease management (eg, fewer patients without active complications at any time).

• The objective of this study was to demonstrate how the use of external data’s long-term survival probabilities can be used when only short-term trial data is available.

Methods

• Considerable evidence is available regarding overall survival data from the COMPLEMENT trial.
• Double-blind, multinational, clinic trial of first-line treatment for chronic lymphocytic leukemia (CLL) patients: randomization to modified schedule chlorambucil (M-schedule) or fludarabine and followed for a median 29 months (range 0.1–112).
• The dataset used comprised of both arms of the COMPLEMENT trial for the present analysis.

• The long-term follow-up study used to guide the extrapolation was the C9011 trial.
• Patients randomized to CHL, fludarabine on fludarabine monotherapy (CHL, M-monotherapy) and followed for the trial duration (data not shown).
• Overall survival was reported for periods of up to 10 years.
• The CHL arm (n = 193) of C9011 was used for the present study to guide the extrapolation of the CHL treatment arm.
• The data could not be used directly as the overall survival rates for the first 4 years were markedly better than those observed for CHL in COMPLEMENT 1.
• The data could also be different in patient population characteristics, the CHL drug, and follow-up duration.

• The Kaplan–Meier method was used to fit the Kaplan–Meier survival curves, and the graphically and statistically identical with the step function. The Kaplan–Meier survival function estimates a survival probability at time .
• Long-term extrapolation for the overall survival in the COMPLEMENT 1 trial, guided by the C9011 data, was estimated using a step approach.
• Stage 1: Parametric survival functions were fitted to the C9011 data and then using an indicator for treatment effect (eg, see Figure 1).
• The average treatment effect of OCHL vs CHL was estimated, and survival analysis including data from both arms of COMPLEMENT 1 and the CHL arm, indicating a treatment effect of 50%.

• The Kaplan–Meier curve (Figure 1) of the estimated survivor function from C9011 (Stage 1) using the same type of function.
• Survival functions were considered:
  - Exponential
  - Weibull
  - Log-logistic
  - Gamma

• The parametric survival functions to the data were graphically and statistically by comparison of Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics.

Results

• Stage 2: parametric survival functions were fitted for the C9011 arm in both arms with an indicator for treatment effect. The results are presented in Table 1 and Figure 2.
• Weibull, gamma, and parametric types provided similar estimates of the hazard rate and Kaplan–Meier estimation were assessed using AIC, BIC (Table 1), visual inspection (Figure 1), and expert opinion.
  - The AIC, BIC, and additional statistical criteria used for this purpose were identical, and the Weibull model was chosen as the most appropriate model, statistically and graphically.

• The Kaplan Meier curve between about 70 and 75 months was poorly fitted by the survival curve, an indicator of drop-out rate on the survival graph, and undulations observed in the Kaplan–Meier data in this region are understandable in other overall survival survival for CLL patients: survival rates were high in the CHL arm compared to the CHL arm.

• The Kaplan–Meier curves estimated for the CHL arm in both arms of the COMPLEMENT 1 trial at 5 years.
• For example: the Weibull function predicted a 20% year survival of 24% for the CHL arm in both arms of the COMPLEMENT 1 trial.

• The survival curves (Figure 1) of the estimated survivor function from C9011 (Stage 1) using the same type of function.
• Stage 2: Exponential, Weibull, Log-logistic, and Gamma were used to evaluate the long-term survival estimated from Stage 1 of the estimated survivor function from C9011 (Stage 1) using the same type of function.

Discussion

• The work explored how to use external long-term follow-up data to guide the extrapolation of overall survival for chronic lymphocytic leukemia (CLL) patients.
• The main findings were:
  - Long-term extrapolation is problematic due to differences in patient population characteristics, the CHL drug, and follow-up duration.
  - The Kaplan–Meier curve was used to estimate overall survival and progression-free survival.
  - The assumption is unreasonable during the common follow-up period.

• Conventional survival function techniques (Stage 1) were produced by using long-term follow-up data (Figure 3).
• A similar approach to that studied in COMPLEMENT 1 trial.
  - No treatment effect was observed for the CHL arm.
  - The results were similar to those for a similar follow-up period in the C9011 trial.
  - The results were similar to those for a similar follow-up period in the C9011 trial.

• The overall survival rate over the first 4 years was markedly higher than the overall survival rate over the first 4 years for the CHL arm.

• The survival rate was >70% at 4 years in both arms.

• Survival predictions guided by the external data were markedly lower than conventional functions fitted only to trial data. For example, the Weibull function predicted a 20% 5-year survival rate of 24% for the CHL arm in both arms of the COMPLEMENT 1 trial.

• Conflicts of Interest

• The authors declare no conflicts of interest.

Supplementary Information

• Table S1: Summary of External Data Used to Guide Extrapolations

Table 1. Kaplan–Meier Estimates and Summary Information for Overall Survival, C9011 and COMPLEMENT 1 Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>COMPLEMENT 1 CHL</th>
<th>C9011 CHL</th>
<th>C9011 OCHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 year</td>
<td>90.01%</td>
<td>73.65%</td>
<td>80.74%</td>
</tr>
<tr>
<td>1 year</td>
<td>86.31%</td>
<td>70.92%</td>
<td>86.31%</td>
</tr>
<tr>
<td>2 years</td>
<td>80.74%</td>
<td>67.02%</td>
<td>84.62%</td>
</tr>
<tr>
<td>3 years</td>
<td>77.42%</td>
<td>63.05%</td>
<td>79.30%</td>
</tr>
<tr>
<td>4 years</td>
<td>73.65%</td>
<td>59.06%</td>
<td>76.66%</td>
</tr>
<tr>
<td>5 years</td>
<td>70.92%</td>
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<td>74.00%</td>
</tr>
</tbody>
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Figure 1. Kaplan–Meier Estimates of Overall Survival and Fitted Parametric Curves

Figure 2. Kaplan–Meier Estimates of Overall Survival and Estimated Kaplan–Meier Curves

Figure 3. Kaplan–Meier Estimates of Overall Survival and Estimated Kaplan–Meier Curves

Figure 4. Comparison of Estimated Functions (Red and Unshadowed Lines: Kaplan–Meier; Black and Shadowed Lines: Weibull)

Figure 5. Comparison of Estimated Functions (Red and Unshadowed Lines: Kaplan–Meier; Black and Shadowed Lines: Weibull)

Figure 6. Comparison of Estimated Functions (Red and Unshadowed Lines: Kaplan–Meier; Black and Shadowed Lines: Weibull)

Table 2. Overview of Study Parameters and Model Parameters

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<td>Survival</td>
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<td>Progression-free survival</td>
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Table 3. Parameter Estimates of Overall Survival and Progression-Free Survival

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Table 4. Survival Analysis Outcomes by External Data

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Table 5. Parameter Estimates of Overall Survival and Progression-Free Survival

Acknowledgements

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• The authors thank Kirin Haag, MPH, for statistical support.

• This study was conducted in compliance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of Interest

• GSK employees and their immediate family members are employees of GSK and who are paid employees of GSK.

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