Estimating Long-term Survival in a Cohort of Allogeneic Hematopoietic Stem Cell Transplant Patients

Poster #3556

Stephen Palmer,[1] Casey Quinn,[2] Crystal Watson,[3] Arie Barlev[3]

[1]Centre for Health Economics, University of York, York, UK; [2]PRMA Consulting, Ltd, Fleet, UK; [3]Atara Biotherapeutics, Inc, South San Francisco, CA, USA

INTRODUCTION

- Allogeneic hematopoietic cell transplantation (HCT) is a common treatment for many hematologic diseases.
- Most deaths occur in the first 2 years after HCT due to relapse, graft-versus-host disease, infections, malignancies, or other toxicities.[1,2]
- Among patients who are alive and recurrence free at 2 years after HCT, survival at 10 years is between 80% and 92%.[2]
- Advances in transplantation practices have led to improved outcomes and more long-term HCT survivors.[2]
- As survival outcomes continue to improve and new treatments emerge, understanding and quantifying the full lifetime benefit of HCT in terms of mean overall survival (OS) is clinically relevant.
- In this analysis, we estimate the mean OS of a cohort of HCT patients.

METHODS

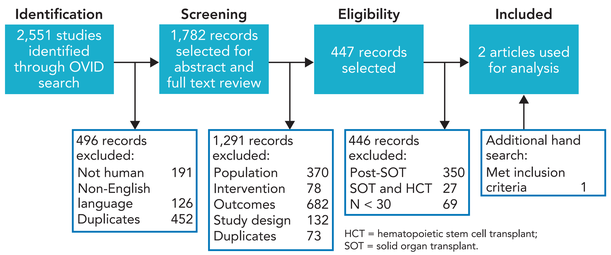
Systematic Literature Review

- The systematic literature review was performed following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
- The scope was defined in terms of Population, Intervention Comparators, Outcomes, and Study design (PICOS) criteria (**Table 1**).
- Using extensive search terms for the indication and study designs, studies were identified using the EMBASE, MEDLINE, and Cochrane databases.
- The literature search was conducted on July 19, 2018 and included studies published between database inception in January 1, 1959 and July 19, 2018.
- Relevant congress abstracts published between January 2015 and June 2018 were also identified.
- The PICOS-based inclusion and exclusion criteria were used to review identified citations.
- No treatment limitations were imposed to ensure inclusion of all relevant evidence, and the study designs were limited to prospective and retrospective observational studies; case reports were included regardless of sample size.
- Two independent reviewers screened all citations and full-text articles; any discrepancies were resolved by a third independent reviewer.

Table 1. PICOS Criteria

Element	Inclusion	Exclusion
Patient Population	• Patients with PLTD after HCT	• Non-human • Not fulfilling inclusion criteria
Intervention and Comparators	• Any therapy for PTLD – Cellular therapy, chemotherapy, immunotherapy, antiviral therapy, etc	• Radiotherapy • Surgery • Palliative therapy
Outcomes Measures	• Treatment pathways • Real-world treatment choices • Treatment sequence • Market shares • Durations • Real-world effectiveness • Overall survival • EBV status	• Any not listed in the inclusion criteria
Study Design	• Large-scale relevant prospective observational studies • Large-scale relevant retrospective studies • Database analyses • Registries • Natural history studies • Non-interventional studies • Any publications presenting disease-specific information	• Notes/comments/letters • Reviews/editorials
Restrictions	• English language • Sample size ≥ 30 subjects with PTLD	• Non-English language studies • Sample size < 30 subjects with PTLD

Figure 1. PRISMA Evidence Flow



HCT = hematopoietic stem cell transplant; SOT = solid organ transplant.

Data Source

- We retrieved only 2 published articles that met the inclusion criteria from the literature review: Uhlin et al, 2014[3] and Wingard et al, 2011[2] (**Table 2**).
- Data from Uhlin et al, 2014 was used to estimate the percentage of patients alive at 2 years after HCT, which was 65%.

Table 2.

	Study	
	Uhlin et al, 2014	Wingard et al, 2011
Database	Karolinska University Hospital in Huddinge, Stockholm	Center for International Blood and Marrow Transplant Research
Single Center or Multi-center	Single center	Multi-center (318 centers worldwide)
Number of Patients	981 patients without complications out of a total of 1,021 patients	10,632 patient records selected out of 31,818 total transplant records
Type of Study	Retrospective chart review	Retrospective analysis using registry data
Study Period	1996–2011	January 1980–December 2003
Overall Survival	1 year = 74% 2 years = 65% 3 years = 62%	For 2-year survivors, the probability of being alive 10 years after HCT was 85%

Long-term Survival Model

- Extracted data were incorporated into a long-term survival model using a step-wise approach:
  - Short-term survival (up to 2 years after HCT) using data reported by Uhlin et al, 2014.
  - Longer-term survival (more than 2 years after HCT) using data reported by Wingard et al, 2011 and the age-adjusted life tables for the general UK population.
  - A lifetime analysis was undertaken for a cohort of patients aged 23.5 years at the time of HCT, calculated from the weighted median age in Wingard et al, 2011.
- Available published data provided OS estimates up to 15 years after HCT, and beyond this time, OS estimates are uncertain.
- To estimate mean OS and address this uncertainty, three different survival scenarios were modeled:
  - Base-case
    - Weibull, exponential, Gompertz, log-logistic, and log-normal parametric functions were used to fit the data published by Wingard et al, 2011 to estimate the survival curve from year 2 after HCT until death.
    - It was assumed that patients have excess mortality for the rest of their lives compared to the general population. To incorporate this excess mortality throughout the patients' lives, the lowest survival was chosen cycle over cycle between the parametric estimate and the age-adjusted life tables.
    - The selection for base-case was decided based on the most conservative estimate and the fewest assumptions.
  - Best-case
    - Assumed that HCT patients were cured and had the same OS as the age-adjusted UK general population 15 years after HCT.
  - Worst-case
    - Assumed that HCT patients carried excess mortality for the rest of their lives (e.g., more than 15 years after HCT).
    - Excess mortality was calculated from Wingard et al, 2011, which showed 20% mortality from year 2–15 after HCT, an order of magnitude greater than the general population (2%).

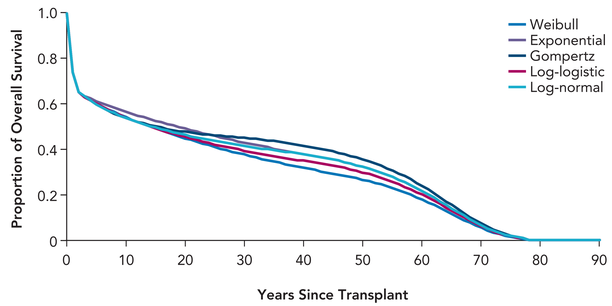
RESULTS

Parametric Models to Establish Base Case

- Parametric models of Weibull, exponential, Gompertz, log-logistic, and log-normal showed mean OS of 25.9, 28.8, 29.5, 27.0, and 28.0 years, respectively (**Figure 2**).
  - Similar "goodness of fit" (AIC [Akaike Information Criterion]/BIC [Bayesian Information Criterion]) were seen with all parametric models.
- Weibull was selected as it was the most conservative estimate of the mean OS and had the fewest assumptions.

OS = overall survival.

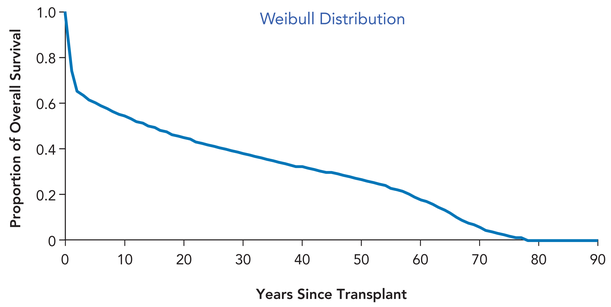
Figure 2.



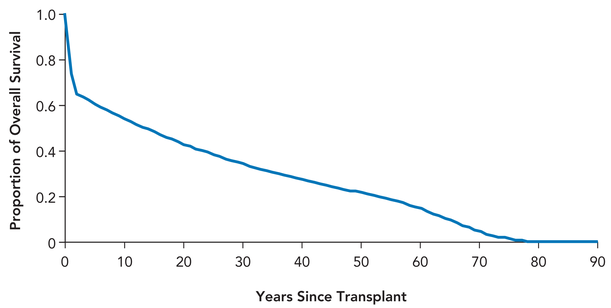
Scenarios

- For a cohort of HCT patients who received their transplant at age 23.5, the estimated mean OS for the base-case survival scenario was 25.9 years after HCT (**Figure 3A**).
- The estimated mean OS for the worst-case survival scenario was 23.9 years when using excess mortality from Wingard et al., 2011 for the rest of the patients' lives (**Figure 3B**).
- The estimated mean OS for the best-case survival scenario was 31.7 years when hazards used from general UK population after 15 years (**Figure 3C**).

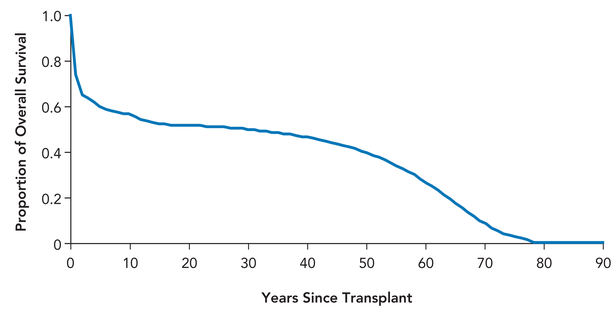
3A. Base-Case Survival Scenario



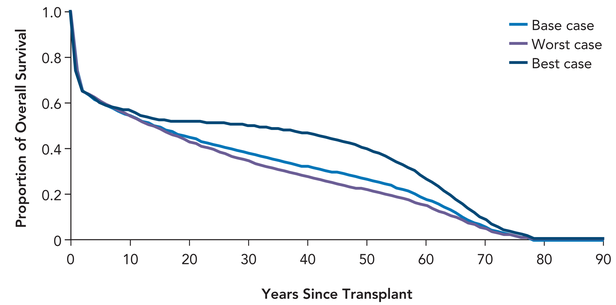
3B. Worst-Case Survival Scenario



3C. Best-Case Survival Scenario



Summary of Survival Scenarios



CONCLUSIONS

- The mean OS for a cohort of HCT patients was estimated to be 25.9 years.
- This estimate helps to understand and quantify the full lifetime survival benefit to HCT patients, including the tail end of the survival curve and the potential added benefits of future treatments after HCT.
- The parametric models revealed a narrow range for the estimated mean OS, minimizing the uncertainty of the results.
- Since the first 2 years after HCT have the highest mortality rate, new treatments that can improve survival during this time may change the impact on the lifetime benefit of the therapy.

REFERENCES

1. Socie´ G, et al. *N Engl J Med.* 1999;341:14–21. 2. Wingard, et al. *J Clin Oncol.* 2011;29:2230-9. 3. Uhlin, et al. *Haematologica.* 2014;99:346-52.

ACKNOWLEDGMENT

We would like to acknowledge Kathryn Boorer, PhD, for her help with medical writing.

DISCLOSURE

Study funded by Atara Biotherapeutics, Inc.

Presented at the American Society of Hematology Annual Meeting; San Diego, CA; December 1–4, 2018.