Comparison of Methods for External Controls Using Real-World Data: A Case study of Tisagenlecleucel

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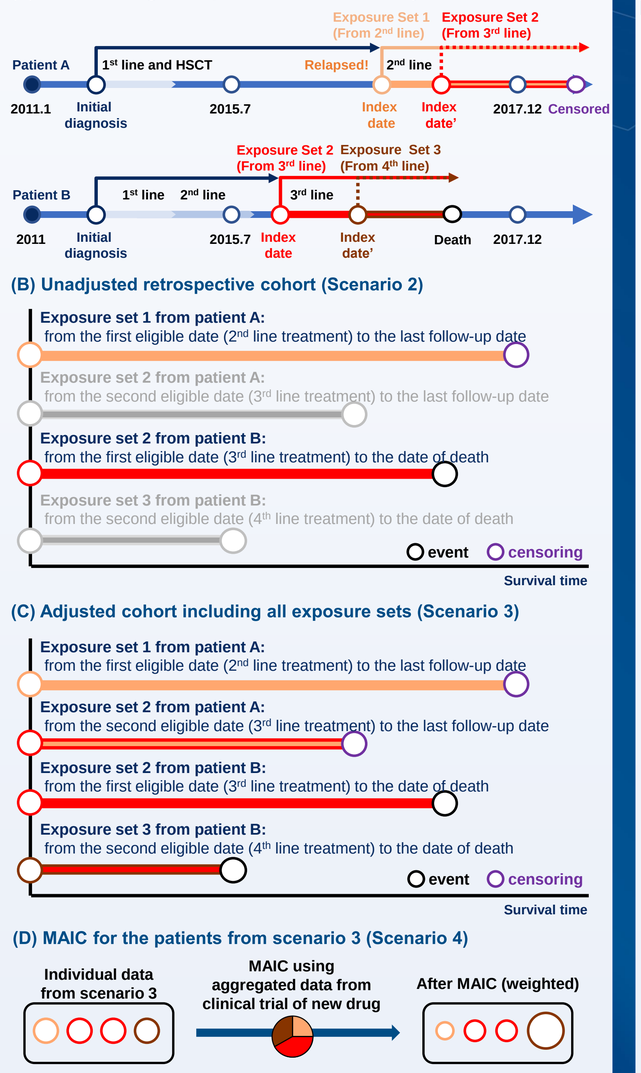
BACKGROUND/ OBJECTIVES

- New drugs approved based on single-arm trials due to ethical reason or rarity of disease should be compared with external controls in health technology assessments.
- Thus, the relative value of the drug could be evaluated differently by the methods of constructing external controls.
- This study investigates a methodology that constructs external controls with better comparability from various sources including real-world data (RWD).

METHODS

- To investigate differences among methodologies that construct external controls, we performed a case study on tisagenlecleucel which was used as curative treatment for the relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
- To compare with the single-arm trial of tisagenlecleucel, we created four scenarios for external controls by conducting a literature review and analyzing the claims data from the Health Insurance Review and Assessment Service (HIRA).
  1) Systematic literature review on the efficacy of salvage chemotherapy for the relevant patients
  2) Unadjusted retrospective cohort of DLBCL (Figure 1B)
  3) Retrospective cohort with adjusting for the time-related bias through including all potential exposure sets (Figure 1C)[1]
  4) Applying matching-adjusted indirect comparison (MAIC) for the adjusted cohort from scenario 3 using baseline characteristics from pivotal trial of tisagenlecleucel, JULIET (Figure 1D)[2]
- We mimicked the eligibility criteria and index period of the single-arm trial (from July 2015 to December 2017) to minimize selection biases when constructing a comparable cohort.[3]
- Then, we measured patient characteristics, median overall survival (OS), and progression-free survival (PFS).

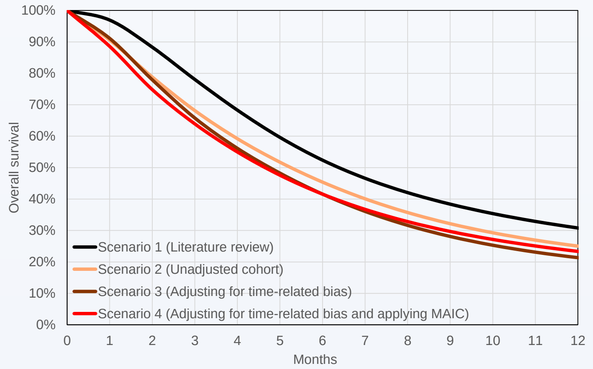
Figure 1. Concept of the scenarios using RWD (Scenario 2 to 4)



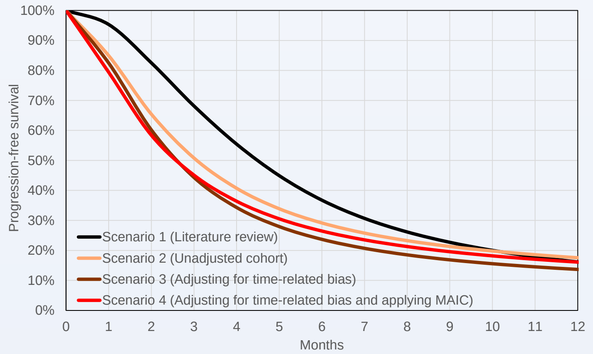
RESULTS

Figure 2. Survivals from each scenarios

(A) Overall survival



(B) Progression-free survival



- The overall survival of tisagenlecleucel was reported as 11.9 months in the single-arm trial, whereas that of external control from the literature review reported 6.3 months (scenario 1).[4,5]
- The OS from the unadjusted retrospective cohort was 4.89 months (Scenario 2 in Figure 2A). Most of patients from unadjusted cohort experienced two lines of previous treatments, which was different from reported baseline characteristics of JULIET trial (Table 1).

Table 1. Baseline characteristics by scenarios

Variables	Pivotal trial of tisagenlecleucel; JULIET	Methods for constructing external controls			
		Scenario 1	Scenario 2	Scenario 3	Scenario 4
Age ≧ 65 years	23%	NR	34%	31%	23%
Patients with transformed FL	19%	4%	4%	4%	19%
Number of previous treatment lines					
1	4%	28%	1%	1%	4%
2	44%	49%	98%	70%	44%
3	31%		0%	22%	31%
4+	20%	<1%	0%	7%	20%
Relapsed after last therapy	45%	NR	30%	26%	45%
Previous autologous HSCT	49%	22%	16%	17%	49%

FL, follicular lymphoma; HSCT, hematopoietic stem cell transplantation

- In scenario 3, patients' previous treatment history became similar to that of the single-arm trial, and the OS decreased to 4.50 months including more progressed records.
- After matching baseline characteristics (scenario 4), treatment history and other clinical characteristics became equal to that of single-arm trial, and the OS was reduced to 4.34 months.
- The PFS showed a similar tendency to decrease survival as comparability improved (Figure 2B).

CONCLUSIONS

- The comparability with single-arm trial showed a difference in the comparative effectiveness.
- It is necessary to ensure the comparability of patients based on MAIC, and the pharmacoepidemiological design to adjust for time-related biases.

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