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Systematic Review of Secondary Primary Malignancies (SPMs) in Patients Treated with Chimeric Antigen Receptor T-cell (CAR-T) Therapies

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Key Takeaway

This research found SPMs to often be not attributed to CAR-T therapy and mostly implicate factors other than the CAR-T treatment itself in the occurrence of SPMs. However, SPMs continue to be a topic of interest in CAR-T treatments and should be diligently monitored, with further investigation focusing on potential causal factors

Conclusions

- Incidence of SPMs in CAR-T treated patients was generally low. In RCTs, CAR-T therapies were not associated with increased risk of overall SPMs; the rates of hematologic SPMs, while low, were generally numerically higher in the CAR T arms. T-cell malignancies were uncommon
- SPMs reported were often not attributed to CAR-T therapy; they were linked to co-existing risk factors such as advanced patient age, prior rounds of chemotherapy and genetic predisposition
- Ongoing evaluations continue to ensure the capture of emerging cases

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Introduction

- CAR-T cell therapies have revolutionized treatment for hematologic malignancies, delivering durable clinical responses by leveraging the patient's immune system to precisely eliminate cancer cells (1,2)
- Despite their effectiveness in relapsed/refractory disease, concerns about secondary primary malignancies (SPMs) have emerged as potential long-term risks (3,4). SPMs, distinct from the original cancer, pose a significant clinical challenge in patient management (5)
- The clinical significance of SPMs is amplified when patients have previously undergone multiple lines of therapy leading to increased oncogenic risk. This is often the case with lymphomas, leukemias and multiple myeloma in which CAR-Ts are approved
- This review aimed to summarize evidence from clinical trials and real-world studies on incidence, time to onset, mortality and causality of SPMs in patients with lymphoma, leukemia or MM treated with an FDA-approved CAR-T therapy

Methods

Study selection

- A systematic literature review (SLR) was conducted in three electronic databases (MEDLINE, Embase, and Cochrane Library) on October 01, 2024 to identify literature published in English and reporting SPM related outcomes for any of the six FDA approved CAR-T treatments (tisagenlecleucel, axicabtagene ciloleucel, brexucabtagene autoleucel, lisocabtagene maraleucel, idecabtagene vicleucel, ciltacabtagene autoleucel)
- Searches in electronic databases were supplemented by manual searches of conference proceedings, clinical trial registries and bibliography of included publications and other published reviews
- No restrictions on study type or geography were applied
- Outcomes of interest included occurrence and incidence of SPM, types of SPM, time to onset of SPM, mortality due to SPM and risk factors for SPM
- A two-stage screening process was conducted: stage 1 involved title and abstract screening, followed by stage 2, which assessed full-text publications. Each stage involved review by two reviewers acting independently; any differences were resolved by a third reviewer

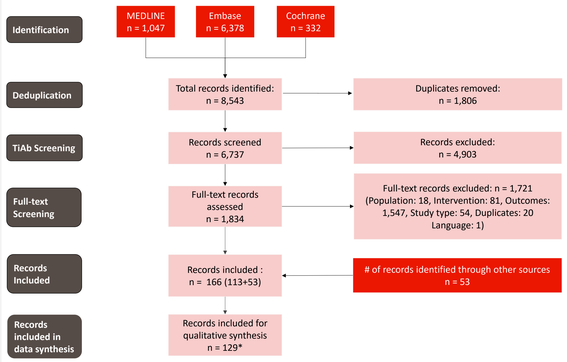
Data synthesis

- A qualitative synthesis of data captured in the review was carried out. Given the heterogeneity in the studies, meta-analysis was not carried out
- Outcomes have been presented in terms of descriptive statistics (median, IQR, range)
- Incidence of SPM has been estimated as number of cases per 100 patient years (PY) by dividing the number of SPM cases reported in a study by number of patients treated with CAR-T and the median follow-up of the study

Results

- Of 8,543 records retrieved, 113 records met the eligibility criteria. In addition, 53 records were identified from other sources, taking the total count of included studies to 166 (**Figure 1**)
- Of these, 129 records with most up to date data from respective studies were selected for synthesis, covering 4 randomized controlled trials (RCTs), 26 clinical trials, 57 observational studies, 5 case series/reports, and 5 pharmacovigilance records (FAERS, Vigibase)
- Studies were based on CAR-T treatments for patients with lymphoma (n=57), multiple myeloma (n=18), or leukemia (n=12); 11 studies had mixed populations
- Median number of prior lines of treatment was ≥3 in more than two-thirds of studies
- Most of the studies included older patients (median age > 60 in more than two-thirds of studies)

Figure 1: PRISMA Flow Diagram Depicting SLR Search Flow



*Only records with unique and most recent data for various outcomes were considered for data synthesis
TiAb, Title and Abstract

Occurrence and incidence of SPMs

- Across all indications, SPMs occurred in a median of 4.5% (IQR: 2.5-8.5%) of patients treated with a CAR-T treatment. Median incidence was 3.1 per 100PY (IQR: 1.4-4.6) (**Table 1**)
- Not counting studies reporting only myeloid SPMs, hematological SPMs accounted for about half of the SPMs (median: 46%, IQR: 25%-95%) across indications (**Table 1**)
- T-cell malignancies were uncommon with the studies reporting a median of 0% (range: 0%-2%) of patients developing a T-cell malignancy post treatment with CAR-T. The incidence of T-cell SPM ranged from 0 – 0.4 cases per 100PY
- Occurrence and incidence of SPMs was consistent across indications: lymphoma (median: 4.7% and 3.1/100PY, respectively), MM (5.9% and 3.2), and leukemia (2.3% and 2.1). The proportion of hematologic SPMs varied, accounting for a median of 46% of SPM cases in lymphoma, 23% in MM, and nearly 100% in leukemia (**Table 1**)

Table 1: Occurrence and incidence of SPMs by tumor type

	Overall	Lymphoma	MM	Leukemia
Occurrence of SPMs				
# studies (# patients)	84 (20,028)	46 (9,523)	17 (2,166)	12 (1,450)
Median (IQR), %	4.5 (2.5-8.5)	4.7 (3.3-8.1)	5.9 (4.2-8.7)	2.3 (1.6-3.1)
Incidence of SPMs				
# studies (# patients)	68 (12,496)	40 (8,510)	16 (2,083)	9 (1,244)
Median (IQR), per 100PY	3.1 (1.4-4.6)	3.1 (1.5-4.3)	3.2 (1.4-6.7)	2.1 (1.1-3.3)
Proportion of hematological SPM of total SPM				
# studies (# patients)	51 (8,573)	27 (5,289)	12 (1,012)	8 (1,206)
Median (IQR), %	46.0 (25.0-95.0)	46.0 (31.0-66.0)	23.0 (0.0-36.0)	100.0 (86.0-100.0)

MM, Multiple myeloma; PY, Patient years; SPM, Secondary primary malignancy

- In RCTs, occurrence (**Table 2**) and incidence of SPMs were comparable between CAR-T and comparator arms
  - Incidence of SPM was estimated to be 1.2 per 100PY (axi-cel) vs 0.5 (standard of care, SoC) in ZUMA-7, 1.2 (liso-cel) vs 1.6 (SoC) in TRANSFORM, 2.8 (ide-cel) vs 1.5 (SoC) in KarMMa-3, and 4.6 (cilta-cel) vs 4.1 (SoC) in CARTITUDE-4

Time to onset of SPMs

- Median time to SPM post-CAR-T infusion spanned a wide range: 3.0-38.4 months
  - Median time to onset of SPM ranged from 3.0 to 31.4 months in lymphoma, 3.4-27.6 months in MM, and 38.4 months in a single leukemia study

Table 2: Occurrence of SPMs in RCTs

RCT	Tx arm	# treated patients	Median FU, months	Any SPM, n (%)	Heme SPM, n (%)	Solid tumor, n (%)
ZUMA-7	Axi-cel	170	47.2	8 (4.7)	3 (1.8)	5 (2.9)
	SoC[a]	168		3 (1.8)	0 (0)	3 (1.8)
TRANSFORM	Liso-cel	92	33.9	3 (3.3)	NR	NR
	SoC[b]	91		4 (4.4)	NR	NR
KarMMa-3	Ide-cel	225	30.9	16 (7.1)	5 (2.2)	11 (4.9)
	SoC[c]	126		5 (4.0)	0 (0)	5 (4.0)
CARTITUDE-4	Cilta-cel	208	33.6	27 (13.0)	7 (3.4)	20 (9.6)
	SoC[d]	208		24 (11.5)	1 (0.5)	23 (11.1)

Axi-cel, axicabtagene ciloleucel; Cilta-cel, ciltacabtagene autoleucel; FU, follow-up; Ide-cel, idecabtagene vicleucel; Liso-cel, lisocabtagene maraleucel; NR, not reported; RCT, randomized controlled trial; SoC, Standard of care; SPM, Secondary primary malignancy; Tx, treatment
a,b. Platinum-based chemoimmunotherapy followed by high dose chemotherapy and stem cell transplant, c. DPd (daratumumab, pomalidomide, and dexamethasone) or DVd (daratumumab, bortezomib, and dexamethasone) or IRd (ixazomib, lenalidomide, and dexamethasone) or Kd (carfilzomib and dexamethasone) or EPd (elotuzumab, pomalidomide, and dexamethasone), d. DPd (daratumumab, pomalidomide and dexamethasone) or PVd (pomalidomide, bortezomib and dexamethasone)

Mortality due to SPMs

- Across 40 studies that reported on SPM-related deaths, there were 131 deaths, representing a median of 1.7% (IQR: 0.9-3.6) of patients treated with CAR-T therapies
  - In lymphoma, SPM-related mortality ranged from 0.2%-4.7% of treated patients (median: 1.5, IQR: 0.9-3.0)
  - In MM, mortality ranged from 0.8%-4.8% (median: 4.1, IQR: 1.7-4.2), primarily due to hematologic SPMs
  - Mortality due to SPM among leukemia patients were reported in 2 studies (0.5% and 2.2%)

Underlying causes for SPMs

- For 432 SPM cases where cause was discussed in the publications, potential contributing factors cited include advanced age (≥65), multiple rounds of prior therapy, smoking history, genetic predispositions (e.g., TP53 mutations, clonal hematopoiesis), and prior stem cell transplantation. In 194 cases, the CAR-T therapy has been explicitly stated to not be a causative factor, while in 3 cases, the SPMs were directly attributed to the CAR-T therapy
- Hematological SPMs shared similar risk factors, with myeloid neoplasms linked to prior genotoxic exposures and genetic predisposition
- Causality was generally considered challenging to establish due to limited genomic testing, small SPM sample sizes, and confounding by extensive prior treatments

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Multiple Myeloma

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