CORRESPONDENCE OPEN

Check for updates

Real-world collection of secondary myeloid neoplasms after CD19 CAR-T cell therapy: first report of the ClonHema study

Bone Marrow Transplantation (2025) 60:702–704; https://doi.org/10.1038/s41409-025-02529-x

To the Editor:

Chimeric Antigen Receptor T cell (CAR-T) therapy is a cutting-edge immunotherapy approved for the treatment of relapsed/refractory B-cell acute lymphoblastic leukemia (ALL), non-Hodgkin lymphomas (NHL), and multiple myeloma. Despite its remarkable efficacy, recent concerns have emerged regarding the risk of secondary neoplasms [1–3], particularly secondary myeloid malignancies (SMNs) [3].

CAR-T-eligible patients are often heavily pretreated, heightening their susceptibility to treatment-related adverse events, including SMN [2, 4, 5]. Specifically, NHL patients undergoing autologous stem cell transplantation (ASCT) face a 3–6% SMN incidence [6], with recent data suggesting a 38-fold increased risk [7]. However, data on SMNs following CAR-T therapy remain limited.

We retrospectively evaluated SMN development after CAR-T therapy in a multicenter, real-world study within the ClonHema trial. This study aimed to collect SMN cases post-CAR-T and prospectively assess clonal hematopoiesis (CH) before CAR-T infusion and at prolonged cytopenia or SMN onset. The study was approved by the local ethics committee (BS-NP5554), and patients provided informed consent in accordance with the Declaration of Helsinki.

Between November 2019 and May 2024, 555 patients received commercial CAR-T cells (axicabtagene ciloleucel [axi-cel], tisagenlecleucel [tisa-cel], and brexucabtagene autoleucel [brexu-cel]) across 16 Italian Centers. CAR-T indications included Diffuse Large B-Cell Lymphomas (DLBCL; $n = 432$, 77.8%), Mantle Cell Lymphomas (MCL; $n = 69$, 12.4%), Primary Mediastinal B-Cell Lymphoma ($n = 17$, 3.0%), Follicular Lymphoma (FL, $n = 15$, 2.7%) and ALL ($n = 22$, 4.0%). All patients underwent lymphodepletion chemotherapy with fludarabine and cyclophosphamide. The median follow-up was of 29 months (IQR 16–41).

Globally, 14 patients (2.5%) developed SMN, including 13 cases of myelodysplastic syndrome (MDS) and 1 case of acute myeloid leukemia (AML). The median time from CAR-T cells infusion to SMN was 7.9 months (IQR 5.8–12.6), with 10 cases (71%) occurring within the first year. Cumulative SMN incidence at 6 months, 1 year, and 4 years reached 1.1%, 1.8%, and 2.7%, respectively (Fig. 1). Two patients with MDS progressed to AML after 6 and 9 months, while two others experienced lymphoma relapse prior to SMN onset.

The median age of patients developing SMN was 61 years (IQR 56.2–65.2), and 57% ($n = 8$) were male. Nine patients had DLBCL, four had transformed DLBCL from FL, and one had MCL. Most (12, 86%) had advanced-stage disease at diagnosis, and 64% ($n = 9$) had an IPI score ≥3. Three patients had bone marrow involvement. The median number of treatment lines before CAR-T was 3 (2–6), and 7 patients (50%) underwent ASCT compared to 27% among those who did not develop SMNs ($p = 0.06$). Before CAR-T infusion, the median white blood cell count was 2.6×10^9/L (IQR 2.1–4.2), the median hemoglobin level was 9.6 g/dL (IQR 8.9–11.1), and platelet count was 102×10^9/L (IQR 71–136). Bone marrow evaluation before CAR-T has been performed in six patients (43%), revealing no morphological abnormalities, although two patients had chromosome 7 deletions (del7). Four out of five patients tested for CH carried mutations in DNMT3A, CBL, JAK3, CSF3R, and TP53.

The development of SMN was not associated with a specific CAR-T product: 6 (3.6%) were treated with Axi-cel, 7 (2.2%) with Tisa-cel, and 1 (1.1%) with Brexu-cel ($p = 0.44$). CRS grade 1–2 was observed in 12 patients (86%), with no grade 3–4, while 29% ($n = 4$) experienced grade 1–3 ICANS. Ten patients received tocilizumab, and four were also treated with dexamethasone. Notably, 71% ($n = 10$) of SMN cases had a high CAR-HEMATOTOX risk score [8], compared to 48% of those without SMN ($n = 240$/500 available patients, $p = 0.04$), suggesting a potential association despite inconsistent prior data [9].

Severe and prolonged neutropenia occurred in 9 patients (64%) within the first 30 days post-CAR-T (Early ICAHT grade 3–4), and 8 patients (57%) experienced late neutropenia beyond day 30 (Late ICAHT grade 3–4). A high early ICAHT score [10] did not correlate with late-onset cytopenia. Low platelet counts at day +90 were observed in 11 patients (79%), compared to 13% (59/450 available) in those without SMN ($p < 0.001$), further supporting its potential association with SMN onset [9]. Half of the patients received granulocyte colony-stimulating factor, and seven received erythropoietin, though none were treated with thrombopoietin mimetics. Among the variables analyzed, elevated CAR-HEMATOTOX scores and thrombocytopenia at 3 months were the only ones significantly associated with SMN development.

At MDS diagnosis, eight patients (62%) had abnormal karyotypes. Among these, 5 (38%) exhibited del7, 2 (15%) presented with a complex karyotype, and 1 showed hyperdiploidy. The AML patient also displayed a complex karyotype. Notably, two patients already had del7 prior to CAR-T therapy. The high frequency of del7 and complex karyotypes (43%, 6/14) aligns with patterns typically observed in therapy-related SMN [11, 12].

NGS analysis at SMN diagnosis was available for 11 patients (79%; Fig. 1). TP53 was the most frequently mutated gene (36%, 1 AML and 3 MDS patients), followed by mutations in DNMT3A, RUNX1, KIT, JAK3, BCOR, EZH2, NPM1, and N136K. Three patients underwent genetic analysis both pre- and post-CAR-T therapy. In one case, DNMT3A and JAK3 clones persisted at SMN onset, with additional mutations in KIT and RUNX1. In another, CSF3R and CEBPA clones present before CAR-T were no longer detectable at SMN onset, while DNMT3A and RUNX1 mutations emerged. A third patient with no detectable clones before CAR-T developed a BCOR mutation after treatment.

Nine patients had intermediate-2 or high IPSS risk MDS (Int-2 = 6 patients, High = 3 patients), while three were Low or Intermediate-1

Received: 12 October 2024 Revised: 17 January 2025 Accepted: 5 February 2025
Published online: 15 February 2025

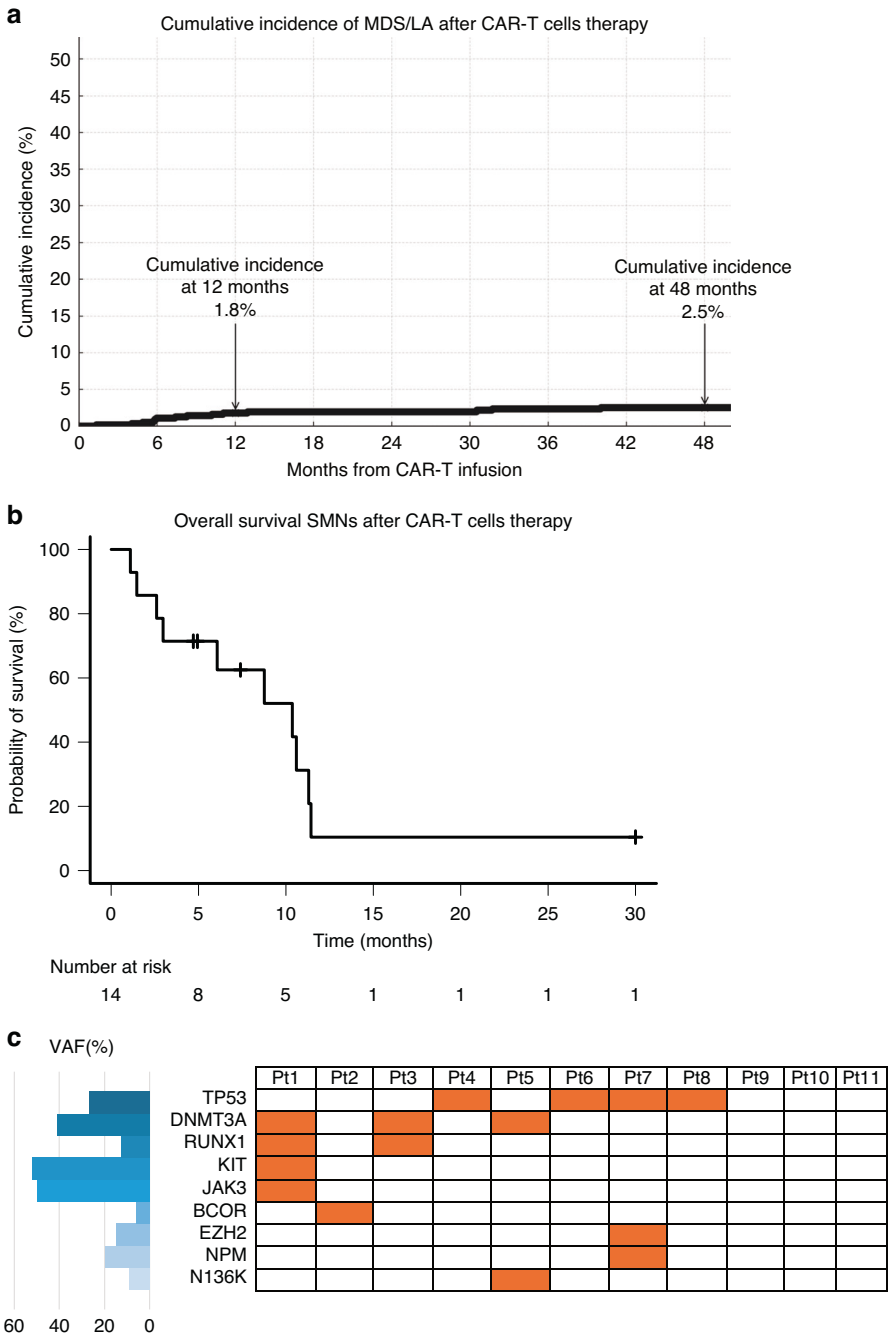

Fig. 1 Development of Secondary Myeloid Neoplasia (SMN) After CAR-T Cell Therapy. a Cumulative incidence of secondary myeloid neoplasms (SMN) following CAR-T therapy across 16 Italian centers. **b** Overall survival curve for patients with SMNs. The median overall survival was 10.4 months (95% CI 2.6–11.3), based on Kaplan–Meier analysis. **c** Mutations detected in 11 patients (79%) tested for clonal hematopoiesis at MDS onset. The Median Variant allele frequency (VAF, %) is displayed on the side.

IPSS risk (one not evaluable). Of the Int-2/High-risk group, three patients were treated with hypomethylating agents, achieved complete response (CR), and subsequently underwent allogenic stem cell transplantation (allo-SCT). Another three patients proceeded directly to upfront allo-SCT, while five (38%) received only supportive care. The patient with AML achieved CR following treatment with azacitidine and venetoclax, and later underwent allo-SCT.

The median follow-up from SMN diagnosis was 6.7 months (IQR 3.4–10.5). Prognosis for patients with SMN was poor, with a median overall survival of 10.4 months (95%CI 2.6–11.3, Fig. 1). Among the Int-2/high-risk MDS group, 78% of patients had died: 4 from transplanted-related causes, 2 from AML progression, and 1 from lymphoma relapse. In contrast, 2 of the 3 Low-Int1 patients remain alive, with 1 death due to lymphoma relapse.

Even for patients undergoing allo-SCT, median survival was only 5.5 months. Of the allotransplanted patients, 83% ($n = 5$) died: 3 (60%) from infections, 1 from multi-organ failure, and 1 from AML progression. Non-relapse mortality (NRM) at 3 months was 37.5 (95% CI 2.8–76.4), and at 6 months it rose to 58.3% (95%CI 6.1–90.1), underscoring the frailty of CAR-T patients undergoing allo-SCT. One patient developed grade-2 acute graft-versus-host disease, which was successfully treated.

Our data confirm that the incidence of SMN following CAR-T therapy is relatively low (2.5%), occurring predominantly within

the first year after CAR-T cell infusion. However, the prognosis remains poor, especially in Int-2/High-risk cases. Even allo-SCT has shown limited success in improving outcomes. Thrombocytopenia at 3 months and elevated CAR-HEMATOTOX scores appear to be predictive of SMN development, though further studies are warranted to validate these findings.

Interestingly, most patients with SMN exhibited del7 and TP53 mutations, some of which were detectable before CAR-T cell therapy. Early detection of CH with high-risk mutations could serve as a critical warning for MDS development. Prospective studies, such as the ClonHema trial, that assess CH are essential for identifying these genetic alterations and determining whether patients with high-risk mutations should receive CAR-T therapy, given the dismal outcomes associated with high-risk SMN.

Mirko Farina[1]✉, Simona Bernardi[1,2], Michele Malagola[1], Alessandro Re[3], Eugenio Galli[4], Marcello Riva[5], Ilaria Cutini[6], Alessandro Leoni[1,2], Massimo Martino[7], Silvia Ferrari[8], Giorgia Battipaglia[9], Mattia Novo[10], Maurizio Musso[11], Giovanni Grillo[12], Stella Santarone[13], Mauro Krampera[14], Andrea Aroldi[15], Nicola Polverelli[16], Luca Arcaini[16,17], Besjana Xhahysa[1,2], Daniele Avenoso[1], Maria Chiara Tisi[5], Patrizia Chiusolo[4] and Domenico Russo[1]

[1]Unit of Blood Diseases and Bone Marrow Transplantation, Cell Therapies and Hematology Research Program, Department of Clinical and Experimental Science, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. [2]Centro di Ricerca Emato-oncologico AIL (CREA), ASST Spedali Civili di Brescia, Brescia, Italy. [3]Lymphoma Unit, SOC of Hematology, ASST Spedali Civili di Brescia, Brescia, Italy. [4]Dipartimento di Scienze di Laboratorio Ed Ematologiche, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Sezione di Ematologia, Dipartimento di Scienze Radiologiche Ed Ematologiche, Università Cattolica del Sacro Cuore, Rome, Italy. [5]Hematology Unit, San Bortolo Hospital, Vicenza, Italy. [6]SOD Terapie Cellulari e Medicina Trasfusionale, Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy. [7]Stem Cell Transplantation and Cellular Therapies Unit (CTMO), Department of Hemato-Oncology and Radiotherapy, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy. [8]Department of Oncology and Hematology, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy. [9]Haematology Department and Department of Clinical Medicine and Surgery, Federico II University of Naples, Naples, Italy. [10]Division of Hematology, AOU Città Della Salute e Della Scienza di Torino, Torino, Italy. [11]UOC di oncoematologia e TMO "La Maddalena", Palermo, Italy. [12]Dipartimento di Ematologia e trapianto di midollo, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy. [13]Hematology Unit, Department of Oncology and Hematology Pescara Hospital, Pescara, Italy. [14]Hematology and Bone Marrow Transplant Unit, Section of Biomedicine of Innovation, Department of Engineering for Innovative Medicine (DIMI), University of Verona, Verona, Italy. [15]Hematology Division and Bone Marrow Transplant Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy. [16]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [17]Department of Molecular Medicine, University of Pavia, Pavia, Italy. ✉email: mirkfar@gmail.com

REFERENCES

1. Elsallab M, Ellithi M, Lunning MA, D'Angelo C, Ma J, Perales MA, et al. Second primary malignancies after commercial CAR T-cell therapy: analysis of the FDA Adverse Events Reporting System. Blood. 2024;143:2099–105.
2. Ghilardi G, Fraietta JA, Gerson JN, Van Deerlin VM, Morrissette JJD, Caponetti GC, et al. T cell lymphoma and secondary primary malignancy risk after commercial CAR T cell therapy. Nat Med. 2024;30:984–9.
3. Hamilton MP, Sugio T, Noordenbos T, Shi S, Bulterys PL, Liu CL, et al. Risk of second tumors and T-cell lymphoma after CAR T-cell therapy. N Engl J Med. 2024;390:2047–60.
4. Accorsi Buttini E, Farina M, Lorenzi L, Polverelli N, Radici V, Morello E, et al. High risk-myelodysplastic syndrome following CAR T-cell therapy in a patient with relapsed diffuse large B cell lymphoma: a case report and literature review. Front Oncol. 2023;13. https://doi.org/10.3389/FONC.2023.1036455.
5. Galli E, Frioni F, Malara T, Attardi E, Bellesi S, Hohaus S, et al. FLT3 mutated acute myeloid leukemia after CD19 CAR-T cells. Mediterr J Hematol Infect Dis. 2024;16. https://doi.org/10.4084/MJHID.2024.029.
6. Zhan Z, Guo W, Wan X, Bai O. Second primary malignancies in non-Hodgkin lymphoma: epidemiology and risk factors. Ann Hematol. 2023;102:249–59.
7. Trab T, Baech J, Jakobsen LH, Husby S, Severinsen MT, Eloranta S, et al. Second primary malignancies in patients with lymphoma in Denmark after high-dose chemotherapy and autologous haematopoietic stem-cell transplantation: a population-based, retrospective cohort study. Lancet Haematol. 2023;10:e838–48.
8. Rejeski K, Perez A, Sesques P, Hoster E, Berger C, Jentzsch L, et al. CAR-HEMATOTOX: a model for CAR T-cell–related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021;138:2499–513.
9. Barone A, Chiappella A, Casadei B, Bramanti S, Ljevar S, Chiusolo P, et al. Secondary primary malignancies after CD-19 directed CAR-T-cell therapy in lymphomas: a report from the Italian CART-SIE study. Br J Haematol. 2024; https://doi.org/10.1111/BJH.19590.
10. Rejeski K, Subklewe M, Aljurf M, Bachy E, Balduzzi A, Barba P, et al. Immune effector cell-associated hematotoxicity: EHA/EBMT consensus grading and best practice recommendations. Blood. 2023;142:865–77.
11. Farina M, Bernardi S, Gandolfi L, Zanaglio C, Morello E, Turra A, et al. Case Report: late onset of myelodysplastic syndrome from donor progenitor cells after allogeneic stem cell transplantation. which lessons can we draw from the reported case? Front Oncol. 2020;10:564521.
12. Strickland SA, Vey N. Diagnosis and treatment of therapy-related acute myeloid leukemia. Crit Rev Oncol Hematol. 2022;171. https://doi.org/10.1016/J.CRITREVONC.2022.103607.

AUTHOR CONTRIBUTIONS

MF, SB, MiM, and DR designed the study and wrote the paper. MF, AR, EG, MR, IC, AL, MasM, SF, GB, MN, MauM, GG, SS, MK, AA, NP, LA, BX, DA, MCT, and PC collected data and wrote the paper. MF performed the statistical analysis. All authors revised the manuscript and accepted the final version of the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Mirko Farina.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.