Hematologic complications in patients exposed to poly-ADP ribose polymerase inhibitors

Poly ADP-ribose polymerase (PARP) inhibitors are a treatment for solid tumors with mutations in *BRCA1, BRCA2*, or other genes conferring homologous repair deficiency.[1] PARP inhibitors are approved for treatment of platinum-sensitive ovarian cancers, and *BRCA1/2* mutated solid tumors, including fallopian tube, breast, prostate, pancreatic, and primary peritoneal cancers.[1-3]

PARP inhibitor trial data, retrospective cohort study, and pharmacovigilance analysis demonstrated an increased likelihood of therapy-related myeloid neoplasms (t-MN) among patients exposed to all PARP inhibitors, particularly olaparib.[4-7] Multiple patient cohorts treated with PARP inhibitors describe t-MN incidence in 1.5% to 8.7% of patients.[5,8,9] These t-MN cohorts largely examine patients with primary ovarian cancer, and demonstrate enrichment in adverse cytogenetic findings, and poor risk *TP53* and *PPM1D* mutations.[5,7-11] Outcomes are generally poor even for patients without evidence of their treated solid tumor, with median overall survival of 4.3 to 18 months.[9,11,12]

The accumulating evidence for t-MN secondary to PARP inhibitor exposure and expanding indications for PARP inhibitor treatment results in frequent hematology referrals. To inform such referrals, we summarized our institutional experience, including clinical data, available germline data, laboratory findings, age, duration of PARP inhibitor exposure, and outcomes of all patients treated with PARP inhibitors who underwent a bone marrow biopsy.

With approval from our Institutional Review Board (IRB), we reviewed institutional records from January 2014 to November 2023. We identified 265 adult patients prescribed a PARP inhibitor for any solid tumor indication and 17 patients who had a bone marrow biopsy after starting treatment. We also reviewed our leukemia registry and identified 5 patients with blood cancer and prior exposure to PARP inhibitors. All diagnoses used the 2022 ICC guidelines.[12] We used the Kaplan-Meier method to assess overall survival and Student *t* test to compare peripheral blood counts between patients with and without a t-MN.

We identified 265 patients treated with PARP inhibitors at our institution and five referred for management of t-MN after PARP inhibitor treatment in community practice; 22 patients had a bone marrow biopsy performed for cytopenias after PARP inhibitor treatment (Figure 1A). Bone marrow biopsies were prompted by unexplained sustained cytopenias or macrocytosis found in the course of treatment. None of these patients had prior cytopenias suggestive of clonal hematopoiesis (CH) or clonal cytopenias of undetermined potential (CCUS), and no next-generation sequencing (NGS) was available to inform the presence or absence of CH/CCUS prior to cancer-directed therapies. NGS described here were obtained from bone marrow biopsy samples. Among the 22 patients with biopsies, 13 (59%) were diagnosed with a t-MN, one (5%) had cytomegalovirus-driven hemophagocytic lymphohistiocytosis (HLH), and one (5%) had a myelophthisic process. Excluding patients with an existing t-MN diagnosis, 6.4% (17/265) of institutional cohort patients underwent bone marrow biopsy. t-MN incidence was 3.0% (8/265) among patients with confirmed PARP inhibitor exposure at our institution (Figure 1B). Bone marrow biopsy resulted in a diagnosis in 59% (10/17), with the remainder attributed to therapy toxicity. t-MN was diagnosed in 47% (8/17, Figure 1C), including 2 t-CCUS patients, 6 therapy-related myelodysplastic syndrome (t-MDS) patients, and one therapy-related acute myeloid leukemia (t-AML) patient. The clinical and laboratory features of these patients are summarized in Table 1 (see *Online Supplementary Table S1* for t-MN details) alongside those of patients who underwent a bone marrow biopsy without a t-MN diagnosis. Compared to the 9 patients without t-MN diagnoses, leukocytes were not reduced (P=0.06), but neutrophils (P=0.03) and platelets (P=0.02) were lower in the t-MN group (Table 1, Figure 1C-F). Median time to t-MN diagnosis was 4.75 years from initial solid tumor diagnosis (Interquartile range [IQR] 3.68 to 7.95 years) and 1.93 years from the start of PARP inhibitor therapy (IQR 1.35 to 4.12 years). The median survival for patients with high-risk t-MN was 159 days (N=9) and 148 days for patients receiving treatment (N=8) (Figure 2A, B). These patients were treated with hypomethylating agents in combination with venetoclax or on clinical trials. None received induction with intensive chemotherapy or allogeneic stem cell transplant.

There was no significant difference in age at biopsy, number of cytopenias, duration of PARP inhibitor exposure, type of PARP inhibitor, solid tumor diagnosis, or the presence of germline mutations between patients with and without t-MN (Table 1). The t-MN that developed in PARP-exposed patients were enriched for *TP53* mutations (N=9/13, 69%), as has been reported by others (Figure 2C).[5,7-9] Of these patients, 4 (44% of *TP53*-mutated and 31% of the total t-MN cohort) had biallelic *TP53* mutations. Similarly, among 11 patients with available data, 8 (77%) had a complex or adverse-risk karyotype, consistent with other studies.[7-9] Of the patients who developed a t-MN, 5 were diagnosed within 60 days of discontinuation of PARP inhibitor (Figure 2D). Eight died of their t-MN, 3 died of their solid tumor, and 2 are still alive. Patients underwent

a diagnostic bone marrow biopsy at time of t-MN diagnosis and subsequent biopsies to assess treatment response. We hypothesized that germline mutations in *BRCA1, BRCA2*, or other DNA damage response genes would increase genomic risk of t-MN development in patients with germline mutations (Figure 2C). However, no significant difference in the distribution of germline mutations was observed across patients with t-MN and those without t-MN (Table 1). Whether patients with germline mutations are at increased risk will require a larger cohort exposure analysis. Risk of t-MN with PARP inhibitor treatment is present regardless of germline mutational status, which is consistent with other single center reports.[13]

PARP inhibitors increase the risk of CH, so we hypothesized that our cohort would be enriched in patients with CH. Except for *TP53*, our institutional NGS panel (*Online Supplementary Table S2*) found CH-associated mutations in only 3 patients with bone marrow biopsies (18%). Patient 5, with a germline *BRCA2* (p.K1381fs*) mutation, had a clonal del(7q) (3.5% of cells by FISH) and no mutations on NGS. A classic CH-associated *DNMT3A* mutation (p.Q816* VAF 7%) was detected in a 45-year-old patient with thrombocytopenia and normal bone marrow findings (*Online Supplementary Table S1*). Patient 10 had a CH-related *TET2* mutation (p.S271fs, VAF 31%) on diagnosis with t-MDS on rucaparib. Mutations in protein phosphatase magnesium-dependent 1 delta (*PPM1D*) following PARP inhibitor maintenance were found in 39% of a separate cohort, but no *PPM1D* mutations were observed in our cohort.[11]

Notably, the t-MN in our patient cohort had a low peripheral blast burden despite adverse-risk molecular characteristics, making bone marrow evaluation essential for t-MN diagnosis in these patients. For patients on PARP inhibitors at the time of t-MN diagnosis, peripheral blasts ranged from 0 to 5%, with a higher bone marrow blast

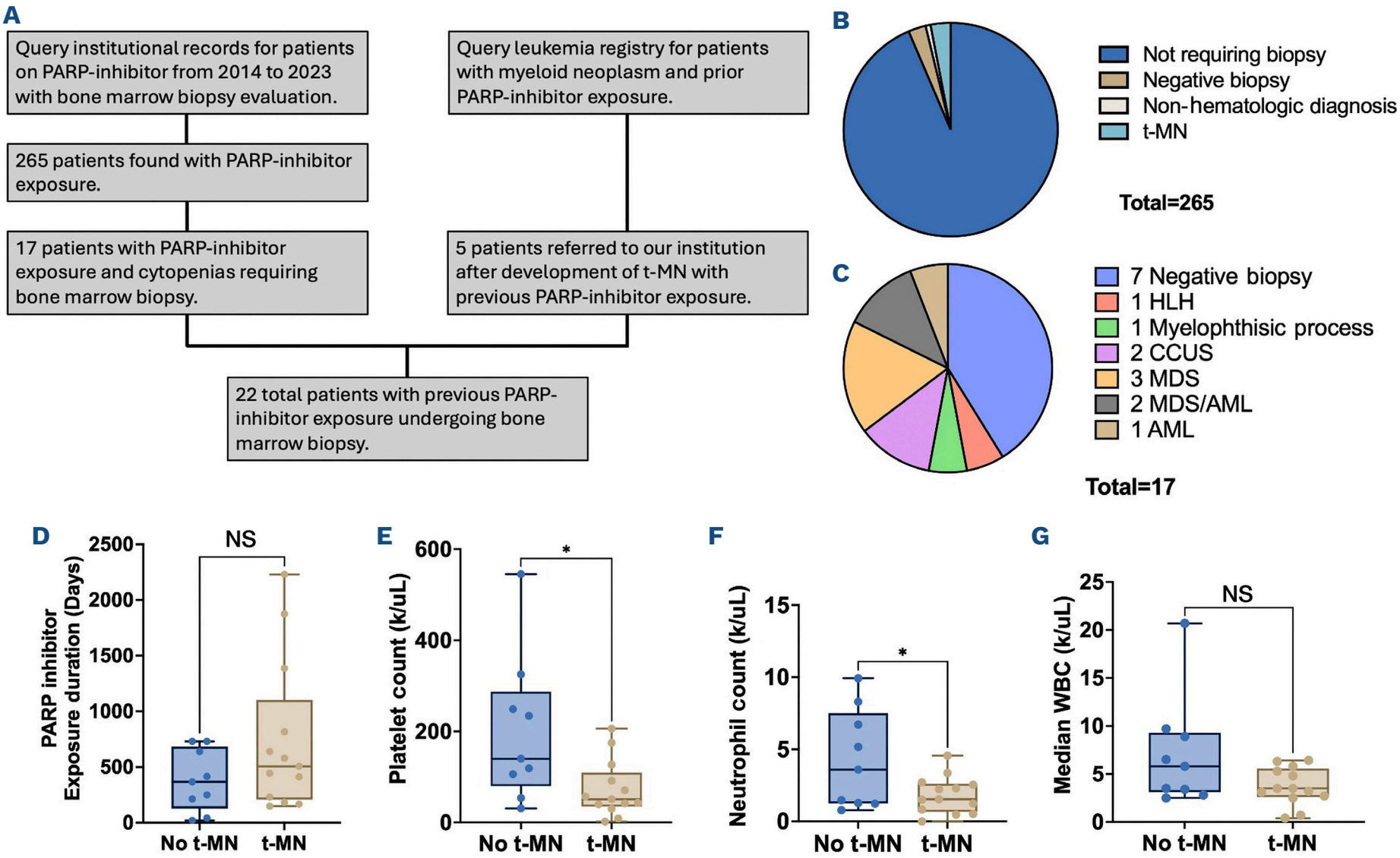

Figure 1. Comparison of clinical features of patients undergoing bone marrow biopsy after poly ADP-ribose polymerase inhibitor exposure. (A) CONSORT plot of patients included in this study. (B) Pie plot showing the proportion of patients who did not undergo bone marrow (BM) biopsies (N=248) and patients who underwent BM biopsies (N=17), those with non-hematologic findings (N=2), negative biopsy (N=7), and therapy-related myeloid neoplasms (t-MN) (N=8). (C) Pie plot showing diagnoses from BM biopsies: no diagnosis (N=7), hemophagocytic lymphohistiocytosis (HLH) (N=1), myelophthisic process (N=1), therapy-related clonal cytopenias of undetermined potential (t-CCUS) (N=2), therapy-related myelodysplastic syndromes (t-MDS) (N=3), t-MDS/acute myeloid leukemia (AML) (N=2), and therapy-related AML (t-AML) (N=1). (D) Duration of poly-ADP-ribose polymerase (PARP) exposure in patients with (gold) and without (blue) diagnoses of t-MN. (E) Platelet count in patients with (gold) and without (blue) diagnoses of t-MN. (F) Neutrophil count in patients with (gold) and without (blue) diagnoses of t-MN. (G) White blood cell (WBC) count in patients with (gold) and without (blue) diagnoses of t-MN. *P<0.05. NS: not significant.

percentage (0-70%). We noted that Patient 13 presented with overt erythroid lineage atypia and a low frequency del(5q) clone after six months of olaparib treatment, leading to a diagnosis of t-MDS. The initial bone marrow noted del(5q) and erythroid hyperplasia and atypia with binucleate pronormoblasts and megaloblastoid precursors, both of which resolved on subsequent bone marrow biopsies three and nine months following olaparib discontinuation (*Online Supplementary Figure S1*). A similar pattern has been reported with PARP inhibitor-associated CH, which can regress with drug discontinuation.[14,15]

In conclusion, this study reinforces the importance of bone marrow biopsy in PARP inhibitor-exposed patients with persistent leukopenia, neutropenia, or thrombocytopenia, even without the presence of peripheral blasts. We found that 6.4% of patients exposed to PARP inhibitors underwent bone marrow biopsies and 3.0% developed t-MN, including t-AML. These patients were enriched with high-risk molecular features, including *TP53* mutations and complex karyotypes, largely consistent with prior reports except for a lack of mutations in *PPM1D*.[5,9,10,15] None of the patients in our cohort underwent allogeneic transplant, but limited cases on PARP inhibitor t-MN cases and transplant data in *TP53*-mutated AML/MDS indicate a high rate of relapse.[12,13] The median survival for our patients with high-risk t-MN was 159 days, which is consistent with other reports and reflects a dire need for novel treatments in *TP53*-mutated myeloid disease.[8-11] *TP53* was the only molecular alteration in most patients, which supports the clonal expansion of either an existing *TP53* clone or therapy-related mutation. However, the small sample size of patients with bone marrow biopsies limited our analysis, and lack of available NGS data at onset of PARP inhibitor treatment does not rule out clonal expansion of existing *TP53* hematopoietic clones, perhaps under selective pressure of PARP inhibitor treatment. This cohort demonstrates the frequent diagnosis of t-MN despite low or absent peripheral blasts, supporting the use of bone marrow biopsy in patients with PARP inhibitor exposure and unexplained cytopenias. t-MN occurred in patients with and without germline mutations, so blood cancer risk in PARP-exposed patients is increased regardless of

Table 1. Laboratory and clinical features of 22 poly-ADP-ribose polymerase inhibitor-exposed patients who underwent bone marrow biopsy evaluation for a therapy-related myeloid neoplasm.

Characteristics at BM biopsy	Patients diagnosed with blood cancer, N=13	Patients without blood cancer N=9	*P*
Leukocyte count, $10^3/\mu L$ (IQR)	3.5 (2.7-5.3)	5.8 (3.4-8.9)	0.06
Median neutrophil count, $10^3/\mu L$ (IQR)	1.5 (0.8-2.5)	3.59 (1.3-6.7)	0.02*
Median hemoglobin, g/dL (IQR)	8.7 (7.5-10.6)	10.2 (7.6-11.4)	0.7
Median MCV, fL (IQR)	91.3 (87.3-113.6)	100.6 (99.6-108.1)	0.5
Median platelets, $x10^9/L$ (IQR)	51 (40-92)	140 (106-249)	0.02*
Median peripheral blasts, % (IQR)	0 (0-2)	0 (0-0)	0.1
N of cytopenias (IQR)	2.3 (2-3)	1.7 (1-2)	0.17
Median age at first cancer diagnosis, years (IQR)	62 (50-65)	56 (50-68)	0.6
Primary tumor type, N (%) Ovarian cancer Breast cancer Prostate cancer Pancreatic cancer	 9 (69) 1 (8) 2 (15) 1 (8)	 8 (89) 1 (11) 0 (0) 0 (0)	0.5
Median age at BM biopsy, years (IQR)	66 (59-72.5)	58 (56-68)	0.65
Known germline mutation, N (%)	8 (61.5)	4 (44.4)	0.4
PARP inhibitor, N (%) Olaparib Rucaparib Niraparib	 10 (83) 1 (8) 1 (8)	 6 (60) 3 (30) 1 (10)	0.4
Median duration of PARP inhibitor exposure, days (IQR)	506 (231-817)	250 (213-639)	0.15

Values in parentheses show the interquartile range (IQR). Student *t* test was used to compare the two groups. BM: bone marrow; MCV: mean corpuscular volume; N: number; PARP inhibitor: poly-ADP-ribose polymerase inhibitor; WBC: white blood cell count. *Denotes statistical significance.

the presence of germline mutations.
Our findings suggest that further research is needed into risk factors for these t-MN and the mechanisms driving PARP inhibitor-associated hematologic malignancies, and that their clinical use should incorporate evaluation for t-MN if chronic cytopenias develop.

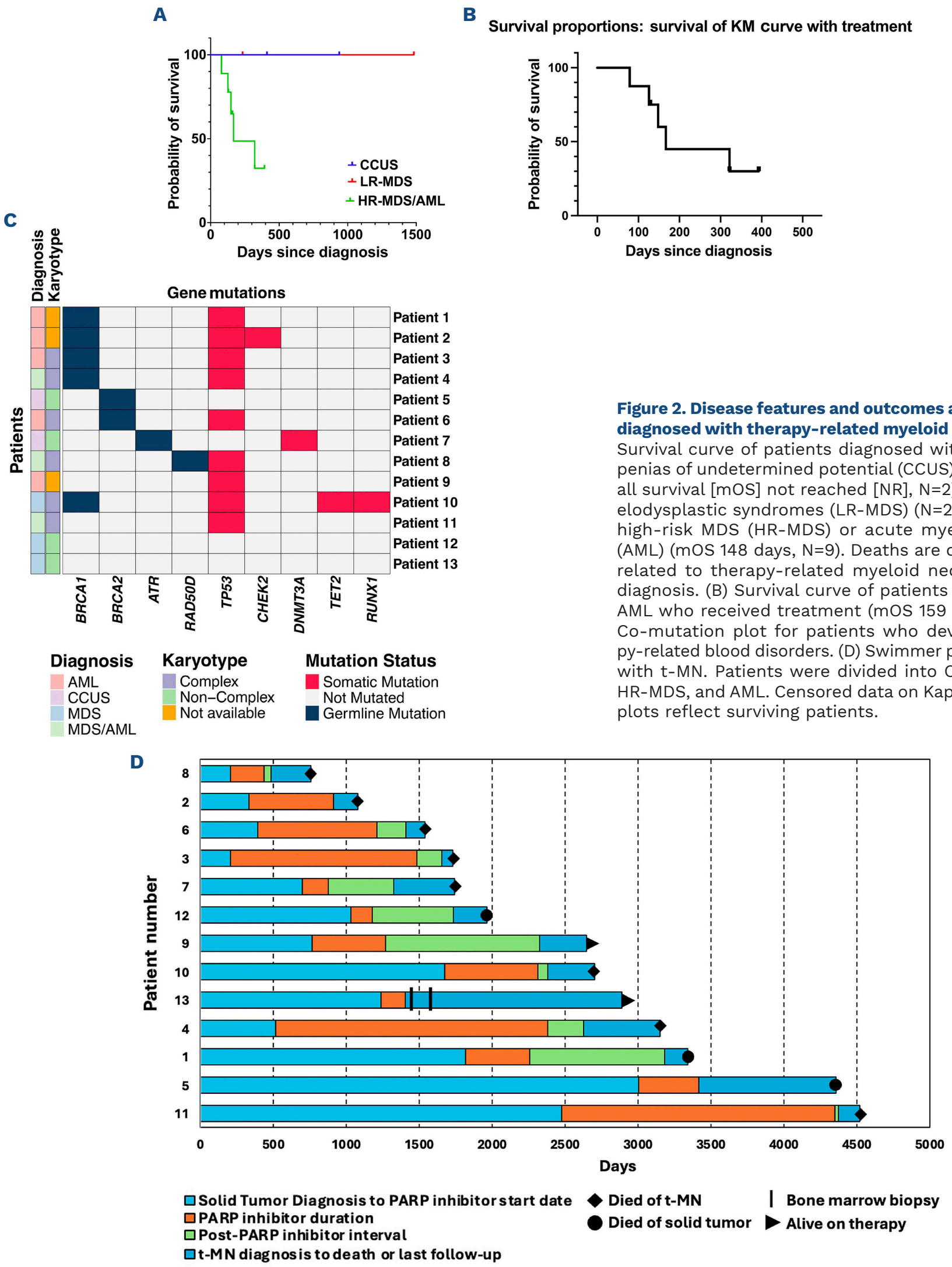

Figure 2. Disease features and outcomes among patients diagnosed with therapy-related myeloid neoplasms. (A) Survival curve of patients diagnosed with clonal cytopenias of undetermined potential (CCUS) (median overall survival [mOS] not reached [NR], N=2), low-risk myelodysplastic syndromes (LR-MDS) (N=2 mOS NR), and high-risk MDS (HR-MDS) or acute myeloid leukemia (AML) (mOS 148 days, N=9). Deaths are censored if unrelated to therapy-related myeloid neoplasm (t-MN) diagnosis. (B) Survival curve of patients with HR-MDS/AML who received treatment (mOS 159 days, N=8). (C) Co-mutation plot for patients who developed therapy-related blood disorders. (D) Swimmer plot for patients with t-MN. Patients were divided into CCUS, LR-MDS, HR-MDS, and AML. Censored data on Kaplan-Meier (KM) plots reflect surviving patients.

Authors

Joseph M. Cannova,[1] Muriel R. Battaglia,[1] Gregory W. Roloff,[1] Sinan Cetin,[1] Michael Tallarico,[2] Wendy Stock,[1] Anand A. Patel,[1] Olatoyosi Odenike,[1] Richard A. Larson,[1] Michael J. Thirman,[1] Mariam T. Nawas,[1] Peng Wang,[3] Melissa Y. Tjota,[3] Jeremy P. Segal,[3] Girish Venkataraman,[3] Adam S. DuVall[1,4] and Michael W. Drazer[1,5]

[1]Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL; [2]Northwest Cancer Centers, Dyer, IN; [3]Department of Pathology, University of Chicago, Chicago, IL; [4]Section of Hematology/Oncology, Department of Pediatrics, University of Chicago, Chicago, IL and [5]Section of Genetic Medicine, Department of Medicine, University of Chicago, Chicago, IL, USA

Correspondence:
M.W. DRAZER - michaeldrazer@uchicagomedicine.org

https://doi.org/10.3324/haematol.2025.288518

Received: June 20, 2025.
Accepted: January 16, 2026.
Early view: January 29, 2026.

Disclosures

GWR reports advisory roles for Autolus and Kite; WS reports advisory roles for Kura, Servier, Newave and Asofarma; AAP reports advisory roles for AbbVie, Celgene/BMS and Sobi, and institutional research funding from Pfizer, Kronos Bio and Sumitomo; OO reports advisory roles for AbbVie, Celgene/BMS, Novartis, Incyte, Kymera therapeutics, Servier and Rigel, data safety board for Treadwell Therapeutics, and institutional research funding from AbbVie, AstraZeneca, Celgene, Curis, Incyte, Shattuck Labs and K-group alpha; MJT reports consulting for AbbVie, AstraZeneca, Celgene, Jannsen, Pharmacyclics and Roche/Genentech, research funding from Gilead, Jannsen, Merck, Nurix, Pharmacyclics, Syndax and TG therapeutics, and institutional research funding from AbbVie; RAL reports consulting for AbbVie, Amgen, Ariad/Takeda, Astellas, Celgene/BMS, Curis, CVS/Caremark, Epizyme, Immunogen, Jazz Pharmaceuticals, Kling Biotherapeutics, MedPace, MorphoSys, Novartis and Servier, institutional clinical research support from Astellas, Celgene, Cellectis, Daiichi Sankyo, Forty Seven/Gilead, Novartis and Rafael Pharmaceuticals, and royalties from UpToDate; ASD reports speaker's fees from CE Concepts; MWD reports consulting or advisory roles for Argenx, honoraria for educational writing from the American Society of Hematology Self-Assessment Program, and honoraria from Novartis.

Contributions

MWD and ASD conceived the study; MWD, ASD, JMC, MRB, SC and GWR collected and analyzed the data; MWD, JMC, GWR, MT, WS, AAP, OO, RAL, MJT, MTN, GV and ASD cared for the patients; GV, PW, MJT and JPS performed molecular pathology testing and reporting; JMC and MWD drafted the manuscript. All authors edited the manuscript.

Acknowledgments

We thank our patients who participated in this research.

Funding

This work was supported by the National Institutes of Health Clinical Therapeutics award (to JMC) and the National Institutes of Health Loan Repayment Program.

Data-sharing statement

Genomic data are available on request to the corresponding author.

References

1. Drew Y, Zenke FT, Curtin NJ. DNA damage response inhibitors in cancer therapy: lessons from the past, current status and future implications. Nat Rev Drug Discov. 2025;24(1):19-39.
2. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. J Clin Oncol. 2015;33(3):244-250.
3. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med. 2015;373(18):1697-1708.
4. Poveda A, Floquet A, Ledermann JA, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22(5):620-631.
5. Marmouset V, Decroocq J, Garciaz S, et al. Therapy-related myeloid neoplasms following PARP inhibitors: real-life experience. Clin Cancer Res. 2022;28(23):5211-5220.
6. Zhao Q, Ma P, Fu P, et al. Myelodysplastic syndrome/acute myeloid leukemia following the use of poly-ADP ribose polymerase (PARP) inhibitors: a real-world analysis of postmarketing surveillance data. Front Pharmacol. 2022;13:912256.
7. Morice PM, Leary A, Dolladille C, et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol. 2021;8(2):e122-e134.
8. Oliveira JL, Greipp PT, Rangan A, Jatoi A, Nguyen PL. Myeloid malignancies in cancer patients treated with poly(ADP-ribose) polymerase (PARP) inhibitors: a case series. Blood Cancer J. 2022;12(1):11.
9. Todisco E, Gigli F, Ronchini C, et al. Hematological disorders after salvage PARP inhibitor treatment for ovarian cancer:

cytogenetic and molecular defects and clinical outcomes. Int J Cancer. 2022;151(10):1791-1803.
10. Martin JE, Khalife-Hachem S, Grinda T, et al. Therapy-related myeloid neoplasms following treatment with PARP inhibitors: new molecular insights. Ann Oncol. 2021;32(8):1046-1048.
11. Chiusolo P, Marchetti C, Rossi M, et al. A common pattern of somatic mutations in t-MDS/AML of patients treated with PARP inhibitors for metastatic ovarian cancer. Am J Hematol. 2022;97(11):E400-E403.
12. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
13. Valenza C, Mongillo M, Gigli F, et al. Germline BRCA pathogenic variants in patients with ovarian cancer and post-poly (ADP-ribose) polymerase inhibitor myeloid neoplasms. ESMO Open. 2024;9(9):103685.
14. Marshall CH, Gondek LP, Daniels V, et al. Association of PARP inhibitor treatment on the prevalence and progression of clonal hematopoiesis in patients with advanced prostate cancer. Prostate. 2024;84(10):954-958.
15. Nuttall Musson E, Miller RE, Mansour MR, Lockley M, Ledermann JA, Payne EM. Monitoring clone dynamics and reversibility in clonal haematopoiesis and myelodysplastic neoplasm associated with PARP inhibitor therapy-a role for early monitoring and intervention. Leukemia. 2024;38(1):215-218.