Therapy-related myeloid neoplasms following treatment with PARP inhibitors: new molecular insights

J.E. Martin, S. Khalife-Hachem, T. Grinda, M. Kfoury, S. Garciaz, F. Pasquier, J. Vargaftig, M. Uzunov, A. Belhabri, S. Bertoli, et al.

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LETTER TO THE EDITOR

Therapy-related myeloid neoplasms following treatment with PARP inhibitors: new molecular insights

Clonal selection is one of the mechanisms leading to therapy-related myeloid neoplasms (TRMN). A preexisting somatic mutation in hematopoietic stem cells [defined as clonal hematopoiesis (CH)] emerging under the pressure of chemotherapy or radiotherapy treatment could ultimately lead to TRMN development.[1] Most of the mutations identified in TRMN, such as *TP53* and *PPM1D*, belong to the DNA damage response (DDR) pathway and are known to confer a dismal prognosis. The poly(ADP-ribose) polymerase inhibitors (PARPi) have shown promising results in several cancers, especially in ovarian cancers (OC).[2] Recently, Morice et al.[3] confirmed in a meta-analysis an increased risk of TRMN after PARPi administration. In this context, we aimed to describe the prevalence and evolution of CH and TRMN following PARPi treatment in patients treated for OC, with the goal of better understanding the molecular mechanisms underlying hematological disease development (Patients and methods and NGS Results, available at https://doi.org/10.1016/j.annonc.2021.04.05).

Firstly, we retrospectively identified, with the help of the UNIHEM group of Unicancer, 20 patients with myelodysplastic syndrome (11; 55%) or acute myeloid leukemia (AML) (9; 45%) occurring during or after PARPi administration (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.04.015). Median duration of PARPi treatment was 17 months (3-57 months). TRMN-PARPi occurred 2 years (range: 0.4-4.8 years) after PARPi initiation and 1.6 months (range: 0.4-17.6 months) after PARPi discontinuation (Figure 1A). All patients had unfavorable karyotypes, of which 19 of 20 (95%) had complex karyotypes; 10 of 12 (83%) harbored next-generation sequencing (NGS) mutations in the DDR genes. Despite 11 (55%) patients with OC in complete remission, median overall survival was 4.3 months (95% confidence interval 2.1 months to not reached). Secondly, we identified 36 OC patients with or without PARPi maintenance treatment and free of hematological disease, to compare occurrence of CH. Median duration of PARPi treatment was 11.2 months (range: 0.4-45.8 months) and Median time between PARPi beginning and NGS, months (range) 8.5 (1.1-15.6). No significant differences in terms of patient characteristics were found between the two groups. CH was found in 14 of 18 patients (78%) in the PARPi group compared to 7 of 18 patients without PARPi maintenance (39%) ($P = 0.018$, Figure 1B; Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.04.015). Twelve (67%) patients treated with PARPi harbored CH mutations in the DDR pathway (Figure 1C) compared to 3 of 18 patients without PARPi maintenance (16.7%) ($P = 0.002$). Lastly, we sequenced nine paired specimens pre-and post-PARPi treatment (Figure 1D for TRMN; Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2021.04.015 for CH) showing that mutations emerged or expanded during PARPi treatment.

Predicting AML was considered hitherto impossible. The democratization of NGS and the description of CH have changed this paradigm. The clinical abruptness of AML contrasts with the biological step-by-step development of the disease. Some patients may have years before a founding clone at a low level, emerging and leading to AML, especially *TP53* mutations.[4] CH incidence is ~38% in gynecological cancer with an enrichment in DDR gene mutations.[5] Our data support the hypothesis that PARPi therapy may act by exerting a selective pressure that boosts clonal expansion, especially *TP53* and *PPM1D* mutations. The clinical benefit of PARPi treatment as a maintenance therapy for OC patients is not questionable but our data raise the question of identification and potential preventive strategies in patients who are considered at high risk of developing TRMN.

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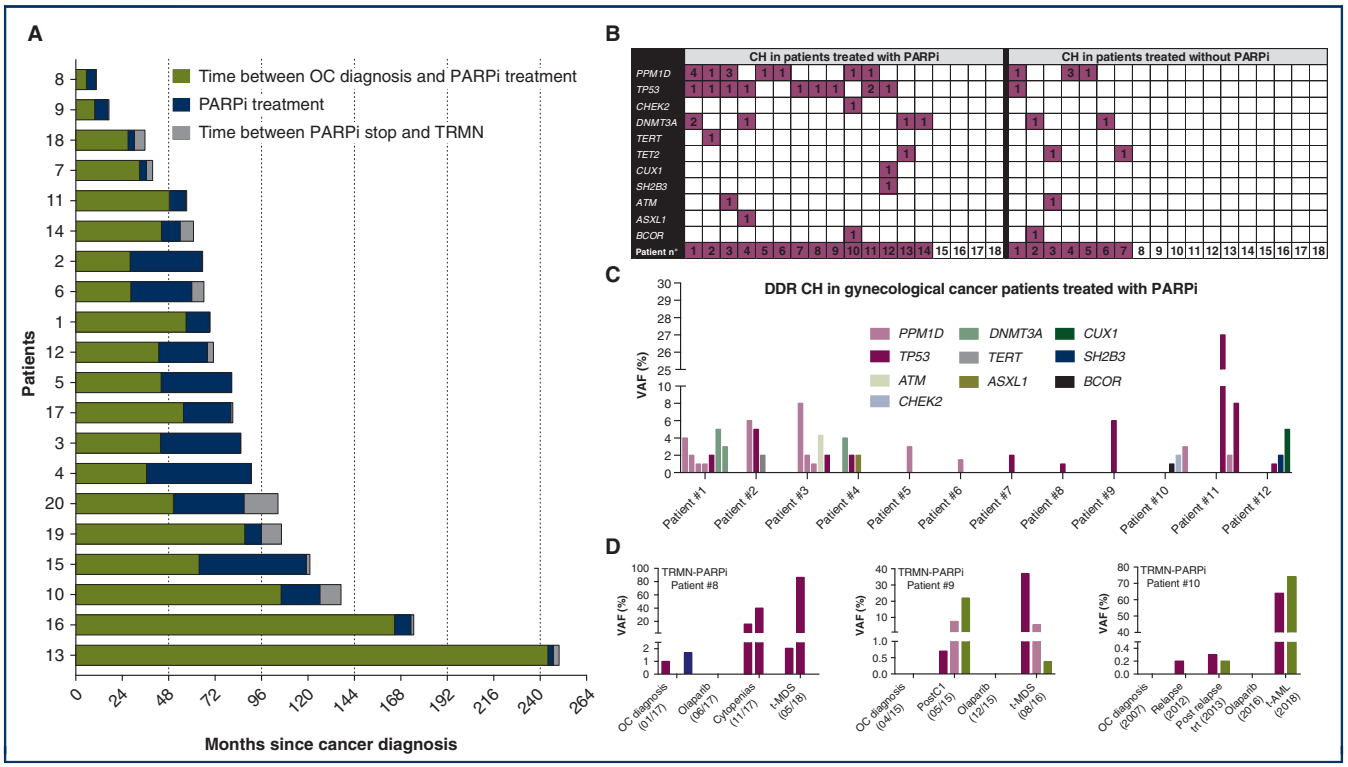

Figure 1. Clinical and molecular characteristics of therapy-related myeloid neoplasm and clonal hematopoiesis of patients treated with PARP inhibitor.
(A) Time between OC diagnosis, PARPi treatment, and TRMN; (B) gene mutations in OC patients without TRMN treated with or without PARPi; (C) DDR gene mutation CH in OC patients following PARPi treatment; and (D) sequential NGS samples from cancer diagnosis to TRMN-PARPi diagnosis.
CH, clonal hematopoiesis; DDR, DNA damage response; NGS, next-generation sequencing; OC, ovarian cancer; PARPi, poly(ADP-ribose) polymerase inhibitors; t-AML, therapy-related acute myeloid leukemia; t-MDS, therapy-related myelodysplastic syndrome; TRMN, therapy-related myeloid neoplasms; trt, treatment; VAF, variant allele frequency.

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