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Review Article

Myeloid neoplasms on poly (ADP-ribose) polymerase inhibitor therapy

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ABSTRACT

Poly (ADP-ribose) polymerase inhibitor (PARPi) therapy is progressively accruing more indications. Given their overall survival benefit in many solid organ tumors, they are here to stay. However, an emerging concern is the risk of therapy-related acute myeloid leukemia. A recent meta-analysis has reported a higher risk of myeloid neoplasms while on PARPi therapy. These patients tend to have underlying tumor protein 53 (TP53) mutated clonal hematopoiesis and have complex karyotypes with poor outcomes. Underlying mechanisms and optimal treatment are currently unknown. In this narrative review, we detail the current evidence available on this entity and compare it with the underlying knowledge of therapy-related myeloid neoplasms.

Keywords: Poly (ADP-ribose) polymerase inhibitors, Acute myeloid leukemia, Myelodysplastic syndromes, Myelodysplastic syndrome, TP53, Clonal hematopoiesis, Complex karyotype

INTRODUCTION

Poly (ADP-ribose) polymerase inhibitors (PARPis), while predominantly being used in patients with solid malignancies with impaired homologous recombination repair, have an upcoming role in patients of acute myeloid leukemia (AML) with runt-related transcription factor 1 (*RUNX1)*-RUNX1 partner transcriptional co-repressor 1 *(RUNX1T1)*/ promyelocytic leukemia (PML)-retinoic acid receptor alpha *(RARα)* fusions or fms like tyrosine kinase 3 (*FLT3)*/isocitrate dehydrogenase 1 (*IDH1)* mutations.[1] However, reports of therapy-related AML on PARPi therapy are a parallel emerging concern. This review details the current evidence about the possible mechanism, clinical features, outcomes, and possible prevention of myeloid neoplasms associated with PARPi therapy.

PRIMER ON THERAPY-RELATED ACUTE MYELOID LEUKEMIA (TAML)

The World Health Organization (WHO) classification of hematological malignancies defines tAML as a "late complication of cytotoxic chemotherapy and/or radiation therapy administered for a prior neoplastic or non-neoplastic disorder."[2]

EPIDEMIOLOGY

The median age of tAML onset is around 60 years.[3] Around 80% of all tAML cases have a history of chemotherapy administration for a prior malignant disorder (solid malignancy: 70% and hematological malignancy: 30%). The remaining 20% of patients have a history of chemotherapy exposure for a

benign disorder/stem cell transplantation for benign disease.[3] Prior chemotherapy exposure leads to a nearly five-fold increase in the risk of tAML, amounting to nearly 30 additional cases of Myelodysplastic syndrome (MDS)/AML/10,000 person-years.[3] Patients receiving therapy for Hodgkin's disease/non-Hodgkin lymphoma/multiple myeloma have a higher risk of tAML/MDS, which is sustained after 5 years of therapy completion as well (in contrast to patients with prior solid organ malignancy).[3]

PATHOGENESIS

The following agents are known to lead to tAML/MDS[2]

- Alkylating agents: Melphalan, cyclophosphamide, nitrogen mustard, chlorambucil, busulfan, carboplatin, cisplatin, Dacarbazine, procarbazine, carmustine, mitomycin C, thiotepa, and Lomustine
- Ionizing radiation therapy (Large fields only, the impact of currently used limited field RT is currently unknown)
- Topoisomerase II inhibitors
- Antimetabolites: Thiopurines, mycophenolate mofetil, and fludarabine
- Anti-tubulin agents: Vinca alkaloids and taxanes.

Although clubbed together, tAML can consist of at least two entities with distinct clinicopathological, molecular, and prognostic features: tAML after alkylator/radiotherapy exposure and tAML after topoisomerase II inhibitor exposure. Cases of tAML with prior alkylator/radiotherapy exposure occur after a 5–7-year latency period, have an antecedent myelodysplastic phase, and are more commonly associated with complex karyotype/deletion 5q/deletion 17p/monosomies, and have an age-dependent risk.[4] On the other hand, patients with prior topoisomerase II inhibitor exposure develop tAML within 1–3 years of exposure, without a prior MDS, and commonly have alterations in the histone-lysine N-methyltransferase 2A (KMT2A) (11q23) or the RUNX1 (21q22) genes.[5] In addition, patients with prior topoisomerase II exposure seem to respond better to anti-leukemic therapy.[6]

Multiple hypotheses attempt to explain the pathogenesis (and susceptibility) of tAML. A higher incidence of underlying mutations involving DNA damage repair/chemotherapy agent metabolism might explain why only a handful minority face this complication.[7] Accumulating DNA aberrations in critical chromosomal regions may also explain this association.[8] More recent work suggests that modulation of underlying clonal hematopoiesis (CH) may have a role. More specifically, chemotherapy leads to the expansion of underlying CH clones with TP53 or PPM1D mutations CH.[9]

CYTOGENETIC FEATURES, MUTATIONAL PROFILE, AND OUTCOMES

More than 90% of all tAML cases have a detectable clonal chromosomal abnormality, with partial loss of chromosome 5/7 and complex chromosomal abnormalities being the most common.[10] In addition, nearly half of all tAML cases have mutations in TP53. Compared to its *de novo* counterpart, tAML also shows enrichment of PPM1D mutations.[11] Other commonly mutated genes in AML with prior chemotherapy exposure include tet methylcytosine dioxygenase 2 (TET2), protein tyrosine phosphatase non-receptor type 11 (PTPN11), IDH1, IDH2, neuroblastoma RAS viral oncogene homolog (NRAS), and FLT3.[6] The outcomes of tAML are poorer compared to its *de novo* counterpart. Patients with adverse cytogenetics or TP53 mutations have particularly poor survival.[4]

PARPI-RELATED MYELOID NEOPLASMS

Does PARPi therapy lead to myeloid neoplasms?

Just like the aforementioned tAML counterparts, myeloid neoplasms after PARPi therapy are rare events, and individual trials are unlikely to be adequately powered to note a difference. However, trials evaluating PARPi maintenance (with the most extended follow-up and patient exposure) hinted at a possible causal link.[12] A meta-analysis subsequently confirmed this association and reported a 2.63 times increased risk of AML and a 2.25 times increased risk of AML/MDS in patients with prior PARPi therapy compared to patients receiving chemotherapy alone.[13] Like its counterparts mentioned above, PARPi therapy expands underlying TP53/Protein Phosphatase, Mg2+/Mn2+ Dependent 1D (PPM1D) mutated clones.[3]

CLINICOPATHOLOGICAL FEATURES

Three studies detail the features of myeloid malignancies in patients with prior PARPi use [Table 1]. The first recent study reported 20 such cases (11 MDS and 9 AML). Almost all patients had received Olaparib for underlying ovarian cancer. The median latency period was 2 years, and 95% of cases had an underlying complex karyotype. Notably, 83% of patients had an underlying mutation involving DNA damage repair machinery. PARPi therapy leads to the expansion of clonal hematopoesis of indeterminate potential (CHIP) clones with mutations in the DNA damage repair (DDR) genes (78% vs. 39%).[14]

More recently, a meta-analysis of prospective trials adding PARPi to cytotoxic chemotherapy and cases reported in the WHO pharmacovigilance database detailed the clinical details of this entity. These patients had a median age of 64 years, 85% had underlying ovarian cancer, and the median therapy duration was 9.8 months (Range: 0.2–66.8 months). The median latency from exposure to myeloid neoplasms was 20.3 months (Range: 18.7–22.1 months). Prior therapy, specific drugs, underlying homologous repair deficient (HRD), or treatment setting (induction vs. maintenance) did not impact the risk of having a subsequent myeloid neoplasm. Clinical features of the cases reported to the VigiBase were also reported. At least 14 of the reported cases

Table 1: Studies reporting characteristics of myeloid malignancies with prior PARP inhibitor use.

Study	Sample size	Underlying malignancy	Agent	Myeloid neoplasm	Cytogenetics	Mutational profile	Status of underlying malignancy	Overall survival (Median)
Martin *et al.*	20	Ovarian	Olaparib (94%) Rucaparib (6%)	AML (45%) MDS (55%)	Complex karyotype: 95%	DDR pathway mutations in 83%	55% in complete remission	4.3 months
Kwan *et al.*	22	Ovarian	Rucaparib	AML (41%) MDS (59%)	Complex karyotype: 53% Alteration in chromosome 5/7: 80%	NR	NR	NR
Morice *et al.*	178	Ovarian (85%) Prostate (7%) Breast (5%) Pancreatic (2%)	Olaparib (75%) Niraparib (18%) Rucaparib (6%) Talazoparib (1%) Veliparib (1%)	AML (44%) MDS (56%)	NR	NR	Response sustained (85%) Progressive disease (15%)	NR (45% died)

PARP: Poly (ADP-ribose) polymerase, AML: Acute myeloid leukemia, DDR: DNA damage repair, MDS: Myelodysplastic syndrome, NR: Not reported

had an antecedent MDS phase, and most cases presented with anemia well into the 7th or 8th month of therapy (unlike the usual drug-related cytopenias). While cytogenetic and molecular profile was not reported, 45% of patients had succumbed to the illness at the time of reporting, with only 9% of patients having improved on therapy.[13]

More recent insights come from the retrospective review of patients enrolled in the rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL) 2/3 studies. Notably, nearly half of the 22 cases reported in these trials (ovarian carcinoma on rucaparib maintenance) had a complex karyotype. On paired sequencing analysis of these patients (along with controls), an underlying TP53 mutated (VAF> 1%) CHIP led to a five-fold increase in the risk of subsequent myeloid neoplasms. In addition, these TP53 mutated CHIP were the only subset of CH to show expansion after PARPi therapy. Furthermore, given the lack of impact of somatic versus germline mutations on the risk of myeloid neoplasms, it seems evident that DDR mutations in the primary malignancy do not portend a higher risk.[15] Of note, the longer median follow-up duration accounts for the preponderance of underlying ovarian cancer in these patients. While the OlympiA trial has reported no increase in cases of MDS or AML as of yet (Median follow-up: 2.5 years, AML cases in Olaparib arm: 2, AML cases in placebo arm: 3), longer follow-up remains prudent.[16] Clinical trials done on patients with prostate cancer have considerably shorter follow-ups. However, while the Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B) trial reported a single case of AML,[17] other trials have not reported any to date.[18-25]

FUTURE DIRECTIONS

Given the capacity of PARPi to prolong survival in many solid organ tumors, they are here to stay.[1] Furthermore, prolonged survival on these drugs may lead to a survivorship bias resulting in a higher incidence of myeloid neoplasms stemming from prior chemotherapy. In this regard, long-term follow-up data of trials using PARPi in frontline settings without prior alkylator/topoisomerase inhibitor exposure (e.g., carcinoma prostate) may shed some light.[23] Until that time comes, optimizing patient selection to maximize the risk-benefit balance in our favor seems prudent. Furthermore, using an underlying TP53 mutated CHIP as a biomarker for patient selection remains an exciting avenue needing further research.

CONCLUSION

PARPi therapy leads to an increased risk of myeloid neoplasms with a comparable latency period and adverse cytogenetic abnormalities. While underlying germline mutations may not impact the risk, mutation profiles of pre-existing CH may modulate the risk, and patients with an underlying TP53 mutated CHIP may be particularly susceptible. More evidence is needed regarding insights for optimal patient selection and treatment.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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