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SHORT COMMUNICATION

Characterization of therapy-related acute leukemia in hereditary breast-ovarian carcinoma patients: role of *BRCA1* mutation and topoisomerase II-directed therapy

Bhausaheb Bagal[1,5] · Rohit Kumar[2] · Tarang Gaur[2] · Vikas Talreja[1] · Avinash Bonda[1,5] · Nikhil Patkar[1,5] · Dhanlaxmi Shetty[1] · Pradnya Kowtal[3] · P. G. Subramanian[1,5] · Sudeep Gupta[4,5] · Rajiv Sarin[3,5] · Syed K. Hasan[1,2,5]

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Abstract

Therapy-related acute leukemias (t-ALs) represent approximately 10–20% of all acute leukemias, are frequently resistant to chemotherapy, and are associated with guarded outcomes. The national comprehensive cancer network data suggest that t-AL cases are diagnosed at increasing rates in breast cancer patients treated with chemotherapeutic agents targeting topoisomerase II. Two cases of *BRCA1*-mutated ovarian and breast carcinoma who developed therapy-related APL and ALL, respectively, following topoisomerase II-directed therapy were characterized. Genomic characterization of therapy-related acute promyelocytic leukemia (t-APL) revealed a unique *RARA* intron 2 breakpoint (Chr17: 40347487) at 3′-end of *RARA* corroborating breakpoint clustering in t-APL following topoisomerase II inhibition. Both cases of this series harbored germline *BRCA1* mutations. The germline *BRCA1* mutation in patient with t-APL was detected in exon 8 (HGVS nucleotide: c.512dupT). This mutation in t-APL is extremely rare. Interestingly, t-ALL patient in this series had a *BRCA1* mutation (HGVS nucleotide: c.68_69delAG; BIC designation: 187delAG) identical to a previously reported case after the treatment of same primary disease. It is unlikely that two breast cancer patients with identical *BRCA1* mutation receiving topoisomerase II-targeted agents for the primary disease developed t-AL by chance. This report highlights the development of t-AL in *BRAC1*-mutated hereditary breast and ovarian cancer patients and warrants further studies on functional consequences of topoisomerase inhibition in this setting.

Keywords Therapy-related leukemia · Germline *BRCA1* · Breast cancer · Topoisomerase II

Introduction

Therapy-related acute leukemias (t-ALs) are well-recognized complications in cancer patients, mainly those diagnosed with highly curable diseases [1]. Breast cancer is by far the most common primary solid tumor reported in patients with t-AL. Breast cancer patients treated with adjuvant therapy are at two-fold increased risk of developing t-AL compared to controls [2, 3]. The t-ALs represent approximately 10–20% of all acute leukemias, is frequently resistant to chemotherapy, and is almost invariably fatal [4–6]. The national comprehensive cancer network data [7] also suggest that the t-AL cases are diagnosed at increasing rates in breast cancer patients treated with chemotherapy. There are several features that distinguish t-AL from de novo AL, including a higher incidence of TP53 mutations abnormalities of chromosomes 5 or 7, complex cytogenetics, and a reduced response to chemotherapy [8]. Treatment-induced

Bhausaheb Bagal and Rohit Kumar have contributed equally to this work.

✉ Syed K. Hasan
shasan@actrec.gov.in

1 Adult Hemato-Lymphoid Disease Management Group, Tata Memorial Hospital, Mumbai 400012, India

2 Cell and Tumor Biology Group, Advanced Centre for Treatment, Research and Education in Cancer, Tata Memorial Centre, Sector 22, Raintree street, Kharghar, Navi Mumbai, Maharashtra 410210, India

3 Genome Biology Group, Advanced Centre for Treatment, Research and Education in Cancer, Navi Mumbai 410210, India

4 Department of Medical Oncology, Tata Memorial Centre, Mumbai 400012, India

5 Homi Bhabha National Institute (HBNI), Anushaktinagar, Mumbai 400094, India

DNA damage has been a focus of research in t-AL. It has also been reported that inefficient DNA damage repair may promote chromosomal aberrations in cancer patients undergoing genotoxic therapies targeting topoisomerase II [9–14]. A comprehensive screening of hereditary breast and ovarian cancer (HBOC) supports the role of deleterious mutations of genes involved in DNA repair and maintenance of genomic integrity in the etiology of t-AL [15]. Here two cases of t-AL arising after HBOC treated with agents targeting topoisomerase II were characterized.

Materials and methods

UPN1

A 38-year-old female was diagnosed in July 2008 with ovarian high-grade serous carcinoma. The genetic counselling and following testing revealed *BRCA1* mutation (c.512dupT) with a strong family history of malignancies (breast and ovarian cancer in maternal and stomach cancer in the paternal side) (Fig. 1a). She received 6 cycles of adjuvant chemotherapy with paclitaxel and carboplatin. Subsequent to first and second relapses, patient was treated with docetaxel-carboplatin and cisplatin-gemcitabine, respectively. At the time of third relapse in October 2013, six cycles of liposomal doxorubicin and paclitaxel were administered. After this line of therapy, she remained in remission for 19 months and later developed brain metastasis in May 2015 (fourth relapse). Following brain metastasis, she was started on oral etoposide. After 1 year of treatment, computed tomography scan revealed progressive disease (fifth relapse). She was started on cisplatin and paclitaxel. She responded to chemotherapy but developed severe myelosuppression, and hence, her chemotherapy had to be stopped. Subsequently, her anemia and thrombocytopenia worsened and peripheral smear revealed 51% abnormal promyelocytes in December 2016. Bone marrow was suggestive of acute promyelocytic leukemia (APL).

UPN2

A 47-year-old female presented with triple-negative breast cancer in June 2016. In view of the strong family history of cancer, genetic counselling and testing were done, which revealed *BRCA1* mutation (c.68_69delAG) (Fig. 1b). She received adjuvant chemotherapy with 4 cycles of anthracycline-based chemotherapy (topoisomerase II inhibitor) followed by 12 cycles of weekly paclitaxel. This was followed by local adjuvant radiotherapy to breast. Her treatment was completed in May 2017. During routine follow-up, a decline in platelet counts was observed in October 2018. The bone

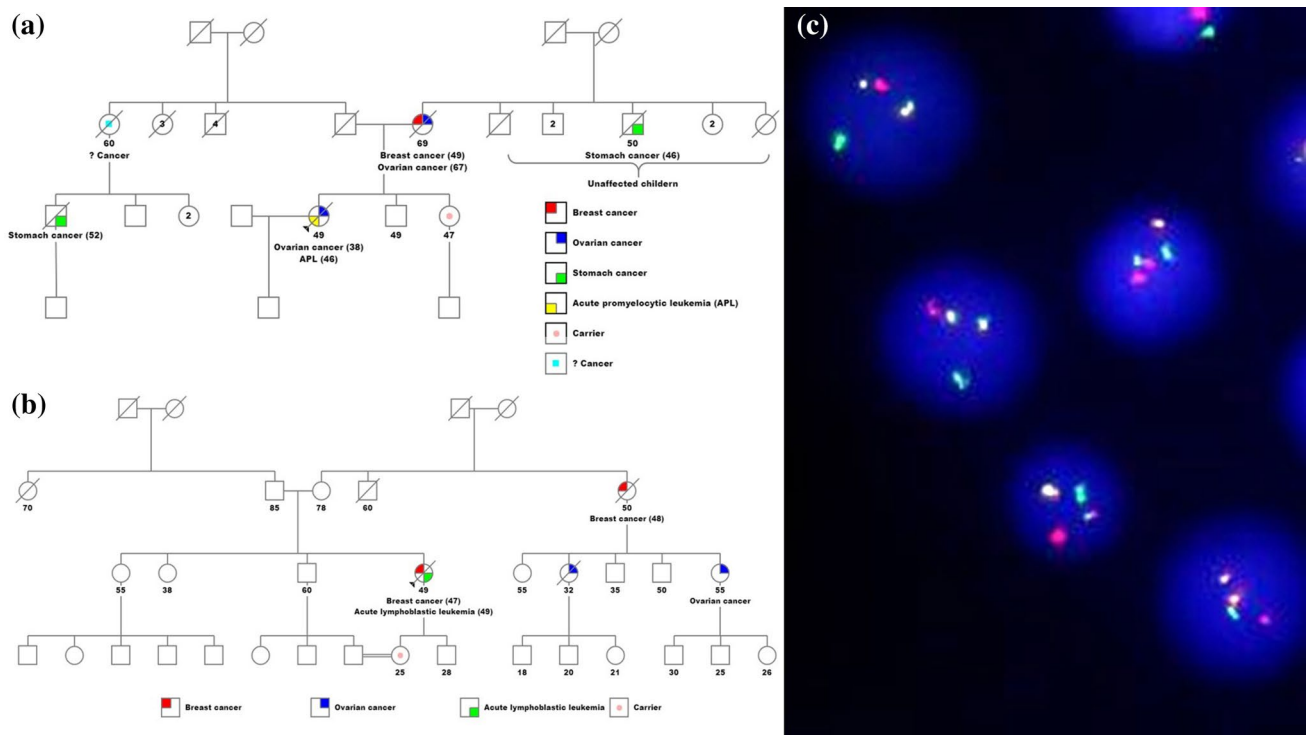

Fig. 1 Pedigrees and fluorescence in situ hybridization (FISH) assay. **a** Pedigree of UPN1. **b** Pedigree of UPN2. **c** Interphase FISH with Abott Molecular LSI *PML-RARA* dual color dual fusion probe showing 2 copies of *PML-RARA* fusion (Yellow signals), one copy of *PML* (Red signal), and one copy of *RARA* (Green signal)

marrow morphology and flow cytometry-based immunophenotyping confirmed the diagnosis of pre-B ALL. The patient was negative for the common translocations by FISH (fluorescent in situ hybridization), and ploidy analysis on 20 metaphases revealed diploidy. The Ph-like ALL FISH panel was also negative. The patient was treated with modified BFM-90 protocol [16] and achieved morphological remission after induction treatment. She was started consolidation in March 2019, and marrow studies at the end of consolidation showed progressive disease (16% blasts and high burden of minimal residual disease). Because of aggressive disease and guarded outcomes, family opted for supportive care and she succumbed to the disease in May 2019.

FISH, qualitative, and quantitative PCR

FISH was performed on an unstimulated bone marrow aspirate using LSI *PML-RARA* dual color dual fusion probe (DCDF) (Abbott Molecular, Abbott Park, IL, USA) for UPN1. Minimum 200 interphase cells were analyzed using GenASIs, Netser-Sereni, Israel software. The standard reference range (threshold) for this probe is 2%. This FISH panel for UPN2 consisted of the *BCR-ABL1*, *TCF3-PBX1* dual color dual fusion probe, MLL rearrangement probe (Abbott Molecular, Abbott Park, IL, USA), and centromeric probes for chromosomes 4, 10, and 17 (ZytoVision, Bremerhaven, Germany). Additionally, DNA ploidy analysis using the Giemsa stain was performed. Besides this, Ph-like ALL characterization was also performed which consisted of *ABL1, ABL2, CRLF2, CSF1R* (ZytoVision, Bremerhaven, Germany), *PDGFRβ* (Leica Biosystems, Nussloch, Germany) dual color rearrangement, and *IKZF1* (Agilent sureFISH, Santa Clara, USA) dual color deletion probe. GenASIs software was used for both FISH and ploidy analyses (GenASIs, Netser-Sereni, Israel).

DNA and RNA were extracted from 200 µL bone marrow sample (UPN1) according to the manufacturer's protocol (QIAamp DNA, RNA extraction kits, Qiagen, GmbH Germany). 1000 ng of total RNA was used for cDNA synthesis using the TaqMan Reverse Transcription Reagent kit (Applied Biosystems). Abelson (*ABL*) gene was used as an internal control to assess the quality of cDNA. Qualitative and quantitative RT-PCR for *PML-RARA* was performed according to BIOMED guidelines [17, 18]. Genomic *PML-RARA* was also quantified using patient-specific primers and probe (designed based on *PML* and *RARA* breakpoints) and fresh aliquots of DNA collected at time of post-induction and during follow-up.

Characterization of the der(15) and der(17) genomic breakpoint junctions of *PML-RARA*

The *PML-RARA* genomic rearrangement was examined in the DNA of UPN1 prepared from leukemic marrow cells cryopreserved at the time of t-APL diagnosis. By the use of a two-step long-range nested PCR assay, the *PML* (3 kb) and *RARA* (16.9 kb) breakpoint spanning DNA regions were covered using 2 *PML* forward primers and 8 *RARA* reverse primers.

Direct DNA sequencing of *PML* and *RARA* genomic breakpoints

PML-RARA PCR products encompassing the breakpoint regions were purified with Qiagen PCR purification kit (Limburg, the Netherlands). To identify the exact location of the *PML* and *RARA* breakpoints, purified PCR products were sequenced. Purified amplicons were directly sequenced using the BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) and resolved on an ABI 3130 automated sequencer (Applied Biosystems) starting with *PML* forward primers and the *RARA* reverse primers. *PML* and *RARA* gene annotations were adapted using the University of California at Santa Cruz (UCSC) Genome Browser Reference Sequence (RefSeq) gene track.

Results and discussion

t(15;17) and sequential monitoring of *PML-RARA*

Cytogenetic analyses by FISH showed evidence of t(15;17) in 80% cells (Fig. 1c). The qualitative and quantitative real-time PCR showed positivity for *PML-RARA* short transcript (bcr3 isoform) and *PML-RARA* normalized copy number (NCN) 2.56%, respectively. The sequential *PML-RARA* monitoring by DNA- and RNA-based real-time PCR is shown in Fig. 2a. The APL was treated with all-trans retinoic acid (ATRA)- and arsenic trioxide (ATO)-based protocol [19]. She had a quick response to ATO-ATRA induction and achieved molecular remission post-induction therapy and later finished her consolidation with ATO-ATRA. While her APL remained in molecular remission, she passed away in March 2019 due to brain metastasis from primary ovarian carcinoma.

Genomic *PML-RARA* breakpoint characterization

By the use of two-step long-range nested PCR assay (Fig. 2b) and direct sequencing, the breakpoint junction nucleotides in *PML* and *RARA* genes were identified (Fig. 2c) in UPN1. After confirming the breakpoint locations in the *PML* and *RARA* loci, patient-specific primers in the vicinity of the breakpoint regions of *PML* and *RARA* were designed. In the patient-specific assay, a fresh aliquot of DNA from UPN1 was used to validate the results of long-range nested PCR. In addition to *PML-RARA*, the reciprocal *RARA-PML* was also

(a)

Date	Type of sample	*PML-RARA* copies (RNA vs DNA)	*ABL* copies (RNA vs DNA)	Normalized copy number (NCN) %
January 2017	Baseline* (Bone marrow)	34900	1371000	2.54
February 2017	Post induction (Bone marrow)	1285 vs 2130	186200 vs 127000	0.69 vs 1.67
September 2017	Follow up# (Bone marrow)	0	1198000	0
April 2018	Follow up# (Bone Marrow)	0	142800	0

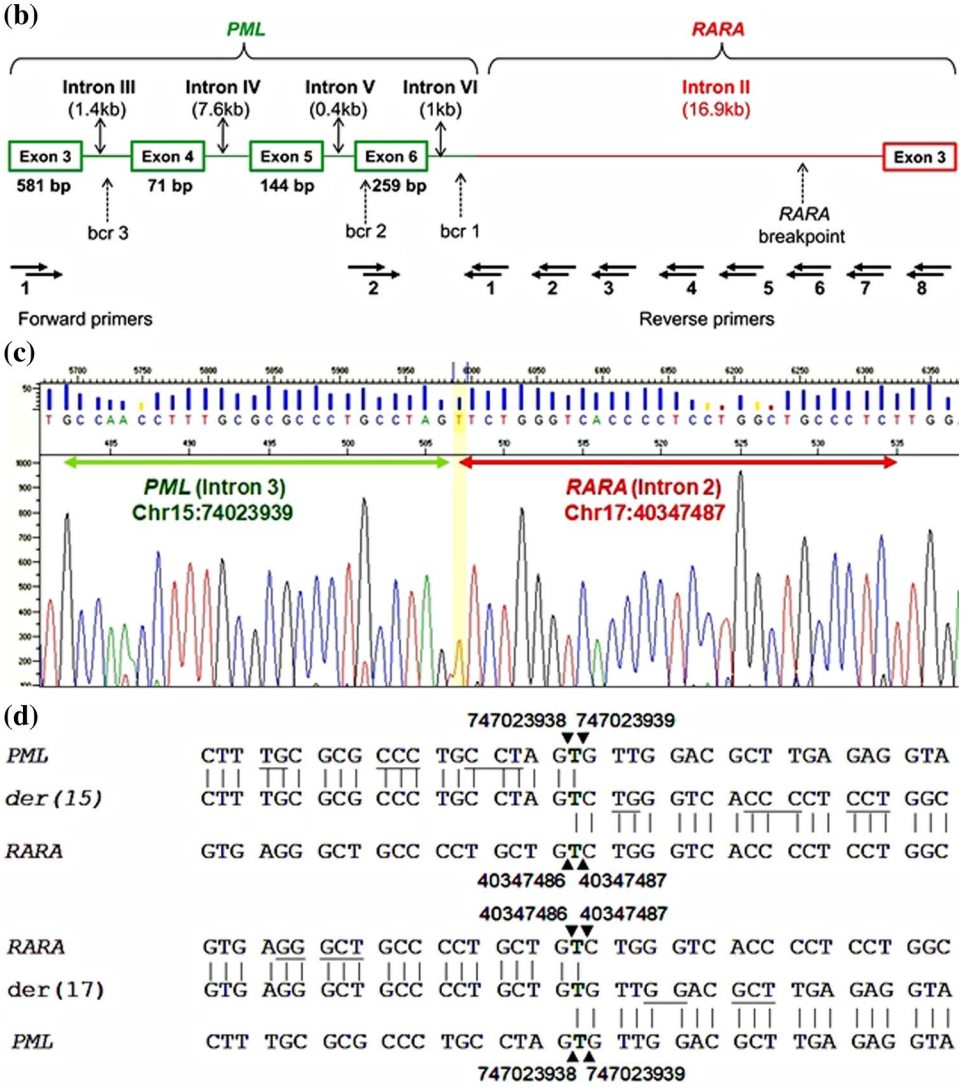

Fig. 2 Molecular characterization and kinetics of *PML-RARA*. **a** *PML-RARA* kinetics by real-time quantitative PCR for UPN1 (*At baseline, only RNA-based RQ-PCR was performed; #Results of RNA-based RQ PCR are shown; however, DNA-based RQ- PCR results were incomplete concordance with RNA-based RQ-PCR data). **b** Positioning of primers for genomic *PML-RARA* amplification by two-step long-range nested PCR assay. Dashed arrows indicate location of breakpoint cluster regions (bcr) at *PML* (green) and *RARA* loci (red). **c** Chromatogram showing the genomic breakpoints at the *PML* and *RARA* loci in UPN1. The presence of common nucleotide (T) at the breakpoint junction precludes the precise location of the breakpoint. *PML* (genomic coordinate chr15: 73994673–74043337) and *RARA* (genomic coordinate chr17: 40309194–40356796) gene annotations were adapted using the University of California at Santa Cruz (UCSC) Genome Browser Reference Sequence (RefSeq) gene track. **d** Perfectly balanced reciprocal translocation in UPN1 without any additional changes in the nucleotides at the breakpoint junction. Underline nucleotides indicate microhomologies at the breakpoint junction

amplified using fresh aliquots of DNA and patient-specific primers. Breakpoint spanning sequences were identified by alignment to the breakpoint cluster regions of *PML* (genomic coordinates chr15:73994673–74043337) and *RARA* (genomic coordinates chr17:40309194–40356796) using the NCBI/alignment tool. In UPN1, the *PML* breakpoint was located in intron 3 at nucleotide position chr15:74023939. The *RARA* breakpoint was in intron 2 at nucleotide position chr17:40347487. The breakpoint junction sequence analysis revealed a common nucleotide (thymine) at the *PML-RARA* junction (Fig. 2d). Two to three bp microhomologies at the breakpoint junction revealed that the DNA repair process in this region was mediated by the error-prone non-homologous end-joining (NHEJ) pathway (Fig. 2d upper and lower panels).

Although the *PML* breakpoint hotspot region in intron 6 has been identified in t-APL cases, there is no such region reported in *RARA* intron 2. However, significant clustering of

RARA breakpoints at 3′-end of intron 2 has been reported in t-APL patients compared to de novo APL cases. The *RARA* breakpoint of UPN2 was found at 3′-end and in extremely close vicinity of a reported case of t-APL. The UPN1 *RARA* breakpoint was only 6 bp upstream of a laryngeal carcinoma patient who developed t-APL [9]. Regarding *RARA* breakpoints distribution, clustering in a 3′-region of intron 2 has been reported in 65% of t-APL as compared to 28% of de novo APL patients [11].

The germline *BRCA1* mutation in UPN1 was detected in exon 8 (HGVS nucleotide: c.512dupT and HGVS protein: p.[Gln172ThrfsTer10]). This mutation in APL or t-APL is extremely rare. One of the first reports of an association between c.512dupT mutation and HBOC was made in 2016 [20]. The latency between the diagnosis of primary malignancy and development of therapy-related acute promyelocytic leukemia (t-APL) was 98 months. This long latency is in contrast to reported topoisomerase II inhibitor-associated t-APL in particular multiple sclerosis where latency interval has been reported less than 12 months [10, 11].

UPN2 *BRCA1* mutation (BIC designation:187delAG; HGVS nucleotide: c.68_69delAG; and HGVS protein: p.[Glu23ValfsTer17]) is identical to a reported t-AL case (UPIN81) following the treatment of the same primary disease [15]. The latencies between the first dose of cytotoxic chemotherapy and the development of t-AL were 29 months (UPN2) and 30 months (previously reported case, UPIN81). It is very unlikely that two breast cancer patients with identical *BRCA1* mutations receiving anthracyclines for the primary disease developed t-AL by chance. In high-risk Ashkenazi Jewish families with a history of HBOC, the incidence of c.68_69delAG is higher as compared to non-Jewish or general population [21].

Therapy-related acute leukemia (t-AL) after HBOC harboring mutations in DNA repair genes, such as *BRCA1* and *BRCA2,* is a probable outcome of cytotoxic therapy, resulting in bone marrow dysfunction. Using therapy-related leukemia registry at the University of Chicago, Churpek et al. [15] identified 88 therapy-related leukemias following breast cancer. Out of 88 breast cancer cases with therapy-related leukemias, only 47 patients had DNA available and 10 (21%) of these cases with available DNA had a germline mutation of *BRCA1* (3 cases), *BRCA2* (2 cases), *TP53* (3 cases), *CHEK2* (1 case), and *PALB2* (1case). Forty three of the 47 with therapy-related leukemia had myeloid neoplasms (MN) and 4 had acute lymphoblastic leukemia (t-ALL). The Breast Cancer Linkage Consortium estimated the risk of leukemia among the probable carriers of a *BRCA1* mutation, relative to non-carriers, and subjects with an unknown mutation status were 0.88 (95% CI: 0.37–2.14) [22]. In a case series, Cole and Strair [23] reported three of six (50%) t-AL patients harboring BRACA1/2 mutations received topoisomerase II inhibitor-based chemotherapy for the breast cancer before development of t-AL. In comparison, estimates in this study are based on a prospective follow-up of women with known *BRCA1* mutation status. Breast cancer patients treated with adjuvant therapy are at a two-fold increased risk of developing t-AL compared to controls. In two extensive analyses reported by Praga et al. [2] and Martin et al. [3], the cumulative risk of t-AL development at 8 years was 0.55% with a high variability between patients receiving standard dose (0.37%) or high cumulative dose (4.97%) of anthracyclines.

Morton et al. [24] identified 801 t-AL cases among 426 068 adults initially treated with chemotherapy for first primary malignancy (9 US population-based cancer registries, 1975–2008). The risk of t-AL was 4.70 times more than expected in the general population ($P < 0.001$). Nearly half of the t-ALs occurred after breast cancer and Non-Hodgkin lymphoma (breast: $n = 223$, SIR = 4.60, EAR = 2.15; NHL: $n = 158$, SIR = 5.85, EAR = 4.81). The patterns of risk generally are consistent with changes in treatment regimens with known cytotoxic agents, such as topoisomerase II inhibitor, that have known leukemogenic potential, although other factors, such as the intensity of treatment and type of primary disease, may have played a role.

Given that these t-AL patients (UPN1 and 2) had multiple lines of therapy for primary malignancy and BRCA-associated breast and ovarian tumors are reported to be more sensitive to chemotherapy, it was decided to treat the t-APL patient (UPN1) with chemo-free regimen [16]. She attended a molecular negativity post-induction and remained in complete molecular remission till the last follow-up for *PML-RARA* monitoring (30 months). However, UPN2 had poor response to therapy with very early progression suggesting relative chemo-resistance. Like breast and ovarian malignancies, whether therapy-related leukemias occurring in *BRCA*-mutated patients are selectively sensitive to Poly (ADP-ribose) polymerase (PARP) inhibitors remains to be explored. There is a report [25] of a *BRCA1*-mutated patient with carcinoma of gallbladder responding to PARP inhibitors may be an attractive option for patients like UPN2 if shown to be active. The occurrence of *RARA* intron 2 breakpoints in the t-APL hotspot region as reported in UPN1 provides a way to distinguish t-APL from a chance of unrelated second malignancy as this may have therapeutic implications. In view of increasingly reported cases of t-AL in *BRCA1*-mutated HBOC patients, close hematological monitoring is suggested following topoisomerase II inhibitor given for the treatment of primary hereditary breast and ovarian carcinoma.

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Author contributions BB, RK, and SKH conducted experiments, data acquisition, and data analyses. TG, VT, AB, and NP contributed to patients' samples, processing and real-time PCR. DS is responsible for cytogenetics; PK and RS contributed to genetic screening of BRCA1. SG and PGS provided clinical data. SKH designed the study and wrote this paper.

Compliance with ethical standards

Conflict of interest The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval Both the patients provided written informed consent in accordance with the Declaration of Helsinki, and the Ethics Committee of Tata Memorial Centre, Mumbai (TMC-IEC III) DCGI registration number: IECIII: ECR/149/Inst/MH/2013 approved this study (IEC reference number 219/2019 dated 24/05/2019).

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