EDITORIAL

TP53 mutations in therapy-related acute myeloid leukemia: still the dark side of the moon?

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Therapy-related acute myeloid leukemia (t-AML) represents 10% to 15% of all newly diagnosed AMLs. The incidence of cases clearly related to a prior therapy for another disease continues to increase, partly because there are more cancer survivors at risk. According to the new 2022 European Leukemia Net classification,[1] t-AML is no longer identified as a separate disease entity, but rather as a diagnostic qualification for disease entities that are essentially characterized by their genetic profile (TABLE 1). Current research suggests that a number of nonexclusive pathways are responsible for t-AML pathogenesis,[2] including: (a) recurrent chromosomal translocations leading to the appearance of fusion oncogenes, (b) induction of genomic instability, (c) chemotherapy- or radiation-induced proinflammatory and proleukemic bone marrow environment, and (d) a selection of pre-existing treatment-resistant hematopoietic cell clones.[2] In t-AML, *TP53* mutations are the most frequently detected somatic mutations, occurring in about 30% of patients.[3] Chemotherapy- and radiotherapy-induced genotoxic damage to hematopoietic stem / progenitor cells (HSPCs) is generally considered responsible for the increased *TP53* mutation rate observed in the t-AML patients as compared with the overall AML patient population. Recently, Wong et al[4] showed that *TP53* mutations in t-AML are present at a lower frequency (0.003%–0.7%) in mobilized blood leukocytes or bone marrow resident progenitor cells 3 to 6 years before the development of t-AML, and sometimes before any chemotherapy. These data suggest a model in which rare HSPCs carrying age-related *TP53* mutations, resistant to chemotherapy, tend to expand preferentially after treatment. In comparison with de novo AML, overall survival (OS) and relapse-free survival are lower in the t-AML patients receiving conventional chemotherapy, with a reported median OS of 10 to 14 months.[5,6] The dismal outcomes documented in this setting are predominantly associated with co-occurring adverse risk factors, such as older age, adverse cytogenetics, adverse somatic mutations, and comorbidities. However, in some studies, t-AML independently correlated with lower OS in multivariate analyses.[5,6]

In this issue of *Polish Archives of Internal Medicine*, Adamska et al[7] present data on a large, retrospective, single-institution AML patient cohort covering a period of over 20 years. Among the 743 patients, 60 (8.1%) were diagnosed with t-AML according to the 2016 World Health Organization criteria. In line with what had been observed in other series, high-risk features, such as a complex karyotype and 17p13 deletion, were detected in 26.8% and 26.7% of the t-AML cases, respectively, while *FLT3-ITD* and *TP53* mutations occurred in 15.4% and 12.5% of the patients, respectively. The authors were also able to confirm the favorable impact of allogenic stem cell transplantation (HSCT) on the survival outcomes (the median OS of all transplanted patients was 47 months). As expected, among the intensively treated t-AML patients, survival was better in those under 64 years of age.

t-AML has been the subject of only a small number of clinical studies, and the choice of induction therapy in the patients without comorbidities is often based on data extrapolation or subset analyses from larger studies.[8] To date, t-AML has not been covered by a special marketing authorization label. In this setting, the National Comprehensive Cancer Network guidelines propose CPX-351 as the preferred first-line intensive induction therapy (category 1A recommendation for patients ≥60 years; category 2B recommendation for patients <60 years). In a phase 3 trial[8] comparing CPX-351 with the standard 7 + 3 regimen in a population of patients with t-AML (n = 62), CPX-351 was associated with a longer median

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TABLE 1 Molecular and cytogenetic characteristics of therapy-related acute myeloid leukemia

Therapy-related AML					
Cytogenetic abnormalities			Gene mutations		
Type of abnormality	Drug correlation	Incidence	Type of mutation	Drug correlation	Incidence
Complex karyotype	Platinum, tamoxifen	26%	*TP53*	Platinum, vinca alkaloids, ImiDs	25%–58%
−5 or 5q−	Platinum, leuprolide, alkylating agents, topoisomerase II inhibitors, tamoxifen	14%	*TET2*	Alkylating agents	15%
−7 or 7q−	Platinum, ImiDs, alkylating agents	20%	*SRSF2*	N/A	5%–7%
t(v;11)(v;q23)	Topoisomerase II inhibitors, anti-CD20 antibody	4%	*EZH2*	Vinca alkaloids, aromatase inhibitors	5%–7%
t(v;21)(v;q22)	Topoisomerase II inhibitors	3%	*PML/RARA*	Mitoxantrone, epirubicin	2%
			PPM1D	Platinum, anti-CD20 antibody	19%
			FLT3	N/A	15%–18%
			NPM1	N/A	7%–9%
			IDH1/2	N/A	9%–15%
			DNMT3A	N/A	15%

Abbreviations: AML, acute myeloid leukemia; ImiDs, immunomodulatory imide drugs; N/A, no data

OS (12.2 vs 6 months, respectively), higher rates of complete response (CR) + complete response with incomplete recovery (CRi) (47% vs 36%) and subsequent HSCT (37% vs 27%). Furthermore, CPX-351 was associated with longer median OS (not reached vs 9.2 months) and median OS landmarked from the date of HSCT (not reached vs 6.6 months) in the subset of t-AML patients achieving CR or CRi (CPX-351, n = 14; 7 + 3, n = 12).[7] Finally, real-world data confirm CPX-351 to be an efficient treatment for high-risk patients with AML, including those with t-AML, with results similar to those of the abovementioned phase 3 trial,[8] allowing to perform HSCT in many patients with a promising outcome after the transplantation.[9,10]

However, a certain amount of data support the hypothesis that resistance to CPX-351 is common in the AML patients with *TP53* mutations. The Dana Farber group[11] presented the results of a study including 309 AML patients randomized at a 1:1 ratio to receive CPX-351 or the 7 + 3 regimen to assess the impact of gene mutations on the outcome. The median OS was longer in the CPX-351 arm among the patients with *DNMT3A* and *TET2* mutations, while it was similar among the patients carrying *TP53* mutations, regardless of the treatment arm (4.5 vs 5.1 months for the CPX-351 arm and the 7 + 3 arm, respectively).[11] In a post-hoc exploratory analysis that led to the approval of venetoclax by the United States Food and Drug Administration, the *TP53* status figured as a significant positive predictor of CR + CRi using univariate logistic regression models.[12] These results suggested improvement in comparison with historical results showing CR rates as low as 28%, although the duration of response was short, in agreement with data reported elsewhere.[13] These data support the concept that the t-AML patients with a *TP53* mutation constitute a distinct subgroup with a very poor prognosis caused by severe chemoresistance, representing an unmet clinical need and openness to innovative therapies. Eprenetapopt (APR-246) is a small-molecule inhibitor that selectively induces apoptosis in *TP53*-mutated cancer cells through the restoration of the wild-type conformation of the mutant 53 protein. In a phase 2 study,[14] eprenetapopt combined with azacitidine was evaluated in 100 elderly patients with a *TP53* mutation and mutant myelodysplastic syndromes or AML; the objective response rate (ORR) was 69%, with a median duration of response (mDOR) of 10.6 months. Magrolimab (Hu5F9-G4) is a monoclonal antibody inhibiting CD47 pathways. In a phase Ib trial,[15] magrolimab combined with azacitidine was assessed in 72 patients with newly diagnosed *TP53*-mutated AML ineligible for intensive chemotherapy. The ORR was 48.6% and the CR rate was 33.3%. The mDOR was 7.7 months with a median OS of 10.8 months. Flotetuzumab is an investigational bispecific Dual-Affinity Re-Targeting (DART) molecule capable of selectively binding CD123 and CD3. In a phase 1/2 study[16] in 38 patients with AML after primary induction failure or early relapse, the ORR was 39% with flotetuzumab at the recommended phase 2 dose of 500 ng/kg/day. These preliminary data confirm the importance of new immune-based therapeutic strategies that might strongly improve outcomes of the patients with t-AML, in which a high proportion of *TP53* mutations is observed.

ARTICLE INFORMATION

DISCLAIMER The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

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