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613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Clinical Characteristics of Patients with TP53 Multihit MDS and AML. a Single-Center Experience

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Introduction

TP53 is a tumor suppressor protein encoded by the *TP53* gene that plays a pivotal role in maintaining genomic stability in response to DNA damage, activates DNA repair programs and triggers cell-cycle arrest. Mutations in TP53 (TP53-mut) are present in approximately 5-10% of *de novo* myelodysplastic syndromes (MDS) and acute myeloid leukemias (AML), and confer an extremely poor prognosis, irrespectively of the treatment administered. The frequency of *TP53* abnormalities increases up to 25-40% in therapy-related MDS and AML, up to 70%-80% in patients with complex karyotype and in patients with loss of chromosome 17/17p, 5/5q, or 7/7q. "Multihit" *TP53*-mut present with the loss of both wildtype *TP53*-alleles, either through point mutations or larger aberrations to chromosome 17, in complex monosomal karyotypes. Recent data strongly support the concept that TP53mut, particularly multi-hit TP53, results in similarly poor clinical outcomes, regardless of its classification as MDS or AML, arguing for a revised *TP53* mutant myeloid entity that includes both MDS and AML. The aim of our analysis is to assess the impact of the multihit *TP53*-mut on clinical outcomes according to the type of treatment received. We will particularly focus on the presence of mono or biallelic mutation status of *TP53* mutation.

Methods

We retrospectively evaluated 42 patients with *TP53* mutated MDS or AML diagnosed from October 2016 to June 2023 in our department at the Catalan Institute of Oncology-L'Hospitalet in Spain. We analyze the prognosis of these two diseases, focusing on single-hit or multi-hit status of *TP53* mutation and treatments received.

Results

Median age at diagnosis was 71 years (range, 44-87 years) with a male predominance (67%). Thirty-five (84%) patients were diagnosed of AML and 7 (16%) of MDS. Among AML patients, 17% had a prior diagnosis of dysplasia, 78% were diagnosed of AML with dysplasia-related changes, 13% with therapy-related neoplasms, and 9% were AML with maturation and/or AML with mutated *NPM1*. Regarding MDS patients, 57% had an excess of blast-2 (EB2) MDS, 43% MDS multilineage dysplasia (MLD) and MDS with excess of blast-1(EB1). Complex karyotype was present in 79% of the patients. The median variant allele frequency (VAF) of *TP53*mut was 36%. Multi-hit *TP53* status was observed in 24 patients (57%). In this group of multi-hit *TP53mut* median age was 72 years (range,44-81 years) with a male predominance (67%), the median VAF of *TP53mut* was 40%. Twenty (83%) patients had MDS diagnosis and 4 (17%) had AML diagnosis; all of them presented complex karyotype. In the whole group the most concurrent mutations associated with *TP53* were *TET2* in 17%, *ASXL1* in 14% and *DNMT3A*, *NRAS* y *CREBBP* in 12% of patients. Intensive chemotherapy (IC) was administrated as first-line treatment in 17% of patients, 45% received hypomethylating agents (HMA) monotherapy, 24% venetoclax-based combination with HMA, and 14% exclusively supportive treatment. 16 patients (38%) achieved a complete response (CR), 44%, 31% and 25% with HMA+venetoclax, IC and with HMA monotherapy, respectively. Eight patients (19%) achieved a partial response (PR), 88% with HMA and 12% with IC, 7 patients (17%) stable disease, 86% with HMA monotherapy and 14% with HMA+venetoclax and 2 patients (5%) were refractory to IC. In 2 patients (5%), disease was not evaluable. The treatment related mortality was 4.2%. Median overall survival (OS) was 12.5 months [IC 95 % (0.0, 23.54)] and median progression free survival (PFS) was 9, 2 months [IC 95% (3.2, 32.6)]. Median OS of patients with multihit *TP53* was 9.8 months, vs 25.7 months in patients with single-hit *TP53*-mut (P=0.026) (Figure1). Median PFS of the patients with multi-hit and single-hit *TP53* was 9.1 and 11.6 months (P=0.07), respectively. The impact of multi-hit *TP53* on OS and PFS according to the treatment received (HMA monotherapy vs HMA + venetoclax vs IC) was not statistically significant, just like in the single-hit *TP53* (Figure1).

Conclusions

The presence of multihit *TP53* -mut is a prognostic variable for survival in our group of patients analyzed with TP53-Mut. Survival is poor, around one year, in this group of patients independently on the treatment strategy received; this fact would call into question the benefit of IC with the toxicity it entails, in this group of patients. Further development of new effective therapies for multihit *TP53*-mut AML and MDS is needed.

Disclosures Sureda Balari: *Pierre Fabre:* Consultancy, Honoraria; *Astra Zeneca:* Consultancy, Honoraria; *Sanofi:* Consultancy, Honoraria; *Kite:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Jannsen:* Consultancy, Honoraria; *MSD:* Consultancy, Honoraria; *BMS/Celgene:* Consultancy, Honoraria, Research Funding; *Takeda:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *GenMab:* Consultancy, Honoraria.

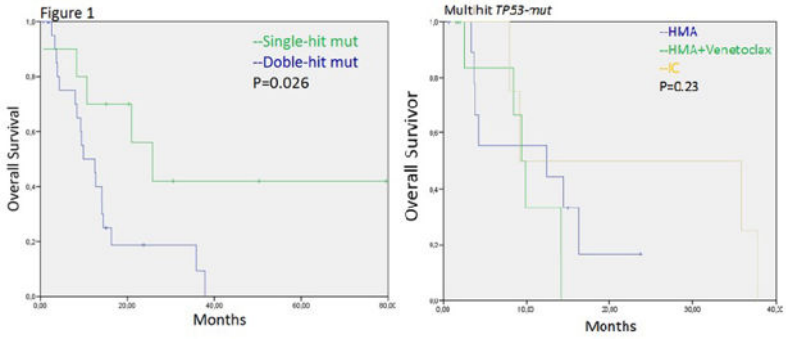

Figure 1

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