ELSEVIER

Blood 142 (2023) 2848–2850

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Poor Prognosis of SRSF2 Gene Mutations in Patients Treated with Venetoclax-Azacitidine (VEN-AZA) for Newly Diagnosed Acute Myeloid Leukemia. a Multicentric Real-Life Study of 117 Patients

Guillaume Berton[1], *Bochra Sedaki*[2], *Erwann Collomb*[3], *Sami Benachour, MD*[2], *Michael Loschi, MD PhD*[4], *Bilal Mohty, MD*[5], *Colombe Saillard, MD*[5], *Yosr Hicheri*[5], *Camille Rouzaud, MD*[5], *Valerio Maisano, MD*[6], *Ferdinand Villetard, MD*[7], *Evelyne D'Incan Corda, MD*[7], *Aude Charbonnier, MD PhD*[5], *Jerome Rey, MD*[5], *Marie Anne Hospital*[7], *Antoine Ittel, PharmD*[8], *Norman Abbou*[9], *Raphaelle Fanciullino*[10], *Bérengère Dadone-Montaudié*[11], *Norbert Vey, MD*[12], *Geoffroy Venton, MD PhD*[13], *Thomas Cluzeau, MDPhD*[14], *Anne Sophie Alary*[15], *Sylvain Garciaz*[12]

[1] Hematology Department, Institut Paoli-Calmettes, Marseille, France
[2] Hematology Department, Nice University Hospital, Cote d'Azur University, Nice, France
[3] Hematology and Cellular Therapy Department, La Conception University Hospital, Marseille, France
[4] Centre Hospitalier Universitaire de Nice, Nice, France
[5] Department of Hematology, Institut Paoli-Calmettes, Marseille, France
[6] Hematology Department, Institut Paoli-Calmettes, Marseille, FRA
[7] Hematology Department, Institut Paoli-Calmettes, Marseille, France
[8] Department of Molecular Biology, Institut Paoli-Calmettes, Marseille, France
[9] CHU Nord, Marseille, France
[10] Aix Marseille Univ, Marseille, FRA
[11] Department of Pathology and Molecular Oncology, Molecular Oncology Unit, Nice University Hospital, Nice, France
[12] Aix-Marseille University, INSERM U1068, CNRS, Institut Paoli-Calmettes, CRCM, Marseille, France
[13] University Hospital Center of Marseille, Marseille, France
[14] Nice University Hospital, Nice, France
[15] Department of Biopathology, Institut Paoli-Calmettes, Marseille, France

Introduction

Spliceosomes are complexes composed of small nuclear RNA that remove introns in protein-encoding genes. Spliceosome mutations (*SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*), are encountered in ~50% of secondary AML cases. Splicing mutations (splice-mut), in particular *SRSF2*, correlate with inferior outcomes to standard induction therapy. A recent report in a cohort of 119 patients, of whom 33 had splice mutations and 24 were SRSF2 mutated, reported the lack of impact of splice-mut on prognosis of AML patients treated upfront with Hypomethylating agents (HMA) + VEN in clinical trials (Lachowiez, C. A. *et al* Blood Adv. 2021).

Aims

We aimed to assess the impact of splice-mut in a population of patients with newly diagnosed acute myeloid leukemia (ND-AML), treated with VEN-AZA.

Methods

We performed a retrospective multicentric study including patients treated in three French centers in Marseille (Institut Paoli-Calmettes, CHU La Conception) and Nice (Hôpital L'Archet). Inclusion criterias were ND AML adult patients treated with VEN (7 to 28 days per cycle) and AZA at conventional doses. Next Generation Sequencing (NGS) was performed at diagnosis and was available for all patients. Data were collected from patients' electronic medical records. Statistical analyses were performed using GraphPad Prism v9.5.1

Results

We included 117 ND-AML patients (median age = 75 yo; range, 32-89) treated with VEN-AZA between October 2019 and March 2023. The five most frequently mutated genes in the whole cohort were *TET2*, *ASXL1*, *TP53* and *RUNX1*in thirty-seven (32%), 36 (31%), 32 (27%) and 31 (26%) patients, respectively. Thirty-four patients (29%) had a mutation in at least one of the spliceosome genes (=Splice-mut), including 20 (17%), 11 (9%), 4 (3%) and 1 (1%) mutations in *SRSF2*, *U2AF1*, *SF3B1* and *ZRSR2*, respectively **(Fig.1)**. Median variant allele frequency (VAF) was 42%, 43% and 26% for SRFS2, *U2AF1* and *SF3B1* respectively. Secondary AML was found in 18 (53%) of the splice-mut AML and 21 (25.3%) of the splice-wt AML groups of patients. Prior

HMA was given in seven (20.6%) patients in the splice-mut versus 6 (7.2%) in the splice-wt cohort. Complex cytogenetics was identified in 7 (20.6%) patients in the splice-mut cohort and 28 (33.7%) in the splice-wt cohort. We found a *TP53* mutation in 17.6% and 31.3% of splice-mut and wt cohorts, respectively. Best overall response rate (= CR, CRi and MLFS) was 72.6%; with CR, CRi and MLFS observed in 63 (54%), 16 (14%) and 6 (5%) patients, respectively. We did not find any difference in response rate between the splice-mut (=73.5%) and splice-wt (72.3%) AML. Prior treatment with hypomethylating agents and *TET2* mutation were the only factors significantly associated with lower response rates (42% vs 82%, p=0.004, and 64% vs 85%, p=0.025, respectively), while *IDH2* mutation was predictive of a better response (100%vs 75%, p=0.037, OR: 9.9 [CI 95% 0.57-173]). Median overall survival (OS) and leukemia-free survival (LFS) for the whole cohort was 10.8 and 7.1 months, respectively. In multivariate analysis taking into account *TP53 and/or* del17p, *NRAS*mut and/or *FLT3-ITD*, *IDH2*mut, complex karyotype, and SRSF2, the only factors predicting OS and LFS were mutations in TP53 and SRSF2 genes. Patients mutated for SRSF2 had a 4.8 months OS and a 5 months LFS compared to 11.3 and 8 months, respectively (p=0.034 and p=0.037), comparable with TP53mut AML patients (**Fig.2**).

Conclusions

*SRSF2*mut seems to be predictive of a worse survival in ND AML treated with VEN-AZA. This finding warrants further exploration in larger cohorts.

Disclosures Loschi: *AstraZeneca:* Honoraria; *BMS:* Honoraria; *Gilead:* Honoraria; *GSK:* Honoraria; *Jazz:* Honoraria; *Kartos:* Honoraria; *Medac:* Honoraria; *MSD:* Honoraria; *Novartis:* Honoraria; *Pfizer:* Honoraria; *Sanofi:* Honoraria; *Sobi:* Honoraria; *Telios:* Honoraria; *Alexion:* Honoraria. **Charbonnier:** *Pfizer, Novartis, Incyte Biosciences:* Honoraria. **Venton:** *Novartis, Abbvie, Jazz, BMS, Janssen, GSK, Astrazeneca, Gilead:* Consultancy. **Cluzeau:** *Novartis:* Consultancy, Speakers Bureau; *Abbvie:* Consultancy, Speakers Bureau; *Jazz Pharma:* Consultancy, Speakers Bureau; *Syros:* Speakers Bureau; *Keros:* Speakers Bureau; *Servier:* Consultancy, Speakers Bureau; *Incyte:* Speakers Bureau; *BMS:* Consultancy, Speakers Bureau.

Fig.1

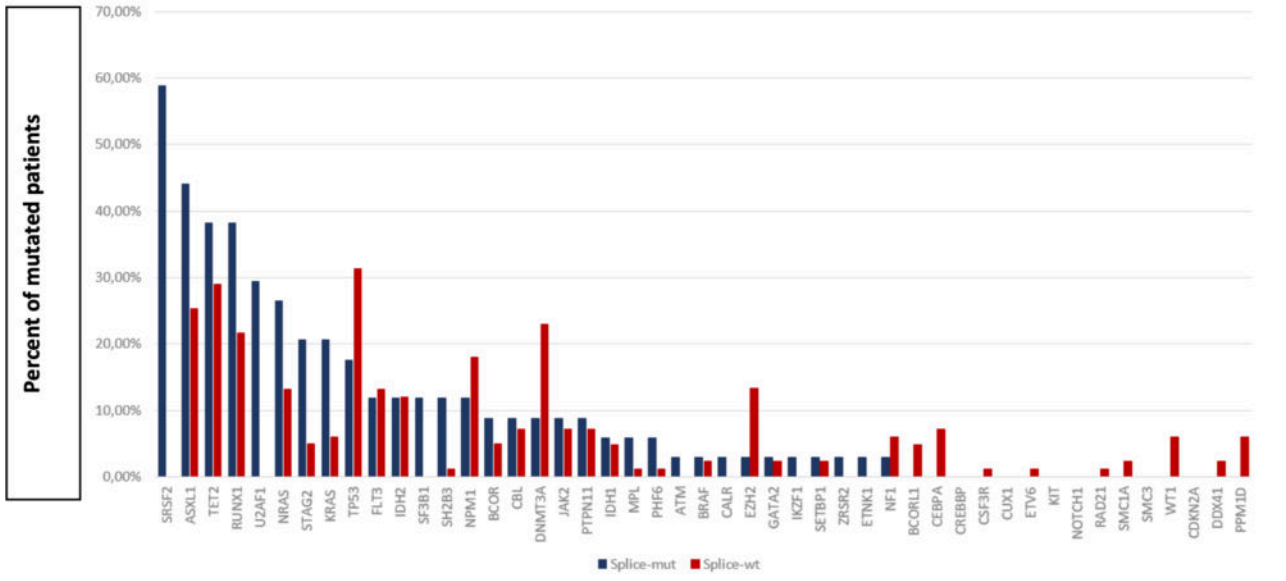

Fig.2

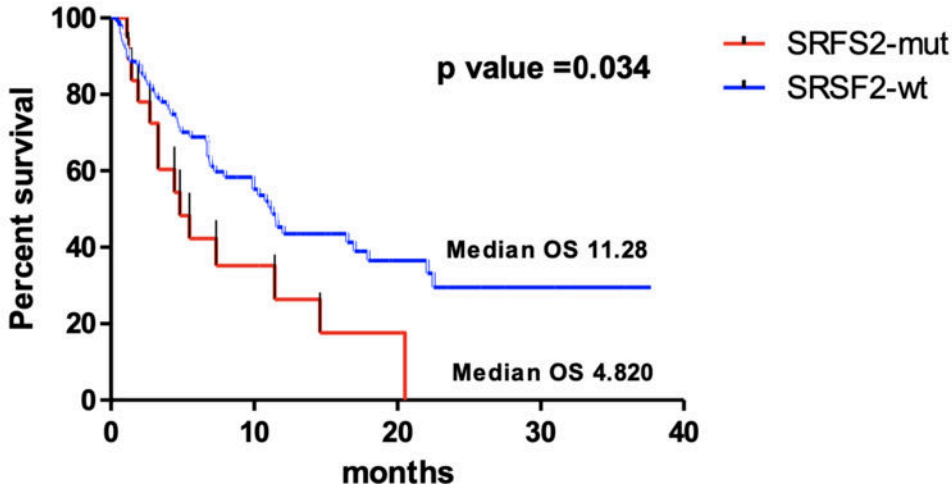

Figure 1

https://doi.org/10.1182/blood-2023-180733