IMPACT OF MYELOID-DERIVED SUPPRESSOR CELLS (MDSC) AND CLINICAL CORRELATES IN ELDERLY PATIENTS AFFECTED BY MYELOPROLIFERATIVE NEOPLASMS (MPNs).

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Background

Myeloproliferative Neoplasms (MPNs) includes polycythemia vera (PV), essential thrombocytemia(ET), primary myelofibrosis (PMF) (Fig.1) and are relatively rare diseases [1]. Median age at diagnosis is around 63–64 years and the incidence increase with age. Given population growth, the effect of aging, and the substantial prolongation of patient survival, the prevalence of diseases is expected to rise, and a large proportion of patients will be elderly. Unfortunately, a large part of patients evolved in acute myeloid leukemia (AML), with very short survival. Cytogenetic and molecular status has a prognostic impact. MPNs, especially myelofibrosis (MF), are recognized to be associated with autoimmune phenomena (Fig.2) , immune derangements in MPN have been much less studied [2]. Myeloid-derived suppressor cells (MDSC) are one type of important immune modulator cell [3].

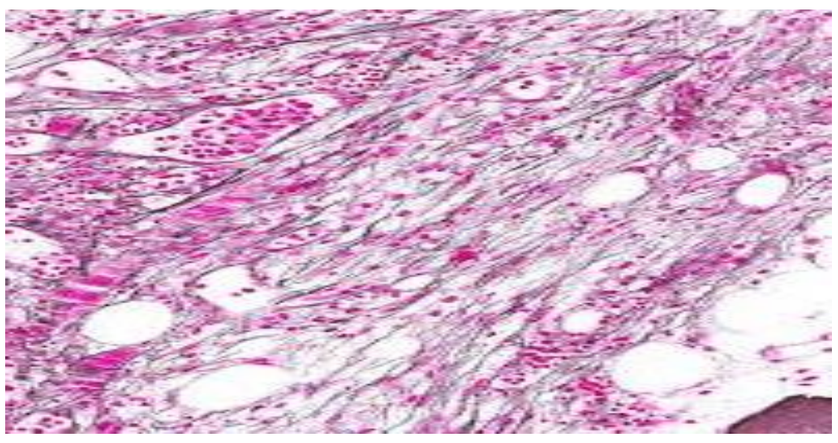

Fig 1. Bone marrow section of PMF

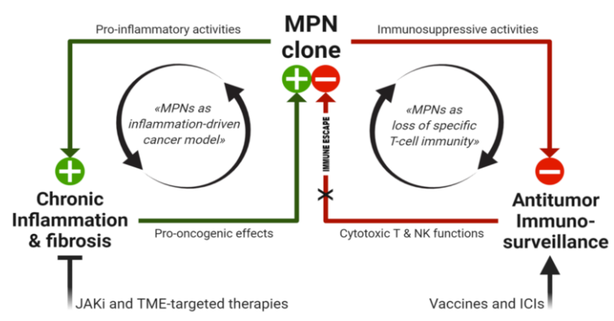

Fig 2. MPNs as inflammation-driven cancer model and loss of T –cell immunity

Aims of project. Based on these assumptions the main objective of this project is to identify and validate the clinical, molecular and cytogenetic features able to impact the survival of elderly myeloproliferative patients, candidates for complex therapies; secondary objective is to study a role of MDSCs in this setting of patients. According to the International System for Human Cytogenetic Nomenclature (ISCN) criteria, and mutational analysis on DNA from peripheral blood or bone marrow cells. Janus-kinase (JAK2V)617F and myeloproliferative leukemia virus (MPL) W515 mutation will be detected by real time-PCR or high-resolution melting analysis. Calreticulin (CALR) mutations will be identified by capillary electrophoresis and bidirectional sequencing and classified as type 1- or type 2-like. Next generation sequencing has been used to detect mutation in selected myeloid genes, including EZH2, ASLX1, IDH1/IDH2 and SRSF2, previously showed to be prognostically informative in MPNs. **Results.** In our prospective monocentre study we enrolled 55 patients including 12 PMF, 10 PV, and 23 ET, 5 with unclassifiable MPN and 5 lymphoproliferative diseases that subsequent we excluded from cytogenetic and molecular analyses (Fig.3). All patients have been enrolled at the moment of diagnosis (from June 2020 to March 2022). Median age was 73 years old; 35 cases presented JAK2 positive, 3 MPL, and 9 CALR mutation. Cytogenetic risk classification showed a favourable risk in 35, unfavourable in 6, very high risk in 5 patients and in 4 patients we didn't get mitoses. No information about overall survival has been requested, due to the status of new diagnosis. In all 55 patients were identified the MDSCs using flow cytometry: no differences in MDSC levels among different MPN categories (Fig.4). The results showed that MDSCs were significantly elevated in MPNs compared with controls. MDSC levels were not correlated with JAK2 status, white blood cells, Hb levels, platelet counts, splenomegaly, degree of bone marrow fibrosis, cytogenetic or molecular information.

Variables	N
Total of patients	55
Age (median)	73 (33-92)
Sex	
Male	26
Female	29
MPNs diagnosis	
PV	10
ET	23
PMF	12
Unclassifiable	5
Lymphoproliferative	5
WBC;/ul (median range)	9400 (1540-15780)
Hb;g/dl (median range)	14 (7,5-18)
HCT; % (median range)	44 (32,8-55)
Cytogenetic	
Normal karyotype	35
Adverse karyotype	6
Very adverse karyotype	5
Molecular informations	
JAK2	35
CARL	9
MPL	3
Triple negative	6
Unclassificable	2
Therapy	
Yes	25
No	30

Fig 3 Preliminary results

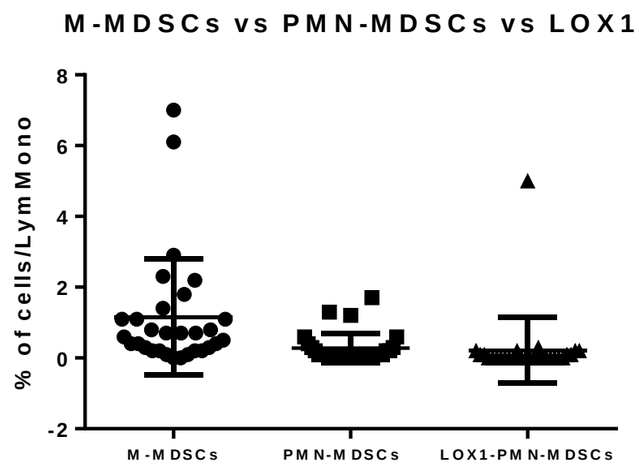

Fig 4 Preliminary results od MDSC detection

Conclusions. More patients are needed to better clarify this issue. In the next future we will correlate the presence of MSCD with p16 as marker of senescence and aging, and we would like to detect the expression of PDL-1 to early identified patients that may be candidate to an early target therapy.

References:

1. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia.

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2. Revised cytogenetic risk stratification in myelofibrosis: analysis based on 1002 informative patients. Tefferi A, Nicolosi M, Mudireddy M, Lasho T et all. Leukemia, 2018 May;32(5):1189-1199.

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