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Running heads: Busulfan and JAK2

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Authorship and Disclosures

MLR was the principal investigator and takes primary responsibility for the paper and coordinated the research ; CS, EC, IB recruited the patients; EP and ED performed the laboratory work for the study; MLR and FF wrote the paper. The authors report no potential conflicts of interest

We read with interest the paper from Kuriakose et al (1) regarding the dramatic decrease of *JAK2V617F* allele burden (AB) observed in five patients with Polycythemia Vera (PV) treated with busulfan (BU). Interestingly, a patient with 100% AB obtained the disappearance of the mutation within 3 months of therapy.

The European Leukemia Net (ELN)(2) has suggested that in MPN patients the molecular response to different cytoreductive drugs is a relevant aspect of the drug efficacy: sustained molecular response has been observed with recombinant Interferon-alpha, pegylated - Interferon-alpha (3) and with hydroxyurea (4) even if not with a general agreement. While, in the past, BU was commonly used in patients with MPN, its use diminished because an increase of leukemogenicity demonstrated in the '90s (5). At present, BU is reserved to elderly patients (6) even if the leukemogenic risk associated with low-dose BU is probably small (7). Therefore, in the JAK2 era, the effect of BU on laboratory data is lacking.

In our large cohort of patients with myeloproliferative neoplasms (MPN), we retrospectively found 6 patients (5 PV and 1 primary myelofibrosis- MF) who received BU as 2nd-3rd line of treatment, in whom *JAK2V617F*- AB was available (table 1).

Kuriakose and colleagues (1) performed the *JAK2* study within 6 and 18 months of BU treatment. In our cohort, two patients had AB higher than 50% while BU was ongoing (24 and 2 months respectively) : in particular, patient GM had 97% AB after long-acting therapy with BU. In the remaining 4 patients, BU was given years before the *JAK2V617F*-AB evaluation (2-9 years) and its molecular effect may have been lost. It is worth noting that patient BR, the only one case in the present cohort who had a *JAK2V617F*-AB lower than 50%, died 4 years after the molecular study because acute leukemia, possibly being one of the cases who lost the *JAK2* mutation when evolved into leukemia (8).

In the absence of a pre-treatment dosage of *JAK2V617F*-AB, it is not possible to ascertain if, in our patients, the AB decreased with BU treatment. However, at least in two patients, as well as in patient n° 6 from Kuriakose (1), BU was not able to obtain a significant effect on *JAK2V617F* -AB: if we consider together both cohorts, the "BU-non-responder" patients pile up 25%. Moreover, the high AB levels found in other patients suggest that, even if they obtained previously significant decreases, after BU suspension the AB grew again.

We conclude that not all patients who had undergone BU therapy have a significant decrease of *JAK2V617F* allele burden. The possible leukemogenic effect of BU is not to be forgotten and has to be taken in due account mainly in patients exposed to recurrent changes of cytoreductive drugs (9).

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Table 1. Demographics and treatment effects of 6 patients treated with busulfan. MPN = myeloproliferative neoplasm; PV = polycythemia vera, MF= primary myelofibrosis. BU= busulfan, HU = hydroxyurea, ³²P = radioactive phosphorus; y = years

Patient	MPN	Age (y) at JAK2 evaluation - Gender	Prior treatment - duration	BU duration	Time elapsed between BU therapy and molecular study	JAK2V617F Allele burden
PV	PV	81 - F	³² P 20 y before HU 5 y	10y (cycles)	9 y	62%
CF	PV	54 - M	HU 5 y	1 y	5 y	76%
BR	PV	71 - F	HU 3 y	3 y	2 y	22%*
VC	PV	78 - F	³² P 10 y before HU 8 y	1 y	2 y	68%
GM	PV	78 - F	HU 10 y	2 y	0 y	97%
VP	MF	62 - F	HU 16 y	2 ms	0 y	51%

*died with acute leukemia 4 years after JAK2 evaluation.