Effect of busulfan on *JAK2*V617F allele burden

We read with interest the paper from Kuriakose *et al.*[1] regarding the dramatic decrease of *JAK2*V617F allele burden (AB) observed in 5 patients with polycythemia vera (PV) treated with busulfan (BU). Interestingly, a patient with 100% AB obtained the disappearance of the mutation within three 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-α, pegylated interferon α[3] and with hydroxyurea[4] even if there is no general agreement about this. While in the past, BU was commonly used in patients with myeloproliferative neoplasms (MPN), the increase of leukemogenicity demonstrated in the 1990s led to a reduction in its use.[5] At present, BU is reserved for elderly patients,[6] even if the leukemogenic risk associated with low-dose BU is probably small.[7] Therefore, in the JAK2 era, there is a lack of laboratory data on the effect of BU.

In our large cohort of patients with MPN, we retrospectively found 6 patients (5 PV and 1 primary myelofibrosis (MF)) who received BU as second- and third-lines of treatment in whom *JAK2*V617F-AB was available (Table 1).

Kuriakose and colleagues[1] performed the JAK2 study within six and 18 months of BU treatment. In our cohort, 2 patients had higher than 50% AB while BU was ongoing (24 and 2 months, respectively). In particular, Patient GM had 97% AB after long-acting therapy with BU (Table 1). In the remaining 4 patients, BU was given years before the *JAK2*V617F-AB evaluation (2-9 years) and its molecular effect may have been lost. It is worth noting that Patient BR, the only case in the present cohort who had a *JAK2*V617F-AB below 50%, died four years after the molecular study from acute leukemia, possibly being one of the cases who lost the *JAK2* mutation when the disease evolved into leukemia.[8]

In the absence of a pre-treatment dosage of *JAK2*V617F-AB, it is not possible to ascertain if, in our patients, the AB decreased with BU treatment. However, at least in 2 patients, as well as in Patient 6 from the study of Kuriakose *et al.*,[1] BU was not able to obtain a significant effect on *JAK2*V617F-AB. If we consider both cohorts together, the "BU-non-responder" patients make up 25%. Moreover, the high AB levels found in other patients suggest that, even if they had previously obtained significant decreases, after BU suspension the AB increased again.

We conclude that not all patients who had undergone BU therapy have a significant decrease in *JAK2*V617F allele burden. We should not forget the possible leukemogenic effect of BU and this has to be taken into due account, particulary in patients who have their cytoreductive drugs repeatedly changed.[9]

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Table 1. Demographics and treatment effects of 6 patients treated with busulfan.

Patient	MPN	Age (y) at JAK2 evaluation (Gender)	Prior treatment duration	BU duration	Time elapsed between BU therapy and molecular study	*JAK2*V617F Allele burden
PV	PV	81(F)	32P 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)	32P 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%

*MPN: myeloproliferative neoplasm; PV: polycythemia vera; MF: primary myelofibrosis; BU: busulfan; HU: hydroxyurea; ^{32}P: radioactive phosphorus; y; years. *Died with acute leukemia 4 years after JAK2 evaluation.*