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634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Exploratory Study on Impact of Comorbid Sleep Apnea Treatment in Patients with Polycythemia Vera and Essential Thrombocythemia

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Background:
Systemic inflammation has been implicated in the progression of myeloproliferative neoplasms (MPNs), polycythemia vera (PV) and essential thrombocythemia (ET). Obstructive sleep apnea (OSA) is a highly prevalent disorder that can lead to TNF-driven systemic inflammation. OSA leads to oxidative stress and NF-kB driven inflammatory gene expression through the mechanistic pathways of intermittent hypoxia and autonomic activation. We therefore sought to understand the prevalence of OSA in patients with MPNs and the feasibility of understanding the impact of treating comorbid sleep apnea in patients with PV and ET.

Methods: Patients with PV and ET diagnosed using the 2008 or 2016 WHO criteria underwent STOP-BANG questionnaires to evaluate for the likelihood of OSA. Based on the finding of 3 or more positive responses on STOP-BANG questionnaire (PLoS One 2015;10:e0143697), patients underwent further evaluation with polysomnography or home sleep apnea test to diagnose OSA at an American Academy of Sleep Medicine-certified sleep laboratory (Figure 1). Patients with apnea-hypopnea index (AHI) of 5 or more events per hour and Eastern Cooperative Oncology Group scale score of 0-2 underwent continuous positive airway pressure therapy (CPAP). Effects of CPAP therapy on MPN-symptom assessment form total symptom scores (MPN-SAF TSS), *JAK2* ^{V617F}, *MPL* and *CALR* allelic burden, and exploratory endpoints of changes in inflammatory and thrombotic markers were ascertained (Figure 1). Comparisons with observational cohorts were planned to ascertain changes in the above endpoints at 0-, 3- and 6-months intervals (Figure 1). Based on a 40% reduction in allele burden (SD of 25%) and correlation of 0.5 between paired measurements, it was estimated that using a paired t-test with 27 evaluable patients will provide a 95% power to detect a 20% change in *JAK2* ^{V617F} burden from 40% to 20%. Similarly, assuming a 50% correlation (SD of 16) between pre- and post-therapy MPN-SAF TSS scores, 27 evaluable patients will provide a 80% power to detect a change of 10 at the two-sided 0.025 significance level.

Results: Screening for OSA in patients with ET and PV revealed a high prevalence of OSA risk based on STOP-BANG scores. 26/29 males (mean age 63.6±11.8 years; BMI 29±3.3) and 16/26 females (mean age 61.5±12.8 years; BMI 28.2±6.5) had STOP-BANG scores of 3 or more. 8 patients with PV and ET have so far been enrolled into this study. 6/8 patients (age ranges from 41-74 years; 4 females and 2 males) with OSA (AHI 5-56 events/hr; 4% oxygen desaturation index 4.7-30/hr) underwent CPAP therapy. 1/6 patients in the CPAP arm did not tolerate CPAP and was excluded. 5/6 patients completed study procedures as did 2 additional patients without OSA in the observational study arm.

Of 5/6 patients undertaking CPAP, 3/5 had the *JAK2* ^{V617F} mutations whereas 2/5 had the *CALR* mutation. *JAK2* ^{V617F} allele burdens at baseline in 2/5 patients were 80.7% and 4% at baseline and reduced to 73% and 1% at 6 months respectively whereas the third patient had undetectable *JAK2* ^{V617F} burdens throughout the study. All except one patient experienced improvement in MPN-SAF TSS scores after 6 months of CPAP therapy. While all 5 patients treated with CPAP showed improvements in C-reactive protein levels, analysis of *NFkB1*, *TNF* and *IL-6* transcript levels showed mixed results. Similar mixed results were found with hypoxia-inducible factor (HIF) target gene expression (*SLC2A1*, *VEGF-A*, *EDN1*) and markers of iron turnover (% transferrin saturation, transferrin, iron and ferritin levels) despite reduction in erythropoietin values in 4/5 patients with CPAP therapy at 6 months.

Conclusions: Given the significant likelihood of OSA in patients with PV and ET (as based on STOP-BANG scores of 3 or more), there is need to evaluate and treat for OSA. Preliminary results show abnormalities in inflammatory markers with reductions in C-reactive protein and erythropoietin levels following CPAP therapy even though mixed results were noted in inflammatory and HIF-target gene transcripts, and markers of iron turnover. Larger studies and longer follow-up are required to understand the impact of OSA on not only the thrombotic and inflammatory milieu in patients with MPNs, but also the benefit of treating on prevention of disease progression and thrombotic manifestations common in MPNs.

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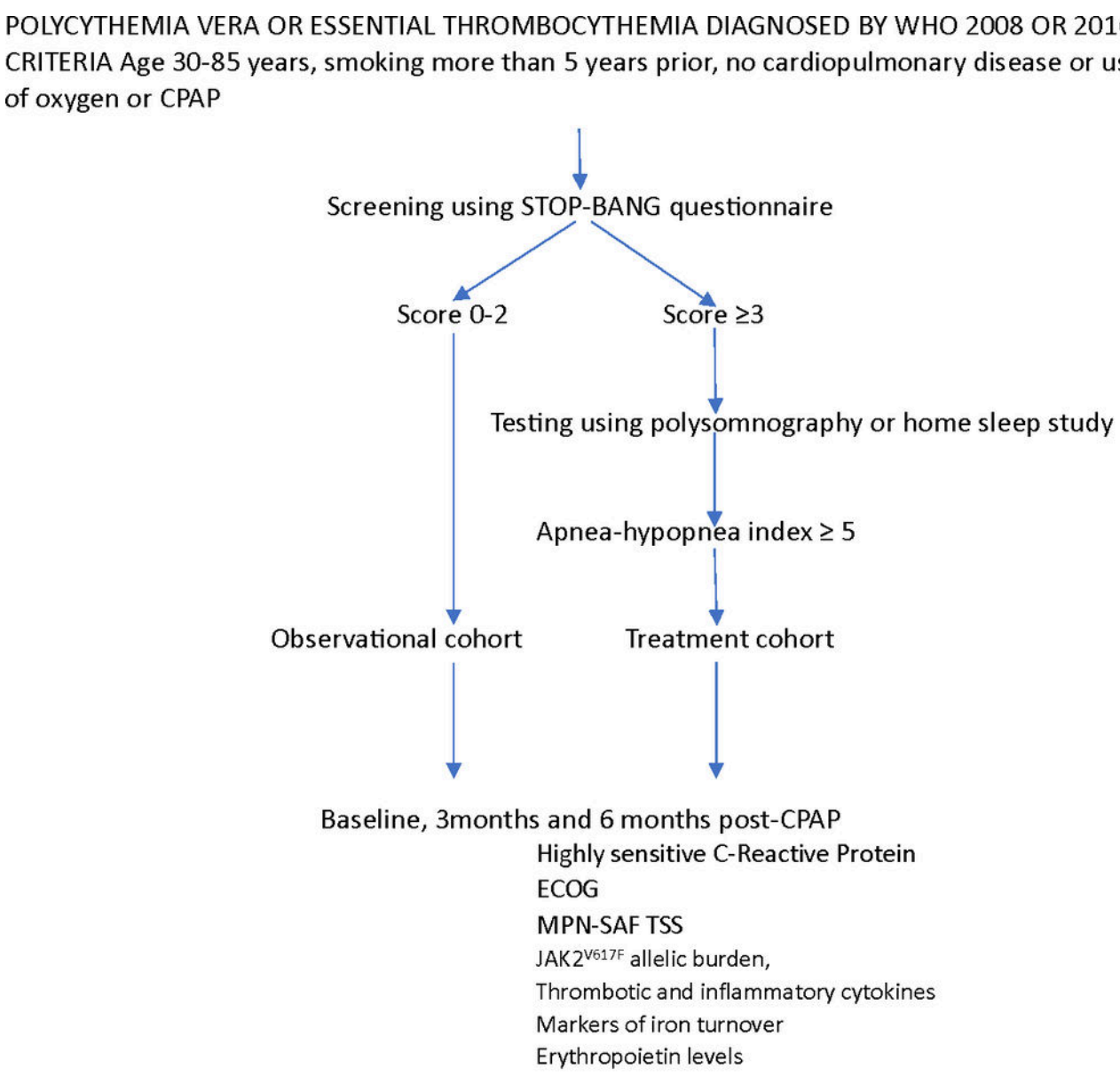

Figure 1. Study design for understanding impact of sleep apnea management in patients with myeloproliferative neoplasms (Essential thrombocythemia and polycythemia vera).

Figure 1

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