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A prospective evaluation of pegylated interferon alfa-2a therapy in patients with polycythemia vera and essential thrombocythemia with a prior splanchnic vein thrombosis

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Introduction

Essential thrombocythemia (ET) and polycythemia vera (PV) are myeloproliferative neoplasms (MPNs) characterized by an increased risk of developing venous and arterial thromboses and of evolution to myelofibrosis or acute leukemia (1). MPNs are recognized as a major cause of splanchnic vein thromboses (SVT), which include hepatic, splenic, portal and mesenteric vein thromboses (2). Patients with SVT are at an increased risk of developing bleeding events and arterial thrombotic events (3), as well as recurrent SVT and the use of anticoagulation and cytoreduction do not clearly modify this risk (3–5).

Management of SVT in MPN patients remains a challenge and most therapeutic recommendations are based on retrospective analyses (6). Recently, De Stefano reported that hydroxyurea failed to prevent recurrent thromboses in the splanchnic vasculature in patients with a prior SVT (7). We conducted a prospective, open-label, multi-center phase II clinical trial of Pegylated Interferon Alfa-2a (PEG) in 20 subjects with SVT and an MPN, who represented a cohort of patients who participated in the Myeloproliferative Disorders - Research Consortium (MPD-RC) 111 trial (). MPD-RC 111 was a prospective study of patients with high-risk ET/PV who were resistant or intolerant to hydroxyurea (HU), but prior HU therapy was not a requirement for patients to enter the SVT cohort. Here we report the outcomes of the 20 SVT patients who were treated with PEG.

Methods

This study was an investigator-initiated phase 2 clinical trial that was performed in compliance with an Investigational New Drug Application and approved by the Program for the Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai and at all participating sites. It was supported by the National Cancer Institute, and PEG was generously supplied by Roche/Genentech.

Patients met 2008 World Health Organization (WHO) criteria for the diagnosis of ET/PV and were treated for up to 12 months with PEG with a primary objective of inducing PR/CR as defined by the European LeukemiaNet (ELN) (8). Patients who achieved PR/CR could continue PEG therapy for a maximum of 4 years on study. Secondary objectives included evaluation of toxicity, safety, tolerability, and impact of PEG on key biomarkers of disease. Survival, incidence of myelodysplastic syndrome (MDS), myelofibrosis (MF), or leukemic transformation (LT) and incidence of major cardiovascular events during therapy with PEG were described.

PEG therapy was initiated at a dose of 45 μg subcutaneously weekly and the dose was titrated upwards each month by 45 μg to induce a CR, to a maximum dose of 180 ug. Clinical and laboratory assessments were conducted as per protocol every month for the first six months and then every three months afterwards.

For the SVT cohort, we estimated a CR +PR rate of 50% with an exact 95% confidence interval equal to the observed rate +/− 22%. Patients who discontinued therapy for any reason were considered to be failures in this intent to treat evaluation. Exact 95% confidence intervals were used to estimate the clinico-hematologic response rate in this SVT cohort.

Patients completed a comprehensive assessment of their MPN-associated symptoms (Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)) (9), an assessment of functionality and quality of life (EORTC QLQ-C30) and five exploratory questions to assess PEG-related side effects on a serial basis (baseline, 3, 6, 9, 12 months). Changes over time were assessed by mixed models adjusting for age.

Myeloid neoplasm associated-gene mutations were detected by next generation sequencing using a targeted-sequencing panel designed to capture 156 genes implicated in the pathogenesis of myeloid malignancies and described elsewhere (10). Pathogenic significance of mutations was determined by previously published criteria (11–13).

Results

A total of 20 subjects with SVT [PV: 13 (65%); ET: 7 (35%)] were enrolled between February 2012 and December 2015. Baseline demographics of these 20 patients are shown in Table 1. At time of enrollment, 18/20 (90%) patients were receiving anticoagulation/antiplatelet therapy including coumadin (n=10), aspirin (n=6), low molecular weight heparin (n=2), and combination coumadin and aspirin (n=1). The median number of weeks on treatment with PEG was 114.2 (11.0–209.9) and 16 (80%) patients received at least 48 weeks of therapy for the analysis of the primary efficacy endpoint. The median dose of PEG administered was 135 μg weekly (45.0–180.0), and treatment was continued to maintain hematologic response.

Mean MPN-SAF Total Symptom Score (TSS) was 15.6 amongst patients with SVT (SD 14.9; range 0–50), which was lower than the mean for non-SVT 111 study participants (n=115, 19.5 [SD 18.4]). Baseline quality of life was not significantly impaired, i.e. mean QLQ-C30 global health status/QOL was 71.7 (SD 19.9), which is similar to the non-SVT

111 study participants (71.6 [SD 20.1]) and a general healthy population (mean 71.2 [SD 22.4] QLQ-C30 Reference Manual 2008).

After 12 months of therapy, the overall hematological response rate (ORR, CR+PR) was 70% (95% CI: 45.7–88.1%), with 3 (15%) CR, 11 (55%) PR and 6 (30%) non-responses (NR). NR in 2 of these 6 patients was observed despite treatment with the maximal dose of 180 ug weekly. Fourteen of 20 patients had the opportunity to receive at least 36 months of treatment and the ORR at 36 months was 42.9% (95% CI: 18.9–70.4%). Reasons for NR (n=8) at 36 months in the 14 patients who had completed sufficient time on study prior to sponsor study closure included lack of response despite maximal PEG dose of 180 ug weekly (n=2), AE at 90, 135, or 180 ug weekly (n=3), pregnancy (n=1), and patient/physician withdrawal (n=2). Of the 9 subjects with ultrasound studies performed at baseline and after 12 months of therapy, the median percent reduction in spleen length by imaging was 0.0% (range, −53.4% to 7.0%). None of the subjects developed MF, MDS, AML or died during the study period.

Treatment-emergent AEs, regardless of attribution, occurring in more than 10% of subjects were infrequent (data not shown). There were three bleeding events; grade 3 esophageal bleeding (n=1), grade 1 gingival bleeding (n=1), and grade 1 microscopic hematuria (n=1). There were no recurrent episodes of SVT. One subject developed a grade 2 deep venous thrombosis (DVT) of the lower extremity one month following discontinuation of PEG therapy. Reasons for study treatment discontinuation included study closure (n=7, 35%), AE (n=4, 20%), non-response (n=3, 15%), patient withdrawal (n=2, 10%), treatment completion per protocol (n=2, 10%), physician decision (n=1, 5%), and pregnancy (n=1, 5%).

Serial MPN-SAF questionnaire completion was achieved in 15 (75%) patients at 12 months. In a mixed model analysis, there were minimal MPN-specific symptom changes observed (however, some improvements in sad mood and sexuality improvement at 9 months were observed). SVT patients did experience statistically significant time-dependent worsening of PEG-related side effects such as flushing, injection site irritation, blurry vision, and visual changes (all $p<0.05$). GHS/QOL stayed relatively stable over time for those patients who continued treatment (p=NS).

Seventeen patients had their mutational status assessed at baseline and all of these patients harbored *JAK2V617F*. The median *JAK2V617F* variant allele fraction at baseline was 15% (range 1% – 76%). *TET2* and *DNMT3A* mutations were the most frequent co-occurring mutational events (Figure 1A). Among the 17 patients harboring *JAK2V617F*, the ORR (CR: 6, PR: 7) was 13/17 (76.5%) at 12 months. Among 14 patients with serial samples (Figure 1B), ELN defined molecular CR/PR was not achieved in any of the evaluable subjects. Four of the 20 patients had baseline karyotypic abnormalities and these abnormalities persisted after 12 and 24 months of treatment in the two patients with available follow-up analyses.

Based on blinded central expert histopathology assessment of bone marrow biopsy specimens from 17 patients (11 PV and 6 ET) with available and adequate materials at 12

months, two subjects attained a pathologic marrow CR. Clinical-hematologic responses in these two subjects were CR and PR.

Conclusion

SVT is a well described complication associated with ET and PV but optimal management remains poorly defined (6). Current recommendations are that these high-risk patients be treated with myelosuppressive therapy (HU or PEG) (14). However, HU has been reported to be ineffective in preventing recurrent SVT (4). Also due to the relative youth of this patient population, there has been a reluctance to treat these patients with HU due to effects on fertility, teratogenicity and fear of possible leukemogenicity (6). Recently, a phase 2 trial of the JAK½ inhibitor ruxolitinib in 9 ET/PV patients with SVT was reported to induce reduction in spleen volume but without any impact on degree of esopahageal varices (15). In this prospective study, PEG therapy was well tolerated in patients with ET/PV and a history of SVT and resulted in a clinical-hematologic ORR of 70% (15% CR and 55% PR) at 12 months of therapy.

PEG therapy for ET/PV patients with SVT had a favorable impact on certain MPN symptoms but was also associated with treatment emergent low-grade toxicities that can abrogate some of those benefits. Regardless, PEG did not clearly diminish QoL. SVT did not recur in any of the patients during a median follow-up of 2.2 years. This prospective study of PEG therapy in MPN patients with SVT demonstrates the feasibility and apparent efficacy of this therapy.

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Conflict of interest: JM reports clinical trial research support paid to the institution from Incyte, Roche, Novartis, CTI Biopharma, Janssen, Merck, Promedior, and Celgene; clinical trial steering committee and scientific advisory board member: Roche, CTI Biopharma, Incyte, and Celgene. MRB reports clinical trial research support paid to the institution from Abbvie, AI, Astellas, Forma, Incyte, Kite and Takeda. MA reports research grant support paid to institution from Incyte, CTI Biopharma, Samus Therapeutics, Janssen, and Gilead. RTS reports consultancy and speaker bureau for Pharmaessentia. RH reports research support from Roche.

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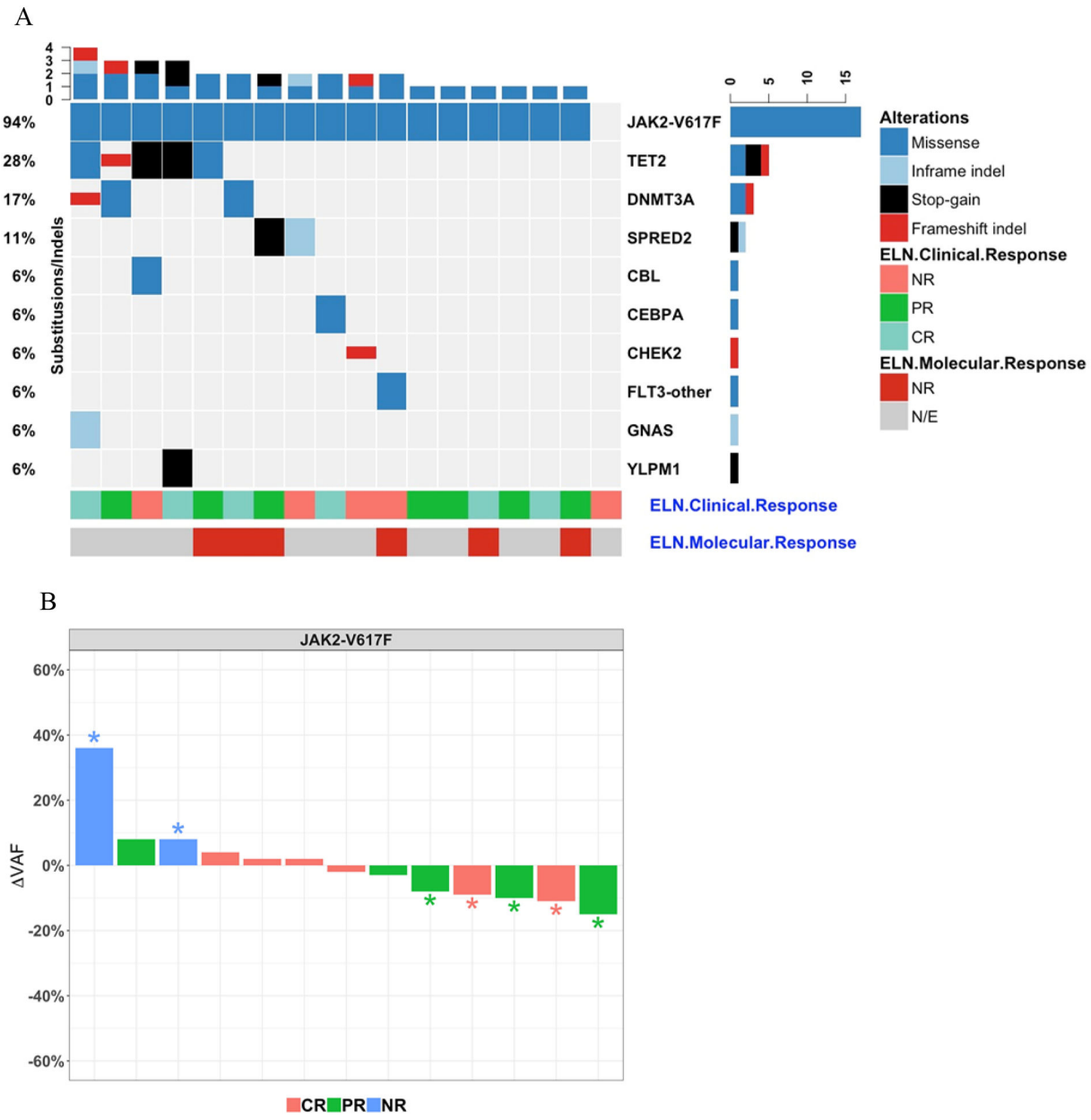

Figure.

1A Oncoprint of identified genomic alterations in 17 baseline samples. Individual genes are represented as rows, and the patients are represented as columns. The bars at the top of the figure indicate the number of somatic alterations that were identified in the corresponding patient at baseline. Different colors distinguish the type of alterations, such as missense (dark blue), stop-gain (black), in-frame indel (light blue), and frameshift indel (red). The genes (rows) are sorted based on the frequency of the gene-level alterations in the cohort, as noted on the left of the figure. The best clinical response of each patient is displayed at the bottom annotation bar according to the key. **1B** *JAK2V617F* variant allele fraction (VAF) waterfall plot. The y-axis indicates absolute change from the baseline VAF. Each bar represents an individual patient and the colors denote best response status (red: CR, green:

PR and blue: NR). The stars highlight patients who have significant change of VAF from baseline. These is a subset of patients for whom the 95% confidence interval of VAF (with respect to the depth of coverage of the mutation in corresponding sample) did not overlap between baseline and last time-points.

Table 1

Baseline clinical variables of 20 ET/PV subjects with splanchnic vein thrombosis receiving pegylated interferon-alfa-2a therapy

Variable	n=20
Gender, female	12 (60.0%)
Essential thrombocythemia/polycythemia vera	7/13
Disease duration (median time since initial diagnosis, mos)	16.4 (0.4–121.9)
Prior MPN-directed therapy	7 (35.0%)
Anagrelide	1 (14.3%)
Hydroxyurea	5 (15.0%)
Therapeutic phlebotomy only	1 (14.3%)
Anticoagulation at time of enrollment	18
Aspirin only	6
Warfarin	10
Low molecular weight heparin	2
ECOG 0	16 (80.0%)
ECOG 1	4 (20.0%)
Splenectomy	4 (20.0%)
Palpable splenomegaly	10 (50%)
Median spleen length by palpation, cm (range) *	3.0 (0.0–11.0)
Median spleen length by imaging, cm (range) *	15.0 (8.0–18.3)
Median WBC x10^9/L, range	7.6 (2.5–23.2)
Median hematocrit, range	42.0 (34.6–48.0)
Median platelets x10^9/L, range	339.0 (149.0–872.0)
Median LDH, range	241.0 (157.0–603.0)
Abnormal karyotype **	4
JAK2V617F ***	17 (100%)
CALR exon 9 ***	0
MPLW515L/K ***	0

* n=14

** 46,XY,del(20)(q11;q13); 46,XX,+1,der(1;7)(q10;p10); 47,XY,+9[2]; 46,XX,del(20)(q11.2q13.1)

*** n=17 with baseline mutational status

WBC white blood cell count, LDH lactate dehydrogenase