PREVALENCE OF SECOND CANCERS IN PATIENTS WITH POLYCYTHEMIA VERA (PV): A RETROSPECTIVE ANALYSIS OF US REAL-WORLD CLAIMS DATA

Naveen Pemmaraju, MD[1], Alina Markova, MD[2], Lucia Masarova, MD[1], Nancy Reaven, MA[3], Susan Funk, MBA[3], Pedro Oyuela, MD[4], Frank Valone, MD[4], Phil Dinh, PhD[4], Lucy Bellamy[4], Nikita Modi, PharmD[4], Arturo Molina, MD, MS, FACP[4] and Suneel Gupta, PhD[4]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Strategic Health Resources, La Canada, CA; [4]Protagonist Therapeutics, Inc., Newark, CA

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INTRODUCTION

- Polycythemia vera (PV) is a chronic myeloproliferative neoplasm (MPN) associated with risk of leukemic or fibrotic progression[1]
- In addition to the known risk of disease transformation, patients with MPNs have a 60% higher risk of developing second non-hematologic cancers compared to matched controls
  - Skin cancers are among the most prevalent second cancers, with a reported 2.8-fold increase in risk of non-melanoma skin cancer (NMSC)[2]
- We used data for 2007-2019 from a large US electronic health records database to examine the overall frequency of second cancers in patients with a primary PV diagnosis and compared those who were treated with hydroxyurea (HU) versus phlebotomy (PHL) only

METHODS

Data Source

- The Optum® MarketClarity Database contains HIPAA-compliant, de-identified data from a cumulative population of >105 million patients in the United States, including those with all insurance types and those who were uninsured (**Figure 1**)

Figure 1. Data Source Methods

Optum® De-identified Electronic Health Records Dataset, (MarketClarity) 2007–2019

- ≥2 PV diagnosis codes with ≥60 days between the first and last diagnosis code in the data period among patients ≥18 years old
- Patients were indexed at the 1st diagnosis code of PV preceded by ≥1 year of EHR data
- ≥1 year of follow-up data (post-index date) was required unless the patient died during this interval
- Exclusions: Patients with pre-index evidence of secondary polycythemia, leukemia, myelodysplastic syndrome, myelofibrosis, or stem cell transplant

- A subset of patients with available pre-index medication data was used to evaluate differences in post-treatment cancer prevalence by treatment groups
- Patients with a minimum of 4 weeks of HU treatment at any time were compared with patients with phlebotomy-only treatment

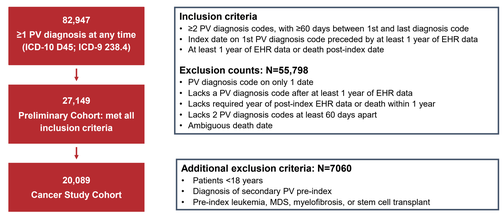
Cancer Outcomes

- Post-index period prevalence of second cancers was evaluated for all patients. Second cancers were identified at first occurrence of a diagnosis code (ICD-9 or ICD-10) for a defined cancer in retrospective electronic health records.
  - ‘Any malignancy’ included over 3000 diagnostic codes
  - ‘Non-AML leukemias’ included 237 diagnostic codes
- Cancer events were counted once per patient, per type of cancer
- Analysis of post-treatment cancer rates used a subset of patients with pre-index medication data in EHR or linked claims data (n=17,402) and excluded non-skin cancer types identified prior to treatment and skin cancer types recurring post-treatment with a gap of <30 days since the prior diagnosis
  - The association of treatment group and second cancers was examined with Chi-square tests
  - Cox Proportional Hazards models were used to evaluate the predictors of incident skin cancers in the post-index period using pre-index treatments and conditions as predictors
  - Covariates included clinical and demographic information (age, sex, race, region, comorbid or pre-existing medical conditions and laboratory values)
  - P-values were not adjusted for multiplicity

RESULTS

- 20,089 patients with PV qualified for this retrospective study (mean age, 63.0 years; 57.8% male; 88.6% Caucasian) (**Figure 2**)

Figure 2. Patient Population



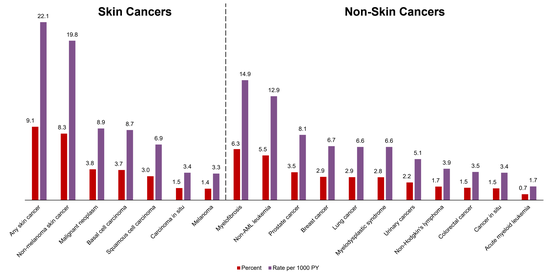
EHR, electronic health record; PV, polycythemia vera; MDS, myelodysplastic syndrome.

- 15.5% of patients (n=3112) had evidence of a pre-index cancer
- Median duration of follow-up was 4.3 years (Q1-Q3 2.4-5.9)

Cancer Prevalence

- 35.7% of patients (n=7181) reported at least one second cancer in the post-index period (“post-index period prevalence”)
- The rate of second cancers in the post-index period was 109.7 events per 1000 patient years (PY)

Figure 3. Post-Index Period Prevalence of Second Cancers in Patients with PV (N=20,089)

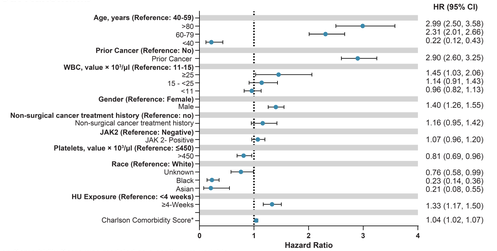


AML, acute myeloid leukemia, PY, patient years.

- The most common non-hematologic malignancies were skin cancers (22.1/1000 PY) followed by prostate cancer (8.1/1000 PY) and breast cancer (6.7/1000 PY) (**Figure 3**)
- 9.1% (1830 patients) reported at least one skin cancer in the post-index period, with 8.3% (1659 patients) experiencing non-melanoma skin cancer (NMSC) and 1.4% (286 patients) experiencing melanoma (**Figure 3**)
  - The post-index period prevalence rate of NMSC was 6-times higher versus the rate of melanoma (19.8 vs. 3.3/1000 PY)
  - Among NMSCs, the rate of basal cell carcinoma was higher than the rate of squamous cell carcinoma (8.7 vs. 6.9/1000 PY). However, the highest rate was observed for non-specific or unspecified malignant neoplasms (8.9/1000 PY).

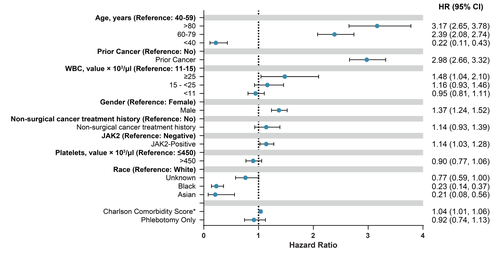
Risk Factors for Skin Cancers

Figure 4. Forest Plot with Predictors of Skin Cancers, Rank-Ordered by Highest Significant HRs, for Patients with Pre-index Medication Data Who Were Exposed to at Least 4+ Weeks of HU Without Ruxolitinib



*Charlson Comorbidity Score was modeled as a continuous variable.
CI, confidence interval; HU, hydroxyurea; HR, hazard ratio; WBC, white blood cell. Model also adjusted for geographical region and smoking status.

Figure 5. Forest Plot with Predictors of Skin Cancers, Rank-Ordered by Highest Significant HRs, for Patients with Pre-index Medication Data Who Received Therapeutic Phlebotomy Only



*Charlson Comorbidity Score was modeled as a continuous variable.
CI, confidence interval; HR, hazard ratio; WBC, white blood cell. Model also adjusted for geographical region and smoking status.

- In Figures 3 and 4, the strongest predictors of skin cancers were older age (>60 years), history of cancer, elevated white blood cell count ≥25 × 10^3/µL, and male sex
- After controlling for demographic and clinical covariates, 4 weeks (minimum) exposure to HU was associated with a higher hazard of incident skin cancers (hazard ratio [HR] 1.33; 95% CI: 1.17, 1.50) (**Figure 4**)
- In contrast, phlebotomy treatment was not associated with incident skin cancers (HR 0.92, 95% CI: 0.74-1.13) after controlling for other covariates (**Figure 5**)

Second Cancers Associated with Common PV Treatments

- Within the subset of 17,402 patients with pre-index medication data, 20.2% (n=3512) were exposed to at least 4 weeks of HU (without ruxolitinib) at any time; 19.0% (n=3314) were treated with phlebotomy only
- The rate of any second malignancy subsequent to treatment was >2.5-times higher in the HU vs. phlebotomy group (140.4 vs. 55.3/1000 PY) (**Table 1**)
- Rates of skin cancers were nearly 2-times higher in the HU vs. PHL group for any skin cancer (31.6 vs. 17.7/1000 PY), NMSC (28.8 vs. 15.7/1000 PY), and melanoma (4.5 vs. 2.9/1000 PY) (**Table 1**)

Table 1. Rates of Second Malignancies in Patients with PV Treated with Hydroxyurea vs. Phlebotomy Only

Malignancy type	Patients treated with hydroxyurea (n=3512)		Patients treated with phlebotomy only (n=3314)		
	Percent	Rate[a]	Percent	Rate[a]	P-value
Any malignancy	50.7	140.4	21.6	55.3	<0.0001
Skin cancer	13.8	31.6	7.4	17.7	<0.0001
Non-melanoma skin cancer	12.7	28.8	6.6	15.7	<0.0001
Malignant neoplasm	6.1	13.4	2.7	6.2	<0.0001
Squamous cell carcinoma	5.7	12.5	2.5	5.8	<0.0001
Basal cell carcinoma	5.5	12.0	3.0	7.0	<0.0001
Carcinoma in situ	3.0	6.5	1.2	2.8	<0.0001
Melanoma	2.1	4.5	1.3	2.9	0.0219
Myelofibrosis	13.8	30.6	2.8	6.4	<0.0001
Non-AML leukemias	11.0	23.9	3.0	6.9	<0.0001
Myelodysplastic syndrome	6.0	13.1	1.1	2.6	<0.0001
Prostate cancer	2.7	5.7	2.8	6.5	0.3184
Lung cancer	2.5	5.4	1.9	4.3	0.1350
Breast cancer	2.4	5.1	1.1	2.5	<0.0001
Urinary cancers	2.0	4.2	1.7	3.9	0.5396
Non-Hodgkin’s lymphoma	1.8	3.8	0.9	2.1	0.0079
Cancer in situ	1.4	3.1	0.6	1.3	0.0017
Acute myeloid leukemia	1.4	2.9	0.5	1.0	0.0001
Colorectal cancer	1.4	2.9	0.8	1.8	0.0581

[a]Rate represents number of events per 1000 patient years.

CONCLUSIONS

- In this large retrospective study of US patients, we found that patients with PV had high rates of secondary malignancies
  - The highest rates were observed for skin cancers, driven by the frequency of NMSC
- Patients treated with HU had nearly twice the rate of skin cancers (including NMSC and melanoma) compared to PHL-only treated patients
- Exposure to HU was a significant predictor of skin cancers after controlling for other demographic and clinical variables
- The strongest predictors of skin cancers were older age (≥60 years), history of malignancy, elevated white blood cell count ≥25 × 10^3/µL, and male sex
- Although the mechanisms contributing to the increased risk of cancers are not fully understood, the inherent risk associated with PV appears to be further increased by exposure to HU

REFERENCES

1. Tefferi A and Barbui T. *Am J Hematol*. 2017;92:94-108.
2. Landtblom AR, et al. *Leukemia*. 2018;32:2203-10.

DISCLOSURES

NP: Membership on an entity’s Board of Directors or advisory committees for Dan’s House of Hope. Consultancy, Membership on an entity’s Board of Directors or advisory committees and Speakers Bureau for Aplastic Anemia & MDS International Foundation, BMS, CancerNet, CareDx, Celgene, Dava Oncology, Harborside Press, Imedex, Intellisphere, Magdalen Medical Publishing, Medscape, Menarini Group, OncLive, Patient Power, PeerView Institute for Medical Education, Physician Education Resource (PER). Other: Leadership for ASH Committee on Communications, ASCO Cancer.Net Editorial Board. Other: Licenses for Karger Publishers. Research Funding for United States Department of Defense (DOD), National Institute of Health/National Cancer Institute (NIH/NCI). Other: uncompensated for HemOnc Times/Oncology Times. **AMa**: Research funding from Incyte Corporation and Amryt Pharma; consults for ADC Therapeutics, Alira Health, AstraZeneca, Protagonist Therapeutics, OnQuality, and Janssen; and receives royalties from UpToDate. **LM**: Nothing to declare. **NR, SF:** Consultants to Protagonist Therapeutics, Inc. **PO, FV, PD, LB, NM, AMo, SG**: Employees of Protagonist and have an equity interest in the company.

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CONTACT INFORMATION

Naveen Pemmaraju, MD (email: NPemmaraju@mdanderson.org), Department of Leukemia, The University of Texas MD Anderson Cancer Center at Houston, TX, 77030, USA or Protagonist Therapeutics, Inc. (email: info@ptgx-inc.com).