race (0.11%) (Supporting Information Figure, chi-square test *P*-value: .0001). In patients with Khorana low risk, 5 (1.6%) patients developed events; in patients with Khorana intermediate risk, 36(3.54%) patients developed events; in patients with Khorana high risk, 14(5.15%) patients developed events (Supporting Information Figure, Mantel–Haenszel test for trend *P*-value: .02).

In Cox proportional hazards model: compared with Whites, Blacks were associated with increased risk for VTE or VTE-related death (AHR: 3.25, 95% CI: 1.12-9.45, *P*-value: .03). There was no difference in risk between Whites and Asians (AHR: 0.92, 95% CI: 0.43-1.94, *P*-value: .82). Patients with Khorana intermediate or high risk, with ECOG score ≥ 2, and patients with ≥ 2 VTE-associated risk factors had increased risk for VTE or VTE-related death (Table 1). Patient's age, sex, cancer stage, the use of cisplatin or use of any bevacizumab, sunitinib, cetuximab, panitumumba or tamoxifen were not associated with increased VTE risk (Table 1).

There are so far few studies conducted in a cancer population which capacitates direct comparisons between Asians and other races outside the United States.[6] The SAVE-ONCO trial control arm was an ideal cohort for us to investigate the effect of race on VTE risk in patients receiving chemotherapy given the homogenized follow-up mandated by study procedures and worldwide enrollment.

Our results demonstrated that after adjustment for baseline characteristics including the Khorana risk score and chemotherapy agents, there was no difference of VTE risk between Asians and Whites. However Blacks had a significantly threefold increased risk of VTE in patients initiating chemotherapy. Certain limitations included that Blacks were underrepresented and our results were a post-hoc analysis.

In conclusion, we found that although Asians might have lower risk of VTE than Whites in the general population,[1] this risk might likely be potentiated by chemotherapy agents in cancer population. Physicians should be aware that VTE is the leading cause of death in outpatient chemotherapy.[2] Future studies are indicated to address the risk of VTE upon starting chemotherapy among different races and ethnicities.

CONFLICT OF INTEREST

A. A. Khorana reports personal fees from Sanofi, personal fees from Janssen, personal fees from Leo Pharma, personal fees from Bayer, personal fees from Pfizer, personal fees from Halozyme, personal fees from Roche, personal fees from AngioDynamics, outside the submitted work.

AUTHOR CONTRIBUTIONS

Conception and Design: Y.W. Chen, A.A. Khorana; Collection and assembly of data: Y.W. Chen, A.A. Khorana; Data Analysis and interpretation: Y.W. Chen, A.A. Khorana; Manuscript writing: Y.W. Chen, A.A. Khorana; Final Approval of manuscript: Y.W. Chen, A.A. Khorana

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

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Recombinant erythropoietin vs. blood transfusion care in infants with hereditary spherocytosis: a retrospective cohort study of A.I.E.O.P. patients (Associazione Italiana Emato-Oncologia Pediatrica)

To the Editor:

In hereditary spherocytosis (HS), erythropoietic responsiveness is frequently blunted and unable to full compensate for hemolysis, with many affected infants requiring transfusions.[1] Some previous reports[2–6] have shown contradictory data about benefits from the use of recombinant human erythropoietin (rHuEPO). In this study performed in A.I.E.O.P. (Associazione Italiana Emato-Oncologia Pediatrica) centers, we compared outcomes between centers using rHuEPO and centers using only

transfusion therapy, by analyzing a group of 48 infants treated with rHuEPO and comparing them with 30 infants supported with packed red blood cells (PRBC; Table 1). Case report forms were sent to participating centers: one for centers treating infants with rHuEPO and the other for centers treating infants with PRBC. To avoid bias, centers treating or having treated randomly some patients with rHuEPO and some patients with PRBC were not included. Patients treated with rHuEPO were included even if already transfused in another hospital before arriving at the center using rHuEPO therapy, and/or if in the course of rHuEPO treatment occasional PRBC transfusions were deemed necessary on the basis of clinical conditions and/or severity of anemia.

We compared the total number of transfusions in the first year of life (TT) in the two groups and also considered another alternative outcome, the total number of transfusions/year in the first year of age from the start of therapy (TTY):

$$\frac{\text{Number of transfusions from start of therapy to one year of age}}{\text{Days from start of therapy to one year of age}} \times 365$$

According to the definition of TTY, transfusions before starting rHuEPO were excluded: all transfusions in the first year of life after the first rHuEPO dose in the rHuEPO group and all transfusions in the first year of life in the PRBC group were included.

Thirty patients (38.4%) received transfusions (PRBC group) and 48 (61.5%) received subcutaneous rHuEPO (rHuEPO group). Less than half (43.7%) of rHuEPO treated patients (21/48) had already received transfusions before arriving at the center using rHuEPO. Median–mean TT in rHuEPO and PRBC group were respectively: 1-1.69 vs. 2-3.23 ($P = .0007711$). Using TTY as outcome, we also found a significant difference: median–mean TTY in rHuEPO and PRBC groups were 0.00-1.05 vs. 2.23-3.62 ($P = 1.14\ e{-}07$) respectively.

Since the median hemoglobin (Hb) value at the last blood count before the start of specific therapy was higher in the rHuEPO group (Table 1), we speculated that some patients in the rHuEPO group could have avoided transfusion even if they had not been treated with rHuEPO. To correct for this potential bias, we repeated our analysis using a subgroup of patients with more comparable disease severity, namely those having Hb values between 6.0 and 8.0 g/dL at the blood count immediately preceding the start of therapy: 19/48 (39.6%) children in the rHuEPO group and 20/30 (66.7%) in the PRBC group were included in this sub-analysis. Statistically significant differences were present for both TT ($P = .002347$, with median and mean in rHuEPO and PRBC group of 1.0-1.4 vs. 3.0-3.4, respectively) and TTY ($P = 2.444\ e{-}05$, with median and mean in rHuEPO and PRBC group of 0.00-0.84 vs. 2.34-2.62, respectively). There was no significant difference in the median age at start of therapy ($P = 0.07$) and above all in Hb value distribution at the last blood count before the start-therapy ($P = .20$).

We performed a bivariate analysis between TTY and Hb values before start-therapy: Hb values were not significantly related to TTY, neither in the whole sample ($P = .11$), nor in each therapy group ($P = .26$ in PRBC group, $P = .53$ in rHuEPO group). We also performed a multiple regression on the whole sample, with TTY as outcome and Hb values before start-therapy and therapy group (rHuEPO and PRBC) as predictor variables: therapy group remained highly significant ($P = .0002$), while Hb value was not significant ($P = .80$).

We examined reticulocytes in the two groups at 30, 90, and 180 days of life (Table 1): the difference was significant only at one month of age, with rHuEPO treated patients showing higher counts ($P = .04717$).

Furthermore, we compared patients who started therapy with higher rHuEPO doses (751-1200 IU/kg/week) to patients treated with lower doses (500-750 IU/kg/week): there was no statistically significant difference both in terms of TT ($P = .50$) and TTY ($P = .58$). No rHuEPO side effects were reported.

The mean duration of rHuEPO treatment was 133 days (19.0 weeks), the mean weekly dose of rHuEPO was 538 IU/Kg and the average number of weekly injections was 2. The mean number of transfusions at under 1 year of age in the rHuEPO and PRBC group was 1.69 and 3.23, respectively. Estimated costs were 913 Euros (153 for rHuEPO + 205 for injections + 510 for 1.7 transfusions) in each rHuEPO treated child, and 2261 Euros (969 for 3.23 transfusions + 1292 for days hospital) in each PRBC treated patient.

TABLE 1 Characteristics of rHuEPO and PRBC groups

	rHuEPO	PRBC	*P*
Female/Male (%)	18/30 (37.5/62.5)	16/14 (53.3/46.7)	$P = .1701$
Median Hb at blood count immediately preceding start-therapy	8.30g/dL	6.85g/dL	$P = 3.355\ e{-}07$
Median age at start-therapy (days)	40	32	$P = .2806$
Median age at stop-therapy (days)	135	124	$P = .5376$
Median reticulocytes at 30 days of life	194.700/μL	80.000/μL	$P = .04717$
Mean reticulocytes at 30 days of life	172.213/μL	101.145/μL	
Median reticulocytes at 90 days of life	192.000/μL	170.200/μL	$P = .3051$
Mean reticulocytes at 90 days of life	233.532/μL	174.971/μL	
Median reticulocytes at 180 days of life	213.500/μL	248.500/μL	$P = .58$
Mean reticulocytes at 180 days of life	228.580/μL	273.141/μL	

The present multicenter study is the first to compare centers adopting transfusions only and centers adopting rHuEPO ± transfusion. We believe it strongly suggests that rHuEPO can reduce the need for blood transfusions in infants with HS. Furthermore our data give some indications about the timing of rHuEPO therapy: at 30 days of life the reticulocyte count is significantly higher in the rHuEPO group, whereas at 180 days it is comparable in the two groups. We can deduce that rHuEPO should be started as early as possible in all infants with anemia at birth or showing a rapid fall in Hb values and that a therapy discontinuation schedule can be based upon the presence of a satisfactory plateau in Hb values at about 5-6 months of age. In conclusion, rHuEPO therapy should be considered in infants suffering from HS, with the aim of improving quality of life and limiting both financial cost and exposure to donor blood products.

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CONFLICT OF INTEREST

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Ibrutinib in very elderly patients with relapsed/refractory chronic lymphocytic leukemia: A real-world experience of 71 patients treated in France: A study from the French Innovative Leukemia Organization (FILO) group

To the Editor:

In first-line therapy, 20% of patient with chronic lymphocytic leukemia (CLL) are even 80 years old or over, rendering therapeutic decisions often challenging. Due to the common comorbidity burden and frequency of adverse cytogenetics associated with this elderly population,