compared with treatment with placebo.[5] These results show that ruxolitinib reduces splenomegaly in patients with thalassemia and suggest that targeting *EPO-EPOR-JAK2-STAT5* axis may limit the excessive proliferation of erythroid progenitors in spleen.

Although there was an increase in hepcidin levels with ruxolitinib treatment in our study, no significant changes in either serum iron or ferritin levels were observed over time. However, increased levels of hepcidin may suggest that the handling of iron absorption could be improved in the long term.

In conclusion, treatment with ruxolitinib in patients with TDT led to a sustained reduction in spleen size, and, hence, could be considered as an option for TDT patients with splenomegaly. Because the major purpose of reducing spleen size in patients with TDT is to improve pretransfusion hemoglobin and related reduction in transfusion needs where ruxolitinib had shown a limited effect, no further phase 3 studies are planned in regularly transfused patients with thalassemia.

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Authorship

Contribution: A.T.T. contributed to study design, data collection, and data interpretation and performed the research. Y.A., Z.K., E.C., A.M., A.K., and N.S. performed research and contributed to data collection and interpretation. S.R. contributed to study design and data interpretation. N.H. contributed to study design and performed statistical analyses. B.G., N.H., and B.M. contributed to data interpretation. All authors were involved in drafting the manuscript and approved the final version.

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Footnotes

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TO THE EDITOR:

Histiocytic sarcoma: a population-based analysis of incidence, demographic disparities, and long-term outcomes

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Histiocytic sarcoma (HS) is a rare hematopoietic neoplasm derived from non-Langerhans histiocytic cells of the monocyte/macrophage system that is diagnosed using immunohistochemistry markers, such as CD68, lysozyme, CD4, and CD163, on the tissue biopsies.[1] HS can occur in isolation or in association with other hematological neoplasms like non-Hodgkin lymphoma (NHL), myelodysplasia, or acute leukemia.[2] HS has variable clinical presentation and outcomes, ranging from localized disease to multiple sites within a single system, to life-threatening disseminated disease (preferentially involving the skin, soft tissue, and gastrointestinal tract).

The exact incidence of HS in adults is unclear, and contemporary clinical data are mostly limited to institutional case series.[2-7] In this study, we used the Surveillance, Epidemiology, and End Results (SEER) Program database (https://seer.cancer.gov/) to study the incidence, clinical presentation, and outcomes of HS.

SEER, a program of the US National Cancer Institute, collects cancer incidence and survival data from population-based cancer registries covering ~28% of the US population. We identified HS cases (age >18 years) that were confirmed histologically using International Classification of Diseases for Oncology, Third Edition histology code 9755/3 from the SEER 18 (1973–2014) registry, and we included cases that were diagnosed after 2000. We calculated the incidence (cases per 1 000 000) and disease-specific survival (DSS) rates using the 2000–2014 SEER 18 registries and age-adjusted those to the US 2000 standard population. Patient-level data were analyzed to determine demographic findings and clinical outcome. We used SEER*Stat (version 8.3.4; https://seer.cancer.gov/seerstat/) for incidence and survival statistical calculations. The SEER*Stat Multiple Primary-SIR tool was used to calculate standard incidence ratios (SIRs) for secondary malignancies by comparing these patients' subsequent cancer diagnoses with the number of cancers that would be expected based on incidence rates for the general US population.

A total of 159 cases with HS were reported in the SEER database between 2000 and 2014. We excluded 1 case that was reported with concomitant myeloid monocytic leukemia because that could be potentially classified as myeloid sarcoma. The median age at diagnosis was 63 years (range, 18-96 years) and was similar in both sexes. The overall incidence of HS was 0.17 per 1 000 000 individuals (95% confidence interval [CI]: 0.14-0.19]. The incidence according to racial groups was: whites, 0.18 (95% CI: 0.15-0.21), African Americans, 0.04 (95% CI: 0.01-0.11), and others (Asian/Pacific Islander/American Indian), 0.12 (95% CI: 0.06-0.21). The incidence was significantly lower among African Americans compared with whites (incidence rate ratio: 0.27; 95% CI: 0.08-0.64; $P = .0009$), and was higher among males (female:male incidence ratio = 0.49; $P = .0001$). The most common sites of the presentation were skin and connective tissue (35.8%), followed by lymph nodes (17%), respiratory system (8.2%), and nervous system (7.5%). Patient characteristics are summarized in Table 1.

The median overall survival (OS) in the entire cohort of HS was 6 months (Figure 1A). Five-year DSS was similar in males (42.3% [95% CI: 29.8-54.2]) and females (33.6% [95% CI: 18.9-48.9]) (Figure 1B). Similarly, median OS was similar among all races (Figure 1C). Although the incidence of HS significantly increased over time ($P = .006$), the 5-year OS was similar between patients diagnosed from 2000 to 2007 and 2008 to 2014 (Figure 1D). The median OS did not differ significantly based on the primary site ($P = .06$). After censoring patients with bone marrow, spleen, and reticuloendothelial system involvement, patients who were managed surgically had a better OS compared with those who were not (hazard ratio: 0.33 [95% CI: 0.21-0.50]; $P < .0001$) (Figure 1E).

After a median follow-up of 7.5 months (range, 0-178 months), 115 patients had died. Among these 115 deaths, 66 (57.3%) were due to a malignancy, either HS alone (n = 24) or in combination with other neoplasms (n = 42). The coexisting malignancies

Table 1. Characteristics of HS patients

Variable	Number
Total number of patients (2000–2014)	159
Median age, y	63 (range, 18-86)
Males	63 (18-95)
Females	63.5 (18-96)
Sex (%)	
Males	99 (62.3)
Females	60 (37.7)
Year of diagnosis (%)	
2000–2007	63 (39.6)
2008–2014	96 (60.4)
Race (%)	
White	138 (86.8)
African American	5 (3.1)
Asian/Pacific Islander	12 (7.5)
American Indian	0 (0.0)
Unknown	4 (2.5)
Site frequencies (%)	
Connective tissue and skin	57 (35.8)
Nodal	27 (17)
Respiratory system (including sinuses)	13 (8.2)
Nervous system	11 (6.9)
GI tract (including hepatobiliary and pancreas)	12 (7.5)
Bone marrow and hematopoietic system	7 (4.4)
Spleen and RES	8 (5.0)

GI, gastrointestinal; RES, reticuloendothelial system.

in patients who died were as follows: NHL (n = 28), acute myeloid leukemia (AML; n = 6 patients), chronic lymphocytic leukemia (n = 3), myeloma (n = 1) mixed germ cell tumor (n = 1), splenic marginal cell lymphoma (n = 1), papillary transitional cell carcinoma of urinary bladder (n = 1), and renal cell carcinoma (n = 1). The median OS was significantly shorter in patients who had concomitant NHL (7 months) and AML (10 months) compared with that of HS alone (16 months) ($P < .001$) (Figure 1F). Compared with the general population, HS patients had an increased risk of developing NHL (SIR: 51.2; $P < .05$). HS occurred as second primary malignancy in 34 cases, which included follicular lymphoma (n = 5), precursor cell lymphoblastic leukemia (n = 4), small B-cell lymphoblastic leukemia (n = 3), breast cancer (n = 3), prostate cancer (n = 5), aleukemic leukemia (n = 1), gall bladder adenocarcinoma (n = 1), and miscellaneous cancers (n = 12). No significant difference in survival was noted whether HS occurred as a first primary malignancy or second primary malignancy ($P = .38$).

The major limitations of our study can be attributed to its derivation from a database, with limited information on the specific therapies received, patient performance status, and comorbidities. Additionally, in the case of patient deaths in the presence of HS and another concomitant, aggressive malignancy, we were unable to ascertain the exact cause of death. Nevertheless, our study provides important insights into disease incidence, clinical

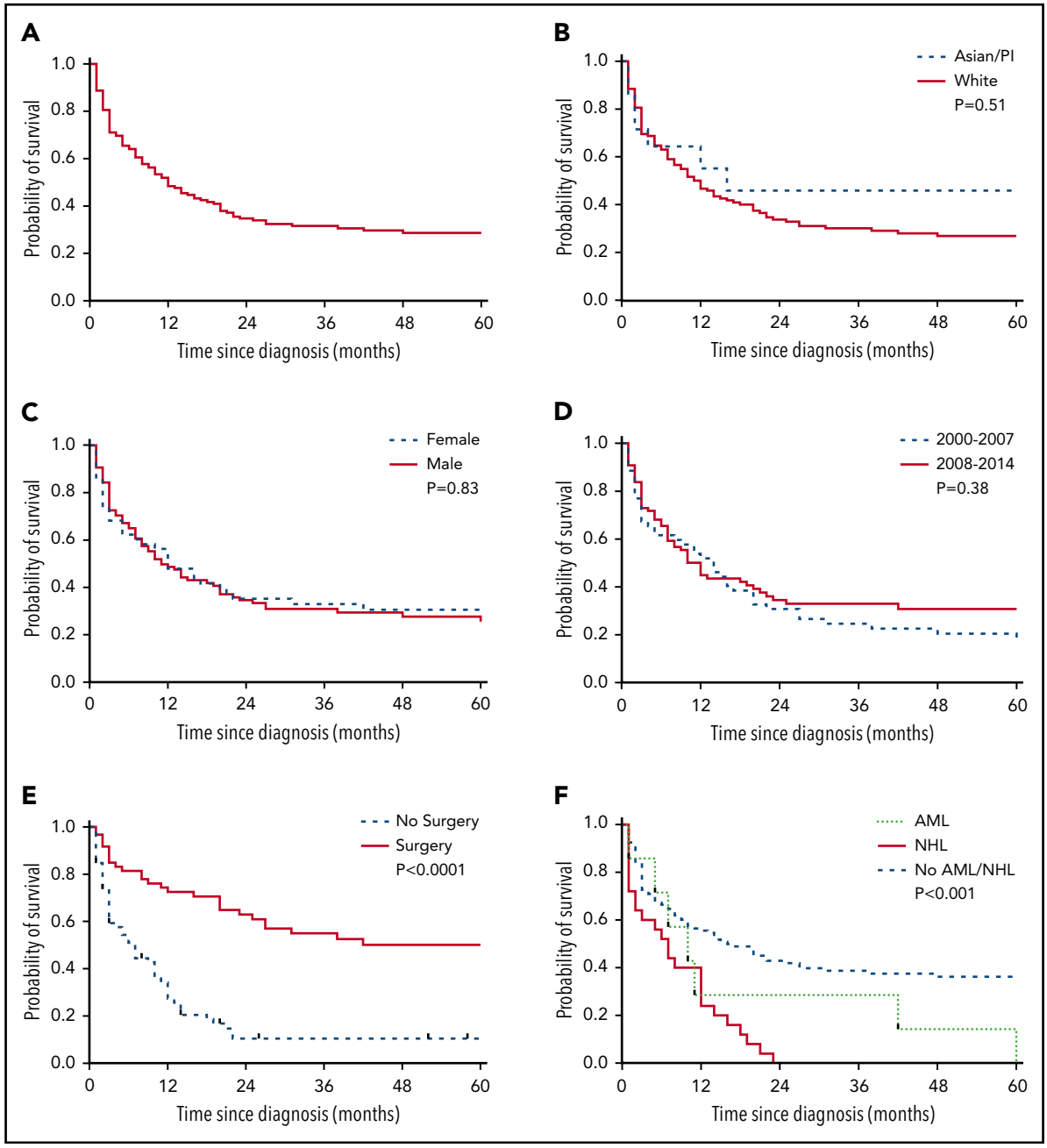

Figure 1. OS analyses by Kaplan-Meier curves in patients with HS. (A) Predicted OS in patients with HS. (B) Comparison of OS by race. (C) Comparison of OS by sex. (D) Comparison of OS of patients diagnosed between 2000 and 2007 and between 2008 and 2014. (E) Comparison of OS based on surgical treatment. (F) Comparison of OS based on the presence of concomitant NHL and AML. $P < .05$ was considered significant. PI, Pacific Islander.

presentation, and patient outcomes, where traditional studies are limited due to the rarity of the condition.

In summary, this study is the largest report on adult HS patients in the United States. It shows that HS is a very rare malignancy that is less common among the African American population and in females. The prognosis was relatively poor for patients who had concomitant hematological neoplasms (NHL and AML). Also, there is an increased risk of subsequent development of NHL. Our study highlights that, despite the rising incidence, there has not been an improvement in survival, clearly emphasizing the unmet need for better therapies for this rare but lethal malignancy.

Authorship

Contribution: A.K., S.H.T., and G.G. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; A.K. and S.H.T. conceptualized and designed the study and drafted the manuscript; A.K., S.H.T., and M.D. contributed to acquisition, analysis, or interpretation of data and statistical analysis; A.K., S.H.T., M.D., G.G., and R.S.G. critically revised the manuscript for important intellectual content; and G.G. supervised the study.

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Footnotes

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