In our experience, ruxolitinib is active in secondary HLH, well tolerated, non-myelosuppressive, and manageable in the outpatient setting. Therefore, we believe these findings support ongoing efforts investigating JAK inhibitors, not only in HLH, but in other HLH-related cytokine-release syndromes, including severe Covid-19.

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AUTHOR CONTRIBUTIONS

A.A., S.A.M., and R.A.W. provided and interpreted data. P.S.B. and R.A.W. analyzed data and drafted the manuscript. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions.

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This trial (NCT02400463) was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent was provided by clinical trial participants.

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REFERENCES

1. Locatelli F, Jordan MB, Allen C, et al. Emapalumab in children with primary Hemophagocytic Lymphohistiocytosis. *N Engl J Med*. 2020; 382:1811-1822.
2. Das R, Guan P, Sprague L, et al. Janus kinase inhibition lessens inflammation and ameliorates disease in murine models of hemophagocytic lymphohistiocytosis. *Blood*. 2016;127:1666-1675.
3. Ahmed A, Merrill SA, Alsawah F, et al. Ruxolitinib in adult patients with secondary haemophagocytic lymphohistiocytosis: an open-label, single-Centre, pilot trial. *Lancet Haematol*. 2019;6:e630-e637.
4. Wilcox RA. Janus Family kinase (JAK) inhibitors in HLH and severe COVID-19. *Am J Hematol*. 2020;95:1448-1451.
5. Bergsten E, Horne A, Arico M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood*. 2017;130:2728-2738.
6. Merrill SA, Naik R, Streiff MB, et al. A prospective quality improvement initiative in adult hemophagocytic lymphohistiocytosis to improve testing and a framework to facilitate trigger identification and mitigate hemorrhage from retrospective analysis. *Medicine*. 2018;97:e11579.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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Depression in adolescents and young adults with heavy menstrual bleeding in a referral clinic setting

To the Editor:

Heavy menstrual bleeding (HMB) is a common problem reported in up to 40% of adolescent females, with a greater frequency in adolescents with bleeding disorders (BDs).[1] Heavy menstrual bleeding is known to negatively affect health due to high rates of associated iron deficiency (ID) and iron deficiency anemia (IDA), both of which have been linked to decreased health related quality of life (HRQOL) in adults.[2] Adolescents with HMB also report decreased HRQOL compared to adolescents without HMB, and on par with or worse than adolescents with cystic fibrosis and juvenile arthritis.[3] Studies suggest that reduction in HMB, and treatment of ID leads to improvement in HRQOL.[1,2] While there is increasing evidence that HMB in adolescents impacts HRQOL negatively, the association with depression and anxiety, is unknown. We conducted a retrospective chart review at the University of Michigan to evaluate the impact of HMB on mental health disorders, specifically

depression and anxiety, in adolescents and young adults. We further evaluated if a BD diagnosis, IDA, or ID were associated with depression and anxiety in this population and compared the prevalence of depression and anxiety to the general age matched US population.

We identified females 9–25 years old with HMB and/or a BD, including a factor deficiency, von Willebrand disease (VWD), a platelet function disorder (PFD), hypo-/dys-fibrinogenemia or immune thrombocytopenia (ITP), evaluated in the pediatric hematology or combined pediatric hematology and gynecology clinic between 2016 and 2020. We defined HMB as bleeding lasting more than seven consecutive days, requiring changing of sanitary products more frequently than every 2 hours, or multiple episodes of bleeding during the month significant enough to impact daily routines (eg, missing school, work or extracurricular activities).[1] Patients were determined to have depression and anxiety if a provider documented these diagnoses in a note in their electronic medical record (EMR), or if they had a Patient Health Questionnaire-9 score greater than 10. Note, ID was defined as a ferritin less than 30 ng/ml, and severe ID as a ferritin less than 15 ng/ml. Also, IDA was defined as ID in addition to a hemoglobin value below the normal age-based range. Severe anemia was defined as a hemoglobin less than or equal to 9 g/dL. Adolescents were defined as patients ages 12–17 years old, and young adults were defined as patients 18–25 years old. Statistical analysis was performed using two proportion z-tests, $z = \frac{(\bar{p}_1 - p_2)^{-0}}{\sqrt{\bar{p}(1-p)(\frac{1}{n_1}+\frac{1}{n_2})}}$, to compare proportions and t-tests, $t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{(\frac{(N_1-1)s_1^2+(N_2-1)s_2^2}{N_1+N_2-2})(\frac{1}{N_1}+\frac{1}{N_2})}}$, to compare means. The University of Michigan Institutional Review Board approved this study.

In total 272 patients were included. Heavy menstrual bleeding was present in 253 patients (93%) and 138 patients (50.7%) were diagnosed with a BD (86.2% of whom had HMB). The mean age of the patients was 16 years and 10 months. The majority of patients were Caucasian (73.5%), 9.2% were African-American, and additional represented races composed 5% or less of the population. Patients were predominantly non-Hispanic (93.8%).

Represented BDs included VWD (68%), PFDs (19%), factor deficiencies (8%), and ITP (5%). The mean age of onset of menarche was 11.8 years, onset of HMB was 13 years, and mean age at initial evaluation for HMB was 14.5 years. Twenty-four patients (9.5%) presented for initial evaluation of a BD in young adulthood.

Overall, 40.1% of patients in this study had a diagnosis of depression, 37.1% had anxiety, 50% were anemic, and 77.6% were iron deficient. The prevalence of depression and anxiety were evaluated in patients with and without IDA and ID and revealed anxiety was more prevalent in patients without ID (p = .049), though no significant difference was seen with regards to depression. Patients with severe anemia or severe ID were not found to have higher rates of depression (p = .73, p = .68 respectively). Rates of depression and anxiety were similar between patients with and without a BD and are presented in Table 1.

Of the patients with HMB, 43.1% had depression and 37.9% had anxiety. Among these patients with HMB, depression was diagnosed in six patients prior to 12 years of age, 79 patients (33%) during adolescence, and 24 (25%) patients during adulthood. Excluding the 16 (14.7%) patients who had onset of depression prior to HMB, the average time from onset of HMB to diagnosis of depression was 2.3 years. Anxiety was present in half the young adult patients vs 32% of patients ages 13 to 17 years.

Patients with HMB with and without a BD were compared, revealing no difference in age at onset of HMB (p = .25) or at initial evaluation for HMB (p = .26) based on the presence of a BD.

TABLE 1 Comparison of patients by bleeding disorder diagnosis and HMB

			Bleeding Disorder			Bleeding Disorder			
		Total	Heavy Menstrual Bleeding	No Heavy Menstrual Bleeding	p-value	Yes	No	p-value	Ongoing Bleeding Disorder Evaluation
Total N (%)		272	119 (43.8)	19 (7.0)		138 (50.7)	77 (28.3)		57 (21.0)
Depression N (%)	Yes	109 (40.1)	58 (48.7)	0 (0)	.00006	58 (42)	28 (36.4)	.42	23 (40.4)
	No	163 (59.9)	61 (51.2)	19 (100)		80 (58)	49 (63.6)		34 (59.6)
Anxiety N (%)	Yes	101 (37.1)	53 (44.5)	5 (26.3)	.14	58 (42)	24 (31.2)	.12	19 (33.3)
	No	171 (62.9)	66 (55.5)	14 (73.7)		80 (58)	53 (68.8)		38 (66.7)
Depression, Anxiety or Both N (%)	Yes	135 (49.6)	69 (58)	5 (26.3)	.01	74 (53.6)	35 (45.5)	.25	26 (45.6)
	No	137 (50.4)	50 (42)	14 (73.7)		64 (46.4)	42 (54.5)		31 (54.4)
Iron Deficiency N (%)	Yes	211 (77.6)	87 (73.1)	7 (36.8)	.002	94 (68.1)	72 (93.5)	.004	45 (78.9)
	No	27 (9.9)	12 (10.1)	6 (31.6)		18 (13.0)	2 (2.6)		7 (12.3)
	Unknown	34 (12.5)	20 (16.8)	6 (31.6)		26 (18.8)	3 (3.9)		5 (8.8)
Anemia N (%)	Yes	136 (50)	54 (45.4)	1 (5.3)	.001	55 (39.9)	49 (63.6)	.02	32 (56.1)
	No	131 (48.2)	62 (52.1)	16 (84.2)		78 (56.6)	28 (36.4)		25 (43.9)
	Unknown	5 (1.8)	3 (2.5)	2 (10.5)		5 (3.6)	0 (0)		0 (0)

However, on average those with a BD were evaluated 1.4 years earlier than those without a BD as 24 (20.2%) patients presented prior to onset of HMB due to a family history of a BD or other bleeding manifestations (p = .006). Interestingly, those without a BD were more likely to be anemic (p = .019) and iron deficient (p = .024) than patients with a BD perhaps due to pre-menarchal anticipatory guidance.

Patients with a BD diagnosis with and without HMB were compared and results are presented in Table 1. Those without HMB on average presented 43 months earlier than those with HMB (p < .001) as 36.8% without HMB presented at a young age due to a family history of a BD vs only 21% of patients with HMB.

Other factors with potential to impact depressive symptoms including sexual activity and use of hormonal medications were also evaluated. Seventy patients (25.7%) were sexually active and were more likely to be depressed than those who were abstinent (p < .001). Hormonal medications were prescribed to 234 (93%) patients for HMB, 45% of whom had a diagnosis of depression.

Therapeutic interventions for patients with depression were evaluated and 63.3% of patients were treated with an antidepressant, 46.8% of whom received concurrent therapy. In addition, 22% of patients were in therapy alone, and 14.7% did not receive any treatment for their depression.

Our study found a higher prevalence of depression in adolescents (33%) and young adults (25%) with HMB than in the adolescent female population in the US (20% in adolescent females, 13.3% in young adults), unrelated to the presence of an underlying BD.[4]

The prevalence of anxiety in our population of patients ages 13 to 17 years old (32%), was similar to the US population (38%), but the percentage of young adults with HMB and anxiety (50%) was twice that of the general adult population (23.4%).[4]

While this study suggests that HMB is associated with depression in adolescents and depression and anxiety in young adults, the etiology of these mood disorders is likely multifactorial. Our results do not suggest that patients with a BD, ID or IDA are more likely to be depressed. This is somewhat contradictory to prior studies which have shown a correlation between IDA and decreased HRQOL, which has been associated with depressive symptoms.[2] Meanwhile anxiety was more prevalent in patients without ID. As only 27 patients in this study were not ID, a larger cohort of patients without ID is needed to validate these findings.

One potential confounding variable in this study was the large proportion of girls treated with hormonal medication. The impact of hormonal medication on mood has been studied extensively and results are contradictory. One study has shown that women taking oral contraceptives for reasons other than contraception, like most of the patients in our study, are more likely to have depression, suggesting the reason for initiation may have more of an impact on mood than the medication itself.[5] Due to our high hormonal treatment rates, we were not able to evaluate if use was associated with depression.

Sexual activity was noted to be associated with depression in this study. While this could confound our data, it is important to note that only 25.7% of patients were sexually active which is far below the US national average where 51.4% of females 15–17 years old, and 91.8% of females 20–24 years report being sexually active.[6]

A significantly higher percentage of our adolescent patients with HMB received treatment for their depression (85.3%) compared to the US population (39.9%).[4] One explanation for this discrepancy is that patients with HMB have higher rates of severe depression requiring therapeutic intervention. Alternatively, patients with HMB, particularly those in our study with access to healthcare, may be more frequently evaluated for depression by health care professionals, increasing opportunities for diagnosis and treatment.

Limitations of our study include that it was retrospective and therefore reliant on provider documentation. In addition, our cohort of women with BDs without HMB was small, and a larger cohort is necessary to further validate our findings in this group.

In conclusion this study demonstrates that mental health screening is imperative in adolescents and young adults with HMB given the high prevalence of depression and anxiety. From our study it is unclear whether the treatment of HMB with hormonal medications could increase or potentially decrease rates of depression. Further longitudinal studies are needed to determine the association between hormonal medications and depression in patients with HMB.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

All authors designed the study and wrote the manuscript. Mary McGrath performed the data collection and analysis. All authors approved the final version of the manuscript for submission.

DATA AVAILABILITY STATEMENT

Author elects to not share data.

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REFERENCES

1. Haamid F, Sass AE, Dietrich JE. Heavy menstrual bleeding in adolescents. *J Pediatr Adolesc Gynecol*. 2017;30:335-340.
2. Nur Azurah AG, Sanci L, Moore E, Grover S. The quality of life of adolescents with menstrual problems. *J Pediatr Adolesc Gynecol*. 2013;26(2):102-108.
3. Peuranpaa P, Helovaara-Peippo S, Fraser I, Paavonen J, Hurskainen R. Effects of anemia and iron deficiency on quality of life in women with heavy menstrual bleeding. *Acta Obstet Gynecol Scand*. 2014;93:654-660.
4. https://www.nimh.nih.gov/health/statistics/index.shtml. Accessed December 02, 2020.
5. Duke JM, Sibbritt DW, Young AF. Is there an association between the use of oral contraception and depressive symptoms in young Australian women? *Contraception*. 2007;75:27-31.
6. Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: men and women 15-44 years of age, United States, 2002. *Adv Data*. 2005;362:1-55.

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Acute myeloid leukemia after age 70 years: A retrospective comparison of survival following treatment with intensive versus HMA ± venetoclax chemotherapy

To The Editor:

Population-based studies indicate a median age of over 65 years for newly diagnosed adult patients with acute myeloid leukemia (AML).[1] The particular scenario is of utmost practical importance considering that such patients, especially those above age 70 years (i.e., "older old" as opposed to "younger old" patients between ages 60–70 years),[1] are typically not offered allogeneic hematopoietic stem cell transplantation (AHSCT), thus compromising their chance for long-term survival. Instead, an increasing number of oncologists are currently preferring to use low-intensity chemotherapy (e.g., hypomethylating agents ± venetoclax) in older old patients with AML, with the intent to prolong short-term survival while at the same time avoid treatment-related morbidity from intensive induction chemotherapy.[2-4] However, while any form of treatment might be better than supportive care in prolonging survival in such patients, the possibility of additional survival benefit from intensive chemotherapy cannot be excluded and should not be ignored.[5] The current study seeks to provide additional information in this regard, based on retrospective analysis of data from 360 newly diagnosed AML patients above age 70 years, seen at our institution between January, 2004 and December, 2017. In addition, we included survival data from a more recent group of 28 newly-diagnosed AML patients above age 70 years (seen between April, 2018 and December, 2019) treated upfront with HMA + venetoclax. Our specific objectives included treatment-annotated survival analysis and determination of prognostic factors.

The current study was approved by the Mayo Clinic institutional review board and included AML patients above age 70 years, who were recruited from institutional databases of cytogenetically annotated patients with World Health Organization classification system-compliant diagnosis of AML, excluding acute promyelocytic leukemia.[6] The diagnosis of AML was further subcategorized into primary, secondary (i.e., with antecedent history of a chronic myeloid neoplasm) and therapy-related. In all instances, bone marrow examination and cytogenetic studies were performed or reviewed at the Mayo Clinic. Cytogenetic risk stratification into favorable, intermediate and adverse groups was based on the 2017 European LeukemiaNet (ELN) recommendations.[6] Commonly available molecular information included *FLT3*-ITD, *NPM1* and *CEBPA* mutational status, in a subset of patients. Follow up information was updated as of November 2020. Type of therapy included induction (or intensive) chemotherapy (often "7 + 3" or equivalent), less intensive chemotherapy often including HMA, and supportive care alone ± hydroxyurea. Information with regard to marrow recovery was collected to evaluate complete remission (CR) or CR with incomplete count recovery (CRi).[6] Statistical analysis considered clinical and laboratory variables at the time of diagnosis and as necessary at the time of follow up or remission. Categorical variables were compared using chi-square statistics. Overall survival was calculated from date of diagnosis to death regardless of cause, and patients who were alive were censored at last follow-up. Survival curves were prepared using Kaplan-Meier method and compared using log-rank test. Multivariable Cox-regression analyses were used to identify independent risk factors. The JMP Pro 13.0.0 software (SAS Institute, Cary, NC, USA) was used for all calculations.

The core group of study patients was comprised of 360 consecutive cases seen between 2004 and 2017 (i.e., before the introduction of venetoclax into our clinical practice); median age at diagnosis was 76 years (range 71–94; males 69%). The AML subtype was primary in 171 (48%) patients, therapy-related in 37 (10%) and secondary in 152 (42%); the latter included post-myelodysplastic syndromes (MDS) in 110 (31%) patients, post-myeloproliferative neoplasm (MPN) in 27 (8%) and post-MDS/MPN in 15 (4%). Cytogenetic information was available in all 360 study patients and included adverse (135 patients; 38%), intermediate (220 patients; 61%) and favorable (five patients; 1.4%) risk categories. *FLT3-ITD/NPM1* mutation information was available in 113 patients and included *FLT3-ITD-/NPM1-* in 77 (68%) patients, *FLT3-ITD-/NPM1+* in 20 (18%), *FLT3-ITD+/NPM1-* in nine (8%) and *FLT3-ITD+/NPM1+* in seven (6%). Mostly single *CEBPA* mutations were seen in eight (13%) of 64 patients tested. Table S1 outlines these clinical characteristics of the study patients above age 70 years ("older old" group; n = 360); compared to their younger counterparts