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Geriatric Hematology Research presented at the 2018 American Society of Hematology Annual Meeting: Young International Society of Geriatric Oncology Perspective Paper

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1. Introduction

The 2018 American Society of Hematology (ASH) Annual Meeting was held from December 1–4th in San Diego, California and brought together N25,000 hematology professionals. One scientific workshop was dedicated to Hematology and Aging [1]. Over 5000 oral and poster abstracts in non-malignant and malignant hematology were submitted. Based on the keywords “older” or “elderly”, Fig. 1 suggests that an increasing number of abstracts submitted focuses on older adults. Here, we review abstracts relevant to geriatric hematology.

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Conflicts of Interest

Dr. Mims served on the advisory board for Astellas, Agios, Abbvie, and PTC Therapeutics, All other authors have no relevant conflicts of interest to report.

2. Acute Myeloid Leukemia

Optimizing treatments for older adults with acute myeloid leukemia (AML) has always been an active area of research. Approximately 10 days prior to ASH, venetoclax, a BCL2 inhibitor, was approved by the United States Food and Drug Administration (FDA) for use in combination with hypomethylating agents (HMA; azacitidine or decitabine) or low-dose cytarabine for patients with AML aged ≥ 75 years or patients ineligible for intensive induction chemotherapy due to co-morbidities. Two studies that led to this approval were presented (Table 1) [2,3]. Pollyea et al. presented data from an open-label, phase 1b, dose escalation and expansion multi-center trial with venetoclax and HMA [azacitidine ($n = 84$) or decitabine ($n = 31$)] for patients aged ≥ 60 with untreated AML ineligible for induction chemotherapy [2]. Complete remission and complete remission with incomplete count recovery (CR/CRi) were 70% in the venetoclax and azacitidine cohort and 74% in the venetoclax and decitabine cohort. Median overall survival (OS) was 14.9 and 16.2 months, and time to response (TTR) was 1.2 and 1.9 months, respectively. Death ≤ 30 days occurred in 2% in the venetoclax and azacitidine cohort and 7% in the venetoclax and decitabine cohort; death ≤ 60 days were 8 and 10%, respectively. In the whole cohort, grade ≥ 3 AEs included febrile neutropenia (44%), anemia (28%), pneumonia (25%), thrombocytopenia (22%), and neutropenia (18%). Strickland et al. presented findings from a phase 1/2 study of venetoclax and low-dose cytarabine in a similar population [3]. Of 82 patients treated with venetoclax at 600 mg, median TTR was 1.4 months, 54% patients achieved CR/CRi, and median OS was 10 months. Most common grade ≥ 3 AEs included febrile neutropenia (43%), thrombocytopenia (38%), neutropenia (27%), and anemia (27%).

Venetoclax was also studied in combination with 5 + 2 chemotherapy in fit, older patients in an on-going phase 1b study [4]. Although fitness was not well-defined, the Eastern Cooperative Oncology Group performance status (PS) inclusion criteria was 0–1. Forty-four patients were included; median age was 72 years and 23% were ≥ 75 years. One dose-limiting hematological toxicity was reported at the 600 mg dose level but maximum tolerated dose had not been reached. CR/CRi rate was 71% (95% in de novo vs. 42% in secondary/therapy-related AML).

The Leukemia and Lymphoma Society's Beat AML presented initial results from their Umbrella study in older adults to determine if patients could be assigned by genetic profiling to a molecularly defined subtype-specific therapy within 7 days [5]. At data-cutoff of April 2018, 268 patients were enrolled; median age was 72 years and 38% were ≥ 75 years. Treatment assignment occurred within 7 days in 97.2% (106/109) of patients in the feasibility phase and 95.2% (200/210) of their overall cohort, confirming the feasibility of a precision medicine treatment assignment trial in newly diagnosed older patients with AML.

Isocitrate dehydrogenase (IDH) inhibitors (FDA approved for relapsed/refractory AML in 2017 and 2018) for upfront treatment of older patients with AML with IDH1/2 mutations were also presented [6,7]. The IDH2 inhibitor enasidenib study was presented by Stein et al. as part of the Beat AML study; median age was 76 years [6]. Twenty-three patients received initial monotherapy and five patients went on to receive HMA in addition to enasidenib after single-agent failure/progression. The CR/CRi rate was 43% with no early death seen and

two patients went on to allogeneic hematopoietic cell transplantation (allo-HCT) after single-agent therapy. Roboz et al. presented a phase 1 dose-escalation and expansion study which included 34 newly diagnosed patients treated with IDH1 inhibitor ivosidenib; median age was 76.5 years and 56% were ≥ 75 years [7]. CR rate was 26.5%, CR with partial hematological recovery (CRh) was 41.2%, and 3 patients received allo-HCT. The results are encouraging and suggest that IDH1/2 inhibitors may be a future frontline option for patients with IDH1/2 mutations.

3. Chronic Lymphocytic Leukemia

Ibrutinib is a Bruton's tyrosine kinase (BTK) inhibitor approved for use in several lymphomas including chronic lymphocytic leukemia (CLL). Although ibrutinib was shown to be superior to chlorambucil in older patients with CLL in the RESONATE-2 trial [8], ibrutinib has not been compared to more commonly used chemoimmunotherapy. In the plenary session, Woyach et al. presented results of the A041202 randomized phase 3 trial that compared ibrutinib alone, ibrutinib-rituximab, and bendamustine-rituximab (BR) in 547 patients; median age was 71 years [9,10]. Two-year progression free survival (PFS) was 87% for ibrutinib alone, 88% for ibrutinib-rituximab, and 74% for BR. Ibrutinib monotherapy demonstrated a significantly lower rate of disease progression or death compared to BR [hazard ratio (HR) 0.39, $p < .001$]; there was no additional benefit to adding rituximab to ibrutinib. There were more grade ≥ 3 hematological adverse events with BR (61% vs. 41% for ibrutinib alone and 39% for ibrutinib-rituximab, $p < .001$), but more grade ≥ 3 non-hematologic adverse events with ibrutinib-containing arms (74% vs. 63% for BR, $p = .04$). Notably, a geriatric assessment (GA) was included for correlative analysis in this study. There were no difference between arms; the mean score for Activities of Daily Living (ADL) was 13.7 (possible range 0–14; higher is better), mean score for Instrumental ADL was 79.7 (possible range 0–100; higher is better), 9.7% had ≥ 1 falls in the last 6 months, 5.4% screened positive for cognitive impairment (using the Blessed Orientation Memory Concentration Test), and 23.9% had $\geq 5\%$ weight loss in the last 6 months. In another phase 3 trial, iLLUMINATE, presented by Moreno et al., the combination of ibrutinib-obinutuzumab was superior to chlorambucil-obinutuzumab in patients aged ≥ 65 years, or < 65 years with pre-existing conditions (median age 71 years) [11]. PFS with ibrutinib-obinutuzumab was not reached compared to 19 months with chlorambucil-obinutuzumab [HR 0.23, $p < .0001$], with similar toxicity profiles.

4. Aggressive Lymphomas

Chimeric antigen receptor (CAR)-T cell therapy continues to garner attention and was further evaluated in older adults. Schuster et al. [12] presented the updated data from the JULIET trial [30] and Sano et al. [13] presented real-world treatment outcomes. In both studies, the outcomes (duration of response and overall survival in Maziarz's study, response in the Sano's study) of patients aged ≥ 65 years and < 65 years with relapsed/refractory large B-cell lymphoma were comparable. Sano et al. reported no difference in CAR-related encephalopathy and cytokine release syndrome in the older and younger age groups (29% vs. 39%, $P = .58$) [13].

5. Multiple Myeloma

For patients with multiple myeloma (MM) ineligible for transplant, conventional full-dose or modified regimens may be used depending on their underlying health/functional status. In a late-breaking abstract, Facon et al. presented results of the MAIA phase 3 trial that included 737 patients with newly diagnosed MM ineligible for transplant; median age was 73 years [14]. Patients were randomized to daratumumab, lenalidomide, and dexamethasone (DRd) or lenalidomide and dexamethasone (Rd). DRd was found to be superior to Rd in terms of median PFS (not reached vs. 31.9 months, HR, 0.56, $p < .0001$) and ORR (93% vs. 81%, $p < .0001$). However, the DRd regimen was associated with higher rates (5% difference) of grade 3/4 pneumonia, neutropenia, and leukopenia.

An interesting frailty-adjusted approach was presented by Larocca et al. [15]; 199 intermediate-fit patients based on the International Myeloma Working Group frailty score were randomized to receive a dose/schedule-adjusted treatment: Rd followed by lenalidomide maintenance (Rd-R) vs. continuous Rd. Event-free survival was superior with Rd-R vs. continuous Rd (9.3 vs. 6.6 months, HR 0.72, $p = .04$). There was no difference in best response rates, PFS, and OS between the two arms. The dose/schedule-adjusted treatment was feasible without compromising the outcomes, and the study supports exploring a frailty-adjusted approach to better balance efficacy and safety in older adults with cancer.

6. Hematopoietic Cell Transplantation

A number of prospective [16] and retrospective [17,18] studies demonstrated that autologous HCT in older patients with MM in the era of novel agents continues to be safe without increased treatment-related mortality and results in high response rates, reinforcing that chronologic age should not be used to determine candidacy for autologous HCT.

The data are less straightforward for allo-HCT. In a multi-center analysis, Devillier et al. showed that allo-HCT for patients aged 60–70 years with AML in first remission resulted in increased non-relapse mortality (NRM) but significantly improved relapse-free survival and OS; 610% of patients without allo-HCT had long-term disease-free survival, suggesting allo-HCT remains the first curative option [19]. In contrast, Sorror et al. conducted a prospective multi-center longitudinal study of 695 patients with AML that included GA [20]. After adjusting for patient-specific GA variables and disease-specific variables, the benefit of HCT over non-HCT therapies seen in initial unadjusted analyses was lost. While these results may reflect improvement in non-HCT therapies, need for longer follow-up given high early NRM rates, and the highly selective transplant eligibility process, there is a need for randomized trials that measure GA variables to better risk-stratify older patients and explore HCT vs. non-HCT strategies. The mixed data may contribute to the uncertainty surrounding HCT in older adults and may introduce barriers to referral to and receipt of HCT, as shown by Loh et al. [21]

7. Geriatric Assessment

Multiple investigators demonstrated diverse ways of utilizing GA, from risk stratification to describing treatment experiences with novel therapies [22–26]. Lin et al. examined the prognostic impact of preallo-HCT GA deficits [Instrumental Activities of Daily Living (IADL) impairment, comorbidity, PS] in older adults and proposed a geriatric vulnerability index that stratifies patients into risk categories [22]. Saillard et al. identified impaired nutritional status as an independent risk factor for OS in a prospective cohort of older patients with AML [23]. In a prospective study of older patients with myelodysplasia receiving azacitidine, Molga et al. found that IADL dependence, cognitive, and mobility impairment predicted therapy discontinuation, and IADL dependence and increased comorbidities predicted worse OS [24]. Huang et al. showed that IADL deficit was associated with inferior PFS and OS, and lower Medical Outcomes Study (MOS) Physical Health scale was associated with increased NRM, inferior OS, and increased length of stay in a prospective cohort of patients aged ≥ 50 who underwent allo-HCT [26]. Based on this, functional status appears to be an important measure, and interventions such as structured exercise may be used to reverse functional impairments, as demonstrated by Rosko et al. [27]. Finally, Klepin et al. evaluated GA measures and patient-reported outcomes (PRO; using the PRO-Common Terminology Criteria for Adverse Events) longitudinally in a phase 1b trial (venetoclax and MEK inhibitor cobimetinib vs. venetoclax and MDM2 antagonist idasanutli) of older patients with AML to offer complementary insight into their treatment experience [25]. Symptoms were found to fluctuate throughout treatment, increased with the start of treatment and decreased towards the end of treatment. These symptoms included nausea, diarrhea, vomiting, decreased appetite, and fatigue. Despite growing research, GA is still under-utilized in clinical practice, and we need to understand the barriers to routine GA utilization and target these barriers, especially in the community oncology setting [28].

8. Conclusions

The growth of geriatric hematology is evidenced by the increasing number of abstracts and the inclusion of GA in therapeutic trials. We hope that like the American Society of Clinical Oncology, ASH will develop a stand-alone track for Geriatric Hematology at its annual meetings.

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Fig. 1.
Number of abstracts with the keyword “older” or “elderly” presented at the 2018 American Society of Hematology Annual Meeting.

Therapeutic clinical trials relevant to older adults with hematologic malignancies presented at the 2018 American Society of Hematology Annual Meeting.

Table 1

Abstract Number/Author	Setting	Design	Demographics	Results
Acute myeloid leukemia				
#285 Pollyea et al. [2]	Untreated AML, aged 60 years, no prior HMA therapy for MDS	Phase 1b, dose-escalation and expansion Venetoclax with azacitidine or decitabine	<i>N</i> = 115 treated at venetoclax 400 mg daily Venetoclax and azacitidine <i>N</i> = 84 Median age: 75 years (range 61–90) Venetoclax and decitabine <i>N</i> = 31 Median age: 72 years (range 65–86)	Venetoclax and azacitidine CR/CRi: 70% Median OS: 14.9 months Death 30 days: 2% Death 60 days: 8% Venetoclax and decitabine CR/CRi: 74% Median OS: 16.2 months Death 30 days: 7% Death 60 days: 10% Transfusion independent in both arms: 52% Toxicity (whole cohort) Grade > 3 AEs: febrile neutropenia (44%), anemia (28%), pneumonia (25%), thrombocytopenia (22%), and neutropenia (18%)
#284 Wei et al. [3]	Untreated AML, aged 60 years, may have prior HMA	Phase 1/2 Venetoclax and low dose cytarabine	<i>N</i> = 82 treated at venetoclax 600 mg daily	CR/CRi: 54% Median OS: 10.1 months Transfusion independent Packed red blood cells: 49% Platelets: 65% Toxicity Grade 3 AEs: Febrile neutropenia (43%), thrombocytopenia (38%), neutropenia (27%), and anemia (27%). Two patients had laboratory evidence of tumor lysis syndrome
#333 Wei et al. [4]	Untreated AML, aged 65 (60 was allowed for monosomal karyotype)	Phase 1b Venetoclax and 5 + 2 induction chemotherapy, 4 cycles of consolidation with venetoclax, cytarabine and idarubicin, followed by 7 cycles of venetoclax maintenance (ongoing)	<i>N</i> = 44 Median age: 72 years (range 63–80)	One hematological DLT MTD not reached CR/CRi: 71% in all patients; 95% in de novo AML and 42% in secondary/therapy-related AML Treatment-related mortality in induction: 7% Toxicity Grade 3 non-hematological AEs induction: neutropenia (56%), sepsis (32%), rapid atrial fibrillation (15%), diarrhea (12%), nausea (10%), and localized infection (10%)
#287 Stein et al. [6]	Newly diagnosed IDH2 mutated AML, aged 60 years	Phase 1b/2 BEAT AML substudy Enasidenib initially, azacitidine may be added if failure to respond by 5 months	<i>N</i> = 23 Median age: 76 years (range 62–84)	CR/CRi: 43% 5 patients went on to combination therapy; 2 went to allogeneic transplant after single-agent therapy Death 28 days: None Toxicity 13/23 (57%) patients experienced 1 serious adverse events; most common were differentiation syndrome (<i>n</i> = 4), sepsis (<i>n</i> = 4), bleeding (<i>n</i> = 3), elevated liver tests (<i>n</i> = 3), and respiratory failure (<i>n</i> = 2). Grade 3 AEs occurring in 20% of patients: fatigue, fever, edema, anorexia, low albumin, low electrolytes, nausea, diarrhea, constipation, insomnia and depression

Abstract Number/Author	Setting	Design	Demographics	Results
#561 Roboz et al.[7]	Newly diagnosed IDH1 mutated AML not eligible for intensive therapy	Phase 1 dose-escalation and expansion Ivosidenib	N = 34 Median age: 76.5 years (range 64–87)	CR: 26.5% CR/CRh: 41.2% 3 patients went to allogeneic transplant after single-agent therapy Toxicity Any AEs occurring in 20% of patients: diarrhea (50.0%), fatigue (44.1%), nausea (38.2%), decreased appetite (32.4%), leukocytosis (26.5%), anemia (26.5%), peripheral edema (26.5%), dyspnea (23.5%), thrombocytopenia (23.5%), hypomagnesemia (23.5%), constipation (20.6%), dizziness (20.6%), and insomnia (20.6%). IDH differentiation syndrome occurred in 17.6%; 8.8% were grade 3
#84 Short et al. [29]	Newly diagnosed AML, aged 60 years and < 60 years if unfit for intensive chemotherapy	Randomized phase 2 study Decitabine 5 vs. 10 days	Decitabine 5 days N = 28 Median age 77 (range 57–86) Decitabine 10 days N = 43 Median age: 78 (range 65–94)	Terminated early for futility. No differences in response rate, early mortality, and OS. No differences in TP53 mutated AML. Decitabine 5 days Death 30 days: 4% Death 60 days: 21% Decitabine 10 days Death 30 days: 9% Death 60 days: 25%
Chronic lymphocytic leukemia				
#6 Woyach et al. [9]	Untreated CLL, aged 65 years	Phase 3 RCT Bendamustine-rituximab vs. ibrutinib vs. ibrutinib-rituximab	N = 547 Median age: 71 years (range 65–89)	Ibrutinib PFS: 87% Grade 3 hematologic AEs: 41% Grade 3 non-hematologic AEs: 74% Ibrutinib-rituximab PFS: 88% Grade 3 hematologic AEs: 39% Grade 3 non-hematologic AEs: 74% Bendamustine-rituximab PFS: 74% Grade 3 hematologic AEs: 61% Grade 3 non-hematologic AEs: 63% Lower rate of disease progression or death in the ibrutinib monotherapy arm; no PFS difference between the two ibrutinib-containing arms. More grade 3 hematologic AEs with BR ($p < .001$), but more grade 3 non-hematologic AEs with ibrutinib-containing arms ($p = .04$)
#642 Moreno et al. [11]	Untreated CLL/SLL, aged 65 years or aged 65 years with coexisting conditions	Phase 3 RCT Ibrutinib-obinutuzumab vs. chlorambucil-obinutuzumab	N = 229 Median age: 71 years (range 40–87)	Ibrutinib-obinutuzumab PFS: notreached Most common serious AEs (3%): pneumonia (5%), atrial fibrillation (4%), febrile neutropenia (4%), and pyrexia (4%). Any grade IRRs: 25%; grade 3 or serious IRR: 3%. AEs leading to discontinuation of ibrutinib: 16%; AEs leading to discontinuation of obinutuzumab: 9% Chlorambucil-obinutuzumab PFS: 19 months Most common serious AEs (>3%): IRRs (7%), febrile neutropenia (6%), pneumonia (4%), tumor lysis syndrome (4%), and pyrexia (3%). Any grade IRRs: 58%; grade 3 or serious IRR: 9%. AEs leading to discontinuation of chlorambucil: 9%; AEs leading to discontinuation of obinutuzumab: 13%

Abstract Number/Author	Setting	Design	Demographics	Results
Aggressive lymphomas				
#1684 Schuster et al. [12]	Relapsed/refractory diffuse large b-cell lymphoma	Single-arm, open-label, phase 2 Tisagenlecleucel	N= 167 Median age: 56 years (range 22–76); 23% aged >75 years	Median duration of response similar by age groups (65 vs. <65 years) 65 years Any grade CRS: 83% Grade 3 CRS: 18% CRS: 58% Grade 3 CRS: 29% <65 years Any grade CRS: 91% Grade 3 CRS: 11% CRS 71% Grade 3 CRS: 39% One patient with a history of autoimmune disease in the elderly group died of hemophagocytic lymphohistiocytosis. Toxicities and median hospitalization due to therapy were comparable between the two groups
Multiple myeloma				
#LBA-2 Facon et al. [14]	Newly diagnosed multiple myeloma, ineligible for transplant	Phase 3 RCT DRd vs. Rd	N= 737 Median age: 73 years (range 45–90)	DRd PFS: notreached ORR: 93% Rd PFS: 31.9 months ORR: 81% DRd regimen was associated with higher rates (5% difference) of grade 3/4 pneumonia, neutropenia, and leukopenia
#305 Larocca et al. [15]	Newly diagnosed multiple myeloma, intermediate-fit older patients based on the International Myeloma Working Group frailty score	Phase 3 RCT Dose/schedule-adjusted Rd followed by lenalidomide maintenance (Rd-R) vs. continuous Rd	N= 199 Median age: 75 in the Rd-R arm, 76 years in the Rd arm 47% in Rd-R vs. 57% in Rd were defined intermediate-fit for age (76 years), and 53% vs. 43% due to an impairment in Charlson Index, ADL, or IADL	Rd-R EFS 9.3 months Adverse events accounting for EFS (any hematologic grade 4, non-hematologic grade 3–4): 30% Continuous Rd EFS: 6.6 months Adverse events accounting for EFS (any hematologic grade 4, non-hematologic grade 3–4): 30% No difference in OS, PFS, or adverse events Toxicity (whole cohort) Most common AEs (<10%): neutropenia, infection, and skin reactions.

Abbreviations: ADL, Activities of Daily Living; AEs, adverse events; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CR, complete remission; CRFS, Chimeric antigen receptor-related encephalopathy syndrome; CRi, complete remission with incomplete count recovery; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; DRd, daratumumab, lenalidomide, and dexamethasone; EFS, event-free survival; HMA, hypomethylating agents; IADL, Instrumental Activities of Daily Living; IRR, infusion-related reactions; IDH, isocitrate dehydrogenase; MDS, myelodysplastic syndrome; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trials; Rd, lenalidomide and dexamethasone; SLL, small lymphocytic lymphoma.