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GERIATRIC ONCOLOGY (AR MACKENZIE, SECTION EDITOR)

Updates on Hematologic Malignancies in the Older Adult: Focus on Acute Myeloid Leukemia, Chronic Lymphocytic Leukemia, and Multiple Myeloma

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Abstract

Purpose of Review Hematologic malignancies are common and difficult to treat in older adults. In this review, we focus on recent updates in diseases with several novel agents relevant to older adults—acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM).

Recent Findings In AML, CPX-351 offers a new induction chemotherapy for secondary AML that prolongs survival, and venetoclax and IDH inhibitors are efficacious and well tolerated. In CLL, chemoimmunotherapy is being replaced by monoclonal antibodies and small molecule inhibitors that are more effective and better tolerated. In MM, new immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies have expanded treatment options for older patients.

Summary The introduction of novel agents has dramatically shifted the landscape of therapeutic options for older adults with hematologic malignancies. Clinical trials in older adults are needed to expand treatment options for these patients.

Keywords Older adults · Geriatric oncology · Acute myeloid leukemia · Chronic lymphocytic leukemia · Multiple myeloma · Novel agents

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Introduction

Many hematologic malignancies are both more common in older adults and more challenging to treat due to higher disease risk and greater difficulty of balancing efficacy with tolerability. Older adults, especially those with comorbidities, have historically been underrepresented in clinical trials, and treatment options were often limited due to decreased tolerance of intensive chemotherapy. However, in recent years, the advent of novel agents that are effective and well tolerated has changed the landscape of therapeutic options for older adults (Table 1). In this review, we will focus on hematologic malignancies that have seen the greatest increase in novel agents relevant to older adults—acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM).

Geriatric Assessment

The first step when treating an older patient with a hematologic malignancy is to evaluate their level of fitness to

Table 1 Novel agents FDA-approved for hematologic malignancies since 2013 and promising new agents for older adults

Drug	Disease	Indication	FDA-approved status
BCL2 inhibitor			
Venetoclax	CLL	Previously treated with or without 17p deletion	April 2016, June 2018
		Previously treated, with rituximab	June 2018
	AML	Treatment-naïve elderly patients ineligible for intensive chemotherapy, with hypomethylating agents or low-dose cytarabine	November 2018
BTK inhibitor			
Ibrutinib	CLL/SLL	Previously treated	February 2014
		With 17p deletion	July 2014
		Untreated, as monotherapy or with bendamustine-rituximab	March 2016
	Mantle cell lymphoma	Previously treated	November 2013
	Waldenstrom macroglobulinemia	As monotherapy	January 2015
		In combination with rituximab	August 2018
	Marginal zone lymphoma	R/R after anti-CD20-based therapy	January 2017
Acalabrutinib	Mantle cell lymphoma	Previously treated	October 2017
FLT3 inhibitor			
Midostaurin	AML	Untreated FLT3-positive	April 2017
Crenolanib	AML	R/R FLT3-positive	December 2017 FDA fast-track therapy designation
Gilteritinib	AML	R/R FLT3-positive	November 2018
Quizartinib	AML	R/R FLT3-positive	November 2018 FDA priority review
HDAC inhibitor			
Panobinostat	MM	R/R, with bortezomib + dexamethasone	February 2015
Hedgehog pathway inhibitor			
Glasdegib	AML	Untreated, patients aged ≥ 75 or ineligible for intensitve chemotherapy	November 2018
IDH inhibitor			
Enasidenib	AML	R/R with IDH2 mutation	August 2017
Ivosidenib	AML	R/R with IDH1 mutation	July 2018
Immunomodulatory drug			
Lenalidomide	Myelodysplastic syndrome	With deletion 5q	December 2005
	Mantle cell lymphoma	R/R	June 2013
	MM	Newly diagnosed, with dexamethasone	February 2015
		As maintenance following autologous stem cell transplant	February 2017
	Follicular lymphoma	Untreated, when used with rituximab showed similar efficacy to chemotherapy with rituximab, although did not meet primary endpoint of superiority [1]	Not FDA-approved, but potential chemotherapy-free first-line option
	Diffuse large B cell lymphoma	As maintenance after first-line R-CHOP in elderly patients aged 60–80 improved PFS but not OS [2]	Not FDA-approved
Pomalidomide	MM	R/R	February 2013
Monoclonal antibody			
Obinutuzumab—anti-CD20	CLL	Untreated, with chlorambucil	November 2013
	Follicular lymphoma	R/R after rituximab-containing therapy, with bendamustine	February 2016
		Untreated, with chemotherapy	November 2017
Ofatumumab—anti-CD20	CLL	R/R	October 2009
		R/R, as maintenance	January 2016
		R/R, with fludarabine + cyclophosphamide	August 2016
Daratumumab—anti-CD38	MM	R/R, as monotherapy	November 2015
		R/R, with lenalidomide + dexamethasone or bortezomib + dexamethasone	November 2016
		R/R, with pomalidomide + dexamethasone	June 2017

Table 1 (continued)

Drug	Disease	Indication	FDA-approved status
		Untreated, ineligible for autologous stem cell transplant, with bortezomib, melphalan, prednisone	May 2018
Elotuzumab—anti-SLAMF7	MM	R/R, with lenalidomide + dexamethasone	November 2015
		R/R, with pomalidomide + dexamethasone	November 2018
Gemtuzumab ozogamicin—anti-CD33	AML	R/R CD33-positive	September 2017
PI3K inhibitor			
Idelalisib	CLL/SLL	R/R	July 2014
	Follicular lymphoma	R/R	July 2014
Duvelisib	CLL/SLL	R/R	September 2018
	Follicular lymphoma	R/R	September 2018
Proteosome inhibitor			
Carfilzomib	MM	R/R, as monotherapy	July 2012
		R/R, with lenalidomide + dexamethasone	July 2015
		R/R, with dexamethasone	January 2016
Ixazomib	MM	R/R	November 2015
Recombinant fusion protein			
Luspatercept	Myelodysplastic syndrome	For low-to-intermediate risk with ringed sideroblasts [3]	Not FDA-approved

This table is not meant to be comprehensive for all upcoming novel agents for hematologic malignancies, only those that are particularly relevant to the treatment of older adults

AML acute myeloid leukemia, *BCL2* B cell lymphoma 2, *BTK* Bruton's tyrosine kinase, *CLL* chronic lymphocytic leukemia, *FDA* United States Food and Drug Administration, FLT3 *fms*-like tyrosine kinase 3, *HDAC* histone deacetylase, *IDH* isocitrate dehydrogenase, *MM* multiple myeloma, *OS* overall survival, *PFS* progression-free survival, *PI3K* phosphoinositide 3-kinase, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, *R/R* relapsed/refractory, *SLL* small lymphocytic lymphoma

determine the most appropriate intensity of therapy. Older adults are often more vulnerable to the toxicities of treatment and consequently experience higher rates of dose reduction and treatment discontinuation, which may impact outcomes. Geriatric assessments (GA) are standardized, comprehensive evaluations of physical function, comorbidities, cognition, nutrition, and mental health that offer a more in-depth evaluation of factors that make a patient vulnerable. GA impairments have been shown to be associated with toxicity and outcomes including mortality in hematologic malignancies and can be used to help with prognostication and treatment decision-making [4, 5]. GA is a part of chemotherapy toxicity scores such as the CARG or CRASH scores, although these tools are validated primarily for solid tumor patients [6, 7]. GA data can be used to classify patients as fit (no significant comorbidities, independent, consider standard therapy); vulnerable/prefrail (some clinically significant comorbidities and/or functional status deficits, standard therapy should be adjusted); or frail (multiple comorbidities, multiple disabilities or geriatric syndromes, consider best supportive care or palliative treatment) [8]. Frailty status can be constructed from a GA with tools such as a deficit-accumulation frailty index [9]. The use of GA for specific diagnoses are discussed in the individual sections.

Acute Myeloid Leukemia

Introduction

AML is a disease of older adults, with a median age at diagnosis of 68 years with nearly 60% of patients aged ≥ 65 years [10]. Older age is associated with poor outcomes due to both increased patient vulnerability (worse performance status, organ dysfunction) and higher risk disease (higher incidence of unfavorable cytogenetics, multidrug resistance) [11]. About 60% of elderly AML patients in the USA do not receive any treatment after diagnosis, even though treatment with either hypomethylating agents (HMA) or intensive chemotherapy improves survival compared to no therapy after adjusting for confounders [12].

Risk Stratification

Prognostic models have been developed for AML based on disease-related and patient-related factors to estimate rates of complete remission (CR) and treatment-related mortality after induction chemotherapy, and some tools are available online (https://www.aml-score.org/) [13, 14]. These models tend to rely on age as a marker of vulnerability, yet chronologic age is simply a surrogate for physiologic age and should not be used as

the sole determinant of patient-related risk [15]. In a prospective study of AML patients aged ≥ 60 treated with induction chemotherapy, GA measures of physical performance (Short Physical Performance Battery < 9) and cognitive impairment (Modified Mini-Mental State Exam < 77) were independently associated with overall survival (OS) after accounting for other tumor and clinical characteristics such as age and performance status [16].

Historically, fit patients are considered for intensive chemotherapy with the possibility of allogeneic stem cell transplantation, while vulnerable/prefrail patients are treated with lower intensity therapies. Recently, with promising data from the new combinations of HMA+venetoclax described here, the standard approach to AML therapy may be changing. Some fit patients may in fact be offered lower intensity therapy, as the outcomes may be comparable or better than with chemotherapy, particularly in certain disease subsets. Not only should fitness be evaluated at treatment initiation, it should be reevaluated for subsequent treatment decisions, since with therapy patients may experience improvements in performance status and organ function, such that "crossover" to become a candidate for higher intensity therapies may be possible (Fig. 1).

Induction Chemotherapy

Induction chemotherapy with the "7+3" regimen of standard dose cytarabine plus an anthracycline has been the standard of care for young fit patients with AML. In older adults, several studies have attempted to address whether an intensive approach improves outcomes compared to lower intensity therapy [17–20]. The best data comes from a retrospective registry study assessing "real-world" outcomes in different areas of Sweden which differed in physician willingness to administer induction chemotherapy. The study found induction chemotherapy was associated with better outcomes even in patients aged 70–79 years old [21]. Thus, 7+3 has been a reasonable standard of care for fit older adults with AML.

Since the 1970s, multiple attempts to improve upon 7+3 have been unsuccessful until recently. CPX-351 (Vyxeos) is a liposomal formulation of cytarabine and daunorubicin in a fixed 5:1 M ratio, chosen for maximal synergy based on in vitro studies. Subset analysis of a phase 2 trial of CPX-351 showed promising results for secondary AML [22]. Subsequently, a randomized phase 3 trial was conducted comparing CPX-351 to 7+3 in patients aged 60–75 with previously untreated secondary AML, which included therapy-related AML and AML with myelodysplasia-related change. CPX-351 achieved superior OS (9.56 vs. 5.95 months, hazard ratio [HR] = 0.69, $p = 0.003$); event-free survival (HR = 0.74, $p = 0.021$); and overall response rate (ORR) (47.7% vs. 33.3%, $p = 0.016$). In addition, the CPX-351 arm had lower 60-day mortality (13.7% vs. 21.2%, $p = 0.097$), and grade 3–5 adverse events were similar in both groups [23••]. CPX-351 is now the new standard of care for older adults with secondary AML.

Post-Remission Therapy

There is currently no clear evidence for a standard chemotherapy-based consolidation in first remission for older adults. For fit older adults, allogeneic stem cell transplantation with reduced-intensity conditioning has produced favorable results with 2-year survival rates of 34–48% [24, 25]. In a prospective biologic assignment study ("donor versus no donor") of patients aged 60–75, preliminary results suggest that compared to chemotherapy consolidation, allogeneic stem cell transplantation demonstrated superior disease-free survival, a nonsignificant trend toward improved OS, but also higher nonrelapse mortality [26]. Thus, transplant should be considered an option for older adults, but patients should be selected carefully as discussed above.

Lower Intensity Therapy

The HMAs azacitidine and decitabine are traditionally the lower intensity agents of choice for older AML patients, based on trials which randomized patients to receive HMA versus conventional

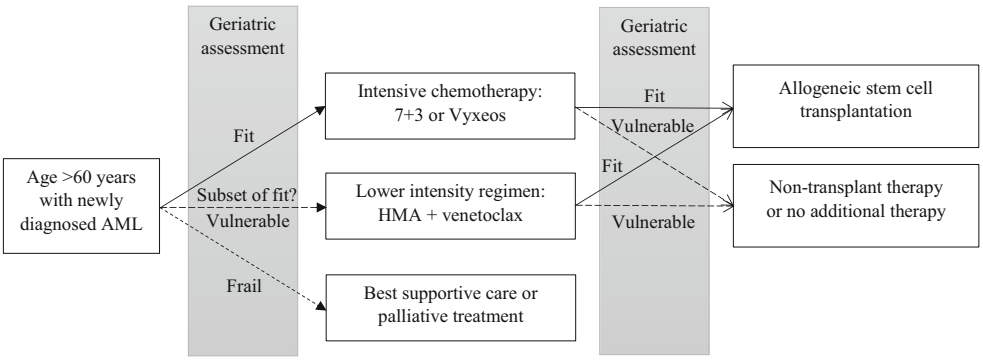

Fig. 1 Treatment framework for older AML patients. This figure provides a framework for considering treatment of an older AML patient. However, based on clinician judgment and patient preference, adjacent treatment options may be appropriate. AML, acute myeloid leukemia; HMA, hypomethylating agents. Adapted from Journal of Geriatric Oncology, 8(6), Li-Wen Huang & Rebecca L. Olin, Emerging therapeutic modalities for acute myeloid leukemia (AML) in older adults, 417–420, ©2017, with permission from Elsevier

care regimens of patient/physician choice of best supportive care, low-dose cytarabine, or induction chemotherapy [20, 27, 28]. One phase 3 study compared azacitidine to a physician preselected conventional care regimen in patients with AML and > 30% bone marrow blasts. Azacitidine resulted in a median OS of 10.4 versus 6.5 months with conventional care regimens, although the primary endpoint was not met ($p = 0.1$). Interestingly, in the group preselected for induction chemotherapy (presumably fit), patients who received azacitidine versus induction chemotherapy had similar median OS (13.3 vs. 12.2 months); however, this study was not powered to detect an OS difference in these subgroups [20].

Venetoclax, a potent BCL2 inhibitor which promotes programmed cell death, is changing treatment options for older AML patients. Data from the expansion cohort of a phase 1b trial combining venetoclax with azacitidine or decitabine in adults aged ≥ 60 with untreated AML ineligible for induction chemotherapy reported complete remission and complete remission with incomplete count recovery (CR/CRi) rates of 70 and 74% in the venetoclax+azacitidine arm and venetoclax+decitabine arm, respectively. Median OS was 14.9 and 16.2 months, and median time to response (TTR) was 1.2 and 1.9 months, respectively. Among patients who achieved CR/CRi, 45% achieved negative minimal residual disease (MRD) [29••, 30, 31]. These results are exciting compared to historical results for HMA monotherapy with ORR ranging 17.8–28% and OS ranging 7.7–10.4 months [20, 28]. Moreover, CR/CRi rates appear consistently impressive in poor risk subgroups such as adverse cytogenetics (67–80%); secondary AML (57–78%); and TP53 (65–86%), as well as good risk subgroups such as IDH-mutated (90–100%) and NPM1 (79–100%) [29••]. These response rates, if ultimately confirmed in larger samples, could potentially support the use of HMA+venetoclax instead of 7+3 even in fit patients.

Venetoclax has also been studied in another phase 1/2 trial combining it with low-dose cytarabine in a similar population; this study reported CR/CRi of 54% and median OS of 10.1 months [32•, 33]. The US Food and Drug Administration (FDA) granted venetoclax accelerated approval in combination with HMA or low-dose cytarabine for the treatment of newly diagnosed AML patients who are ≥ 75 or ineligible for induction chemotherapy in 2018. Phase 3 trials are ongoing to compare the combination of venetoclax+azacitidine to azacitidine alone (NCT02993523) and venetoclax+low-dose cytarabine to low-dose cytarabine alone (NCT03069352).

Glasdegib, a Hedgehog pathway inhibitor, is another novel agent that is augmenting the efficacy of lower intensity therapies. In a randomized phase 2 trial of patients with untreated AML or high-risk myelodysplastic syndrome unsuitable for intensive chemotherapy, glasdegib with low-dose cytarabine improved OS (8.8 vs. 4.9 months, HR = 0.51, $p = 0.0004$) and CR rates (17% vs. 2.3%, $p < 0.05$) compared to low-dose cytarabine alone [34]. Glasdegib was FDA-approved for patients who are ≥ 75 years old or ineligible for induction chemotherapy in 2018.

Relapsed/Refractory

Relapsed/refractory AML is particularly difficult to treat, and median OS was only 3.3 months in a phase 3 trial involving investigator's choice of salvage regimen [35]. Novel agents have been approved for relapsed/refractory AML in the last few years, expanding treatment options for older adults.

Isocitrate dehydrogenase (IDH) mutations occur in about 20% of myeloid malignancies [36]. In preclinical studies, IDH mutations led to the arrest of differentiation of hematopoietic cells, and IDH inhibition restored myeloid differentiation. A phase 1/2 study of IDH2 inhibitor enasidenib in patients with relapsed/refractory IDH2-mutated AML reported an ORR of 40.3% and median OS of 9.3 months [37••]. Enasidenib was FDA-approved for relapsed/refractory IDH2-mutated AML based on these results, and a phase 3 trial is ongoing to compare enasidenib to conventional care regimens in patients aged ≥ 60 with relapsed IDH2-mutated AML (NCT02577406). The IDH1 inhibitor ivosidenib has also been FDA-approved for IDH1-mutated relapsed/refractory AML, based on a phase 1 trial which demonstrated an ORR of 41.6% and median OS of 8.8 months [38••]. Both IDH inhibitors were well tolerated in an older study sample (median ages 70 and 68 years) and are particularly attractive as orally administered single-agent regimens. Enasidenib and ivosidenib are also being studied in the frontline setting, with early results showing CR/CRi of 43% for IDH2 mutant AML and CR and CR with partial hematological recovery (CR/CRh) of 41.2% for IDH1 mutant AML, respectively [39, 40].

Upcoming Clinical Trials

In addition to the ongoing clinical trials discussed above, the Leukemia and Lymphoma Society Beat AML trial is an exciting collaborative clinical trial in newly diagnosed AML patients aged ≥ 60. In this trial, patients undergo genetic screening upfront and are assigned one of several available treatment arms based on their individual genetic profile. This innovative trial design is a potential model for future trials investigating novel agents [41].

Chronic Lymphocytic Leukemia

Introduction

CLL is the most prevalent leukemia in the western countries with a median age at diagnosis of 70 years [10]. Because CLL is often diagnosed at an early asymptomatic stage, the age at treatment initiation is even higher. In older adults with CLL, the treatment goal is to maximize life expectancy while

maintaining function and quality of life. Thus, efficacy and tolerability must be balanced carefully when choosing a treatment regimen.

Risk Stratification

Prognostic models comprised of clinical parameters and CLL-specific biomarkers such as the CLL International Prognostic Index (CLL-IPI) should be used to evaluate disease-specific prognosis [42]. In addition, comorbidities should be evaluated, since they may impact treatment tolerance and need for dose reductions or treatment discontinuation. The Cumulative Illness Rating Scale (CIRS) has been used most frequently in CLL trials, although no comorbidity score has been validated in CLL.

One study evaluated the use of a GA in older CLL patients. Impaired functional status (Timed Up and Go test, Instrumental Activities of Daily Living) was associated with treatment delays, and impaired physical function (Timed-Up-and-Go test) and cognitive function (Dementia Detection Test) were associated with inferior OS [43]. The International Society of Geriatric Oncology Task Force has recommended the routine use of a GA for older patients with CLL and suggested treatment options based on level of fitness [44].

Chemoimmunotherapy

For decades, chlorambucil had been the standard of care for CLL. When purine analog-based regimens such as fludarabine-cyclophosphamide-rituximab (FCR) became the preferred frontline regimen for younger, fit CLL patients, older patients were noted to derive less benefit [45–47]. In studies using FCR, age ≥ 70 was associated with inferior response, and older patients were more likely to discontinue therapy earlier due to progression or other adverse events [45]. Although fludarabine-based therapies resulted in higher ORR and CR rates than chlorambucil in older treatment-naïve patients, this did not translate into improved progression-free survival (PFS) or OS, and the HR for OS trended toward favoring chlorambucil [48]. In the CLL10 trial comparing FCR with bendamustine-rituximab, FCR resulted in significantly longer PFS in patients aged ≤ 65, but not in patients aged > 65. In addition, in patients aged > 65, the FCR group experienced more adverse events and treatment discontinuations [49•]. Thus, FCR is not recommended for older patients or patients with significant comorbidities.

With the development of several novel agents for CLL, treatment options that are better tolerated have emerged for older adults. These novel agents are continually moving from the relapsed/refractory setting where they were originally studied to the frontline setting, so they will be discussed by drug class rather than line of therapy.

Monoclonal Antibodies

In addition to rituximab, new monoclonal antibodies against CD20 (obinutuzumab, ofatumumab) have been developed. To address the question of how to treat older patients with comorbidities, the phase 3 CLL11 trial focused on treatment-naïve CLL patients with comorbidities (median age 73) and compared the combination of obinutuzumab-chlorambucil (G-Clb) with rituximab-chlorambucil (R-Clb) and chlorambucil (Clb) alone. Both R-Clb and G-Clb improved PFS over Clb alone, and G-Clb provided an OS advantage compared to Clb alone, with deeper and longer remissions than R-Clb. The rate of MRD negativity was significantly higher after G-Clb than R-Clb (in bone marrow 19.5% vs 2.6%, $p < 0.001$; in peripheral blood 37.7% vs. 3.3%, $p < 0.001$) [50]. This was the first study to show an OS benefit for older CLL patients with comorbidities compared to chlorambucil. Toxicities of obinutuzumab in combination with different chemotherapy backbones were generally manageable [51].

Ofatumumab improves PFS but not OS when combined with chlorambucil compared to chlorambucil alone in untreated CLL patients who are poor candidates for fludarabine-based therapy [52].

Small Molecule Inhibitors

Perhaps, the most exciting advance for older CLL patients is the introduction of novel small molecule inhibitors (Table 1). These inhibitors are targeted and therefore generally better tolerated than cytotoxic chemotherapy, and they have the added benefit of being oral therapy; however, the need for indefinite therapy is a potential downside.

Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor which acts downstream of the B cell receptor pathway, has produced remarkable results in CLL, including in patients with del(17p) or TP53 mutations for whom chemoimmunotherapy is less effective. Ibrutinib has been FDA-approved as monotherapy or in combination with bendamustine-rituximab. In a phase 1/2 trial in older treatment-naïve patients, ibrutinib monotherapy was shown to induce ORR of 84% (CR 29%), 5-year PFS of 92%, and 5-year OS of 92%. Toxicities were mainly grade 1–2, and grade ≥ 3 toxicity diminished over time [53, 54••]. Following these promising results, the RESONATE-2 trial compared ibrutinib to chlorambucil in older treatment-naïve CLL patients and found that ibrutinib was associated with superior ORR (86% vs. 35%, $p < 0.001$); median PFS (not reached vs. 18.9 months, HR = 0.16, $p < 0.001$); and OS (24-month OS 98% vs. 85%, HR = 0.16, $p = 0.001$) [55]. Recently, a randomized phase 3 trial in untreated CLL patients aged ≥ 65 compared ibrutinib alone or in combination with rituximab to bendamustine-rituximab. Two-year PFS was higher with ibrutinib alone (87%, HR = 0.39, $p < 0.001$) and ibrutinib-rituximab (88%, HR = 0.38, $p < 0.001$) compared to bendamustine-rituximab (74%); there was no

additional benefit of adding rituximab to ibrutinib. The ibrutinib-containing regimens were associated with fewer grade ≥ 3 hematologic adverse events compared to bendamustine-rituximab (40% vs. 61%) but more grade ≥ 3 nonhematologic adverse events (74% vs. 63%), with hypertension and infection being most common [56••, 57].

Idelalisib inhibits phosphoinositide 3-kinase-δ (PI3K-δ), which plays a role in the proliferation and survival of B cells. In a phase 2 study in treatment-naïve adults aged ≥ 65, idelalisib with rituximab produced a promising ORR of 97% and 3-year PFS of 83% [58]. A phase 3 trial tested the addition of idelalisib to rituximab for treating relapsed/refractory CLL in patients ineligible for chemotherapy. The addition of idelalisib significantly improved ORR (81% vs. 13%, $p < 0.001$); PFS (HR = 0.15, $p < 0.001$); and OS (HR = 0.28, $p = 0.02$) compared to rituximab monotherapy without increasing adverse events [59]. However, due to observations of increased mortality from infections in trials, a warning was placed for use in the frontline setting, and idelalisib is only FDA-approved for relapsed CLL in combination with rituximab.

Duvelisib, a new dual inhibitor of PI3K-δ and -γ, was found to be active in a phase 1 trial of relapsed and treatment-naïve CLL patients aged ≥ 65 [60]. A recent phase 3 DUO trial showed that in patients who have received ≥ 2 lines of therapy (median age 69), duvelisib compared to ofatumumab achieved superior ORR (78% vs. 39%) and longer PFS (16.4 vs. 9.1 months, HR = 0.40) [61]. Based on these results, the FDA-approved duvelisib for CLL patients who have received ≥ 2 lines of therapy.

The BCL2 inhibitor venetoclax discussed previously for AML was first found to be effective for CLL. In phase 1 studies of relapsed CLL, venetoclax monotherapy and venetoclax-rituximab were found to produce high response rates, including high CR and MRD negativity rates [62•, 63]. In a phase 3 trial in relapsed CLL patients, compared to bendamustine-rituximab, venetoclax-rituximab resulted in significantly longer 2-year PFS (36.3% vs. 84.9%, HR = 0.17, $p < 0.001$) and 2-year OS (86.6% vs. 91.9%, HR = 0.48). Venetoclax-rituximab was associated with an impressive ORR of 92.3% with peripheral blood MRD negativity in 62.4%. Subgroup analyses show that the PFS benefit is consistent in those aged ≥ 65 [64••]. Venetoclax has been FDA-approved as monotherapy or in combination with rituximab for relapsed CLL. Tumor lysis syndrome was reported in early studies with venetoclax, but with a gradual dose ramp-up and tumor lysis prophylaxis, venetoclax was able to be administered safely even in older adults with comorbidities.

Upcoming Clinical Trials

The ongoing CLL14 trial compares venetoclax-obinutuzumab with chlorambucil-obinutuzumab in treatment-naïve patients with comorbidities. Safety and efficacy results from the run-in phase of the trial show that venetoclax-obinutuzumab achieved an ORR of 100%, including 92% MRD negativity at 3 months after end of treatment [65]. Recent phase 2 studies investigating the combination of ibrutinib-venetoclax have reported high rates of MRD negativity in both untreated and relapsed CLL [66•, 67, 68].

The deep responses achieved by these combinations of novel agents are exciting and raise the possibility of treatment-free intervals for patients with relapsed CLL, but longer follow-up is needed to evaluate the durability of such responses. Ongoing phase 3 studies will further investigate the efficacy of these combinations compared to other regimens, including one trial in patients aged ≥ 65 or younger patients with comorbidities (NCT03462719).

Multiple Myeloma

Introduction

MM has a median age at diagnosis of 69 years, and nearly two thirds of patients are aged ≥ 65 at the time of diagnosis [10]. In the last two decades, we have seen an influx of new treatment options for MM, and the survival for younger MM patients has improved dramatically; however, survival benefit for older patients has lagged behind [69, 70]. Improved risk stratification for older adults is critical for selecting the right therapy for each individual patient.

Risk Stratification

Similar to the approach with other hematologic malignancies, age alone should not be used to determine the therapeutic approach for older patients. Instead treatments for MM should be tailored to individual patient characteristics and preferences. In addition to an evaluation of the disease risk with the Revised International Staging System (R-ISS) [71], a GA should be performed to gauge the patient's ability to tolerate treatment. There are several instruments developed specifically for myeloma patients such as the IMWG frailty index (http://www.myelomafrailtyscorecalculator.net/), R-MCI (http://www.myelomacomorbidityindex.org/en_calc.html), and the Mayo frailty index. The IMWG frailty index, based on age, functional status, and comorbidities, was developed to predict mortality and toxicity. Those who were frail were more likely to experience grade 3–4 nonhematologic toxicity, early treatment discontinuation, inferior PFS, and inferior OS [72]. This tool was subsequently prospectively validated and compared to the Revised Myeloma Comorbidity Index (R-MCI) in newly diagnosed MM patients, which is determined by age, performance status, and organ function [73]. Finally, the Mayo frailty index, which uses the biomarker NT-proBNP in addition to age and performance status, is another method to assess patient frailty. These frailty indices should guide

transplant eligibility and selection of the number, type, and dosage of drugs [74•]. As an example, a recent phase 3 trial used the IMWG frailty index to evaluate a frailty-adjusted treatment approach for intermediate-fit patients and found that a dose/scheduled-adjusted approach was more feasible with comparable outcomes to a full-dose treatment approach [75].

Transplant-Eligible

Some have hypothesized that the lagging survival benefits for older patients despite recent advances in MM treatment may be due to the historical restriction of autologous stem cell transplantation (ASCT) to those aged < 65 [69, 70]. Early studies of ASCT in older adults produced conflicting data [76, 77]. However, more recent data in both retrospective [78–80] and prospective studies [81, 82] show ASCT in older adults, including those aged ≥ 70, is feasible and safe. Efficacy was similar to that seen in younger cohorts, and ASCT was associated with improved survival compared to nontransplant strategies. The decreased toxicity in recent studies may be due to improved patient selection and supportive care. Thus, age alone should not be an exclusion for ASCT, and older adults should be evaluated carefully for their candidacy for ASCT.

Transplant-Ineligible—Initial Therapy

For patients who are deemed ineligible for ASCT, melphalan-prednisone (MP) was the standard of care for patients aged ≥ 65 for decades. With the introduction of immunomodulatory drugs and proteasome inhibitors, MP-based triplet regimens with the addition of thalidomide [83, 84], bortezomib (VMP) [85, 86], or lenalidomide [87] demonstrated better outcomes than MP alone in older or transplant-ineligible patients with newly diagnosed MM. For example, the phase 3 VISTA trial in transplant-ineligible patients with newly diagnosed MM found that, compared to MP, VMP improved median time to progression (16.6 vs. 24.0 months, HR = 0.48, $p < 0.001$) and OS (HR = 0.61, $p = 0.008$) [85]. However, triplet regimens were consistently associated with greater toxicity.

The success of novel agents prompted exploration of alkylator-free regimens for transplant-ineligible patients. Studies found that lenalidomide-dexamethasone produced PFS similar to or better than alkylator-containing triplet regimens [88, 89•]. Lenalidomide-dexamethasone (Rd) became the new standard of care for elderly MM patients who are transplant-ineligible. A phase 3 trial compared the triplet regimen of bortezomib-lenalidomide-dexamethasone (VRd) to Rd doublet in patients with newly diagnosed MM of all ages not planned for immediate ASCT, and VRd was found to prolong PFS (43 vs. 30 months, HR = 0.712, $p = 0.0018$) and OS (75 vs. 64 months, HR = 0.709, $p = 0.025$) with benefit maintained after age-adjusted multivariate analysis, although greater toxicity was seen in the VRd group [90•].

In the phase 3 UPFRONT trial based in a community setting, patients who were transplant-ineligible due to age ≥ 65 or comorbidities received bortezomib-dexamethasone (VD), VD-thalidomide (VTD), or VD-melphalan (VMP). The three regimens produced similar PFS and OS. Interestingly, although VTD produced a higher ORR (VTD 80%, VD 73%, VMP 70%), it did not translate into longer PFS, possibly due to higher toxicity from thalidomide and more frequent treatment discontinuations [91]. This community-based study highlights the challenges of balancing efficacy with toxicity in elderly patients. Combinations with more drugs is almost certainly more active against the disease, but if the increased activity comes at the cost of dose reductions and treatment discontinuation, then the overall efficacy for the patient is compromised.

The phase 3 ALCYONE trial explored the addition of daratumumab to VMP in newly diagnosed, transplant-ineligible MM patients. The daratumumab group demonstrated superior 18-month PFS (71.6% vs. 50.2%, HR = 0.50, $p < 0.001$); ORR (90.9% vs. 73.9%, $p < 0.001$); and MRD negativity rates (22.3% vs. 6.2%) compared to the control group. Subgroup analysis showed that the PFS benefit was consistent in those aged ≥ 75. The daratumumab group experienced more infusion-related reactions and grade 3–4 infections [92••]. Recently, the phase 3 MAIA study evaluated the addition of daratumumab to Rd (DRd) in newly diagnosed, transplant-ineligible MM patients, with median age 73 and 44% aged ≥ 75. Compared to Rd, DRd was found to improve median PFS (not reached vs. 31.9 months, HR = 0.55, $p < 0.0001$) and rates of very good partial response or better (47.6% vs. 24.7%, $p < 0.0001$). The DRd group had higher rates (≥ 5% difference) of grade 3/4 pneumonia, neutropenia, and leukopenia [93••].

Transplant-Ineligible—Maintenance Therapy

Similar to younger patients, maintenance therapy has been found to be beneficial in older transplant-ineligible MM patients. The phase 3 MM-015 trial in transplant-ineligible patients found that adding lenalidomide maintenance to melphalan-prednisone-lenalidomide induction significantly prolonged PFS (31 vs. 14 months, HR = 0.49, $p < 0.001$), regardless of age [87]. The phase 3 FIRST trial of patients aged ≥ 65 or otherwise transplant-ineligible found that continuous Rd given until disease progression, compared to 18 cycles of Rd, resulted in similar ORR, but longer PFS (25.5 vs. 20.7 months, HR = 0.71, $p < 0.001$) and longer duration of response (35.0 vs. 22.1 months, HR = 0.60, $p < 0.001$). The reduced risk of progression was seen even in those aged ≥ 75 [88, 94•]. The benefit of novel agent-based continuous therapy was further corroborated in a pooled analysis of three phase 3 trials which showed improved PFS and also OS with continuous as opposed to fixed duration therapy [95].

Table 2 Subgroup analyses of older adults in recent randomized controlled phase 3 trials for relapsed/refractory multiple myeloma

Clinical trial Comparisons	No. of patients (no. aged ≥ 65)	mPFS (months)	HR (95% CI) in entire study	HR (95% CI) in age ≥ 65
PANORAMA1 [96]				
Panobinostat, bortezomib, dexamethasone	387 (162)	11.99	0.63 (0.52–0.76)	0.72 (0.53–0.96)
Bortezomib, dexamethasone	381 (161)	8.08		
ASPIRE [97]				
Carfilzomib, lenalidomide, dexamethasone	396 (185)	26.3	0.69 (0.57–0.83)	0.85 (0.65–1.11)
Lenalidomide, dexamethasone	396 (208)	17.6		
ELOQUENT-2 [98]				
Elotuzumab, lenalidomide, dexamethasone	321 (187)	19.4	0.70 (0.57–0.85)	0.65 (0.50–0.85)
Lenalidomide, dexamethasone	325 (183)	14.9		
CASTOR [99]				
Daratumumab, bortezomib, dexamethasone	251 (119)	NR	0.39 (0.28–0.53)	0.35 (0.22–0.57)
Bortezomib, dexamethasone	247 (122)	7.2		
POLLUX [100]				
Daratumumab, lenalidomide, dexamethasone	286 (153)	NR	0.37 (0.27–0.52)	*65–74 years*: 0.40 (0.24–0.67)
Lenalidomide, dexamethasone	283 (143)	18.4		*≥ 75 years*: 0.11 (0.02–0.51)
TOURMALINE [101]				
Ixazomib, lenalidomide, dexamethasone	360 (192)	20.6	0.74 (0.59–0.94)	*> 65–75 years*: 0.83 (crosses 1)
Lenalidomide, dexamethasone	362 (186)	14.7		*> 75 years*: 0.87 (crosses 1)

This table is created for the purpose of summarizing results of recent trials, not comparing results across trials. Cross-trial comparisons should not be made

CI confidence interval, *HR* hazard ratio, *mPFS* median progression-free survival, *NR* not reached

Relapsed/Refractory

The last few years has seen an explosion of novel agents for the treatment of relapsed/refractory MM, such as panobinostat, carfilzomib, elotuzumab, daratumumab, and ixazomib. While none of these studies were specific to the older population or those with comorbidities, subgroup analyses of those aged ≥ 65 are promising, particularly for daratumumab (Table 2). In these studies, toxicity was not analyzed by age, so it is unclear whether older patients experienced more adverse events.

Upcoming Clinical Trials

While results of novel agents in older patients are promising, clinical trials specifically for older, frail adults are needed. A few ongoing trials focus on the older MM population, including a study in patients aged 60–75 comparing a transplant (Rd induction followed by ASCT and maintenance) versus nontransplant strategy (Rd until progression) (NCT01090089). Furthermore, a prospective clinical trial using frailty assessments to determine treatment selection is needed.

Conclusion

The recent introduction of several novel agents for hematologic malignancies has dramatically expanded therapeutic options for older adults. In untreated AML, CPX-351 (Vyxeos) offers a new induction chemotherapy for secondary AML that prolongs survival compared to 7+3 with similar toxicity, while venetoclax in combination with HMAs have been shown to be highly active, raising the possibility that the standard approach to AML therapy may change in the future such that lower intensity therapy may be better even for some fit patients. IDH inhibitors (enasidenib, ivosidenib) are well-tolerated oral regimens for relapsed/refractory AML. In CLL, chemoimmunotherapy is being replaced by monoclonal antibodies (rituximab, obinutuzumab) and small molecule inhibitors (ibrutinib, venetoclax, idelalisib, duvelisib) that are more effective and better tolerated. In MM, immunomodulatory drugs (lenalidomide, pomalidomide); proteasome inhibitors (bortezomib, carfilzomib, ixazomib); HDAC inhibitors (panobinostat); and monoclonal antibodies (daratumumab, elotuzumab) have expanded treatment options for newly diagnosed transplant-ineligible or relapsed/refractory patients. Although there are many promising new agents, not all of them have been specifically studied in older adults. Clinical trials designed for older adults, including a treatment approach adapted to GA-based fitness level, are needed to continue to improve treatment options for older adults with hematologic malignancies.

Compliance with Ethical Standards

Conflict of Interest Sandy W. Wong has received research funding from Janssen, Celgene, and Roche.

Charalambos Andreadis has received research funding from Celgene, GlaxoSmithKline, Novartis, Amgen, and Pharmacyclics; has received compensation from Amgen for service as a consultant and from Celgene, Gilead, Pharmacyclics, and Genentech for service on advisory boards. His spouse is also an employee of Genentech.

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- • Of importance
- •• Of major importance

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phase 3 trial for untreated CLL patients aged ≥65, ibrutinib alone or in combination with rituximab was compared to bendamustine-rituximab and with each other. Two-year PFS was higher with ibrutinib alone (87%, HR = 0.39, $p < 0.001$) and ibrutinib-rituximab (88%, HR = 0.38, $p < 0.001$) compared to bendamustine-rituximab (74%); there was no additional benefit of adding rituximab to ibrutinib. The ibrutinib-containing regimens were associated with fewer grade ≥3 hematologic adverse events compared to bendamustine-rituximab (40% vs. 61%) but more grade ≥3 nonhematologic adverse events (74% vs. 63%), with hypertension and infection being most common. The results of this study suggest there is no longer a role for cytotoxic chemotherapy for older patients with CLL.

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24.7%, $p < 0.0001$). The DRd group had higher rates (≥ 5% difference) of grade 3/4 pneumonia, neutropenia, and leukopenia. This data support the addition of daratumumab to standard of care combinations in patients with newly diagnosed MM ineligible for transplant.

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