Leucemias agudas en el paciente añoso.

Acute Myelogenous Leukemia in the Elderly.

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Introduction

Acute myelogenous leukemia (AML) is the most common adult leukemia, a biologically diverse clonal neoplasm of the marrow. Our understanding of leukemia biology has led to the concept that AML is characterized by a distinct set of cytogenetic and molecular abnormalities, immunologic features, and cellular morphology that describe subtypes with unique clinical features predictive of response to therapy and relapse-free survival. These diverse features have allowed for disease classification that has prognostic implications, and that offer the possibility of specific therapeutic targets for development of novel treatment strategies that may be subtype-specific. The molecular signatures create the potential to develop therapies that minimize cross-reaction with normal hematopoiesis. AML in the elderly (usually described at AML in patients age greater than 60 years) has been recognized as a distinct entity when compared to AML in younger individuals. In this article we discuss data that summarizes the poor prognosis of AML in the elderly, current treatment strategies, and a focus on novel treatment approaches for this age group.

AML is the most common type of acute leukemia occurring in adults, with 20,830 new cases estimated to occur in 2015.(1) Adults over the age of 60 comprise more than two-thirds of this group,(2) with a median age of onset of about 65.(1,3) The incidence of AML increases with age, such that the incidence is 4 cases per 100,000 among those in their 50s, and over 20 cases per 100,00 in Americans in their 80s.3 In addition, the incidence of AML is rising in the elderly population.(4) In the elderly, the frequency of favorable transloca-
tions and mutations is low; the proportion of unfavorable karyotypes and adverse-risk molecular features is high. In addition, the incidence of secondary AML increases with age, along with a higher rate of clinical multidrug resistance. Although there has been some improvement in the outcome of patients diagnosed with AML over the past several decades, this trend toward increased survival is not seen among older individuals. Furthermore, the risk of treatment-related comorbidity may outweigh the response expected in older patients. Nonetheless, treatment should not be based on age alone, but an overall assessment of the patient’s comorbidities, level of risk associated with cytogenetic and mutational profile, and performance status.

Studies have shown that about half of elderly patients with AML achieve complete response after treatment, but when analyzing subgroups, this trend is variable based on the intensity of therapy and preexisting comorbidities. Historical data indicate that a large percentage of elderly AML patients are not referred to a subspecialist and do not receive chemotherapy at all. Additionally, observational studies of the elderly suggest a very poor general prognosis. For example, Medicare claims analysis demonstrates median survival of two months, with as few as 6% of patients alive at 2 years. These data indicate the need for development of new and effective treatment strategies for older patients.

This review presents both conventional and novel treatment approaches for elderly patients with AML, with mention of agents that have potential for positive outcomes in ongoing clinical trials. Treatment options include conventional treatments, agents complementary to conventional treatments, alternatives to conventional induction therapies, post-induction treatment, and relapsed disease.

**Disease and host-related factors**

Although the largest proportion of AML cases in the elderly are idiopathic, with a significant number of patients have AML secondary to radiation therapy, chemotherapy, or progression from myelodysplastic syndrome (MDS). Secondary AML comprises 24 to 56% of AML diagnosed in elderly patients. Leukemia cells in older patients are more likely to be resistant to standard chemotherapy, perhaps due to multidrug resistant genetics. Aside from underlying disease features, aggressive treatment regimens in the elderly have been shown to produce higher morbidity and lower survival when compared to younger patients. Intensive chemotherapy may not be the optimal treatment strategy for older patients who often have multiple comorbidities and decreased bone marrow reserve. Older age alone is a poor prognostic factor. There have been multiple characteristics that have been identified in older patients presenting with AML (Table 1).

Elderly patients who possess malignant cells characterized by one of the favorable balanced translocations t(8;21), t(15;17) or inversion 16, have a relatively good complete remission (CR) rate. The AML11 trial reported CR of 72%, with a five-year survival rate of only 34% after conventional treatment. These favorable cytogenetic features are more common in younger individuals, which contribute toward their better overall survival. An intermediate-risk group is consists of patients with normal cytogenetics, trisomy of chromosome 8, and several other common numerical abnormalities. Disease characterized by adverse karyotypes includes monosomies of chromosome 5 or 7, deletions of the long arm of chromosome 5, or 3q abnormalities. The majority of elderly patients fall within the intermediate- or adverse-risk groups. CR rates for intermediate-risk disease is estimated to be about 57%, and five-year survival between 10% and 15% with conventional treatment. Many patients with intermediate-risk normal karyotype AML have disease characterized by unfavorable molecular features. Patients in the poor-risk group CR rates of 26% and five-year survival of less than five percent with conventional treatment have been reported. Several algorithms were developed in the past that attempt to assist clinical decisions to proceed with certain therapies. One of these models has been validated in a small cohort of elderly patients other than that used during development of the model. However, larger validation studies were needed prior to widespread use of this model. At the beginning of this decade, there was a publication and subsequent validation of an algorithm regarding full treatment for AML in elderly patients with good performance status. Multivariate regression analysis and subsequent independent validation on a large cohort of patients determined factors such as etiology of AML, blood counts, age, and body temperature to be significant factors that influence treatment outcome. However, this predictive tool does not fully account for cytogenetic and molecular profiles. In our opinion, this tool is suboptimal due to the high predictive value of molecular profiles, which are emerging as the lead factors in determining treatment decisions and outcome. There are data to suggest that the global assessment by an experienced Hematologist may best determine who is a candidate for cytoreductive induction therapy.
Acute promyelocytic leukemia (APL) should be mentioned due to its favorable prognosis. Regimens containing all-trans retinoic acid (ATRA) have been shown to be effective. Although APL has the potential for high initial mortality during the peri-induction timeframe due to life-threatening coagulopathy, the combination of ATRA, cytotoxic therapy, and perhaps arsenic trioxide have proven curative. The prognosis of APL in the elderly is poorer than that of younger patients after treatment with all-trans retinoic acid plus chemotherapy due to a significantly higher mortality during induction and consolidation therapy, mainly due to deaths from sepsis following chemotherapy-induced myelosuppression. A recent small study showed that single-agent arsenic trioxide is safe and effective and may produce long-term durable remission. Such therapy could be used as first-line treatment for elderly patients with de novo APL.

Treatment of newly diagnosed AML
Induction chemotherapy is tolerated poorly in the elderly population in comparison to younger adults. Options for newly diagnosed AML in the elderly include conventional intensive chemotherapy, low-intensity induction chemotherapy, non-myelosuppressive agents, colony-stimulating factors, supportive care, or clinical trials. Foregoing induction chemotherapy in this age group has been resulted in low survival rates and poor quality of life. As we shall discuss, other treatment strategies have shown promise in the elderly.

Conventional chemotherapy
Induction chemotherapy is used for cyttoreduction and restoration of normal bone marrow function. In the older leukemia population, a wide range of CR rates have been reported, ranging from 30 and 60% after conventional chemotherapy. Conventional treatment includes an anthracycline plus cytarabine, a standard against which other therapies are compared. In the large Eastern Cooperative Oncology Group (ECOG) study of older adults, regimens containing daunorubicin, idarubicin or mitoxantrone for three days, combined with seven days of cytarabine, all showed similar CR and overall survival rates of about 42% and 7.5 months, respectively. In the AML11 trial that included a large cohort of elderly patients, three regimens were compared: daunorubicin, cytarabine, thioguanine; daunorubicin, cytarabine, etoposide; and mitoxantrone and cytarabine. The rate of CR was the highest in the first group (62%) when compared to the latter two compared (50% and 55%); however, there was no difference in survival at five years. However, more recently long-term outcomes have demonstrated idarubicin to be superior to daunorubicin in patients 50-65 years of age. The authors concluded that among older patients with AML, younger age, favorable-risk AML, and treatment with idarubicin predict better long-term outcomes. Nonetheless, a meta-analysis of 65 randomized trials comparing different induction regimens to standard-dose daunorubicin plus cytarabine in patients over age of 60 showed that compared with the reference induction, significant differences exist in outcomes after specific induction regimens, although most regimens appeared to have similar efficacy profiles. Furthermore, It has been shown that escalation of the dose of daunorubicin to 90 mg/m² from 45 mg/m² in the first induction cycle, effects a more rapid response and a higher response rate than does the lower dose, without additional toxic effects. Whether 90 mg/m² is superior to a conventional dose of 60 mg/m² remains an open question. Other trials studying variations of the aforementioned regimens have yielded similar results. Table 2 provides a summary of induction regimen trials. Colony-stimulating factors had no impact on survival in the ECOG study. Pairing cytarabine with an additional agent affords the best treatment outcomes. Conventional chemotherapy has been demonstrated to provide a CR in 40-60% of elderly patients. However, only 10–20% of those who achieve CR live more than 3 years from the time of their diagnosis. Favorable response to induction chemotherapy is a good prognostic indicator and is correlated with the best long-term outcomes, while those with partial or no response do poorly even with additional chemotherapy. This is in contrast to the first CR rates of 80% and long-term survival of 40% in children and young adults. Conventional intensive therapy may be an appropriate option for elderly patients with zero or one adverse prognostic factor.

Agents complementary to conventional chemotherapy
The addition of bortezomib to standard 7+3 cytarabine-daunorubicin induction chemotherapy for AML resulted in an encouraging remission rate of 65%. The maximum tested dose of bortezomib administered in combination with intermediate dose cytarabine (2 gm/m²) for remission consolidation was 1.3 mg/m² and proved tolerable. Further testing of this regimen is planned. Gemtuzumab ozogamicin is a CD33 antibody-targeted chemotherapy agent, consisting of an anti-
body attached to a calicheamicin, a potent antitumor antibiotic that cleaves double-stranded DNA. The addition of gemtuzumab ozogamicin to conventional chemotherapy has shown conflicting results. In the AML16 trial, untreated patients with AML or high-risk myelodysplastic syndrome (median age, 67 years) were randomly assigned to receive induction chemotherapy with either daunorubicin/araC or daunorubicin/clofarabine, with or without gemtuzumab on day 1 of the first course of therapy. There was no difference in the primary endpoint of overall survival, but there was a superior outcome in regard to 3-year cumulative incidence of relapse and 3-year survival. In the ALFA0701 trial, the addition of gemtuzumab ozogamicin on days 1, 4, 7 to cytarabine + daunorubicin regimen led to significant improvements in 2-year relapse-free and overall survival. However, the AML17 trial demonstrated different results when gemtuzumab ozogamicin was added at days 1 and 15 to mitoxantrone, cytarabine and etoposide regimen. The induction and 60-day mortality rates were higher in the gemtuzumab arms without a significant difference in overall survival at median follow-up 5 years.

The purine nucleoside analog clofarabine has been evaluated in combination with cytarabine. The most recent study was a phase II trial, which was closed early due to high mortality and toxicities. This was in contrast to earlier studies that had shown clofarabine plus low-dose cytarabine resulted in roughly 60% complete remissions with acceptable toxicity and induction mortality in elderly AML patients not suitable for intensive chemotherapy. FLT3 mutations, which result in unregulated cell proliferation, have been identified in up to one-third of AML cell lines. It has been demonstrated that elderly AML patients with NPM1-mutated/FLT3-wildtype genotype have significantly improved outcomes compared with patients with other NPM1/FLT3 mutated genotypes when treated with cytotoxic chemotherapy. Several oral agents that inhibit FLT3 activity, such as Tandutinib, Lestaurtinib, Midostaurin and Quizartinib are currently under clinical investigation as single agents or complementary to traditional chemotherapies. Although studies have demonstrated decreases in bone marrow and peripheral blast counts with these agents, most notably in patients whose leukemia characterized by a FLT3 internal tandem duplication. Some suggest that the single-agent activity of these drugs may be unfavorably affected by a number of factors, including insufficient inhibitory drug levels, the emergence of alternate leukemia cell-survival pathways, inherent resistance, and selection for novel FLT3 mutations that will compromise drug-target interaction.

Multidrug resistance (MDR) is a significant problem in AML in the elderly. One mechanism of MDR has been investigated by the effect of reducing peak drug levels, sequential phase II studies using continuous-infusion daunorubicin and cytarabine without and then with cyclosporin were performed in older patients with AML. The addition of cyclosporin did not cause undue toxicities, produced a similar CR rate, and improved relapse-free survival. However, further correlate analyses did not identify a subpopulation specifically benefitting from the addition of cyclosporin. Another approach may be to utilize drugs not susceptible to efflux, such as the liposomal cytarabine-daunorubicin nanoparticle from Celator. Modulation of MDR is an area of active research, and future agents will most likely be utilized in specific subsets of patients that can be predicted to respond favorably.

Hematopoietic growth factors as adjuncts to chemotherapy has been a controversial topic. Many studies assessing the role of hematopoietic growth factors (GM-CSF, G-CSF, and glycosylated G-CSF) failed to show any significant improved response to chemotherapy, decrease in treatment-related mortality, or difference in overall survival. However, a panel created by the American Society of Clinical Oncology (ASCO) has published guidelines on this topic, which refers to reduction in febrile neutropenia as an important clinical outcome that justifies the use of colony stimulating factors (CSFs), regardless of impact on other factors. To develop and update to the original guidelines, an ASCO expert panel conducted a formal systematic review of relevant medical literature published from October 2005 through September 2014. The updated recommendations include primary prophylaxis with a CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy in patients who have an approximately 20% or higher risk for febrile neutropenia on the basis of patient-, disease-, and treatment-related factors. Nevertheless, it is also recommended that consideration should be given to alternative, equally effective, and safe chemotherapy regimens not requiring CSFs support when available. In addition, tbo-filgrastim and filgrastim-sndz are now included in the agents of choice. Although the update did not address the use of CSFs in adults with AML, they did recommend that prophylactic CSFs for patients with diffuse aggressive lymphoma age ≥65 years treated with curative chemotherapy...
should be considered, particularly in the presence of comorbidities.\(^{47}\) The risk of febrile neutropenia during treatment of AML with chemotherapy is higher than 20%. In the previous recommendations from 2006, the panel also observed that patients older than 55 years are likely to benefit most from the use of CSF.\(^{48}\) The recommendation in older patients likely stemmed from the relatively higher incidence of both febrile neutropenia and substantial comorbidities.

**Alternatives to conventional induction chemotherapy**

Additional chemotherapeutic agents have been evaluated in the elderly, all of which have shown similar response rates when compared to the data available for the aforementioned traditional agents. In addition to being evaluated as a agent complementary to cytarabine chemotherapy, clofarabine has been assessed as an alternate monotherapy in elderly patients with AML. Clofarabine is a purine nucleoside analogue with several mechanisms of action that has shown promise in elderly patients with AML. Inhibition of ribonucleotide reductase, incorporation into DNA, and induction of apoptosis are all thought to be part of the mechanism of action.\(^{49}\) Clofarabine was shown to double the response rate when compared to cytarabine without an improvement in survival, but with increased incidence of GI side effects.\(^{50}\) A phase II study of 112 elderly patients with at least one unfavorable prognostic factor demonstrated an overall response rate of 46%. Furthermore, the response rate did not seem to be affected by multiple unfavorable prognostic factors.\(^{51}\) Data from larger trials may further define the role of clofarabine monotherapy.

Intensive chemotherapy may not be a reasonable option for a large proportion of the elderly population, due to co-morbidities and the potential for treatment-related mortality. As an alternative, low-dose cytarabine has been studied in elderly patients, demonstrating superior CR rates when compared to supportive care with hydroxyurea.\(^{52}\) However, patients with adverse cytogenetics did not benefit from low-dose cytarabine. Another study examined low-dose cytarabine in comparison to intensive chemotherapy with cytarabine and rubidazon, and found no differences in survival in elderly patients.\(^{53}\) Low-dose cytarabine is easily administered subcutaneously, assuming one can overcome the logistical challenges of giving drug once or twice daily for up to ten days in the outpatient setting.

Cloretazine is a novel alkylating agent that can be given as a single dose in the clinic. It cannot, however, be considered a non-myelosuppressive drug. The CR rate has been reported to be 28% regardless of underlying cytogenetic risk group.\(^{54}\) A subsequent study of single-agent, single-dose cloretazine in elderly patients with de novo poor-risk AML demonstrated an overall response rate was 32%, with 20 patients (23%) achieving CR. Twelve (14%) patients died within 30 days of receiving therapy. The authors concluded that cloretazine has significant single-agent activity in elderly patients with poor-risk AML. Adverse events were predominantly myelosuppressive and respiratory. Response rates are consistent across a spectrum of poor-risk features, however, the response rate, and potential for pulmonary toxicity did not allow for a recommendation for approval.\(^{55}\)

Decitabine is an agent that reverses DNA methylation, and has been studied in de novo and relapsed AML. Promoter hypermethylation of tumor suppressor genes is thought to play an important role in survival of AML cells. In a phase II trial of elderly patients, decitabine was administered for 5 consecutive days per cycle, with each cycle repeating every 4 weeks until they experienced unacceptable toxicity or disease progression. A mean of 3 cycles resulted in a 25% overall response rate. An encouraging finding was that the response rate was observed irrespective of poor-risk cytogenetics and also in those with a history of myelodysplastic syndrome.\(^{56}\) More recently, a phase III trial compared the efficacy and safety of decitabine with treatment choice in older patients with newly diagnosed AML and poor- or intermediate-risk cytogenetics. Treatment choice consisted of supportive care or daily cytarabine as a subcutaneous injection for 10 consecutive days every 4 weeks. There was no significant improvement in overall survival, although there was a significant increase in remission rate in favor of decitabine (p = 0.001).\(^{57}\)

Azacitidine is another demethylating agent that functions similar to decitabine. It has received FDA approval for the treatment of MDS. Data from relapsed patients and pilot studies of newly diagnosed AML demonstrate that azacitidine has potential in the treatment of previously untreated AML.\(^{58}\) The combination of decitabine or azacitidine with a histone deacetylase inhibitor is being evaluated after a cohort study demonstrated potential as an alternative therapy for patients with AML secondary to MDS.\(^{59}\)

Targeting gain-of-function mutations is one approach that received interest in the past. Tipifarnib is an orally active farnesyl transferase inhibitor that
may have a role in treating elderly patients, with one study demonstrating an overall response rate of 23% in previously untreated patients with adverse cytogenetics. Other studies have shown mixed results with this agent. However, a phase III study comparing tipifarnib to best supportive care (including hydroxyurea) in elderly patients demonstrated an 8% complete response rate, substantially lower than that observed previously.

Post-induction therapy
Following successful induction therapy, it is likely that a clinically relevant population of leukemia cells persist. For adult patients tolerating intensive induction chemotherapy and achieving CR, the induction phase of treatment is followed by intensive consolidation chemotherapy, usually in the form of high-dose cytarabine, with or without an anthracycline, or with hematopoietic stem cell transplantation from an histocompatible allogeneic donor. Many elderly patients are deemed unsuitable candidates for conventional consolidation therapy and transplantation due to comorbidities. Alternative options have been pursued, although with limited success. Alternatives include less intensive consolidative chemotherapy, non-myelosuppressive therapy, or clinical trials of maintenance. For elderly patients tolerating intensive induction chemotherapy, and with favorable cytogenetics and functional status, it may be appropriate to pursue traditional consolidation therapy with two cycles of intermediate-dose cytarabine with or without an anthracycline. Alternatively, some experts have suggested a consolidation regimen of daunorubicin for two days and cytarabine for five days as a reasonable option for those tolerating intensive induction chemotherapy.

Long-term survival in the elderly population is possible, supported by data from the Cancer and Leukemia Group B (CALGB) studies. They demonstrate that if remission can be sustained for three to four years following consolidation, long-term disease-free survival is common, and relapse rates are relatively less likely to occur. Following consolidation therapy, attempts have been made to maintain remission with various therapies, although these attempts have been largely unsuccessful. A study adding interleukin-2 (IL2) maintenance therapy to conventional or intensified chemotherapy regimens in older adults (age 50–70) did not demonstrate any benefit. A phase III trial of IL2 combined with histamine dihydrochloride (HDC) for maintenance therapy demonstrated improved leukemia-free survival in some elderly patients, but was unable to demonstrate improvement in overall survival. Attempts at using immunotherapy to target AML cells has been studied over the past several decades. The ability of lymphocytes to induce an anti-leukemia effect has been well demonstrated in trials of donor lymphocyte infusions (DLI) in relapsed patients following allogeneic transplantation. While beneficial, this effect is often complicated by graft versus host disease (GVHD) and infections. The efficacy of donor lymphocyte infusions has been limited to some large retrospective series.

It is thought that in the setting of relapsed leukemia, malignant cell proliferation may outpace donor lymphocyte antineoplastic processes. This has led to attempts at cytoreduction with chemotherapy or stem cell transplant prior to lymphocyte infusion. The impact of risk stratification–directed interventions was studied in patients with AML, along with MDS and ALL. 814 patients were prospectively followed after allogeneic transplantation in first or second complete remission. Of those with minimal residual disease after transplantation (n=105), approximately half received donor lymphocyte infusions and others underwent IL2 treatment. Results favored those receiving lymphocyte infusions, in which they had a significant advantage in overall and disease-free survival at 3 years. Those who received lymphocyte infusion reached survival outcomes similar to those who had no evidence of residual disease after transplant. The authors concluded that risk stratification–directed interventions with modified lymphocyte infusion in patients with standard-risk acute leukemia who are MRD positive after transplantation may improve transplantation outcomes. Although not studied specifically in the elderly, this strategy may be beneficial in our population of interest if the technology is refined further in the future. Vaccination trials have attempted to harness autologous mononuclear cells in order to mount an immune response against leukemia cells. Manipulation of dendritic cells, functioning as antigen-presenting cells, generated from autologous leukemia blasts is being studied. A recent phase I/II trial showed that in 30 patients who were injected with dendritic cells containing Wilms tumor protein WT1 mRNA, results showed that the strategy is feasible, safe, creating an immunogenic response. A phase III study involving elderly patients in first complete remission or adults in second complete remission receiving a vaccine containing the leukemia-associated antigen PR1 is currently underway.

Allogeneic and autologous stem cell transplants are additional post-induction immunologic treatment
approaches for elderly patients. In the past, allogeneic bone marrow transplantation was reserved for patients under the age of 50, mostly due to concerns about profound immunosuppression in patients who have more of a propensity for infectious complications superimposed upon morbidity from GVHD. For patients in advanced CR considered as potential candidates for transplantation, there is no alternative treatment available that clearly prolongs CR duration. There are also concerns about profound immunosuppression in patients who may have a greater impact on outcome than conditioning intensity. A large retrospective study of patients at international sites between ages 40 to 79 years reviewed outcomes in patients who underwent nonmyeloablative HCT, for which outcomes were assessed in four separate age cohorts (40 to 54; 55 to 59; 60 to 54; 65 and over). Univariate analyses demonstrated that there were no age group differences in several outcomes, including non-relapse mortality, grade 2 to 4 acute GVHD, chronic GVHD, or relapse. The authors concluded that older age alone should not be considered a contraindication to transplantation. Another retrospective study collected data from patients aged 50 to 70 years with AML in first complete remission compared the outcome in elderly patients with AML in first complete remission who were treated with chemotherapy. The cumulative incidence of relapse in the HCT group was significantly lower than that in the chemotherapy group (22% versus 62%). Overall survival was significantly improved in the HCT group. The authors concluded that the introduction of appropriate treatment strategies that include allo-HCT may improve the outcome in elderly patients with AML at first complete remission. Although the retrospective design is inherently associated with selection bias, these data suggest that better than any novel agent, allogeneic transplant applied to selective older patients may have the greatest impact on survival at this time.

The use of allogeneic HCT from matched unrelated donors, as opposed to sibling donors, has made transplant feasible for more AML patients. Retrospective data for patients over the age of 50 with intermediate- or poor-risk cytogenetics suggest that donor type is not a major prognostic factor. This increases the potential options for elderly patients in the post-consolidation timeframe. Autologous transplants have the advantage of avoiding long-term immunosuppressive therapy. The disadvantages of autologous transplants include the lack of graft-versus leukemia effect. A large retrospective study of patients aged 50 and older with de novo AML compared autologous peripheral blood stem cell transplantation (PBSCT) to RIC allogeneic human leukocyte antigen (HLA)-identical PBSCT. Although the allogeneic transplant group consisted of patients with more advanced disease at the time of transplant, patients undergoing allogeneic transplant showed a lower risk for relapse without increased non-relapsed mortality. Furthermore, the allogeneic group demonstrated superior leukemia-free survival and overall survival.

Importantly, it appears that age does not adversely affect mobilization of peripheral blood stem cells in autologous stem cell transplantation. This continues to be a relevant finding because the age limit at which stem cell transplantation is being performed continues to increase. Quality of life in regard to transplant is also an area that deserves mention. A study assessing transplant type and the associated quality of life looked at allogeneic BMT, autologous BMT, or intensive chemotherapy (four courses). The findings demonstrated significant impairment in quality of life for those undergoing allogeneic BMT.

**Treatment of relapsed disease**

Relapsed AML in younger patients is typically treated with chemotherapy followed by allogeneic HCT. However, transplantation in older adults has limitations, associated with very-high treatment-related mortality. For patients 60 and older, who are considered fit enough, the NCCN recommends treating relapsed disease with salvage therapy, such as 1) clinical trial agents, 2) chemotherapy followed by matched-sibling or alternative donor HCT, or 3) best supportive care. For patients who experience late relapse (> 12 months) consideration should be given to repeating the previous successful induction regimen.
Clofarabine combined with cytarabine has been examined in relapsed patients with AML specifically. A phase III trial randomized clofarabine and cytarabine versus cytarabine alone in adult patients over the age of 55 with relapsed AML, or AML refractory to up to two prior treatment regimens. Although the primary endpoint of overall survival did not differ between arms, the combination significantly improved overall response rates and event free survival. However, the drug did not receive a recommendation for regulatory approval.

Gemtuzumab ozogamicin (GO) which targets CD33 has been more promising. Approximately 90% of AML patients have blast cells that are CD33 positive. However, there is a considerable degree of cross-reactivity due CD33 being present on normal progenitor hematopoetic cells as well, which has led to substantial toxicities. Gemtuzumab was approved, for a period in the United States and subsequently withdrawn, for treatment of elderly patients with relapsed CD33+ AML, where it demonstrated a 30% response rate. A study of predominantly elderly sample demonstrated that lower doses of gemtuzumab resulted CR of 26%, with limited toxicities. Therefore, reduced-dose GO may be an option that warrants further evaluation for the elderly population. The combination of fludarabine, cytarabine, and idarubicin with or without GO was studied in adults with a wide age range, in relapsed/refractory AML. Results showed that concurrent administration of G-CSF led to improvements in reported outcomes; however, the addition to gemtuzumab did not lead to substantial differences. A recent phase I/II study investigated combination vorinostat, azacitidine, and GO in 52 adults aged 50 years or over with acute myeloid leukemia requiring therapy for first relapse or primary refractory disease. Median overall survival was significantly longer for the 18 patients achieving complete remission, which indicate that this combination has activity in our population of interest.

Conclusion
Acute myeloid leukemia in the elderly poses significant treatment challenges. Poor physiologic reserve, unfavorable cytogenetic profiles, and poor response to conventional chemotherapy contribute to inferior outcomes observed in these patients compared to their younger counterparts. This has led to a search for novel treatments, some of which have demonstrated great promise. Many patients will be candidates for clinical trials rather than conventional therapy, largely based on initial cytogenetic testing or poor response to induction chemotherapy. Current and developing research focuses upon identifying subgroups of patients that benefit more from specific chemotherapeutic agents based on clinical, as well as biologic features. A potential regulatory pathway that is based on targeting certain molecular features in high-risk populations has been the trend in recent years. Treating elderly patients with AML outside of a clinical trial is challenging. It requires identifying comorbidities and biologic disease features to develop a plan as diverse as induction with hypomethylating agents or post-induction allogeneic transplantation.

Declaration of conflict of interest:
I have a small amount of stock and I derive research support from Amgen.

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