Leucemias agudas en el paciente añoso.

Acute Myelogenous Leukemia in the Elderly.

Caspian Oliai, Gary Schiller

Department of Internal Medicine, Division of Hematology/Oncology
David Geffen School of Medicine at University of California, Los Angeles

GSchiller@mednet.ucla.edu

CONFERENCIA

HEMATOLOGÍA, Vol 19: 147 - 161
Número Extraordinario
XXII CONGRESO
Octubre 2015

Palabras clave: Leucemia mieloblastica aguda,
Anciano,
nuevos tratamientos,
factores de riesgo.

Keywords: AML,
Elderly,
Novel therapy,
Risk factors.

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.[5] 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,[5] 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.[6] 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.[7] Leukemia cells in older patients are more likely to be resistant to standard chemotherapy, perhaps due to multidrug resistant genetics.[7] 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.[8,9] 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.[2] 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.[10] 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.[10,11] 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.[10]

Several algorithms were developed in the past that attempt to assist clinical decisions to proceed with certain therapies.[12-16] One of these models has been validated in a small cohort of elderly patients other than that used during development of the model.[12] 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.[17] 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 (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 coagulaopathy, the combination of ATRA, cytotoxic therapy, and perhaps arsenic trioxide have proven curative. [18] 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.[23]

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-myelosupressive 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.[2,8] As we shall discuss, other treatment strategies have shown promise in the elderly.

Conventional chemotherapy

Induction chemotherapy is used for cytoreduction 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.[5] 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.[25] 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. [37] 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.[26] However, more recently long-term outcomes have demonstrated idarubicin to be superior to daunorubicin in patients 50-65 years of age.[27] 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.[28] Furthermore, It has been shown that escalation of the dose of daunorubicin to 90 mg/m^2 from 45 mg/m^2 in the first induction cycle, effects a more rapid response and a higher response rate than does the lower dose, without additional toxic effects.[29] Whether 90 mg/m^2 is superior to a conventional dose of 60 mg/m^2 remains an open question. Other trials studying variations of the aforementioned regimens,[30] 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.[26] 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. [2,7,31] 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.[32,33] This is in contrast to the first CR rates of 80% and long-term survival of 40% in children and young adults.[34] Conventional intensive therapy may be an appropriate option for elderly patients with zero or one adverse prognostic factor. [10,35]

Agents complementary to conventional chemotherapy

The addition of bortezomib to standard 7+3 cytarabine-daunarubicin 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/m^2) for remission consolidation was 1.3 mg/m^2 and proved tolerable. Further testing of this regimen is planned.[36]

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 gemtuzubmab 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.[37] 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.[38] 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.[39]

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.[40] 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.[41]

FLT3 mutations, which result in unregulated cell proliferation, have been identified in up to one-third of AML cell lines.[42] 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.[43] 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.[7,44] 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.[7]

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.[45] 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.[25,46] 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.[47] 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 rubidazone, 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.[60] 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.[61]

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-myelosupressive 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.[62] 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.[63]

Following consolidation therapy, attempts have been made to maintain remission with various therapies, although these attempts have been largely unsuccessful.[64] 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.[65] 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.[66]

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.[67] 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.[68,69] 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.[70] 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.[71] 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.[72] For patients in advanced CR considered as potential candidates for transplantation, there is no alternative treatment available that clearly prolongs CR or prevents relapse in AML.[73] It is imperative that oncologists critically assess whether the benefits of transplantation outweigh the risks, as allogeneic transplant can certainly be applied to patients well over age 60. Allogeneic transplantation following reduced intensity conditioning (RIC) is an approach that uses agents such as fludarabine (a purine analog), antibodies like alemtuzumab or antithymocyte globulin, and low-dose irradiation. Some trials have also used alkylating agents such as melphalan or busulfan. Reduction in toxicity from conventional chemotherapy makes RIC an important strategy to assess. Retrospective data has suggested that nonmyeloablative transplants are not likely to be inferior to myeloablative transplants in patients over age 50.[73,74] These data suggest that once initial remission is achieved, the graft-versus-leukemia effect may have a greater impact on outcome than conditioning intensity.[75] 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 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.[75] Another retrospective study collected data from patients aged 50 to 70 years with AML in first complete remission compared the outcome in 152 patients who underwent allo-HCT to 884 patients 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.[76] 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.[77]

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.[78] 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.[78]

Importantly, it appears that age does not adversely affect mobilization of peripheral blood stem cells in autologous stem cell transplantation.[79] 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.[80]

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 relapase (> 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.[81] 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.[82] 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.[83] A study of predominantly elderly sample demonstrated that lower doses of gemtuzumab resulted CR of 26%, with limited toxicities.[84] 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.[85] 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.[86]

Purine analogs fludarabine, and cladribine increase cytotoxic effect of Ara-C in leukemic blasts and inhibit DNA repair mechanisms; therefore its association with Ara-C and mitoxantrone results in a synergistic effect. In a multicenter phase II study evaluating the efficacy and toxicity of cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF was performed on poor-risk patients with relapsed/refractory AML. There was a good response, in which 58% of 118 patients achieved a complete response after 1 to 2 cycles of the regimen.[87] However, overall survival was related to age and poor karyotype on multivariate analysis, both of which are the concerning factors in our population of interest.

The combination of azacitidine and donor lymphocyte infusions as first salvage therapy for relapse after allogeneic HST was studied in 28 patients with AML in a prospective single-arm multicenter phase-II trial. Overall response rate was 30% and 5 patients remained in complete remission after 2 years with acceptable safety profile.[88] This combination is an encouraging potential option after allogeneic transplant.

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.

References

1. American Cancer Society. Cancer Facts & Figures 2015. Atlanta: American Cancer Society; 2015.
2. Lowenberg B., Downing J.R., and Burnett A.: Acute Myeloid Leukemia. New England Journal of Medicine 1999; 341: pp. 1051-1062.

3. Ries LG, Melbert D, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD, INTER REF: http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER web site, 2007.
4. R. Pazdur, et al., Cancer Management: A Multidisciplinary Approach 8 edition. CMP Healthcare Media, Oncology Publishing Group: Manhasset NY, 369–385.
5. Appelbaum FR, Gundacker H, Head DR, Slovak ML, Willman CL, Godwin JE, Anderson JE, Petersdorf SH. Age and acute myeloid leukemia. Blood. 2006 May 1;107(9):3481-5.
6. Menzin J., Lang K., Earle C.C., et al: The outcomes and costs of acute myeloid leukemia among the elderly. Archives of Internal Medicine 2002; 162: pp. 1597-1603.
7. Stone R.M., O'Donnell M.R., and Sekeres M.A.: Acute myeloid leukemia. Hematology 2004; undefined: pp. 98-117.
8. Lowenberg B., Zittoun R., Kerkhofs H., et al: On the value of intensive remission induction chemotherapy in elderly patients of 65+ years with acute myeloid leukemia: a randomized phase III study of the European Organization for Research and Treatment of Cancer Leukemia Group. Journal of Clinical Oncology 1989; 7: pp. 1268-1274.
9. Tilly H., Castaigne S., Bordessoule D., et al: Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. Journal of Clinical Oncology 1990; 8: pp. 272-279.
10. Grimwade D., Walker H., Harrison G., et al: The predictive value of hierarchical cytogenetic classification in older adults with acute myeloid leukemia (AML): analysis of 1065 patients entered into the United Kingdom Medical Research Council AML11 trial. Blood 2001; 98: pp. 1312-1320.
11. Grimwade D., Walker H., Oliver F., et al: The importance of diagnostic cytogenetics on outcome in AML: analysis of 1,612 patients entered into the MRC AML 10 trial. The Medical Research Council Adult and Children's Leukemia Working Parties. Blood 1998; 92: pp. 2322-23.
12. Johnson P.R., Ryder W.D., and Yin J.A.: Validation of a model to predict survival in elderly patients with acute myeloid leukaemia. British Journal of Haematology 1995; 90: pp. 954-956.
13. Johnson P.R., and Yin J.A.: Prognostic factors in elderly patients with acute myeloid leukaemia. Leukemia and Lymphoma 1994; 16: pp. 51-56.
14. Kantarjian H., O'brien S., Cortes J., et al: Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer 2006; 106: pp. 1090-1098.
15. Grigg A.P., Reynolds J., McQuillan A., et al: Prognostic features for response and survival in elderly patients with de novo acute myeloid leukemia treated with mitoxantrone and intermediate dose cytarabine. Leukemia and Lymphoma 2005; 46: pp. 367-375.
16. Johnson P.R., Hunt L.P., and Yin J.A.: Prognostic factors in elderly patients with acute myeloid leukaemia: development of a model to predict survival. British Journal of Haematology 1993; 85: pp. 300-306.
17. Krug U, Röllig C, Koschmieder A, Heinecke A, Sauerland MC, Schaich M, Thiede C, Kramer M, Braess J, Spiekermann K, Haferlach T, Haferlach C, Koschmieder S, Rohde C, Serve H, Wörmann B, Hiddemann W, Ehninger G, Berdel WE, Büchner T, Müller-Tidow C; German Acute Myeloid Leukaemia Cooperative Group; Study Alliance Leukemia Investigators. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet. 2010 Dec 11;376(9757):2000-8.
18. Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, Ferrara F, Fazi P, Cicconi L, Di Bona E, Specchia G, Sica S, Divona M, Levis A, Fiedler W, Cerqui E, Breccia M, Fioritoni G, Salih HR, Cazzola M, Melillo L, Carella AM, Brandts CH, Morra E, von Lilienfeld-Toal M, Hertenstein B, Wattad M, Lübbert M, Hänel M, Schmitz N, Link H, Kropp MG, Rambaldi A, La Nasa G, Luppi M, Ciceri F, Finizio O, Venditti A, Fab-

biano F, Döhner K, Sauer M, Ganser A, Amadori S, Mandelli F, Döhner H, Ehninger G, Schlenk RF, Platzbecker U; Gruppo Italiano Malattie Ematologiche dell'Adulto; German-Austrian Acute Myeloid Leukemia Study Group; Study Alliance Leukemia. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med. 2013 Jul 11;369(2):111-21.

19. Fenaux P., Chevret S., and de Botton S.: Treatment of older adults with acute promyelocytic leukaemia. Best Practice and Research Clinical Haematology 2003; 16: pp. 495-501.
20. Sanz M.A., Vellenga E., Rayon C., et al: All-transretinoic acid and anthracycline monochemotherapy for the treatment of elderly patients with acute promyelocytic leukemia. Blood 2004; 104: pp. 3490-3493.
21. Mangelli F., Latagliata R., Avvisati G., et al: Treatment of elderly patients (> or = 60 years) with newly diagnosed acute promyelocytic leukemia. Results of the Italian multicenter group BIMEMA with ATRA and idarubicin (AIDA) protocols. Leukemia 2003; 17: pp. 1085-1090.
22. Ades L., Chevret S., De Botton S., et al: Outcome of acute promyelocytic leukemia treated with all transretinoic acid and chemotherapy in elderly patients: the European group experience. Leukemia 2005; 19: pp. 230-233.
23. Zhang Y, Zhang Z, Li J, Li L, Han X, Han L, Hu L, Wang S, Zhao Y, Li X, Zhang Y, Fan S, Lv C, Li Y, Su Y, Zhao H, Zhang X, Zhou J. Longterm efficacy and safety of arsenic trioxide for firstline treatment of elderly patients with newly diagnosed acute promyelocytic leukemia. Cancer. 2013 Jan 1;119(1):11525.
24. Lowenberg B., Suciu S., Archimbaud E., et al: Mitoxantrone versus daunorubicin in in induction-consolidation chemotherapy—the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian hemato-Oncology Cooperative Hovon Group. Journal of Clinical Oncology 1998; 16: pp. 872-881.
25. Rowe J.M., Neuberg D., Friedenberg W., et al: A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. Blood 2004; 103: pp. 479-485.
26. Goldstone A.H., Burnett A.K., Wheatley K., et al: Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: the results of the United Kingdom Medical Research Council AML11 trial. Blood 2001; 98: pp. 1302-1311.
27. Gardin C, Chevret S, Pautas C, Turlure P, Raffoux E, Thomas X, Quesnel B, de Revel T, de Botton S, Gachard N, Renneville A, Boissel N, Preudhomme C, Terré C, Fenaux P, Bordessoule D, CelliLebras K, Castaigne S, Dombret H. Superior long-term outcome with idarubicin compared with high-dose daunorubicin in patients with acute myeloid leukemia age 50 years and older. J Clin Oncol. 2013 Jan 20;31(3):3217.
28. Ziogas DC, Voulgarelis M, Zintzaras E. A network meta-analysis of randomized controlled trials of induction treatments in acute myeloid leukemia in the elderly. Clin Ther. 2011 Mar;33(3):254-79.
29. Löwenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A, Sonneveld P, Maertens J, JongenLavrencic M, von LilienfeldToal M, Biemond BJ, Vellenga E, van Marwijk Kooy M, Verdonck LF, Beck J, Döhner H, Gratwohl A, Pabst T, Verhoef G; DutchBelgian Cooperative Trial Group for HematoOncology (HOVON); German AML Study Group (AMLSG); Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group. Highdose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med. 2009 Sep 24;361(13):123548.
30. Anderson J.E., Kopecky K.J., Willman C.L., et al: Outcome after induction chemotherapy for older patients with acute myeloid leukemia is not improved with mitoxantrone and etoposide compared to cytarabine and daunorubicin: a Southwest Oncology Group study. Blood 2002; 100: pp. 389-3876.
31. 40. Fey M.F.: ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of acute myeloblastic leukaemia

(AML) in adult patients. Annals of Oncology 2003; 14: pp. 1161-116.

32. Kantarjian H., O'brien S., Cortes J., et al: Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer 2006; 106: pp. 1090-1098.
33. Bow E.J., Stuherland J.A., Kilpatrick M.G., et al: Therapy of untreated acute myeloid leukemia in the elderly: remission-induction using a non-cytarabine-containing regimen of mitoxantrone plus etoposide. Journal of Clinical Oncology 1996; 14: pp. 1345-1352.
34. Hann I.M., Stevens R.F., Goldstone A.H., et al: Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia. Results of Medical Research Council's 10th AML trial (MRC AML10). Adult and Childhood Leukaemia Working Parties of the Medical Research Council. Blood 1997; 89: pp. 2311-2318.
35. Wahlin A., Markevarn B., Golovleva I., et al: Prognostic significance of risk group stratification in elderly patients with acute myeloid leukaemia. British Journal of Haematology 2001; 115: pp. 25-33.
36. Attar EC, Johnson JL, Amrein PC, Lozanski G, Wadleigh M, DeAngelo DJ, Kolitz JE, Powell BL, Voorhees P, Wang ES, Blum W, Stone RM, Marcucci G, Bloomfield CD, Moser B, Larson RA. Bortezomib added to daunorubicin and cytarabine during induction therapy and to intermediate-dose cytarabine for consolidation in patients with previously untreated acute myeloid leukemia age 60 to 75 years: CALGB (Alliance) study 10502. J Clin Oncol. 2013 Mar 1;31(7):923-9.
37. Burnett AK, Russell NH, Hills RK, Kell J, Freeman S, Kjeldsen L, Hunter AE, Yin J, Craddock CF, Dufva IH, Wheatley K, Milligan D. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. J Clin Oncol. 2012 Nov 10;30(32):3924-31.
38. Castaigne S, Pautas C, Terré C, Raffoux E, Bordessoule D, Bastie JN, Legrand O, Thomas X, Turlure P, Reman O, de Revel T, Gastaud L, de Gunzburg N, Contentin N, Henry E, Marolleau JP, Aljijakli A, Rousselot P, Fenaux P, Preudhomme C, Chevret S, Dombret H; Acute Leukemia French Association. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. Lancet. 2012 Apr 21;379(9825):1508-16.
39. Amadori S, Suciu S, Stasi R, Salih HR, Selleslag D, Muus P, De Fabritiis P, Venditti A, Ho AD, Lübbert M, Thomas X, Latagliata R, Halkes CJ, Falzetti F, Magro D, Guimaraes JE, Berneman Z, Specchia G, Karrasch M, Fazi P, Vignetti M, Willemze R, de Witte T, Marie JP. Sequential combination of gemtuzumab ozogamicin and standard chemotherapy in older patients with newly diagnosed acute myeloid leukemia: results of a randomized phase III trial by the EORTC and GIMEMA consortium (AML-17). J Clin Oncol. 2013 Dec 10;31(35):4424-30.
40. Martínez-Cuadrón D, Montesinos P, Oriol A, Salamero O, Vidriales B, Bergua J, Herrera P, Vives S, Sanz J, Carpio C, Rodríguez-Veiga R, Moscardó F, Sanz MA. Phase II trial to assess the safety and efficacy of clofarabine in combination with low-dose cytarabine in elderly patients with acute myeloid leukemia. Ann Hematol. 2014 Jan;93(1):43-6.
41. Faderl S, Ravandi F, Huang X, Garcia-Manero G, Ferrajoli A, Estrov Z, Borthakur G, Verstovsek S, Thomas DA, Kwari M, Kantarjian HM. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome. Blood. 2008 Sep 1;112(5):1638-45.
42. Knapper S., Burnett A.K., Littlewood T., et al: A phase 2 trial of the FLT3 inhibitor lestaurtinib (CEP701) as first-line treatment for older patients with acute myeloid leukemia not considered fit for intensive chemotherapy. Blood 2006; 108: pp. 3263-3270.
43. Daver N, Liu Dumlao T, Ravandi F, Pierce S, Borthakur G, Pemmaraju N, Nazha A,Faderl S, Jabbour E, GarciaManero G, Cortes J, Kantarjian H, QuintásCardama A. Effect of NPM1 and FLT3 mutations on the outcomes of elderly patients with acute myeloid leukemia receiving standard chemothera-

py. Clin Lymphoma Myeloma Leuk. 2013 Aug;13(4):43540.

44. Fischer T, Stone RM, Deangelo DJ, Galinsky I, Estey E, Lanza C, Fox E, Ehninger G, Feldman EJ, Schiller GJ, Klimek VM, Nimer SD, Gilliland DG, Dutreix C, Huntsman-Labed A, Virkus J, Giles FJ. Phase IIB trial of oral Midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3) and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome with either wild-type or mutated FLT3. J Clin Oncol. 2010 Oct 1;28(28):4339-45.

45. Chauncey TR, Gundacker H, Shadman M, List AF, Dakhil SR, Erba HP, Slovak ML, Chen IM, Willman CL, Kopecky KJ, Appelbaum FR. Sequential phase II Southwest Oncology Group studies (S0112 and S0301) of daunorubicin and cytarabine by continuous infusion, without and with ciclosporin, in older patients with previously untreated acute myeloid leukaemia. Br J Haematol. 2010 Jan;148(1):48-58.

46. Stone R.M., Berg D.T., George S.L., et al: Granulocyte-macrophage colony-stimulating factor after initial chemotherapy for elderly patients with primary acute myelogenous leukemia. New England Journal of Medicine 1995; 332: pp. 1671-1677.

47. Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015 Jul 13. pii: JCO.2015.62.3488. [Epub ahead of print] PubMed PMID: 26169616.

48. Smith T.J., Khatcheressian J., Lyman G.H., et al: Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. Journal of Clinical Oncology 2006; 24: pp. 3187-3205.

49. Kantarjian H.M., Jeha S., Gandhi V., et al: Clofarabine: past, present, and future. Leukemia & Lymphoma 2007; 48: pp. 1922-1930.

50. Burnett AK, Russell NH, Hunter AE, Milligan D, Knapper S, Wheatley K, Yin J, McMullin MF, Ali S, Bowen D, Hills RK; UK National Cancer Research Institute AML Working Group. Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival. Blood. 2013 Aug 22;122(8):1384-94.

51. Kantarjian HM, Erba HP, Claxton D, Arellano M, Lyons RM, Kovascovics T, Gabrilove J, Craig M, Douer D, Maris M, Petersdorf S, Shami PJ, Yeager AM, Eckert S, Abichandani R, Faderl S. Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors. J Clin Oncol. 2010 Feb 1;28(4):549-55.

52. Burnett A.K., Milligan D., Prentice , et al: A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. Cancer 2007; 109: pp. 1114-1124.

53. Tilly H., Castaigne S., Bordessoule D., et al: Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly. Journal of Clinical Oncology 1990; 8: pp. 272-279.

54. Giles F., Rizzieri D., Karp J., et al: Cloretazine (VNP40101M), a novel sulfonylhydrazine alkylating agent, in patients age 60 years or older with previously untreated acute myeloid leukemia. Journal of Clinical Oncology 2007; 25: pp. 1-2.

55. Schiller GJ, O'Brien SM, Pigneux A, Deangelo DJ, Vey N, Kell J, Solomon S, Stuart RK, Karsten V, Cahill AL, Albitar MX, Giles FJ. Single-agent laromustine, a novel alkylating agent, has significant activity in older patients with previously untreated poor-risk acute myeloid leukemia. J Clin Oncol. 2010 Feb 10;28(5):815-21.

56. Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. J Clin Oncol. 2010 Feb 1;28(4):556-61.

57. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J,

Gau JP, Chou WC, Buckstein R, Cermak J, Kuo CY, Oriol A, Ravandi F, Faderl S, Delaunay J, Lysák D, Minden M, Arthur C. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol. 2012 Jul 20;30(21):2670-7.

58. Maslak P., Chanel S., Camacho L.H., et al: Pilot study of combination transcriptional modulation therapy with sodium phenylbutyrate and 5-azacytidine in patients with acute myeloid leukemia or myelodysplastic syndrome. Leukemia 2006; 20: pp. 212-217.

59. Tan P, Wei A, Mithraprabhu S, et al. Dual epigenetic targeting with panobinostat and azacitidine in acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood Cancer Journal*. 2014;4(1):e170-. doi:10.1038/bcj.2013.68.

60. Harousseau J.L., Lancet J.E., Reiffers J., et al: A phase 2 study of the oral farnesyltransferase inhibitor tipifarnib in patients with refractory or relapsed acute myeloid leukemia. Blood 2007; 109: pp. 5151-5156.

61. Harousseau JL, Martinelli G, Jedrzejczak WW, Brandwein JM, Bordessoule D, Masszi T, Ossenkoppele GJ, Alexeeva JA, Beutel G, Maertens J, Vidriales MB, Dombret H, Thomas X, Burnett AK, Robak T, Khuageva NK, Golenkov AK, Tothova E, Mollgard L, Park YC, Bessems A, De Porre P, Howes AJ; FIGHT-AML-301 Investigators. A randomized phase 3 study of tipifarnib compared with best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia in patients 70 years or older. Blood. 2009 Aug 6;114(6):1166-73.

62. Stone R.M., and Mayer R.J.: The approach to the elderly patient with acute myeloid leukemia. Hematology/Oncology Clinics of North America 1993; 7: pp. 65-79.

63. Schiffer C.A., Dodge R., and Larson R.A.: Long-term follow-up of Cancer and Leukemia Group B studies in acute myeloid leukemia. Cancer 1997; 80: pp. 2210-2214.

64. Saunter C., Alberto P., Berchtold W., et al: Long-term results of two Swiss AML studies. Haematology and Blood Transfusion 1987; 30: pp. 38-44.

65. Pautas C, Merabet F, Thomas X, Raffoux E, Gardin C, Corm S, Bourhis JH, Reman O, Turlure P, Contentin N, de Revel T, Rousselot P, Preudhomme C, Bordessoule D, Fenaux P, Terré C, Michallet M, Dombret H, Chevret S, Castaigne S. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol. 2010 Feb 10;28(5):808-14.

66. Brune M, Castaigne S, Catalano J, Gehlsen K, Ho AD, Hofmann WK, Hogge DE, Nilsson B, Or R, Romero AI, Rowe JM, Simonsson B, Spearing R, Stadtmauer EA, Szer J, Wallhult E, Hellstrand K. Improved leukemia-free survival after post-consolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. Blood. 2006 Jul 1;108(1):88-96.

67. Kolb H.J., Schmid C., Barrett A.J., et al: Graft-versus-leukemia reactions in allogeneic chimeras. Blood 2004; 103: pp. 767-776.

68. Kolb HJ, Schattenberg A, Goldman JM, Hertenstein B, Jacobsen N, Arcese W, Ljungman P, Ferrant A, Verdonck L, Niederwieser D, van Rhee F, Mittermueller J, de Witte T, Holler E, Ansari H; European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood. 1995 Sep 1;86(5):2041-50.

69. Collins RH Jr, Shpilberg O, Drobyski WR, Porter DL, Giralt S, Champlin R, Goodman SA, Wolff SN, Hu W, Verfaillie C, List A, Dalton W, Ognoskie N, Chetrit A, Antin JH, Nemunaitis J. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol. 1997 Feb;15(2):433-44.

70. Yan CH, Liu DH, Liu KY, Xu LP, Liu YR, Chen H, Han W, Wang Y, Qin YZ, Huang XJ. Risk stratification-directed donor lymphocyte infusion could reduce relapse of standard-risk acute leukemia patients after allogeneic hematopoietic stem cell transplantation. Blood. 2012 Apr 5;119(14):3256-62.

71. Van Tendeloo VF, Van de Velde A, Van Driessche A, Cools N, Anguille S, Ladell K, Gostick E, Vermeulen K, Pieters K, Nijs G, Stein B, Smits EL, Schroyens WA, Gadisseur AP, Vrelust I, Jorens PG, Goossens H, de Vries IJ, Price DA, Oji Y, Oka Y, Sugiyama H, Berneman ZN. Induction of complete and molecular remissions in acute myeloid leukemia by Wilms' tumor 1 antigen-targeted dendritic cell vaccination. Proc Natl Acad Sci U S A. 2010 Aug 3;107(31):13824-9.

72. Fey M.F.: ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of acute myeloblastic leukaemia (AML) in adult patients. Annals of Oncology 2003; 14: pp. 1161-1162.

73. Alyea E.P., Kim H.T., Ho V., et al: Comparative outcome of nonmyeloablative and myeloablative allogenic hematopoietic cell transplantation for patients older than 50 years of age. Blood 2005; 105: pp. 1810-1814.

74. Scott B.L., Sandmaier B.M., Storer B., et al: Myeloablative vs nonmyeloablative Allogenic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. Leukemia 2006; 20: pp. 128-135.

75. McClune BL, Weisdorf DJ, Pedersen TL, Tunes da Silva G, Tallman MS, Sierra J, Dipersio J, Keating A, Gale RP, George B, Gupta V, Hahn T, Isola L, Jagasia M, Lazarus H, Marks D, Maziarz R, Waller EK, Bredeson C, Giralt S. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. J Clin Oncol. 2010 Apr 10;28(11):1878-87.

76. Kurosawa S, Yamaguchi T, Uchida N, Miyawaki S, Usuki K, Watanabe M, Yamashita T, Kanamori H, Tomiyama J, Nawa Y, Yano S, Takeuchi J, Yakushiji K, Sano F, Uoshima N, Yano T, Nannya Y, Moriuchi Y, Miura I, Takaue Y, Fukuda T. Comparison of allogeneic hematopoietic cell transplantation and chemotherapy in elderly patients with non-M3 acute myelogenous leukemia in first complete remission. Biol Blood Marrow Transplant. 2011 Mar;17(3):401-11.

77. Schetelig J, Bornhäuser M, Schmid C, Hertenstein B, Schwerdtfeger R, Martin H, Stelljes M, Hegenbart U, Schäfer-Eckart K, Füssel M, Wiedemann B, Thiede C, Kienast J, Baurmann H, Ganser A, Kolb HJ, Ehninger G. Matched unrelated or matched sibling donors result in comparable survival after allogeneic stem-cell transplantation in elderly patients with acute myeloid leukemia: a report from the cooperative German Transplant Study Group. J Clin Oncol. 2008 Nov 10;26(32):5183-91.

78. Herr A.L., Labopin M., Blaise D., et al: HLA-identical sibling allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning compared to autologous peripheral blood stem cell transplantation for elderly patients with de novo acute myeloid leukemia. Leukemia 2007; 21: pp. 129-135.

79. Ferrara F., Viola A., Copia C., et al: Age has no influence on mobilization of peripheral blood stem cells in acute myeloid leukemia. Hematological Oncology. 2007; 25: pp. 84-89.

80. Watson M., Buck G., Wheatley K., et al: Adverse impact of bone marrow transplantation on quality of life in acute myeloid leukaemia patients; analysis of the UK Medical Research Council AML 10 Trial. European Journal of Cancer 2004; 40: pp. 971-978.

81. Faderl S, Wetzler M, Rizzieri D, Schiller G, Jagasia M, Stuart R, Ganguly S, Avigan D, Craig M, Collins R, Maris M, Kovacsovics T, Goldberg S, Seiter K, Hari P, Greiner J, Vey N, Recher C, Ravandi F, Wang ES, Vasconcelles M, Huebner D, Kantarjian HM. Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: results from the CLASSIC I Trial. J Clin Oncol. 2012 Jul 10;30(20):2492-9.

82. Pagano L., Fianchi L., Caira M., et al: The role of Gemtuzumab Ozogamicin in the treatment of acute myeloid leukemia patients. Oncogene 2007; 26: pp. 3679-3690.

83. Bross P.F., Beitz J., Chen G., et al: Approval summary: Gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clinical Cancer Research 2001; 7: pp. 1490-1496.

84. Taksin A.L., Legrand O., Raffoux E., et al: High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the ALFA group. Leukemia 2007; 21: pp. 66-77.

85. Martin MG, Augustin KM, Uy GL, Welch JS, Hladnik L, Goyal S, Tiwari D, Monahan RS, Reichley RM, Cashen AF, Stockerl-Goldstein K, Westervelt P, Abboud CN, Dipersio JF, Vij R. Salvage therapy for acute myeloid leukemia with fludarabine, cytarabine, and idarubicin with or without gemtuzumab ozogamicin and with concurrent or sequential G-CSF. Am J Hematol. 2009 Nov;84(11):733-7.

86. Walter RB, Medeiros BC, Gardner KM, Orlowski KF, Gallegos L, Scott BL, Hendrie PC, Estey EH. Gemtuzumab ozogamicin in combination with vorinostat and azacitidine in older patients with relapsed or refractory acute myeloid leukemia: a phase I/II study. Haematologica. 2014 Jan;99(1):54-9.

87. Wierzbowska A, Robak T, Pluta A, Wawrzyniak E, Cebula B, Hołowiecki J, Kyrcz-KrzemieńS, Grosicki S, Giebel S, Skotnicki AB, Piatkowska-Jakubas B, Kuliczkowski K, Kiełbiński M, Zawilska K, Kłoczko J, Wrzesień-KuśA; Polish Adult Leukemia Group. Cladribine combined with high doses of arabinoside cytosine, mitoxantrone, and G-CSF (CLAG-M) is a highly effective salvage regimen in patients with refractory and relapsed acute myeloid leukemia of the poor risk: a final report of the Polish Adult Leukemia Group. Eur J Haematol. 2008 Feb;80(2):115-26

88. Schroeder T, Czibere A, Platzbecker U, Bug G, Uharek L, Luft T, Giagounidis A, Zohren F, Bruns I, Wolschke C, Rieger K, Fenk R, Germing U, Haas R, Kröger N, Kobbe G. Azacitidine and donor lymphocyte infusions as first salvage therapy for relapse of AML or MDS after allogeneic stem cell transplantation. Leukemia. 2013 Jun;27(6):1229-35.