Editors' Choice

INVITED REVIEW ARTICLE

Nagoya J. Med. Sci. **82**. 151–160, 2020
doi:10.18999/nagjms.82.2.151

How to improve outcomes of elderly patients with acute myeloid leukemia: era of excitement

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ABSTRACT

Among elderly patients with acute myeloid leukemia (AML), especially those who are unfit for intensive chemotherapy, a policy of reduced-intensity chemotherapy or conservative observation has been chosen, resulting in unmet medical needs. Clinical trials using anticancer drugs including antimetabolites or drugs targeted to cell cycle-related molecules failed to show superiority over conventional treatments. Recently, drugs targeted to Bcl-2, SMO, FLT3, and IDH1/2 have been shown to prolong overall survival alone or in combination with reduced-intensity chemotherapy. These treatments are likely to reshape the therapeutic landscape of AML, which will be personalized for individual patients based on leukemia genetics.

Keywords: elderly patients, acute myeloid leukemia, chemotherapy, molecule-targeted drug, prognosis

Abbreviations:
AML: acute myeloid leukemia
SEER: Surveillance, Epidemiology, and End Results
US: United States
JALSG: Japan Adult Leukemia Study Group
allo-HCT: allogeneic hematopoietic cell transplantation
OS: overall survival
AZA: azacitidine
CCR: conventional care regimens
DAC: decitabine
APL: acute promyelocytic leukemia
LDAC: low-dose cytarabine
HMA: hypomethylating agents
CR: complete remission
CRi: complete remission with incomplete count recovery
ATRA: all-*trans* retinoic acid
ATO: arsenic trioxide
Plk: polo-like kinases
FDA: Food and Drug Administration
PMDA: Pharmaceuticals and Medical Devices Agency
SMO: smoothened

Received: December 4, 2019; accepted: December 16, 2019
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INTRODUCTION

Acute myeloid leukemia (AML) is a malignant disease that mainly affects the elderly.[1-4] According to the Surveillance, Epidemiology, and End Results (SEER) in the United States (US),[1] the median age of AML patients is 68 years. In Japan, a similar national cancer registration system has begun but is not yet fully available. The median age of AML patients was 61.3 years (range, 15 to 96 years) according to the JALSG CS-07 study,[4] in which more than 3,000 patients with AML and high-risk myelodysplastic syndromes (MDS) were prospectively registered in a survey of 117 institutions of the Japan Adult Leukemia Study Group (JALSG) from 2007 to 2011. Because the JALSG consists of regional leukemia centers, patients tend to be younger than those in the general population. In many countries, the population aging will increase elderly patients with AML.

The characteristics of AML vary with age.[2-7] AML in elderly patients is associated with higher rates of antecedent hematologic disorders and a history of chemotherapy and/or radiotherapy for prior cancer. Elderly patients have a higher proportion of unfavorable cytogenetics and tend to overexpress P-glycoprotein, a plasma membrane protein that actively removes drugs from leukemia cells.[6] The spectrum of driver gene mutations in elderly AML patients also differs from that in younger patients.[7] Patient-related factors, such as poor general condition, severe comorbidities, organ dysfunction, and low socioeconomic status, also make clinical management of AML in elderly patients difficult.[3,5,6]

The treatment strategy for AML has not changed for several decades. For patients with AML who are considered fit for intensive chemotherapy, the standard induction therapy consists of anthracycline and cytarabine, known as the 7+3 regimen.[8,11] After complete remission has been achieved, consolidation chemotherapy and, in cases of intermediate- or high-risk AML, allogeneic hematopoietic cell transplantation (allo-HCT) are recommended. Intensification of these regimens, expansion of allo-HCT, and progress in supportive care have improved the outcome of AML (Figure 1).[1,9,10] As described below, however, the majority of elderly patients with AML are unfit for intensive chemotherapy.

Here I review the clinical development of new treatments for elderly patients with AML.

OUTCOME OF ELDERLY PATIENTS WITH AML

Overall survival (OS) of elderly patients with AML decreases with age,[1,2,4,6,8] and there has been little improvement in the survival rate for a long time.[1,9] According to US SEER data, the 2-year survival rate for patients over 65 years old has improved from 7.4% to 14.2% over the past three decades but has remained at around 5% for those for over 75 years old (Figure 2).[1] One of the reasons why the outcome has not improved more is that more than half of AML patients in the US over the age of 65 do not receive chemotherapy within 3 months after diagnosis.[2] According to the JALSG CS-07 study,[4] 25% of elderly patients with AML, except for those with acute promyelocytic leukemia (APL), did not receive any chemotherapy as initial treatment. The remaining 32% and 42% of patients received intensive chemotherapy and reduced-intensity chemotherapy, respectively. As described above, it should be noted that the patient population of JALSG may show selection bias compared with that in the US.

In patients for whom intensive chemotherapy is contraindicated, the treatment choices are reduced-intensity chemotherapy, best supportive care, or enrollment in clinical trials.[3,11] Although there are data that low-dose cytarabine (LDAC) therapy prolongs survival in elderly patients with AML, the rate of complete remission (CR) was as low as 18%, and the 1-year survival rate

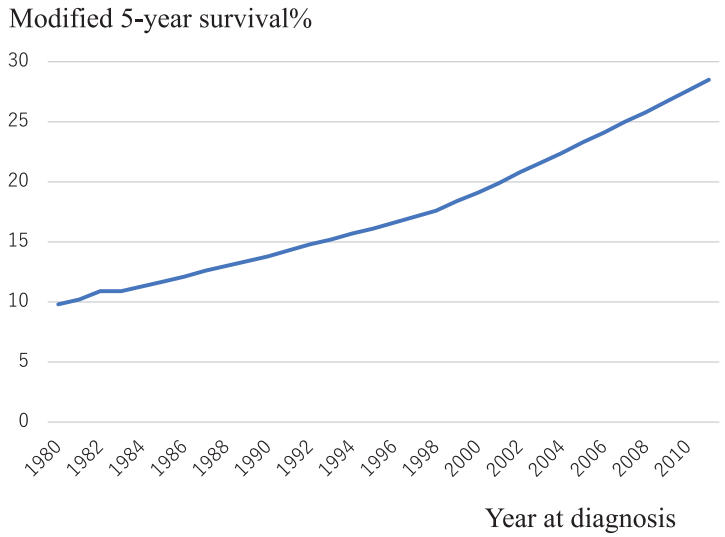

Fig. 1 5-year relative survival percent from 1980 to 2011, according to SEER 9 database[1]

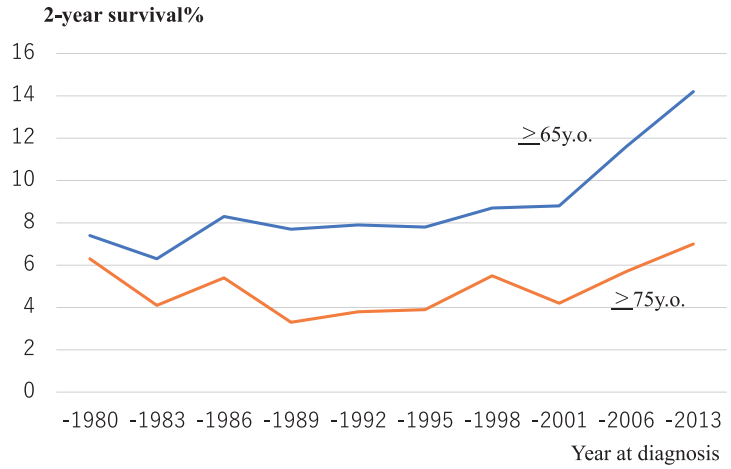

Fig. 2 2-year survival percent from 1980 to 2013, according to SEER 9 database[1]

was 25%.[12] According to recent US data,[2] the median OS for elderly patients receiving intensive chemotherapy, hypomethylating agents (HMA), and no treatment was 18.9, 6.6, and 1.5 months, respectively. Accordingly a goal of new drug therapy for elderly patients with newly diagnosed AML is to achieve survival for more than 6 months.

HYPOMETHYLATING AGENTS

One of the promising HMA is azacitidine (AZA). In high-risk MDS patients, whose blast% is 10% to 30%, AZA prolonged OS compared with conventional care regimens (CCR)[13] (Table 1). Since AML was redefined as a blast% of 20% or more by the WHO 2001 classification,[14] it

Table 1 Trials using HMAs

Treatments	Conditions	Age	N	Outcomes (m)	Reference
Decitabine vs. treatment choice (supportive care or Ara-C)	Newly diagnosed AML (poor or intermediate-risk)	73 (64–91)	485	OS (med.): 7.7 vs 5.0 (p=0.108); CR+CRp: 17.8% vs 7.8%; Early death: 9% vs 8% (Ara-C)	Kantarjian et al JCO 2012[17]
Azacitidine vs. Conventional care	Newly diagnosed AML (blasts > 30%)	75 (64–91)	488	OS (med.): 10.4 vs 6.5 (p=0.101); CR+CRi: 27.8% vs 25.1%; Early death: 7.5% vs 11.7%	Dombret et al Blood 2015[16]
Guadecitabine vs. DEC, AZA or LDAC	Newly diagnosed AML	76 (56–94)	815	OS (med.): 7.10 vs 8.47; CR: 19.4% vs 17.4%	Fenaux et al EHA 2019[18]

is now the consensus that AZA is the first choice for AML with a blast% of less than 30%.[11,15] Based on these findings, a prospective study was conducted to determine whether AZA therapy was superior to CCR for elderly patients with newly diagnosed AML with a blast% of 30% or more. However, the response rate and OS did not differ between the AZA and CCR groups.[16] Prior to this study, another HMA, decitabine (DAC), was studied in elderly patients with newly diagnosed AML who were at poor or intermediate risk in randomization with the doctor's treatment choice of supportive care or LDAC.[17] The results were negative. A second-generation HMA, guadecitabine, was studied in patients with newly diagnosed AML who were unfit for intensive chemotherapy in comparison with physician-chosen treatment with DEC, AZA, or LDAC. The study found no significant differences in OS or CR between patients receiving guadecitabine and patients receiving other drugs.[18]

ANTICANCER AND CELL-CYCLE-TARGETING DRUGS

Three drugs have been developed for relapsed or refractory AML: elacytabine, a fatty acid derivative of cytarabine; clofarabine, a purine nucleoside analog; and vosaloxine, a topo-II inhibitor (Table 2a). Although studies of these drugs included younger patients, the median age was over 60 years. The elacytabine study found no benefit.[19] In studies of clofarabine and vosaloxin, the response rates were superior to those of controls, but the OS was not significantly different from those of controls.[20,21]

CPX-351, a dual-drug liposomal encapsulation of cytarabine and daunorubicin at a 5:1 molar ratio,[22] and lomustine, an alkylating agent of the nitrosourea type, have been developed for untreated AML. In a randomized phase II study of patients age 60 to 75 years with newly diagnosed AML, CPX-351 showed promising results in a subgroup of patients with secondary AML.[23] A phase III study was then conducted to compare the efficacy and safety of CPX-351 with conventional 7+3 therapy. CPX-351 improved the response rate and OS, and did not increase the rate of early death.[24] Based on these results, CPX-351 was approved by the US Food and Drug Administration (FDA) for the treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes. This drug is beneficial for patients for whom intensive chemotherapy, such as 7+3, is indicated, and its usefulness and safety for unfit

Table 2 Trials using anticancer and cell-cycle-targeting drugs

Table 2a

Treatments	Conditions	Age	N	Outcomes (m)	Reference
Elacytabine vs investigator choice	Relapsed/refractory (2nd or more salvage)	62 (19–89)	381	CR+CRi: 23% vs 21%; OS (med.): 3.5 vs 3.3 (p=0.96); Early death: 17% vs 15%	Roboz et al JCO 2014[19]
Clofarabine + Ara-C vs Ara-C alone	Relapsed or refractory (1st salvage)	67 (55–86)	320	CR+CRi: 46.9% vs 22.9% (p=<0.01); OS (med.): 6.6 vs 6.4 (p=1.0); Early death: 16% vs 5% (p<0.01)	Faderl et al JCO 2012[20]
Vosaroxin + Ara-C vs placebo + Ara-C	Relapsed or refractory (1st salvage)	60.6 ± 12.0	711	CR: 30% vs 16% (p<0.0001); OS (med.): 7.5 vs 6.1 (p=0.06); Early death: 8% vs 7% (p<0.01)	Ravandi et al Lancet Oncol 2015[21]

Table 2b

Treatments	Conditions	Age	N	Outcomes (m)	Reference
Volarsatib + LDAC vs placebo + LDAC	Unfit AML	75 (65–93)	666	CR+CRi: 25.2% vs 16.8% (p=0.071); Median OS: 4.8 vs 6.5; AE (Grade 5): 27.9% vs 15.2%	Dohner et al EHA 2016[30]

patients should be considered carefully. Patients 60 years of age or older with untreated AML who were fit to receive chemotherapy and who were without unfavorable cytogenetics were randomly assigned to receive standard chemotherapy plus lomustine or chemotherapy only. The CR + CR with incomplete count recovery (CRi) ratio was higher in the lomustine group (84.7% vs. 74.9%, $P = 0.01$), in spite of a higher rate of early death in the group (8% vs. 4%, not significant). The OS did not significantly differ between the two groups.[25]

Aurora and polo-like kinases (Plk) are important enzymes that control the cell cycle, especially in the G2/M phase, and are considered crucial targets for cancer therapy.[26] Barasertib, a prodrug of a potent and selective inhibitor of aurora B kinase, was compared with LDAC in a randomized phase II study. A significant improvement in CR + CRi was observed in the barasertib group (35.4% vs. 11.5%, $P < 0.05$).[27] However, the subsequent phase III study did not show an improvement in OS (data not published). Volasertib is a potent and selective Plk-inhibitor that causes mitotic arrest followed by the induction of apoptosis.[28] A randomized phase II study suggested that adding volasertib to LDAC improved survival.[29] However, the subsequent phase III study found that the volasertib plus LDAC group had a better response but that OS was unexpectedly inferior to that in the placebo plus LDAC group (Table 2b).[30] This was probably due to an increase in adverse events, including infection.[30]

Except for CPX-351, none of the new anticancer agents and targeted drugs that inhibit the cell cycle have significantly improved the prognosis of AML compared with LDAC therapy or conventional care. The fact that the only exception is CPX-351 suggests that these drugs may require delivery systems such as liposomes and nanoparticles, to discriminate leukemia cells from normal hematopoietic cells.[22]

Table 3 Clinical studies for elderly patients with APL

Group	Age	N	Regimen	CR	outcome	Reference
PETEMA	> 60 y.o.	104	ATRA+anthracyclin	84%	79% (6y-DFS)	Blood, 2004[34]
German	> 60 y.o.	98	ATRA+chemotherapy	82%	45% (7y-OS)	Ann Hematol, 2013[38]
European	> 60 y.o.	129	ATRA+chemotherapy	86%	57.8% (4y-OS)	Leukemia, 2005[37]
Harbin	> 60 y.o.	33	ATO	87.9%	69.3% (10y-OS)	Cancer, 2013[33]
GIMEMA	> 60 y.o.	134	ATRA+Idarubicine	86%	81% (3y-OS)	Leukemia, 2003[33]
JALSG	> 60 y.o.	46	ATRA+chemotherapy	89%	63% (10y-OS)	Cancer Science, 2012[36]
MDA et al	> 60 y.o.	52	ATRA+ATO+GO	96%	74% (5y-OS)	Blood, 2017[39]

GO: gemtuzumab ozogamicin

LESSON FROM ATRA AND ARSENIC TRIOXIDE

Data on treatment choice from the JALSG CS-07 study showed that most elderly patients with APL were treated, indicating the need for a more effective and less toxic therapy for AML other than APL.[4]

All-*trans* retinoic acid (ATRA) induced differentiation and apoptosis in APL cells without hematopoietic hypoplasia in a PML-RARα-dependent manner.[31,32] In combination with chemotherapy, ATRA significantly improved the outcome of APL patients and now contributes to make APL a curable leukemia, not only in younger patients but also in elderly patients (Table 3).[33-39] Arsenic trioxide (ATO), another APL-specific drug,[31,32] further improved OS in combination with ATRA.[40] ATRA and ATO have different modes of action and do not show cross-resistance. Moreover, they have relatively low toxicity. These are the reasons why elderly APL patients have improved outcomes with ATRA+ATO regimen.

NEWLY APPROVED MOLECULE-TARGETED DRUGS

In 2018, glasdegib was approved by the US FDA for use in combination with LDAC in patients with newly diagnosed AML who are 75 years of age or older or who have complications that preclude intensive induction therapy. Glasdegib is a small-molecule inhibitor of smoothened (SMO) in the sonic hedgehog pathway. SMO is expressed in many types of cancer, including leukemia, and is considered to be associated with self-renewal and treatment resistance of leukemia cells.[41,42] The approval is based on a trial including patients aged 75 years or older or patients who were not fit to receive intensive chemotherapy due to organ failure or poor performance status (Table 4a). LDAC plus glasdegib was superior to LDAC alone and prolonged OS from 4.9 to 8.8 months.[43]

In the same year, venetoclax was approved in combination with AZA or DEC or LDAC for the treatment of patients with newly diagnosed AML who are 75 years of age or older or who have comorbidities that preclude the use of intensive chemotherapy. Venetoclax is a BH3 domain mimetic selectively targeting Bcl-2 protein, which plays an important role in cell survival in AML

Table 4 Trials of recently FDA-approved drugs for elderly patients with AML

Table 4a

Treatments	Conditions	Age	N	Outcomes (m)	Reference
Glasdegib + LDAC vs. LDAC	Newly diagnosed AML & high-risk MDS	77 (58–92)	132	OS (med.): 8.8 vs 4.9 (p=0.0004); CR: 17.0% vs 2.3% (p<0.05)	Cortes et al Leukemia 2019[43]

Table 4b

Treatments	Conditions	Age	N	Outcomes (m)	Reference
Venetoclax + DEC or AZA	AML without prior therapy for AML	74 (65–86)	145	CR+CRi: 67%; Median CR+CRi duration: 11.3; Median OS: 17.5	DiNardo et al Blood 2019[45]

as well as in lymphoid malignancies.[44] Approval was based on a nonrandomized clinical trial of venetoclax in combination with AZA or DEC in patients newly diagnosed with AML (Table 4b). A total of 67% of patients achieved CR + CRi, and patients with poor-risk cytogenetics and those 75 years of age or older had CR + CRi rates of 60% and 65%, respectively. The median duration of CR + CRi was 11.3 months, and the median OS was 17.5 months.[45] In Japan, phase II studies of these two drugs are ongoing.

PRECISION MEDICINE AND LEUKEMIA

Recent advances in genome studies and high-throughput technology have enabled us to obtain genome information from AML cells in the clinical setting.[46,47] In addition, recent clinical studies have led to novel therapies, most of which are indicated on stratification of actionable gene mutations.[48] *FLT3*, a gene coding receptor tyrosine kinase, which has a role in proliferation and survival of hematopoietic stem/progenitor cells, is mutated in nearly 30% of cases of AML.[49,50] Mutated FLT3 protein mediates constitutive active signals in leukemia cells. Clinically, AML with *FLT3* mutation is associated with leukocytosis and a poor prognosis. The *FLT3* mutation is slightly less frequent in elderly than in younger AML patients, but the prognosis is dismal for both elderly and younger patients.

In 2017, the US FDA approved midostaurin, a multitarget tyrosine kinase inhibitor that is active against FLT3, for the treatment of *FLT3*-mutated AML. Approval was based on a phase III study in which patients 18 to 59 years of age with newly diagnosed AML harboring *FLT3* mutations were randomly assigned to receive standard chemotherapy plus either midostaurin or a placebo.[51] There is no indication for midostaurin in elderly patients with AML because it is combined with intensive chemotherapy.

Gilteritinib is a dual tyrosine kinase inhibitor of FLT3 and AXL that was approved by the Pharmaceuticals and Medical Devices Agency (PMDA) and the US FDA in 2018. The current indication is relapsed or refractory AML with *FLT3* mutation. Although the patients in the phase I/II study were elderly, with a median age of 62 to 65 years,[52] the efficacy and safety of gilteritinib in the elderly must be followed carefully.

IDH1/2 are metabolic enzymes that convert isocitrate to α-ketoglutarate in the TCA cycle. Point mutations in *IDH1/2* lead to aberrant enzymes that convert isocitrate to 2-hydroxyglutarate, an oncometabolite that increases methylation of DNA and histone and that is associated with

differentiation block of hematopoiesis.[53] In 2017, the US FDA approved enasidenib, a small-molecule inhibitor of mutant IDH2 protein, for patients with R/R *IDH2*-mutated AML. In a phase I/II study of enasidenib in patients with R/R AML, the overall response rate was 40.3%, with a median response duration of 5.8 months.[54] Enasidenib was also studied in elderly patients with newly diagnosed *IDH2*-mutated AML. The CR rate was 30.8% and the median OS was 11.3 months, and treatment-related grade 3 or 4 adverse events were observed in 49% of patients.[55] In 2018, ivosidenib, a small-molecule inhibitor of IDH1 mutants, was approved by the US FDA for the treatment of R/R AML with *IDH1* mutations. Ivosidenib was studied in a phase I dose-escalation and dose-expansion study of patients with *IDH1*-mutated AML. CR and overall response were observed in 21.6% and 41.6% of patients, respectively, and the median duration of these responses was 8.2 months.[56]

Currently, various strategies with combinations between a molecule-targeted drug and HMA are being studied in elderly patients and patients unfit for intensive chemotherapy. In the future, if the drug best suited for AML can be selected for each patient instead of giving up because the patient is of advanced age, the treatment of elderly AML patients will change significantly. This is an exciting time.

ACKNOWLEDGMENTS

JALSG data was provided by Professor Yasushi Miyazaki in Nagasaki university.

CONFLICT OF INTEREST

T. Naoe received lecture fees from Astellas Pham Inc., Nippon Shinyaku Co. and Bristol-Myers Squibb, and honoraria from Sysmex Co. Pfizer Inc., Otsuka Pham Inc. FujiFilm Co. and Eisai Co.

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