Best Practice & Research Clinical Haematology 32 (2019) 101105

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Acute myeloid leukemia: How to treat the fit patient over age 75?

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ARTICLE INFO

Keywords:
Acute myeloid leukemia
AML
Elderly
Glasdegib
Venetoclax

ABSTRACT

Survival rates for patients with acute myeloid leukemia (AML) older than 75 years are still quite dismal. Recent approvals, therefore, of two agents specifically to treat older patients—glasdegib and venetoclax—have created excitement among the medical community. Clinical data, particularly complete response (CR) rates and CR with incomplete hematologic recovery (CRi), look quite promising and are reviewed here. Yet the question remains whether fit elderly patients should receive combination therapy containing the newer agents, particularly since intensive chemotherapy remains the only treatment that has demonstrated the ability to achieve long-term disease-free survival.

Introduction

A retrospective analysis conducted more than 10 years ago confirmed that older patients with acute myeloid leukemia (AML) are a unique group of patients in terms of disease biology. The analysis included 968 patients enrolled on 5 different Southwest Oncology Group trials and evaluated whether the nature of AML changes with age [1]. The investigators found that patients older than 75 have differences in disease features at presentation (Table 1). Those older than 56 years had lower white blood cell counts at presentation than younger patients and a greater percentage had multidrug resistance. Patients older than 75 had the worst cytogenetic risk group distribution.

Risk

Older patients have an increased risk of *TP53*, *ASXL1*, and *TET2* alterations, but these are not necessarily exclusive to those over age 75 [2]. While performance status is more predictive than age for early death at any Eastern Cooperative Oncology Group (ECOG) performance status level, older patients have a higher 30-day mortality rate at all levels [1]. This, however, is most notable in a group with poor performance status. Patients older than 75 with a performance status of ECOG 2 have a 50% chance of early death from induction chemotherapy, and those in ECOG 3 have an 82% 30-day mortality rate. This 75-year-old group is high risk both biologically and in terms of their tolerance of chemotherapy.

Scores for fitness have been developed and most of them incorporate age [3–10]. SEER (Surveillance, Epidemiology and End Results) data indicate 5-year survival for AML is poor for those over age 75 (Fig. 1) [11]. Based on the most recent survey, 2.6% of AML patients 75 years or older survive 5 years.

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https://doi.org/10.1016/j.beha.2019.101105

Table 1
SWOG retrospective analysis showing age and disease features at presentation [1].

Age (years)	< 56	56–65	66–75	> 75
Number pts	323	183	199	54
Karyotype (%)	16	5	5	4
Favorable	46	55	55	44
Intermediate	33	38	39	50
Unfavorable	16	34	32	48
WBC(× 1000 μL)	18.6	12.0	10.0	12.7
MDR + (%)	33	62	61	57

MDR, multidrug resistance; pts, patients; WBC, white blood cell count.
An analysis by the Southwest Oncology Group found that patients older than 75 have differences in disease features at presentation, including karyotype, white blood cell counts, and multidrug resistance.

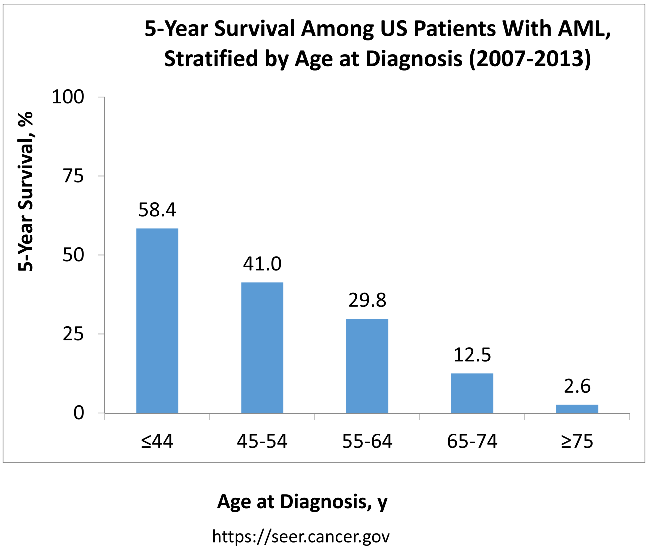

Fig. 1. 5-year survival for patients with AML [11].
SEER (Surveillance, Epidemiology and End Results) data indicate 5-year survival for AML patients 75 years or older is 2.6%.

Recent drug approvals

On November 21, 2018, the US Food and Drug Administration (FDA) approved two drugs—venetoclax and glasdegib—particularly for AML patients who are 75 years or older or who have comorbidities that preclude the use of intensive chemotherapy. Venetoclax was approved in combination with azacitidine or decitabine or low-dose cytarabine, and glasdegib in combination with low-dose cytarabine.

The FDA approval of glasdegib, a hedgehog inhibitor, was based on a multicenter, open-label trial (NCT01546038) [12]. One hundred fifteen patients with newly diagnosed AML were evaluated. Patients had to be 75 years or older, or have severe cardiac disease, an ECOG performance status of 2, or baseline creatinine of greater than 1.3 mg/dL. Patients were randomized 2:1 to receive glasdegib 100 mg daily with low-dose cytarabine (20 mg) twice daily (n = 77) on days 1–10 of a 28-day cycle or low-dose cytarabine alone (n = 38) in 28-day cycles until disease progression or unacceptable toxicity. With a median follow-up of 20-months, median survival was 8.3 months for the combination arm (95% CI: 4.4, 12.2) versus 4.3 months for the single-agent low dose cytarabine arm with a hazard ratio of 0.46 (95% CI: 0.30, 0.71; $P = 0.0002$).

The FDA approval of venetoclax was based on two open-label nonrandomized trials in patients with newly diagnosed AML [13]. Again, the studies used for this approval included patients who were either 75 years or older or had comorbidities that precluded the use of intensive induction. The data considered for FDA approval was based solely on efficacy—the rate of CR and CR duration.

One of these nonrandomized trials of venetoclax (400 mg daily dose) was in combination with azacitidine or decitabine (NCT02203773). Most patients (n = 67) received azacitidine, and they achieved a 37% CR rate with a median rate of duration of 5.5 months. Patients treated with decitabine (n = 13) had a 54% CR rate with a duration of remission of 4.7 months. The other nonrandomized, open-label study used for approval was venetoclax (600 mg daily dose) in combination with low-dose cytarabine (NCT02287233). Of the 61 older patients treated, 21% achieved a CR. The median duration of remission for them was 6 months (range, 0.03–25 months).

Early data presented in 2017 at the European Hematology Association meeting [14] included 100 patients treated with either decitabine or azacitidine and venetoclax at doses of 400 or 800 mg. CR plus CRi (CR with incomplete hematologic recovery) rates ranged between 55% and 70% in the different arms, with an overall CR/CRi rate of 68%. Responses were achieved in all cytogenetic risk groups and in primary and secondary AML. Most importantly, patients achieved a response after one to two cycles, not the traditional four to six cycles seen with hypomethylating agents alone. Median overall survival at that time, after being followed for a median of 9 months, was 79% at 6 months (95% CI: 70%, 86%) and 70% at 12 months (95% CI: 59%, 79%). Median overall survival had not yet been reached.

Additional data on these agents have been collected since their approval, and now for many AML patients over age 70 or 75 they have become the de facto treatment of choice. And the question is, should they be? A review of some of the newer data may assist in the decision making.

Newer data

Since the approval of venetoclax, investigators have published additional data on the dose escalation and expansion phases of the combination trial with azacitidine or decitabine, in which patients were treated at either 400, 800 or 1200 mg of venetoclax [15,16]. About 35% of patients were over age 75 and 16% had a performance status of ECOG 2. Venetoclax was well-tolerated. Gastrointestinal side effects and cytopenias were the most significant adverse events. The 30-day mortality was 3.4% and the 60-day mortality rate was 6%. Almost half the patients (46%) required some dose interruption because of myelosuppression or adverse events.

For patients over age 75, CR/CRi rates were no different than those for younger patients. The CR/CRi rates were also the same for de novo and secondary and for intermediate- and poor-risk disease. The duration of remission was good for patients with Cr/CRi, particularly for the doses that are now being used. Median duration of response for the 400 mg combination with decitabine has not yet been reached. Durable remissions were achieved in all patient subgroups, regardless of whether AML was secondary, intermediate risk, de novo, or poor cytogenetics, although remissions in patients with poor cytogenetics were shorter.

In patients who were CR/CRi, minimal residual disease (MRD) negativity was achieved by 45% of in the 400 mg plus azacitidine group and 32% in the 400 mg plus decitabine group. MRD negativity was defined as $< 10^{-3}$ leukemic cells at any measurement, centrally assessed by multicolor flow cytometry from bone marrow aspirates.

When one looks at historic controls of a hypomethylating agent (HMA) alone compared with venetoclax plus an HMA in patients with a median age in the mid-70s, the combination appears better than azacitidine alone. The combination produced a CR/CRi rate of 67% compared to 28% with a hypomethylating agent alone [16,17]. A recently published study of low-dose cytarabine with venetoclax reported a CR/CRi rate of 70% [18]. In this study, about half the patients were 75 years or older and about 30% had a performance status of 2 or 3. Complete responses occurred in all cytogenetic risk groups regardless of whether patients had received prior HMAs and in de novo and secondary AML. The median duration of remission with the venetoclax/low-dose cytarabine combination was about 8 months, and the median overall survival was about 10 months. Patients who achieved a CR did best in terms of survival. It is unclear what benefit is seen in those who are not able to achieve at least a CRi, but there does seem to be some benefit in CRi.

New standard of care for older patients?

So does this mean all patients over the age of 75 should get one of these therapies? Should they get an HMA plus venetoclax, or low-dose cytarabine plus venetoclax, or low-dose cytarabine plus glasdegib? These approved therapies for patients over the age of 75 now exist, with data that look quite promising in terms of CR and CRi.

Long-term ECOG ACRIN data demonstrate that improvements in survival have been made over the decades for patients age 60 or older [19]. Survival for older patients has improved both overall and from the time of achieving CR compared to previous decades. The ALFA-1200 study evaluated intensive chemotherapy in older patients with a median age of 68 years (range, 60–85) [20]. Patients received idarubicin at 12 mg/m^2 with cytarabine at 200 mg/m^2, followed by high-dose cytarabine consolidation. Patients had a 22.5 months median survival with a CR/CRp (CR with incomplete platelet recovery) rate of 72%. The study included patients with favorable, intermediate, and unfavorable risk and a few who had poor performance status at the time they went on study. The induction death rate was 8.5%, 60-day mortality 9.4%, and median overall survival was 20.7 months.

The Intergroup trial E2906, an ECOG-ACRIN Cancer Research Group trial, provided a bit more information on what can be expected from intensive chemotherapy in an older patient population [21]. The study evaluated daunorubicin and cytarabine versus clofarabine in AML patients 60–69 years and 70 or older. Clofarabine was chosen because it was promising in patients unfit for chemotherapy, regardless of cytogenetics or performance status, and the hope was clofarabine could possibly produce even better results in patients who were fit. Patients in the daunorubicin/cytarabine arm who achieved a CR or CRi then received high-dose cytarabine consolidation. Those in the clofarabine arm who achieved remission only received clofarabine consolidation. The weighted analysis demonstrated no improvement for clofarabine over daunorubicin and cytarabine. Patients treated with clofarabine had a median survival of 9.99 months compared with 13.8 months in the daunorubicin/cytarabine arm. And importantly, those patients age 75 or older had a survival plateau out to 40 months, with about 35%–40% experiencing long-term disease-free survival with standard intensive chemotherapy treated with daunorubicin and cytarabine.

About 40% (n = 67) of the 157 patients analyzed achieved MRD-negative status in both the daunorubicin/cytarabine arm and in the clofarabine arm. There was no difference by induction therapy arm and no difference in MRD status according to patients' baseline clinical criteria. More women achieved MRD-negative status than men. Those patients who were MRD negative had a better long-term disease-free survival than those who were MRD positive. Interestingly, this benefit was most evident in patients in the

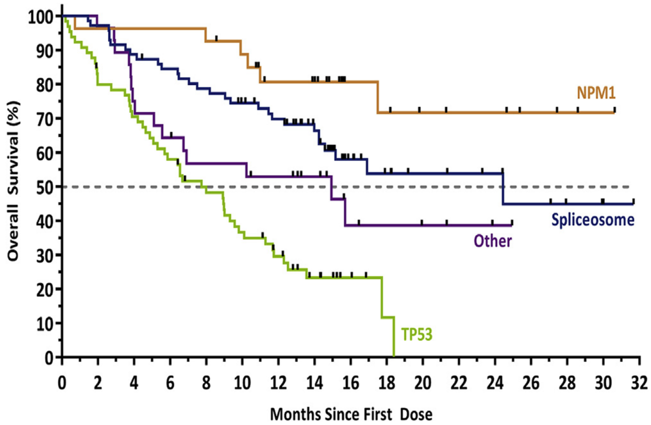

Fig. 2. Overall survival with venetoclax combinations by molecular subgroup [25].
Overall survival with venetoclax is subject to many of the same issues experienced with other regimens. For example, patients with *TP53* mutation do not do well with this agent.

clofarabine arm, perhaps because those in the daunorubicin/cytarabine arm who were MRD positive were most likely salvaged by the high-dose cytarabine consolidation. Those patients who received clofarabine only and were MRD positive only got additional clofarabine. So those patients did not get much benefit from the post remission therapy.

So, why and how do we compare the HMAs with intensive chemotherapy? Two French propensity score matching analyses have examined studies using high-dose intensive chemotherapy versus HMAs [22,23]. The conclusion is that comparing the two therapies is like comparing apples to oranges—the therapies are not used in the same patient populations. The patients being treated with intensive chemotherapy are not the same as those being treated with HMAs. This means that using the data available right now to establish which regimen is superior is very difficult to do. A direct comparison of international phase 3 trial data with registry data from the Austrian Azacitidine Registry of the AGMT Study Group has shown that age, poor performance status, and NCCN (National Comprehensive Cancer Network) cytogenetic risk are predictors of HMA response [24]. However, not as many patients with a poor performance status have been treated on the HMA clinical trials. In evaluating the data with HMA and venetoclax it is important to recognize again that patient populations and disease response criteria differ from those treated on intensive chemotherapy trials.

Overall survival with venetoclax and HMA does also , unfortunately, seem to be subject to many of the same issues experienced with other regimens (Fig. 2) [25]. For example, patients with *TP53* mutation unfortunately do not do well with this agent. Identifying patient populations and molecular subgroups that would clearly benefit from venetoclax combinations is yet to be accomplished.

Conclusion

So, what are we left with? First, intensive chemotherapy remains the only treatment that has demonstrated the ability to achieve long-term disease-free survival with a defined course of therapy. Second, lower intensity therapies provide an option with less toxicity, but what that means in terms of long-term disease-free survival is not clear. If one uses time without symptoms or treatment as the standard measure, it is not very achievable with the lower intensity therapies because patients must continue treatment. The new agents, however, are promising with high CR rates. Third, it's not certain which patient populations benefit from one approach versus another. Fourth, as transplant is not offered to patients over age 75, we are left with a patient population for which we must decide what the optimal post remission therapy is with these lower intensity therapies. Is continued treatment necessary for patients getting low-intensity therapy? Particularly those who are MRD negative? Or should we be giving these patients standard consolidation in order to make it so that they don't need long-term therapy with these low-intensity therapies? And this would be the case particularly since the patients have gone through the period where they were at highest risk and now don't have active leukemia? These questions and more remain to be answered by the medical community.

Disclosures

Consulting/Honoraria: Pfizer, Agios, Daichi Sankyo, Jazz.
Contracted research: Onconova, Seattle Genetics, Kura, Cyclacel, Celgene, Hoffman La Roche, Biosight.

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