For reprint orders, please contact: reprints@futuremedicine.com

Early mortality and survival in older adults with acute myeloid leukemia

Manisha Pant¹ & Vijaya Raj Bhatt^{*.2}

¹Department of Internal Medicine, Staten Island University Hospital, 475 Seaview Ave, Staten Island, NY, USA

²Department of Internal Medicine, Division of Hematology-Oncology, University of Nebraska Medical Center, Omaha, NE 68198-7680, USA

* Author for correspondence: Phone: +1 402 559 5166; Fax: +1 402 559 6520; vijaya.bhatt@unmc.edu

“Overall care of older patients with AML may improve with refined risk-stratification and personalized therapy based on the principles of geriatric medicine.”

Keywords: acute myeloid leukemia • chemotherapy • geriatric assessment • hematopoietic cell transplant • novel therapy • older adult • survival

Acute myeloid leukemia (AML) is a disease of older adults [1] and has a median age of 68 years at the time of diagnosis. The management of AML in older patients (>60 years) is far from optimal and often associated with poor outcomes. Over half of the older patients do not receive initial chemotherapy [1,2], remission rate is lower than in younger patients and lasts shorter duration, and long term survival is dismal. For example, 5-year survival is over 50% for patients aged 15–24 years that drops steadily to 13% for patients between 60 and 69 years of age and 3% for those aged 70–79 years [3]. Functional status varies widely even in older patients with similar biological age and affects outcome. For instance, data from the Southwest Oncology Group trials demonstrated that the early mortality at 1 month for patients older than 75 years is 14% with Eastern Cooperative Oncology Group performance score of 0 versus 82% for a score of 3 [4]. Higher incidence of comorbidities negatively affects outcomes [1]. This is reflected by a higher 8-week mortality (30 vs 19%) in patients with a higher modified Charlson Comorbidity Index of >1 versus ≤ 1, respectively [5]. Comorbidities may lead to poor tolerance of chemotherapy, enhanced toxicity, particularly following intensive chemotherapy and a lower rate of complete response. Malnutrition, decreased immunity with increased susceptibility to infection, cognitive decline and social isolation pose increased risk of toxicity from chemotherapy.

Older adults have higher rates of multidrug resistance compared with the younger patients (57 vs 33%) [4]. The proportion with unfavorable cytogenetics increases with age, whereas translocation associated with favorable response drops. AML in younger patients may result from a limited number of mutational events restricting diversity of leukemic subclones and leaving many cell functions intact including mechanism of apoptosis. AML in the older patients, however, may arise due to string of mutational events producing multiple leukemic subclones giving rise to chemoresistance. Patients with pre-existing myelodysplastic or myeloproliferative disorders (i.e., secondary AML) have higher probability of harboring poor cytogenetics, which translates to poor survival. Also, the presence of secondary AML type mutations, commonly observed in older patients, is associated with poor chances of achieving remission and long-term disease control [6].

Overall care of older patients with AML may improve with refined risk-stratification and personalized therapy based on the principles of geriatric medicine. For example, careful assessment of comorbid conditions is vital in older patients. Comprehensive geriatric assessment is also valuable in determining tolerance to various intensities of chemotherapy. Geriatric assessment evaluates multiple health domains including comorbidities, polypharmacy, cognitive, nutritional, psychological, functional and social status, and can predict tolerance of chemotherapy better than chronological age and performance status alone [7–9]. A multidisciplinary leukemia care team may perform a comprehensive geriatric assessment to identify and address cognitive impairment, depression and various geriatric syndromes. Physical, psychological and neurocognitive prehabilitation may improve quality of life, chemotherapy tolerance and mortality. It should be stressed that such assessment should be done on an ongoing basis as clinical conditions could change over time.

Patients with intermediate or high-risk cytogenetics have a poor median and long-term survival with chemotherapy alone. In fit patients with higher risk disease, treatment approach should allow patients to proceed to an allogeneic hematopoietic cell transplant [10]. This is important since the probability of long-term disease control is higher with transplant. However, for various reasons, the utilization of transplant is poor in real world [11,12]. For patients with favorable cytogenetics, complete remission may be achieved in up to 80% patients with chemotherapy alone and survival is much higher than other risk groups [13,14]. Consequently, these patients are generally treated with chemotherapy alone. In many patients, even if transplant or cure is not possible, goal should be to achieve a complete remission, which extends survival, improves quality of life, decreases hospitalization and reduces need for transfusions [15,16]. For some patients, poor functional status and multiple comorbidities may preclude the use of chemotherapy, and in such cases, supportive care or comfort care may be appropriate. Integrating palliative care team as part of advance care planning early in the disease process is desirable in most patients.

Intensive chemotherapy is frequently utilized to achieve remission, however, less intensive therapy such as decitabine or azacitidine are equally valuable. In a retrospective study from MD Anderson Cancer Center, hypomethylating agent achieved survival comparable to that achieved with intensive chemotherapy [17]. This has also been demonstrated in an international Phase III trial among older patients aged ≥ 65 years. In this study, azacitidine resulted in similar outcomes to conventional care regimens (intensive chemotherapy, low-dose cytarabine or best supportive care), as well as to intensive chemotherapy in a subset analysis [18]. The results are in part related to poor tolerance and increased toxicities with intensive chemotherapy.

Given poor survival with currently available therapies, drug development is important in this field. Older adults may benefit from low-intensity therapy options. The role of agents such as hypomethylating agents (decitabine, or azacitidine), and gemtuzumab ozogamicin are well established. 10-day decitabine has shown good results, especially in patients with complex cytogenetics and TP53 mutation [19–21]. Guadecitabine, which is a novel second generation hypomethylating agent is associated with an overall response rate of 57% and median overall survival of 10 months in patients unfit for intensive therapy [22]. A number of other novel drugs and targeted agents such as vasaroxin (a quinolone derivative), CPX351 (liposomal formulation of cytarabine and daunorubicin), volasertib (selective inhibitor of Plk1, Plk2 and Plk3), tyrosine kinase or FLT3 ITD inhibitors, IDH 1/2 inhibitors and antibody–drug conjugate such as vadastuximab talirine are in development. Some of these agents have already shown preliminary evidence of efficacy. Given poor outcomes with cytotoxic chemotherapy alone, participation in the clinical trials should be strongly encouraged to improve the outcomes of older patients with AML.

Financial & competing interests disclosure

This work was supported in part by 2016–2017 Physician-Scientist Training Program Grant to VR Bhatt from the College of Medicine, University of Nebraska Medical Center. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

- 1 Bhatt VR, Shostrom V, Giri S *et al.* Early mortality and overall survival of acute myeloid leukemia based on facility type. *Am. J. Hematol.* 92(8), 764–771 (2017).
- 2 Upadhyay S, Dahal S, Khanal N, Bhatt VR, Silberstein PT. Chemotherapy in elderly patients with acute myeloid leukemia (AML): analysis of socioeconomic factors using National Cancer Data Base (NCDB). *Blood* 124(21), 5267 (2014).
- 3 Shah A, Andersson TM, Racher B, Bjorkholm M, Lambert PC. Survival and cure of acute myeloid leukaemia in England, 1971–2006: a population-based study. *Br. J. Haematol.* 162(4), 509–516 (2013).
- 4 Appelbaum FR, Gundacker H, Head DR *et al.* Age and acute myeloid leukemia. *Blood* 107(9), 3481–3485 (2006).
- 5 Etienne A, Esterni B, Charbonnier A *et al.* Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. *Cancer* 109(7), 1376–1383 (2007).
- 6 Lindsley RC, Mar BG, Mazzola E *et al.* Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood* 125(9), 1367–1376 (2015).
- 7 Muffy LS, Kocherginsky M, Stock W *et al.* Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. *Haematologica* 99(8), 1373–1379 (2014).
- 8 Tawfik B, Pardee TS, Isom S *et al.* Comorbidity, age and mortality among adults treated intensively for acute myeloid leukemia (AML). *J. Geriatr. Oncol.* 7(1), 24–31 (2016).

- 9 Klepin HD, Geiger AM, Tooze JA *et al*. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood* 121(21), 4287–4294 (2013).
- 10 Goyal G, Gundabolu K, Vallabhajosyula S, Silberstein PT, Bhatt VR. Reduced-intensity conditioning allogeneic hematopoietic-cell transplantation for older patients with acute myeloid leukemia. *Ther. Adv. Hematol.* 7(3), 131–141 (2016).
- 11 Meyers J, Yu Y, Kaye JA, Davis KL. Medicare fee-for-service enrollees with primary acute myeloid leukemia: an analysis of treatment patterns, survival, and healthcare resource utilization and costs. *Appl. Health Econ. Health Policy* 11(3), 275–286 (2013).
- 12 Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica* 97(12), 1916–1924 (2012).
- 13 Gardin C, Chevret S, Pautas C *et al*. 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.* 31(3), 321–327 (2013).
- 14 Lowenberg B, Ossenkoppele GJ, Van Putten W *et al*. High-dose daunorubicin in older patients with acute myeloid leukemia. *N. Engl. J. Med.* 361(13), 1235–1248 (2009).
- 15 Juliusson G, Antunovic P, Derolf A *et al*. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood* 113(18), 4179–4187 (2009).
- 16 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. *J. Clin. Oncol.* 7(9), 1268–1274 (1989).
- 17 Quintas-Cardama A, Ravandi F, Liu-Dumlao T *et al*. Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia. *Blood* 120(24), 4840–4845 (2012).
- 18 Dombret H, Seymour JF, Butrym A *et al*. International Phase III study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* 126(3), 291–299 (2015).
- 19 Blum W, Garzon R, Klisovic RB *et al*. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc. Natl Acad. Sci. USA* 107(16), 7473–7478 (2010).
- 20 Blum W, Klisovic RB, Hackanson B *et al*. Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia. *J. Clin. Oncol.* 25(25), 3884–3891 (2007).
- 21 Ritchie EK, Feldman EJ, Christos PJ *et al*. Decitabine in patients with newly diagnosed and relapsed acute myeloid leukemia. *Leuk. Lymphoma* 54(9), 2003–2007 (2013).
- 22 Stein EM, Tallman MS. Emerging therapeutic drugs for AML. *Blood* 127(1), 71–78 (2016).