

## POINT Better the cure you know: why patients with AML $\geq 60$ years of age should be offered early allogeneic stem cell transplantation

Siok-Keen Tey,<sup>1-3</sup> and Steven W. Lane<sup>1-3</sup>

<sup>1</sup>Division of Cancer Care Services, Royal Brisbane and Women's Hospital, <sup>2</sup>Cancer Program, QIMR Berghofer MRI, and <sup>3</sup>University of Queensland Medical School, Herston, Brisbane, Australia

*This article has a companion Counterpoint by Deeg.*

### Introduction

Acute myeloid leukemia (AML) is a disease predominantly affecting older patients. AML has a median age at diagnosis of 69 years with poor long-term survival rates in patients  $>60$  years.<sup>1</sup> After many decades of incremental gains, predominantly through improvements in supportive care and chemotherapy permutations, there have recently been a number of major breakthroughs leading to improved survival in older patients, specifically, venetoclax combinations,<sup>2,3</sup> liposomal chemotherapy compounds,<sup>4</sup> novel targeted inhibitors,<sup>5</sup> and maintenance therapy.<sup>6</sup> However, these novel agents with high short-term response rates and improved overall survival have not yet delivered on durable long-term, treatment-free survival (ie, cure). Patients who have relapsed or refractory disease have poor outcomes, which has not improved significantly over time,<sup>7</sup> and salvage with novel agents typically yielded median survival of  $<6$  months.<sup>8-10</sup> Concurrently, gains have been achieved in allogeneic hematopoietic stem cell transplantation (allo-HSCT) outcomes and applicability through improved supportive care and changes in the transplant approach, including the use of reduced-intensity conditioning and alternative donors.<sup>11</sup> These have broadened the application of allo-HSCT at many large transplant centers to include patients up to 75 years of age.<sup>12,13</sup> Older patients at highest risk of adverse transplant outcome are also at highest risk of disease progression and death from AML in the absence of allo-HSCT.<sup>14</sup> Early referral for consideration of allo-HSCT remains essential to identify those patients who will benefit from transplantation in first remission, and to leverage the favorable short-term responses and tolerability of novel treatment algorithms into long-term cure.

### Limitations of risk prediction and novel agents in older patients with AML

AML is a highly heterogeneous disease, and prognosis after chemotherapy treatment can be divided into favorable, intermediate, and adverse based on cytogenetic and molecular classifications, such as the European Leukemia Network 2017 (ELN2017) consensus statement.<sup>15</sup> The ELN2017 prognostic tool performed extremely well in patients aged 18 to 60, reflecting the usual cohorts found in large clinical trials,<sup>16</sup> but was unable to reliably identify patients  $>60$  years old who would have long-term survival after chemotherapy, even in so-called favorable risk cohorts.<sup>17</sup> In particular, patients  $>60$  years old with mutations in NPM1 alone, or in combination with low allelic ratio FLT3<sup>ITD</sup> mutations, had poor outcomes with median survival  $\sim 2$  years.<sup>17</sup> Older patients have enrichment for adverse karyotypic/molecular profiles, which portends even poorer prognosis motivating calls for dynamic tools incorporating clinical, genetic, and therapeutic factors to stratify risk.<sup>18</sup> These poor outcomes have motivated the clinical development of novel agents in older patients with AML. So far, these treatments have inherent limitations, as they need to be ongoing and do not show a plateau in long-term survival representing "cure." CPX351 is a novel liposomal combination of daunorubicin and cytarabine, which improved response rate and overall survival in patients aged 60 to 75 years old compared with standard 7 + 3 induction chemotherapy. Despite this, the median duration of remission was similar between groups (6 to 7 months). Venetoclax, a novel BCL2-inhibitor, has shown efficacy in older patients with AML combined with azacitidine<sup>2</sup> or cytarabine.<sup>3</sup> In phase 3 trials, venetoclax combinations were able to induce response rates of 50% to 70% and improved overall survival, but it is unclear whether a plateau in long-term survival will be seen. Moreover, patients need to remain on treatment indefinitely. Maintenance oral azacitidine (CC486) has been used to prevent AML relapse after induction chemotherapy for older patients. Again, this approach was able to improve survival compared with placebo, but there was no plateau with median relapse-free survival extended from 4.8 months in placebo to 10.2 months with CC486.<sup>6</sup> Targeted small molecules such as FLT3 inhibitors have substantial efficacy in older patients with AML and improve survival in patients with relapsed or refractory disease. However, FLT3 inhibitors also do not result in long-term

survival in older patients.<sup>5,19</sup> In aggregate, these novel agents show striking efficacy and short-term responses in older patients with AML; however, they do not routinely lead to cure.

### Evidence for allo-HSCT in older patients with AML

Allo-HSCT remains the most effective postremission therapy for intermediate- and high-risk AML. Retrospective analyses have shown that this holds true for older patients, and the National Comprehensive Cancer Network guidelines state that reduced-intensity allo-HSCT is a feasible option in older patients age  $\geq 60$  years, particularly those in complete response (CR) with minimal comorbidities.<sup>20</sup> In a large multicenter study comparing outcomes for older patients with AML (age 60 to 77 years) receiving allo-HSCT with those treated with chemotherapy consolidation, allo-HSCT was associated with superior long-term overall survival (OS; 29% vs 13.8% at 5 years).<sup>21</sup> In the CIBMTR study of patients aged 60 to 70 years, including only those who maintained first remission for at least 4 months to account for transplant bias, reduced-intensity allo-HSCT was associated with superior 3-year leukemia-free survival compared with postremission chemotherapy (32% vs 15%).<sup>22</sup> Similar benefits were observed in big data analysis from the Surveillance, Epidemiology, and End Results–Medicare database.<sup>23</sup> The CALGB also examined 114 patients between the ages of 60 and 74 with reduced-intensity conditioning allo-HSCT for AML in first complete remission, and 2-year OS was 48%.<sup>24</sup> This was similar to data from an EBMT AML working group analysis that showed 2-year OS of 50% in 50- to 69-year-olds and 38% in  $\geq 70$ -year-olds.<sup>25</sup> A post hoc analysis performed by the AML 2004 East German AML study group also suggested improved survival for allo-HSCT compared with consolidation chemotherapy.<sup>26</sup> Consequently, transplantation in  $>60$ -year-olds is routine in most institutions, including in the  $>70$ -years age group,<sup>12,27</sup> with progressive improvements in outcomes over time.<sup>27</sup> Judicious patient selection that balances treatment-related toxicity or mortality, with the beneficial immunological effect that reduces relapse, remains the holy grail in allo-HSCT. Age is a risk factor for both nonrelapse mortality (NRM) and disease relapse after allo-HSCT. However, the factors governing these risks are becoming much better understood as are the ways to mitigate them. Age as an independent risk factor for NRM exists in a continuum from the age of 20,<sup>28</sup> without a clear point at which the risk accelerates. Its effect has been approximated to an additional score of 1 to the hematopoietic cell transplantation comorbidity index for all adults aged  $\geq 40$  years.<sup>28</sup> Beyond 40 years, increasing age to 65 years and beyond has only a modest impact on NRM and other transplant-related outcome for AML and myelodysplastic syndrome.<sup>29</sup> The utility of geriatric assessment and the effectiveness of intervention are being actively studied (BMT CTN 1704; clinicaltrials.gov NCT03992352).<sup>30</sup> Interestingly, a recent multi-institutional retrospective study showed that cognitive performance was predictive of NRM,<sup>31</sup> although this will need to be prospectively confirmed. These studies will refine our understanding of which age-associated functional changes should and should not be considered barriers to transplantation.

### Toward deeper remission, less intense conditioning, and reduced posttransplant relapse

Although age in itself is not an independent risk factor for posttransplant relapse, the intensity of transplant conditioning matters,<sup>32,33</sup> and older patients are less likely to tolerate intensive conditioning. Important advances have been made in the use of reduced-intensity and nonmyeloablative conditioning (NMA) and selection based on

disease risk, including minimal residual disease (MRD) status. NMA conditioning with fludarabine plus 2 Gy total body irradiation is well tolerated and can cure  $\sim 35\%$  to 40% of older patients with favorable or intermediate-risk cytogenetics who are in morphological remission.<sup>29,34</sup> NMA haploidentical transplantation with posttransplant cyclophosphamide is well tolerated even among patients  $>60$  years with reported NRM of  $<10\%$  and OS of 38% at 3 years.<sup>35</sup> Newer conditioning approaches, such as fludarabine plus treosulfan<sup>36</sup> and CD45-targeted radiotherapy,<sup>37</sup> have shown promising results and present further opportunity to improve outcome.

The impact of transplant conditioning on relapse risk is greatest in patients who are not in remission or have detectable MRD. Patients without detectable MRD by next-generation sequencing have equivalent transplant outcomes following myeloablative or reduced-intensity conditioning, with counterbalancing effects on relapse and NRM, leading to similar overall survival.<sup>32</sup> Achieving a MRD<sup>-</sup> state prior to allo-HSCT predicts excellent long-term outcomes,<sup>38</sup> for example, patients who had undetectable NPM1 mutation prior to allo-HSCT had OS 83% vs 45% for those who were MRD<sup>+</sup>.<sup>32</sup> The potential for newer agents to deliver deeper remission thus present the opportunity to consolidate these gains with allo-HSCT. In the phase 3 CPX-351 study, there was a trend toward higher allo-HSCT rate in older patients achieving CR after treatment with CPX-351 compared with conventional 7 + 3 induction, and their posttransplant outcomes were better with median OS not reached at 2 years.<sup>4,39</sup> This was largely driven by large improvement in NRM, suggesting better tolerability of subsequent allo-HSCT.<sup>40</sup> Although MRD data were not prospectively collected in this study, “real-world” data have shown that CPX-351 could eradicate MRD and help facilitate allo-HSCT, with significantly longer OS in transplanted patients (median not reached vs 9.3 months).<sup>41</sup> Similarly, venetoclax combinations have a striking ability to deliver deep, MRD<sup>-</sup> remissions in NPM1<sup>mutant</sup> AML while also delivering less treatment-related toxicity, an ideal pretransplant regimen.<sup>42</sup> Beyond remission induction, the field is now moving rapidly toward defining the role of posttransplant relapse-prevention strategies with FLT3 inhibitors and small molecules, and also hypomethylating agents and immunotherapeutic approaches.<sup>43-45</sup>

### Conclusion

We are entering an exciting new phase in AML therapy. Rather than sounding the death knell of allo-HSCT, the emerging access to a raft of highly active agents to induce deep molecular remissions with reduced toxicity will facilitate greater access of older patients to curative allo-HSCT. Prospective studies will be required to test the outcomes of allo-HSCT after novel low-intensity approaches vs standard induction chemotherapy. Age increases the likelihood of adverse disease biology and transplant-related complications; however, these therapeutic developments, coupled by the broader availability of molecular MRD monitoring both before and after transplantation, can be leveraged to further improve transplant outcome by informing patient selection, choice of conditioning, and posttransplant optimization of graft-versus-leukemia effect. We anticipate that older patients are the most likely to benefit, and it may be that improved upfront therapy will drive broader access to allo-HSCT and improve long-term survival for patients  $>60$ -years-old with AML.

## Acknowledgments

The authors thank David Curtis and David Ritchie for providing helpful comments and reviewing the manuscript.

This work was supported by an Australian National Health and Medical Research (NHMRC) Centre for Research Excellence Grant (GTN 1135107).

## Authorship

Contribution: S.-K.T. and S.W.L. wrote and reviewed the paper.

## References

1. Oran B, Weisdorf DJ. Survival for older patients with acute myeloid leukemia: a population-based study. *Haematologica*. 2012;97(12):1916-1924.
2. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med*. 2020;383(7):617-629.
3. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. *Blood*. 2020;135(24):2137-2145.
4. Lancet JE, Uy GL, Cortes JE, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. *J Clin Oncol*. 2018;36(26):2684-2692.
5. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. *N Engl J Med*. 2019;381(18):1728-1740.
6. Wei AH, Döhner H, Pocock C, et al; QUAZAR AML-001 Trial Investigators. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. *N Engl J Med*. 2020;383(26):2526-2537.
7. Ganzel C, Sun Z, Cripe LD, et al. Very poor long-term survival in past and more recent studies for relapsed AML patients: The ECOG-ACRIN experience. *Am J Hematol*. 2018;93(8):1074-1081.
8. DiNardo CD, Rausch CR, Benton C, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. *Am J Hematol*. 2018;93(3):401-407.
9. Gaut D, Burkenroad A, Duong T, Feammelli J, Sasine J, Schiller G. Venetoclax combination therapy in relapsed/refractory acute myeloid leukemia: a single institution experience. *Leuk Res*. 2020;90:106314.
10. Tenold ME, Moskoff BN, Benjamin DJ, et al. Outcomes of adults with relapsed/refractory acute myeloid leukemia treated with venetoclax plus hypomethylating agents at a comprehensive cancer center. *Front Oncol*. 2021;11:649209.
11. Cornelissen JJ, Blaise D. Hematopoietic stem cell transplantation for patients with AML in first complete remission. *Blood*. 2016;127(1):62-70.
12. Phelan R, Arora M, Chen M. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2020.
13. Rashidi A, Ebadi M, Colditz GA, DiPersio JF. Outcomes of allogeneic stem cell transplantation in elderly patients with acute myeloid leukemia: a systematic review and meta-analysis. *Biol Blood Marrow Transplant*. 2016;22(4):651-657.
14. Cornelissen JJ, Gratwohl A, Schlenk RF, et al. The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach. *Nat Rev Clin Oncol*. 2012;9(10):579-590.
15. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
16. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-464.
17. Straube J, Ling VY, Hill GR, Lane SW. The impact of age, NPM1<sup>mut</sup>, and FLT3<sup>ITD</sup> allelic ratio in patients with acute myeloid leukemia. *Blood*. 2018;131(10):1148-1153.
18. Short NJ, Tallman MS, Pollyea DA, Ravandi F, Kantarjian H. Optimizing risk stratification in acute myeloid leukemia: dynamic models for a dynamic therapeutic landscape. *J Clin Oncol*. 2021;39(23):2535-2538.
19. Schlenk RF, Weber D, Fiedler W, et al; German-Austrian AML Study Group. Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD. *Blood*. 2019;133(8):840-851.
20. Tallman MS, Wang ES, Altman JK, et al; OCN. Acute myeloid leukemia, version 3.2019, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2019;17(6):721-749.
21. Ustun C, Le-Rademacher J, Wang H-L, et al. Allogeneic hematopoietic cell transplantation compared to chemotherapy consolidation in older acute myeloid leukemia (AML) patients 60-75 years in first complete remission (CR1): an alliance (A151509), SWOG, ECOG-ACRIN, and CIBMTR study. *Leukemia*. 2019;33(11):2599-2609.
22. Farag SS, Maharry K, Zhang MJ, et al; Acute Leukemia Committee of the Center for International Blood and Marrow Transplant Research and Cancer and Leukemia Group B. Comparison of reduced-intensity hematopoietic cell transplantation with chemotherapy in patients age 60-70 years with acute myelogenous leukemia in first remission. *Biol Blood Marrow Transplant*. 2011;17(12):1796-1803.
23. Medeiros BC, Satram-Hoang S, Hurst D, Hoang KQ, Momin F, Reyes C. Big data analysis of treatment patterns and outcomes among elderly acute myeloid leukemia patients in the United States. *Ann Hematol*. 2015;94(7):1127-1138.
24. Devine SM, Owzar K, Blum W, et al. Phase II study of allogeneic transplantation for older patients with acute myeloid leukemia in first complete remission using a reduced-intensity conditioning regimen: results from Cancer and Leukemia Group B 100103 (Alliance for Clinical Trials in Oncology)/Blood and Marrow Transplant Clinical Trial Network 0502. *J Clin Oncol*. 2015;33(35):4167-4175.
25. Ringdén O, Boumendil A, Labopin M, et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients age >69 years with acute myelogenous leukemia: on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow

- Transplantation. *Biol Blood Marrow Transplant*. 2019;25(10):1975-1983.
26. Niederwieser D, Al-Ali HK, Krahl R, et al. Hematopoietic stem cell transplantation (HSCT) compared to consolidation chemotherapy (CT) to increase leukemia free survival (LFS) in acute myelogenous leukemia (AML) patients between 60 and 75 years irrespective of genetic risk: report from the AML 2004 of the East German Study Group (OSHO). *J Clin Oncol*. 2016;34(15 suppl):e18501-e18501.
  27. Muffy L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. *Blood*. 2017;130(9):1156-1164.
  28. Sorror ML, Storb RF, Sandmaier BM, et al. Comorbidity-age index: a clinical measure of biologic age before allogeneic hematopoietic cell transplantation. *J Clin Oncol*. 2014;32(29):3249-3256.
  29. McClune BL, Weisdorf DJ, Pedersen TL, et al. 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;28(11):1878-1887.
  30. Muffy LS, Kocherginsky M, Stock W, et al. Geriatric assessment to predict survival in older allogeneic hematopoietic cell transplantation recipients. *Haematologica*. 2014;99(8):1373-1379.
  31. Olin RL, Fretham C, Pasquini MC, et al. Geriatric assessment in older alloHCT recipients: association of functional and cognitive impairment with outcomes. *Blood Adv*. 2020;4(12):2810-2820.
  32. Hourigan CS, Dillon LW, Gui G, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. *J Clin Oncol*. 2020;38(12):1273-1283.
  33. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol*. 2017;35(11):1154-1161.
  34. Gyurkocza B, Storb R, Storer BE, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia. *J Clin Oncol*. 2010;28(17):2859-2867.
  35. Kasamon YL, Bolaños-Meade J, Prince GT, et al. Outcomes of nonmyeloablative HLA-haploidentical blood or marrow transplantation with high-dose post-transplantation cyclophosphamide in older adults. *J Clin Oncol*. 2015;33(28):3152-3161.
  36. Beelen DW, Trensche R, Stelljes M, et al. Treosulfan or busulfan plus fludarabine as conditioning treatment before allogeneic haemopoietic stem cell transplantation for older patients with acute myeloid leukaemia or myelodysplastic syndrome (MC-FludT.14/L): a randomised, non-inferiority, phase 3 trial. *Lancet Haematol*. 2020;7(1):e28-e39.
  37. Vo P, Gooley TA, Rajendran JG, et al. Yttrium-90-labeled anti-CD45 antibody followed by a reduced-intensity hematopoietic cell transplantation for patients with relapsed/refractory leukemia or myelodysplasia. *Haematologica*. 2020;105(6):1731-1737.
  38. Buckley SA, Wood BL, Othus M, et al. Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis. *Haematologica*. 2017;102(5):865-873.
  39. Lin TL, Rizzieri DA, Ryan DH, et al. Older adults with newly diagnosed high-risk/secondary AML who achieved remission with CPX-351: phase 3 post hoc analyses. *Blood Adv*. 2021;5(6):1719-1728.
  40. Uy GL, Newell LF, Lin T, et al. Long-term outcomes of allogeneic hematopoietic cell transplantation in patients enrolled in CPX-351-301, a randomized phase 3 study of CPX-351 versus 7 + 3 in older adults with newly diagnosed, high-risk and/or secondary AML [abstract]. *Blood*. 2020;136(suppl 1). Abstract 44-45.
  41. Chiche E, Rahmé R, Bertoli S, et al. Real-life experience with CPX-351 and impact on the outcome of high-risk AML patients: a multicentric French cohort. *Blood Adv*. 2021;5(1):176-184.
  42. Tiong IS, Dillon R, Ivey A, et al. Venetoclax induces rapid elimination of NPM1 mutant measurable residual disease in combination with low-intensity chemotherapy in acute myeloid leukaemia. *Br J Haematol*. 2021;192(6):1026-1030.
  43. Loke J, Malladi R, Moss P, Craddock C. The role of allogeneic stem cell transplantation in the management of acute myeloid leukaemia: a triumph of hope and experience. *Br J Haematol*. 2020;188(1):129-146.
  44. Scott BL. Allogeneic stem cell transplantation for high-risk acute leukemia and maintenance therapy: no time to waste. *Blood Adv*. 2020;4(13):3200-3204.
  45. Soiffer RJ. Maintenance therapy for high-risk acute leukemia after allogeneic hematopoietic cell transplantation: wait a minute. *Blood Adv*. 2020;4(13):3205-3208.

DOI 10.1182/bloodadvances.2021004829

© 2022 by The American Society of Hematology. Licensed under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0), permitting only noncommercial, nonderivative use with attribution. All other rights reserved.