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The Bottom Line

Allogeneic Transplantation for Older Patients with Acute Myeloid Leukemia: The Dawn of a New Era

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Outcomes among older patients with acute myeloid leukemia (AML) remain dismal over the last few decades based on many registry-based studies, largely due to the general higher disease risk, co-existing medical comorbidities, compromised performance status, and the inability to deliver curative intent, allogeneic hematopoietic cell transplantation (alloHCT) to the majority of these patients [1]. AlloHCT is effective in curing selected older patients with AML who can achieve disease remission as compared to non-HCT therapies [2–4], yet chronologic age alone, "ageism", has been consistently found to be the most common barrier for referring older patients with advanced hematologic malignancies for consideration of alloHCT [5].

There is light at the end of the tunnel, however. In this issue of the journal, Mau L et al. used Medicare claims data to examine trends and factors associated with alloHCT utilization among Medicare beneficiaries with AML and estimated unmet need for alloHCT in the modern era (2010-2016). They found that alloHCT utilization rate had increased gradually over time among Medicare beneficiaries with AML, culminating in 15.8% within 6 months and 20% within 1 year of AML diagnosis. The lower likelihood of receiving alloHCT within 1 year of AML diagnosis was associated with earlier year of diagnosis, older age, non-white race, certain geographic regions, higher comorbidity burden, and lower household income. Moreover, using either the claims data approach or the NMDP (National Marrow Donor Program) methodology, the authors estimated that there was 43-44% of unmet need among AML patients who could benefit from alloHCT, albeit with a downward trend over time.

How do we account for these improvements, and can we expect the trend to continue? There are many reasons to be optimistic. First, we are in an era of unprecedented, rapidly expanding treatments for AML, many of them specifically targeting the older patient population. Since the approval of hypomethylating agents in the early 2000s as the low intensity AML treatment and after the study period described in this manuscript, we have witnessed a period of breakthrough drug approvals for AML including B-cell lymphoma 2 (Bcl-2) inhibitor, venetoclax; two FMS like tyrosine kinase 3 (FLT-3) inhibitors, midostaurin and gilteritinib; two isocitrate dehydrogenase (IDH) inhibitors, ivosidenib (IDH1 inhibitor) and enasidenib (IDH2 inhibitor); the anti-CD33 antibody-drug conjugate, gemtuzumab ozogamicin; the oral hypomethylating agent azacytidine Onureg (as maintenance treatment); the liposomal formulation of cytarabine and daunorubicin, Vyxeos; and the hedgehog signaling pathway inhibitor, glasdegib [6]. While these new agents are not considered curative treatment, they are generally better tolerated than traditional intensive induction therapies such as "7+3", and generally more effective when combined than traditional low intensity, single hypomethylating agent. Perceivably, these drugs could improve upon the meager 30-40% complete remission rate following initial treatment we see with older AML patients, and perhaps more promisingly, safer bridging therapy to curative alloHCT [7,8].

In parallel to this improvement in AML therapeutics, we are also learning to select more appropriate older patients and take better care of them during the intensive treatment phase using geriatric assessment (GA)- based strategies [9]. GA is a multidimensional, multidisciplinary, comprehensive, and holistic assessment to evaluate an older person's functional and cognitive ability, physical mobility, mental health, and socioenvironmental circumstances, and to design optimization strategies, both of which are now increasingly utilized for peri-transplant evaluation and management of older patients with hematologic malaignancies [10]. Several common geriatric deficits including functional impairment, cognitive impairment, and polypharmacy have been shown to be associated with alloHCT outcomes including survival and treatment-related toxicities [11]. Moreover, a GA-guided, outpatient clinic-based, multidisciplinary pre-transplant optimization program for older patients has been shown to effectively reduce transplant-related mortality and improve survival in a pre- and post-study design [12]. Despite these advances, however, many barriers exist to fully integrate GA into transplant practice including physician perception, time, staffing, and knowledge base [13].

Finally, and perhaps most importantly, we are also seeing significant improvements in alloHCT outcomes in recent years [14,15], especially for older patients [16]. These improvements could be attributed to the development of reduced-intensity

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and non-myeloablative conditioning regimens [17,18], advances in supportive care such as newer anti-microbials, better prophylaxis and treatment of graft-versus-host disease, and more recently, increased donor choices across the HLA barrier [19]. Specifically for older patients, the recent development of treosulfan-based conditioning regimen with reduced toxicity and improved anti-leukemia activity, as well as potential antibody-based conditioning strategies may further improve tolerability of alloHCT for older patients [20,21]. Lastly, the role of maintenance therapy post-alloHCT may be of heightened importance in older patients, given the generally higher disease risk and lower intensity of conditioning even with positive measurable residual disease (MRD+) remission status prior to alloHCT [22,23].

With these advances, we are seeing the dawn of a new era for older AML patients with improved ability to effectively bring them to the curative intent alloHCT and take them through the intensive alloHCT procedure. Despite these advances, however, many barriers identified in this manuscript and others will continue to exist. We must leverage these AML treatment advances to educate clinicians, patients, and caregivers on selecting appropriate induction regimen, integrating GA across the treatment continuum, and making early alloHCT referrals to maximize their chance for cure. Clinicians, professional societies, and policy makers should also have keen awareness to these social economical barriers and to develop systemic changes to address them to improve patient outcomes.

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