Best Practice & Research Clinical Haematology 32 (2019) 101110

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

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

What have we learned from transplanting older patients?☆

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ARTICLE INFO

Keywords:
Acute myeloid leukemia
Reduced intensity conditioning
Haploidentical
Umbilical cord blood
Transplant related mortality
Older patient

ABSTRACT

Aggressive curative therapies have now been extended to patients older than 65 years, a fast-growing segment of the population. As the number of allogeneic transplants in patients older than age 65 is increasing, attention is now focused on improving outcomes in this group. This paper discusses important aspects of allogeneic transplant in the older patient, focusing on donor and patient selection, choice of conditioning regimen and graft source, and the importance of timely access to a transplant center.

Introduction

At the turn of the 21st century, 13% of the American population was represented by people older than 65 years of age. The birth rate grew in the 1950s during the post-World War II "baby boom." Therefore, the population over age 65 in the US is expected to increase to 20% by 2050, with an estimated population of around 70 million [1–4]. Similar demographic changes are seen in other economically developed countries. These demographic shifts create an increased incidence of diseases that are more common in the elderly population. Increasing age is an important risk factor for cancer, including leukemia. Approximately 60% of newly diagnosed cancer patients are aged over 65, and 70% of cancer deaths are in patients over age 65 [3,5]. With improved longevity, there is an increased interest in extending aggressive curative therapies including allogeneic stem cell transplantation. In this paper, we discuss the trends in allogeneic transplantation, factors that affect outcomes, and challenges that are encountered in this population. Finally, we discuss what we have learned that may help us care for future patients.

Trends in allogeneic transplantation for older patients with acute leukemia

Allogeneic hematopoietic cell transplantation (HCT) is a curative therapy for patients suffering from acute myeloid leukemia (AML). Patients over age 60 have a high risk of relapse after induction and consolidation chemotherapy, so these patients are prime candidates for HCT. The therapeutic effect is primarily achieved by the combination of conditioning chemotherapy or radiation and the graft-versus-leukemia effect [6]. Introduction of reduced intensity conditioning (RIC) regimens played a pivotal role in extending therapeutic efficacy of transplant to patients > 65 years. RIC is associated with lower treatment-related mortality (TRM) when compared to myeloablative conditioning regimens (MAC) [7–9]. High resolution HLA typing has led to comparable outcomes for matched unrelated and matched related donor transplants, thereby increasing the donor pool [10,11].

Acute myeloid leukemia remains the most common indication for an allogeneic transplant in adults. The number of allogeneic

☆ The views expressed in this article are that of the authors and do not reflect the position of the Center for International Blood and Marrow Transplant Research.

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https://doi.org/10.1016/j.beha.2019.101110

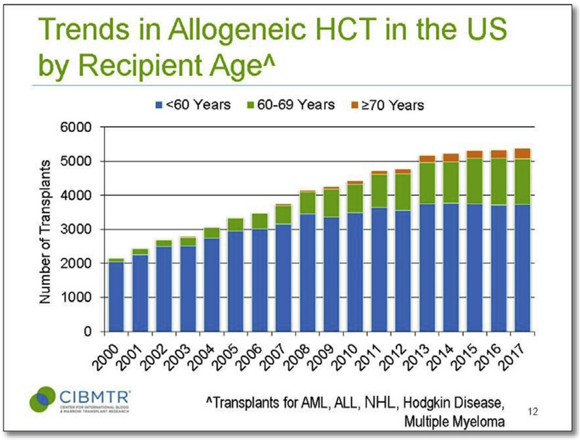

Fig. 1. Trends in allogeneic HCT in the US by recipient age [12].
The number of allogeneic transplants for malignant hematologic diseases continued to rise in patients older than 60 years between 2000 and 2017. In 2017, 31% of allogeneic transplant recipients were 60 years and older. The number of allogeneic transplants for malignant hematologic diseases continued to rise in patients older than 60 years between 2000 and 2017. In 2017, 31% of allogeneic transplant recipients were 60 years and older.

transplants for treatment of malignant diseases such as AML, acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), Hodgkin disease(HD), and multiple myeloma (MM) in patients older than 60 years continues to increase every year, as shown in Fig. 1. Data available from the Center for International Blood and Marrow Transplant Registry (CIBMTR) shows that the rate of HCT in this population has increased from 5% in 2000 to 31% in 2017. Rate of HCT in patients 70 years and older has also increased from 0.4% in 2000 to 6% in 2017 [12]. This is a paradigm shift considering that induction chemotherapy therapy was usually not offered to patients older than 60 years in the 1990s. Data obtained from the Swedish acute leukemia registry showed that patients up to 80 years of age benefited from induction therapy as compared to palliative care [13]. These results were also confirmed by retrospective analysis through the Surveillance Epidemiology and End Results (SEER) database, which showed that elderly patients, especially in the age group of 64–69 years and 70–74 years, had an increased overall survival after receiving induction therapy when compared to those receiving supportive care. The 2-year survival in patients in this database who received an allogeneic transplant was 50% and 30.5% respectively, in the above-mentioned age groups [14].

Muffly and colleagues recently summarized the CIBMTR experience for patients ages 70 and older receiving HCT. AML and myelodysplastic syndrome (MDS) are the most common indications for transplants in this group. One thousand one hundred six patients ages 70 and older have been transplanted in the time period from 2000 to 2013.The percentage of transplants occurring in this age group has increased from 0.1% in 2000 to 3.9% percent in 2013 [15].

Outcomes of allogeneic transplantation in older patients

Patients up to age 75 years with AML who achieve a remission after induction therapy and who have few comorbidities should be considered for HCT, as it may be the only curative option [16]. Retrospective comparison of outcomes between chemotherapy consolidation versus HCT in this age group show a superior long-term overall survival (OS) with HCT. Ustun et al. compared the outcomes between the 2 modalities in patients aged 60–75 years, with AML in first complete remission (CR1). Outcomes of patients who underwent chemotherapy consolidation in the Alliance, Eastern Cooperative Oncology Group (ECOG), and Southwest Oncology Group (SWOG) trials (N = 211) were compared to outcomes of patients receiving HCT (the data obtained from CIBMTR) during the time period from 2004 to 2013. As expected, HCT was associated with worse OS in the first 9 months (HR = 1.52, P = .02), due to higher toxicity. However, OS at 5 years was superior in the transplantation arm (29% vs 13.8%). These findings were attributed to a lower rate of relapse. Most importantly, age was not a predictor of poor outcome in the multivariate analysis [17]. Data from CIBMTR on outcomes of HCT in the older population show a steady improvement in 2-year OS over time, 26% (CI 29%–36%) in 2000–2007 to 39%(CI 35%–42%) in 2008–2013. In the modern era (2008–2013), multivariate analysis of OS showed that higher HCT comorbidity index ≥ 3 (HR 1.27, P = .006), umbilical cord graft (HR 1.97, P = .0002), and myeloablative conditioning (HR 1.61, P = .0002) were associated with increased mortality [15].

Factors influencing transplant outcomes

Choice of donors for transplant in the elderly

The trends of the different donor sources utilized for HCT, obtained from CIBMTR is depicted in Fig. 2 [12]. At present the unrelated donor transplant represents the largest group. The number of unrelated donor (URD) transplants has surpassed the number of HCT from matched related donors after 2006 and the gap between these two types of approaches peaked in 2012. After 2012, the

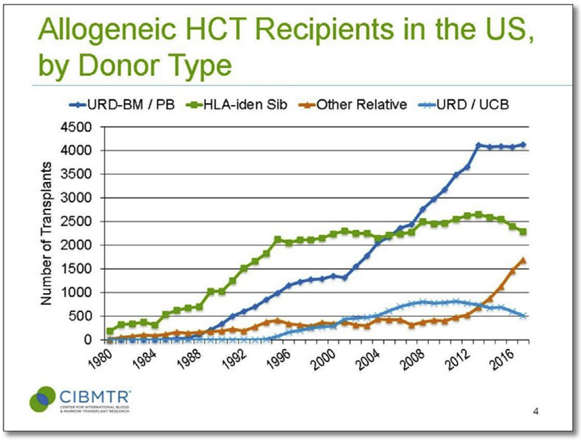

Fig. 2. Trends in utilization of available donor sources for transplantation [12].
Recipients of unrelated donor transplants represent the largest group of allogeneic transplant recipients in the United States. BM, bone marrow; iden Sib, identical sibling; PB, peripheral blood; UCB, umbilical cord blood; URD, unrelated donor.

numbers of URD and HLA-identical sibling transplants has shown a downward trend in absolute numbers. HCT performed with alternative donors are increasing. From 2003 to 2011, there was a steady increase in the numbers of HCT using umbilical cord blood as a result of several published studies demonstrating its benefit in both children and adults [18–21]. From 2012 onward, there was an increase in the numbers of transplants from 'Other Relatives, representing haploidentical transplant.' In 2014, the numbers of transplants using 'Other Relatives' surpassed the total numbers of umbilical cord transplants performed in the US, accounting for 11% of all allogeneic transplants performed in the US. In 2017, this is the only group of donor type that is increasing with all other donor types showing decline or stability in use [12]. Cord blood transplants continue to play an important role in the non-Caucasian population. Data from the National Marrow Donor Program (NMDP) show that cord blood is an important graft source in an ethnically diverse society. In 2017, umbilical cord blood transplants represented 29% of unrelated transplants facilitated by NMDP for Black/African Americans. Umbilical cord blood transplants represented 9% of unrelated transplants facilitated by NMDP for Caucasian patients (Fig. 3) [22].

The success of post-transplant cyclophosphamide in haploidentical transplantation has led to the creation of a younger, alternate donor pool that can be collected within 2–3 weeks. Patients in their 70s often have siblings who may not be ideal donors; however, their children are likely to be healthier donors, providing a higher cell dose and ease of availability. A retrospective single institution study showed a lower OS in patients over 65 years with haploidentical transplants when compared to patients aged younger than 65 years. However, there was no difference in OS between matched unrelated donor (MUD) and haploidentical transplants in the elderly

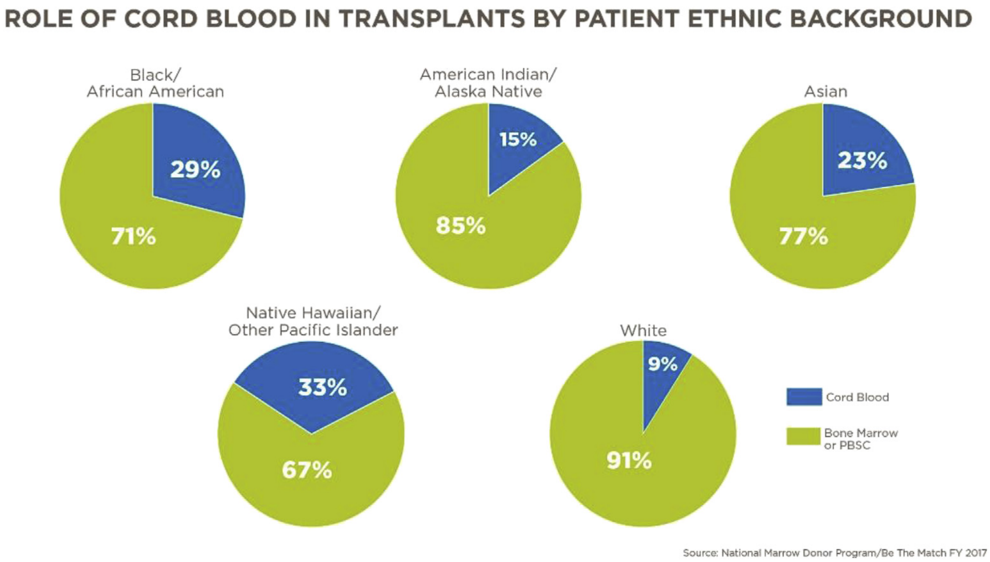

Fig. 3. Use of umbilical cord blood by race/ethnicity [22].
Data from the National Marrow Donor Program (NMDP) show that cord blood is an important graft source in an ethnically diverse society.

population after Disease Risk Index (DRI) and age matching [23]. Analysis from the European Bone Marrow Transplant (EBMT) group also shows comparable outcomes between MUD and haploidentical transplants, reporting OS of 39% at 2 years [24]. Relapse continues to be the main contributing factor to treatment failure. Older age, poor performance status and advanced disease were also associated with poor overall survival.

Conditioning regimens

There have been multiple retrospective studies that have compared RIC versus MAC for HCT. These studies have predominantly shown higher relapse rates with RIC regimens, but higher treatment-related mortality with MAC regimens, thereby resulting in similar OS with both regimens [25–31]. Randomized prospective trials have, however, yielded mixed results. Total body irradiation (TBI)- based MAC(12 Gy and cyclophosphamide) and RIC (8 Gy and fludarabine) regimens showed no difference in progression-free survival (PFS), relapse, and OS [32]. The Bone Marrow Transplant-Clinical Trials Network (BMT-CTN) 0901 showed higher relapse-free survival (RFS) with MAC regimens (68.7 vs 47.6%, $P < .01$) as compared to RIC in patients with AML CR1 and MDS [33]. Eapen et al. performed a CIBMTR-based retrospective study of HCT outcomes associated with specific MAC and RIC regimens. Investigators analyzed 1258 patients with AML and 951 patients with MDS with a median age of 58 years. The study showed comparable (44%) 3-year disease-free survival with high-intensity busulfan (4)/cyclophosphamide, fludarabine/busulfan (4), and reduced-intensity fludarabine, melphalan (140 mg/m^2).The study also showed a higher incidence of relapse with reduced-intensity fludarabine/busulfan (Flu/Bu2) (46%) and Flu/Bu2 + antithymocyte globulin (56%), suggesting that higher-intensity regimens are associated with improved disease-free survival and could be considered in older patients with good performance status [34].

Most of the HCT data in older patients focuses on AML, but acute lymphoid leukemia (ALL) is also an indication for HCT in older patients. Survival for patients over age 60 with ALL without HCT is less than 20%. Cure rates of over 90% have been achieved in children with ALL with the use of combination chemotherapy, but the success has been less impressive in adults [35,36]. OS has been improved in the younger adult population with the use of pediatric or pediatric-inspired regimens, usually containing asparaginase [37]. Fathi and colleagues have used an intensive induction chemotherapy regimen containing asparaginase to achieve remission, followed by HCT, in older patients with ALL. This approach has shown not only feasibility but also improvement in 2-year DFS (52%) when compared to the historical controls [38].

RIC regimens for HCT in ALL have shown a 3-year OS of 38% with a 47% relapse rate. The mortality was higher in adults older than 66 years with a relative risk (RR) of 1.51 (95% CI: 1.00–2.29, $P = .05$) and patients with advanced disease, RR of 2.13 (95% CI: 1.36–3.34, $P = .001$) [39]. Overall data suggest that myeloablative conditioning could be an option in older patients with good performance status and organ function. Other factors in addition to age, such as the comorbidity score, may help to determine which patients will benefit from a more intense conditioning regimen.

Access to care

Easy accessibility and timely referral to a transplantation center play a crucial role in providing curative options to leukemia patients, who are usually diagnosed in the community. Various socioeconomic, healthcare, and patient-associated factors contribute to the challenge in accessing transplant centers. Elderly patients may have a lower rate of referral for aggressive curative therapy. In a survey of 1200 hematologist-oncologists practicing in the community, patients older than 60 years had a much higher rate of non-referral to a transplant center compared to patients 30–60 years, (odds ratio [OR] 8.3, CI 5.9–11.7, $P < .0001$). Insurance coverage (coverage versus no coverage) and race/ethnicity (African American versus Caucasian) were other factors which influenced non-referral to transplant centers [40].

Preliminary work from our center investigated access to transplant care for patients living in the state of Virginia [41]. In collaboration with Be the Match (National Marrow Donor Program), an “unmet” need was determined by estimating the number of patients eligible for an allogeneic transplant based on the SEER database, which provided the number of patients diagnosed with AML, and published guidelines for transplant indications. The data for number of patients who received allogeneic transplantation for AML was obtained from the CIBMTR. The unmet need was calculated by subtracting the group that actually received a transplant from the group that was eligible. This study compared variations in rate of allogeneic transplantation based on geographic region. The highest rate of transplant, 31%, was noted in the Southwest County, with an unmet need of 58%, while the lowest rate of transplantation, 8%, was seen in the Southside County (unmet need 88%). Race/ethnicity was the only socioeconomic factor that significantly correlated with HCT rate. Regions having a higher population of African Americans had a lower rate of transplant ($P = .0334$). Other socioeconomic factors such as median income, marital status, private versus public insurance, education, or gender did not correlate with HCT rate in this preliminary analysis [41].

What have we learned: future directions

Considerable advances have been made in the field of allogeneic transplantation for older patients, especially in reducing toxicity that may be associated with conditioning regimens. Further advances in patient access, patient selection, and reduction of relapse will contribute to the improvement of OS in this growing population. Outcomes in HCT have been shown to depend more on the physiological age than merely chronological age. The HCT-CI score developed by Sorror et al. is a widely used clinically applicable score, which addresses risks based on medical comorbidities. A higher score has been shown to correspond with lower OS [42]. The HCT-CI has also been combined with geriatric assessment measures, such as instrumental activities of daily living, gait speed, mental health, and C–reactive protein levels and has shown to predict OS, particularly in patients over 60 years old.

Relapse remains the biggest cause of treatment failure, and therefore myeloablative regimens should be considered in patients who are fit to tolerate this approach. In an effort to reduce relapse, there are multiple ongoing trials evaluating the efficacy and tolerability of maintenance therapy post allogeneic transplantation. These include trials investigating targeted agents, such as the FLT-3 inhibitor sorafenib [43–47]. Other studies analyze the impact of hypomethylating agents and histone deacetylase inhibitors on post-transplant relapse and survival [48,49]. Additional approaches investigate the role of chimeric antigen receptor (CAR) T-cell therapy, either post-transplant or as a bridge to transplant [50–52]. Increasing awareness among health care providers on prompt and timely referral will play an important role in increasing the opportunity for older patients to receive aggressive curative therapy.

Declaration of competing interest

Drs. Ballen and Varadarajan have no relevant financial relationships with any commercial interest.

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