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Full Length Article
Analysis

An Analysis of the Worldwide Utilization of Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

Molly C. Tokaz[1,2,3,*], Helen Baldomero[4], Andrew J. Cowan[1,2], Wael Saber[5], Hildegard Greinix[6], Mickey B.C. Koh[7,8], Nicolaus Kröger[9], Mohamad Mohty[10], Sebastian Galeano[11], Shinichiro Okamoto[12], Naeem Chaudhri[13], Amado J. Karduss[14], Fabio Ciceri[15], Vergílio Antonio R. Colturato[16], Selim Corbacioglu[17], Alaa Elhaddad[18], Lisa M. Force[19], Cristóbal Frutos[20], Andrés Gómez-De León[21], Nada Hamad[22], Nelson Hamerschlak[23], Naya He[4], Aloysius Ho[24], Xiao-jun Huang[25], Ben Jacobs[26], Hee-Je Kim[27], Minako Iida[28], Leslie Lehmann[29], Regis Peffault de Latour[30], Mary-Elizabeth M. Percival[2,3], Martina Perdomo[31], Walid Rasheed[13], Kirk R. Schultz[32], Adriana Seber[33,34], Bor-Sheng Ko[35], Anderson João Simione[36], Alok Srivastava[37], Jeff Szer[38,39], William A. Wood[40], Yoshihisa Kodera[28], Arnon Nagler[41], John A. Snowden[42], Daniel Weisdorf[43,44], Jakob Passweg[4], Marcelo C. Pasquini[5], Anna Sureda[45], Yoshiko Atsuta[47], Mahmoud Aljurf[13], Dietger Niederwieser[46,47,48]

[1] *Division of Medical Oncology, University of Washington, Seattle, Washington*
[2] *Division of Hematology, University of Washington, Seattle, Washington*
[3] *Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, Washington*
[4] *University Hospital Basel, Center for International Blood and Marrow Transplant Research, Switzerland*
[5] *Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin*
[6] *Medical University of Graz, Division of Hematology, Graz, Austria*
[7] *Infection and Immunity Clinical Academic Group, St George's Hospital and Medical School, London, United Kingdom*
[8] *Academic Cell Therapy Facility and Programme Health Sciences Authority, Singapore*
[9] *UKE Hamburg, Germany*
[10] *Sorbonne University, Hospital Saint Antoine, Paris, France*
[11] *Latin American Blood and Marrow Transplantation Group - LABMT Hospital Británico, Montevideo, Uruguay*
[12] *Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan*
[13] *King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia*
[14] *Clínica Las Américas, Latin AmericanBlood and Marrow Transplantation Group- LABMT, Medellín, Colombia*
[15] *University Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Milan, Italy*
[16] *Hospital Amaral Carvalho, Jaù, Brazil*
[17] *University of Regensburg, Regensburg, Germany*
[18] *African Blood and Marrow Transplantation Group - AfBMT; Department of Pediatric Oncology and Stem Cell Transplantation Unit, Cairo University, Cairo, Egypt*
[19] *Division of Pediatric Hematology-Oncology, Department of Pediatrics and Department of Health Metrics Sciences, University of Washington, Seattle, Washington*
[20] *Instituto de Prevision Social, Asunción, Paraguay*
[21] *Hospital Universitario Dr. José Eleuterio González, Monterrey, México*
[22] *Department of Haematology, St. Vincent's Hospital Sydney, School of Clinical Medicine, Faculty of Medicine and Health, UNSW, School of Medicine, University of Notre Dame Australia, Sydney, Australia*
[23] *Hospital Israelita Albert Einstein, São Paulo, Brazil*
[24] *Department of Haematology, Singapore General Hospital, Singapore*
[25] *Department of Hematology, Peking University Institute of Hematology, Beijing, China*
[26] *University of Pennsylvania, Philadelphia, Pennsylvania*
[27] *Catholic Hematology Hospital, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[28] *Department of Promotion for Blood and Marrow Transplantation, Aichi Medical University School of Medicine, Nagakute, Japan*
[29] *Dana Farber/Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts*
[30] *Saint-Louis Hospital, Paris, France*
[31] *Hospital Británico, Montevideo, Uruguay*
[32] *BC Children's Hospital/UBC, Vancouver, British Columbia, Canada*
[33] *Latin American Blood and Marrow Transplantation Group–LABMT, Bern, Switzerland*

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*Correspondence and reprint requests: Molly C. Tokaz, Division of Medical Oncology, University of Washington, Seattle, WA 98105.
E-mail address: mtokaz@uw.edu (M.C. Tokaz).

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[34] Hospital Samaritano - Americas, Sao Paulo Brazil and Pediatric Oncology Institute–Graacc–Unifesp, São Paulo, Brazil
[35] Department of Hematological Oncology, National Taiwan University Cancer Center, Taipei, Taiwan
[36] Hospital Amaral Carvalho, Jau, Brazil
[37] Christian Medical College, Vellore, India
[38] Australasian Bone Marrow Transplant Recipient Registry (ABMTRR), St. Vincent´s Hospital Sydney, Sydney, New South Wales, Australia
[39] Peter MacCallum Cancer Center and Royal Melbourne Hospital, Parkville, Victoria, Australia
[40] CIBMTR, University of North Carolina, Chapel Hill, North Carolina
[41] The Chaim Sheba Medical Center, Tel-Hashomer, Israel
[42] Department of Hematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom
[43] CIBMTR (Center for International Blood and Marrow Transplant Research), National Marrow Donor Program/Be The Match, Minneapolis, Minnesota
[44] University of Minnesota, Minneapolis, Minnesota
[45] Clinical Hematology Department, Institut Català d'Oncologia-Hospitalet, IDIBELL, Universitat de Barcelona, Barcelona, Spain
[46] University Leipzig, Leipzig, Germany
[47] Japanese Data Center for Hematopoietic Cell Transplantation, Department of Registry Science for Transplant and Cellular Therapy, Aichi Medical University School of Medicine, Nagakute, Japan
[48] KaunoKlinikos University of Health Sciences, Kaunas, Lithuania

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A B S T R A C T

Acute myeloid leukemia (AML) has an aggressive course and a historically dismal prognosis. For many patients, hematopoietic stem cell transplantation (HSCT) represents the best option for cure, but access, utilization, and health inequities on a global scale remain poorly elucidated. We wanted to describe patterns of global HSCT use in AML for a better understanding of global access, practices, and unmet needs internationally. Estimates of AML incident cases in 2016 were obtained from the Global Burden of Disease 2019 study. HSCT activities were collected from 2009 to 2016 by the Worldwide Network for Blood and Marrow Transplantation through its member organizations. The primary endpoint was global and regional use (number of HSCT) and utilization of HSCT (number of HSCT/number of incident cases) for AML. Secondary outcomes included trends from 2009 to 2016 in donor type, stem cell source, and remission status at time of HSCT. Global AML incidence has steadily increased, from 102,000 (95% uncertainty interval: 90,200-108,000) in 2009 to 118,000 (104,000-126,000) in 2016 (16.2%). Over the same period, a 54.9% increase from 9659 to 14,965 HSCT/yr was observed globally, driven by an increase in allogeneic (64.9%) with a reduction in autologous (−34.9%) HSCT. Although the highest numbers of HSCT continue to be performed in high-resource regions, the largest increases were seen in resource-constrained regions (94.6% in Africa/East Mediterranean Region [AFR/EMR]; 34.7% in America-Nord Region [AMR-N]). HSCT utilization was skewed toward high-resource regions (in 2016: AMR-N 18.4%, Europe [EUR] 17.9%, South-East Asia/Western Pacific Region [SEAR/WPR] 11.7%, America-South Region [AMR-S] 4.5%, and AFR/EMR 2.8%). For patients <70 years of age, this difference in utilization was widened; AMR-N had the highest allogeneic utilization rate, increasing from 2009 to 2016 (30.6% to 39.9%) with continued low utilization observed in AFR/EMR (1.7% to 2.9%) and AMR-S (3.5% to 5.4%). Across all regions, total HSCT for AML in first complete remission (CR1) increased (from 44.1% to 59.0%). Patterns of donor stem cell source from related versus unrelated donors varied widely by geographic region. SEAR/WPR had a 130.2% increase in related donors from 2009 to 2016, and >95% HSCT donors in AFR/EMR were related; in comparison, AMR-N and EUR have a predilection for unrelated HSCT. Globally, the allogeneic HSCT stem cell source was predominantly peripheral blood (69.7% of total HSCT in 2009 increased to 78.6% in 2016). Autologous HSCT decreased in all regions from 2009 to 2016 except in SEAR/WPR (18.9%). HSCT remains a central curative treatment modality in AML. Allogeneic HSCT for AML is rising globally, but there are marked variations in regional utilization and practices, including types of graft source. Resource-constrained regions have the largest growth in HSCT use, but utilization rates remain low, with a predilection for familial-related donor sources and are typically offered in CR1. Further studies are necessary to elucidate the reasons, including economic factors, to understand and address these health inequalities and improve discrepancies in use of HSCT as a potentially curative treatment globally.

Acute myeloid leukemia (AML) is a neoplasm of the myeloid lineage with an aggressive course and a historically dismal prognosis across all ages, but especially in patients >60 years of age [1–3]. As of 2017, AML accounted for 23.1% of leukemia diagnoses worldwide [4], with a reported 29.5% five-year overall survival rate (2012 to 2018), the lowest of any hematologic malignancy [5,6]. Globally, an 87.3% increase in incident cases in AML has been seen over the past 3 decades [7]. This rise in incidence has been noted in regions dominated by low- and middle-resource countries such as Latin America and East Asia [7], which may reflect improvements in access to care, diagnosis, and patient tracking. However, there continue to be great disparities in AML outcomes depending on resource availability. Within the United States, disparities remain in treatment options and outcomes in centralized (largely urban) versus community treatment sites, with reported early mortality rates in AML of 12% in National Cancer Institute–designated centers versus 24% in non-National Cancer Institute–designated centers [8] and significant differences noted in race-associated survival in Black young adult AML patients as compared to their White counterparts [9]. Globally, this disparity in outcomes is magnified; nonbiologic disease risk factors such as socioeconomic status, education, and access to services disproportionately increase cancer-related mortality in low- and middle-income countries [10].

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the best option for cure in patients with intermediate- and adverse-risk AML in first complete remission (CR1) or any patient with relapsed/refractory disease [3,11]. AML is the most frequently reported indication for allogeneic HSCT; in 2018, 38% of all allogeneic HSCT performed in Europe were for AML and worldwide 37.3% of allogeneic HSCT performed in 2016 were for AML [12,13]. Advances in conditioning regimens have improved tolerability and allowed expanded use in older patients up to age 75 and, in some cases, beyond [14–18]. In addition to allogeneic HSCT, autologous HSCT can be used as a

consolidative treatment to prolong relapse-free survival; however, global frequency and utilization for this indication is on the decline [12,19–21]. The timing of these consolidative transplantations as upfront (CR1) versus as salvage (in non-CR1) remains a topic of debate with implications on resource prioritization and utilization [22,23]. The capacity of a region to perform HSCT, along with a family's ability to financially access HSCT in many locations, determines curability of high-risk patients. No studies to date address the global utilization patterns of HSCT for AML.

Much of what we know about HSCT for AML is derived from general data regarding the use of HSCT across disease indications. Overall, the use of HSCT in the global setting is on the rise for all indications, with an estimated 77.6% increase from 2006 to 2016 [12,24]. With the unique operational, financial, and technical challenges inherent to HSCT [19,25,26], there is great regional disparity in HSCT uptake for all indications with reported transplant rates (TR) ranging from 0.1 to 1001 per 10 million inhabitants, with no transplantations happening in countries with a population of less than 300,000 inhabitants [24,27]. Our study aims to describe the numbers of allogeneic and autologous HSCT performed for AML by world region and to explore donor type stem cell source and disease stage to understand availability and utilization of HSCT to inform potential future expansion efforts for increased HSCT availability worldwide.

METHODS

Study design and data sources

This is a retrospective analysis of global AML incidence in relation to AML transplantation activity from 2009 to 2016.

Global AML incidence data was obtained using the Global Burden of Disease (GBD) 2019 Results Tool (https://vizhub.healthdata.org/gbd-results/) for the years 2009 to 2016 for both sexes combined and across all ages, as well as separated into <70 years and 70+ years of age groups. These were downloaded by World Health Organization (WHO) region and then collated to align with Worldwide Network for Blood and Marrow Transplantation (WBMT) designated regions as described below. HSCT activity was collected by the WBMT, which included total numbers of HSCT per year for AML by WBMT designated region, as well as stem cell source; donor type; disease stage (e.g., at CR1 or non-CR1) and type of transplant (allogeneic versus autologous). HSCT utilization by year and by region were calculated by using the numbers of HSCT relative to AML incident cases.

Participating groups

Participating Groups, Continents, Countries, and Teams Organizations providing information to the WBMT include the European Society for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplantation, the Asian Pacific Blood and Marrow Transplant Group, the Australasian Bone Marrow Transplant Recipient Registry, the Eastern Mediterranean Blood and Marrow Transplant Group, the Latin American Bone Marrow Transplantation Group, the African Blood and Marrow Transplantation Group, and the Cell Therapy Transplant Canada.

Data Collection

A retrospective survey of HSCT activities was collated by the WBMT through well-established international and regional organizations and, where no organizations were in place, directly from the transplantation centers. A list of WBMT participating countries is given in Supplemental Table S2. Informed consent from the individual patients was waived because no individualized data were transferred to the investigators. Global activities included numbers of HSCT for AML by WHO-aligned WBMT regional designations from 2009 to 2016. The registry included all HSCTs for AML separated by HSCT in CR1 and non-CR1. Stem cell source was obtained by region and year for both autologous and allogeneic HSCT and separated into bone marrow (BM), peripheral blood stem cell (PBSC), and cord blood sources from related or unrelated donors. The years 2009 to 2016 were selected to maximize region specific reporting of the full analyzed variables in this paper. Data collection for WBMT changed in 2009 to include transplantation timing (CR1 versus non-CR1) and the year 2016 represented the most recent compilation of data available from WBMT reporting organizations.

Global AML incidence estimates by year and WHO region were obtained from the GBD Study 2019 for the year 2016 using the GBD Results Tool. A comprehensive description of GBD 2019 cancer estimation has been previously described (https://jamanetwork.com/journals/jamaoncology/fullarticle/2787350). This included data from both sexes combined, for all ages, and age divided into the populations <70 and ≥70 years of age. This age breakdown was chosen to reflect age categorizations used in the HSCT literature to differentiate between younger and older patient cohorts. WHO regions were used for the GBD incidence analysis; WBMT reporting countries were characterized and separated by their GBD WHO region, and these WHO regions were then combined, where appropriate, to correspond with larger WBMT regional designations (ie combining WHO regions of SEAR and WPR to SEAR/WPR WBMT region) (Supplemental Figure S1 and Table S2). The decision was made to separate the United States and Canada from the Americas WHO regional designation to capture the disparate financial and infrastructure capacities of these 2 regions (North America and Latin America). For this, USA and Canada country level incidence data were combined and subtracted from the Americas incidence data to create the WBMT regional designations of AMR-N (USA + Canada) and AMR-S (Latin America). Thus the WBMT combined regions included USA/Canada (AMR-N); Latin America (AMR-S); African Region/Eastern Mediterranean Region (AFR/EMR); European Region (EUR); and South-East Asian Region/Western Pacific Region (SEAR/WPR); Supplemental Figure 1. Statistical analysis was conducted in R Core Team 2020 [28].

RESULTS

Global incidence and use of HSCT for AML

The global reported incidence of newly diagnosed AML has been steadily increasing from an annual incidence of 102,000 (95% uncertainty interval: 90,200 to 108,000) in 2009 to 118,000 (104,000 to 126,000) in 2016 (16.2% increase) (Table 1).

Alongside this global increase in AML diagnoses, there was a significant increase in the number of total transplantations performed for AML from 2009 to 2016. Total global HSCT (including both allogeneic and autologous) demonstrated a 54.9% increase in number during that time frame. The highest numbers of total HSCT for AML are being performed in regions with higher resources, with the highest number in EUR (n = 6238 in 2016) followed by SEAR/WPR (n = 4572) and AMR-N (n = 3223) with far fewer in AMR-S (n = 502) and AFR/EMR (n = 430) (Table 1). Despite these smaller gross total HSCT numbers, the largest percent change in HSCT was seen in AFR/EMR with a 94.6% increase in total HSCT as compared to 34.7% increase in AMR-N over the same period. AMR-S had a 46.8% increase in total HSCT numbers from 2009 to 2016 despite the relatively low gross use reported (Table 1). The region of highest use (EUR) showed 53.0% growth in total HSCT from 2009 to 2016 as compared to 74.1% growth in the SEAR/WPR Region (second highest gross use region; see Table 1).

The 54.9% global increase in HSCT use was the result of a 64.9% increase in the use of allogeneic HSCT across all regions, countered by a simultaneous −34.9% reduction in autologous HSCT globally across the same time period (Table 1, Figure 1a, Figure 2a). The largest percent increase in only allogeneic HSCT was reflected by AFR/EMR (111.9%) with the smallest percent increase in AMR-N (42.5%) (Table 1, Figure 1a). This reflects the overall global trend: in 2016, 95.8% of HSCT for AML were allogeneic, with highest percentage in AMR-N (99.2%) and lowest in AMR-S (93.2%). The decreasing number of autologous transplantation was observed in all regions except in SEAR/WPR, which has an increase in use between 2009 and 2016 (18.2%) although with stably low numbers, Table 1.

Utilization of HSCT in AML

Total HSCT utilization (number of HSCT/ AML incident cases by region) rose from 9.5% to 12.6% from 2009 to 2016 (Table 1). Highest total HSCT utilization rates were seen in AMR-N (18.4% in 2016) followed by EUR (17.9% in 2016) with lowest rates in AFR/EMR (2.8% in 2016) and AMR-S (4.5% in 2016). SEAR/WPR showed the greatest change in utilization rate from 2009 to 2016, increasing from 7.7% to 11.7% (Table 1).

Table 1
Global Trends in Total Number of Allogeneic, Autologous, and Total (Allo + Auto) HSCT (n), Total Number of AML Cases for All Ages and <70 (n), and Total HSCT Utilization for All Ages and <70 From 2009 to 2016 by Region

	Total Number of HSCT			Total Number of AML cases		Total HSCT utilization	
	Allogeneic (n)	Autologous (n)	Total (n)	All Ages (n)	Age <70 (n)	All Ages (%)	Age <70 (%)
AFR/EMR (Africa & Eastern Mediterranean)							
2009	194	27	221	12,700	11,700	1.7%	1.9%
2016	411	19	430	15,300	14,100	2.8%	3.0%
Percent change	111.9%	−29.6%	94.6%	21.0%	20.8%	–	–
AMR-N (North America)							
2009	2244	149	2393	14,900	7320	16.0%	32.7%
2016	3198	25	3223	17,500	8020	18.4%	40.2%
Percent change	42.5%	−83.2%	34.7%	17.0%	9.6%	–	–
AMR−S (Latin America)							
2009	270	72	342	9590	7730	3.6%	4.4%
2016	468	34	502	11,200	8660	4.5%	5.8%
Percent change	73.3%	−52.8%	46.8%	16.8%	12.0%	–	–
EUR (Europe)							
2009	3546	531	4077	30,400	17,000	13.4%	24.0%
2016	5911	327	6238	34,900	17,500	17.9%	35.6%
Percent change	66.7%	−38.4%	53.0%	14.8%	3.1%	–	–
SEAR/WPR (South-East Asian & Western Pacific)							
2009	2436	190	2626	34,000	25,900	7.7%	10.1%
2016	4346	226	4572	39,200	28,600	11.7%	16.0%
Percent change	78.4%	18.9%	74.1%	15.3%	10.5%	–	–
Global							
2009	8690	969	9659	102,000	69,800	9.5%	13.8%
2016	14,334	631	14,965	118,000	77,100	12.6%	19.4%
Percent change	64.9%	−34.9%	54.9%	16.2%	10.5%	–	–

For patients <70 years of age, highest total HSCT utilization rates were seen in AMR-N, rising from 32.7% to 40.2% from 2009 to 2016 followed by EUR (24% to 35.6%) with lower utilization rates in SEAR/WPR (10.1% to 16.0%) and significantly lower rates in AMR-S (4.4% to 5.8%) trailed by AMR/EMR (1.9% to 3%) (Table 1).

The highest regional utilization for allogeneic HSCT across all ages was represented by the higher resource regions of AMR-N and -EUR, where the utilization rate (number of HSCT/AML incident cases by region) of allogeneic HSCT from 2014 to 2016 ranged from 18.3% to 18.5% (Figure 1b). AFR/EMR had the lowest utilization of allogeneic HSCT, with only 2.7% of estimated new cases receiving an allogeneic HSCT in 2016, a 1.1% increase in utilization from 2009 to 2016. Similarly, AMR-S reported a rate of only 4.2% of regional AML cases receiving an allogeneic HSCT in 2016 (1.4% utilization; see Figure 1b).

For patients <70 years of age, AMR-N had the highest allogeneic HSCT utilization rate, increasing from 2009 to 2016 (30.6% to 39.9%); rates in EUR were slightly lower (20.9% to 33.8%) and much lower utilization were observed in SEAR/WPR (9.4% to 15.2%), AMR-S (3.5% to 5.4%), and AFR/EMR (1.7 to 2.9%) (Figure 1c).

Globally, autologous HSCT utilization for AML remained low (0.5% globally in 2016) although with a slightly increased uptake in younger patients (<70 years of age) (0.8% globally in 2016), although with similarly decreasing use across all regions except SEAR/WPR from 2009 to 2016 (Figure 2b, 2c). In SEAR/WPR, there was a stably low utilization rate for autologous HSCT from 0.5% to 0.7% utilization rate (indexing to 226 total autologous HSCT in 2016; Figure 2a, 2b).

Remission status at time of HSCT

In all regions, the percentage of total HSCT done in CR1 has become increasingly common from 2009 to 2016, increased from 44.1% to 59.0% of total global HSCT performed for AML per year (Figure 3). The proportion of transplantation in CR1 was most pronounced in AFR/EMR where 72.4% to 77.4% of total HSCT happened in CR1 between 2009 to 2014. Although there was a slight downtrend in early HSCT in AFR/EMR from 2015 to 2016 (65.5% to 69.1%), it remains the region with highest overall CR1 HSCT rates from 2009 to 2016 (Figure 3). Conversely, the lowest rates of HSCT in CR1 occurred in AMR-N although with a steady trend toward early transplantation (53.4% in 2009, 62.2% in 2016). Like AMR-N, EUR saw a steady rise in HSCT in CR1 from 2009 to 2016 (from 60.7% to 72.2%). AMR-S had an oscillating percentage HSCT in CR1 from the 65.2% (2009) to 54.9% (2013) increasing back to 60.0% (2016). Unfortunately, incomplete reporting from SEAR/WPR prevent full comparative analysis, but for years of complete reporting (2013 to 2015) percentage of total HSCT in CR1 ranged from 54.1% to 58% (Figure 3).

Donor type for allogeneic HSCT

Patterns of allogeneic HSCT by donor type in AML vary widely across regions; see Table 2. In 2009, there was a slight predilection for unrelated donor HSCT (4516 [52.0%] unrelated versus 4174 [48%] related] globally, with a steady shift toward related donor HSCTs in ensuing years [in 2016: 7531 related versus 6803 unrelated]). In SEAR/WPR, specifically, there was a steady increase in related donor HSCT from 2009 to 2016 (48.3% to 62.3%); Table 2. In AFR/EMR, >95% of transplantations for AML were from related donor sources (95.9% in 2016), a figure similarly reflected in AMR-S (79.9% in 2016). In contrast, AMR-N and EUR represented a more balanced distribution of donor sources with a slight preference for Unrelated Donor transplant (URD) (in 2016: 56.4% URD in AMR-N and 55.0% URD in EUR). In AFR/EMR, the preponderance of related

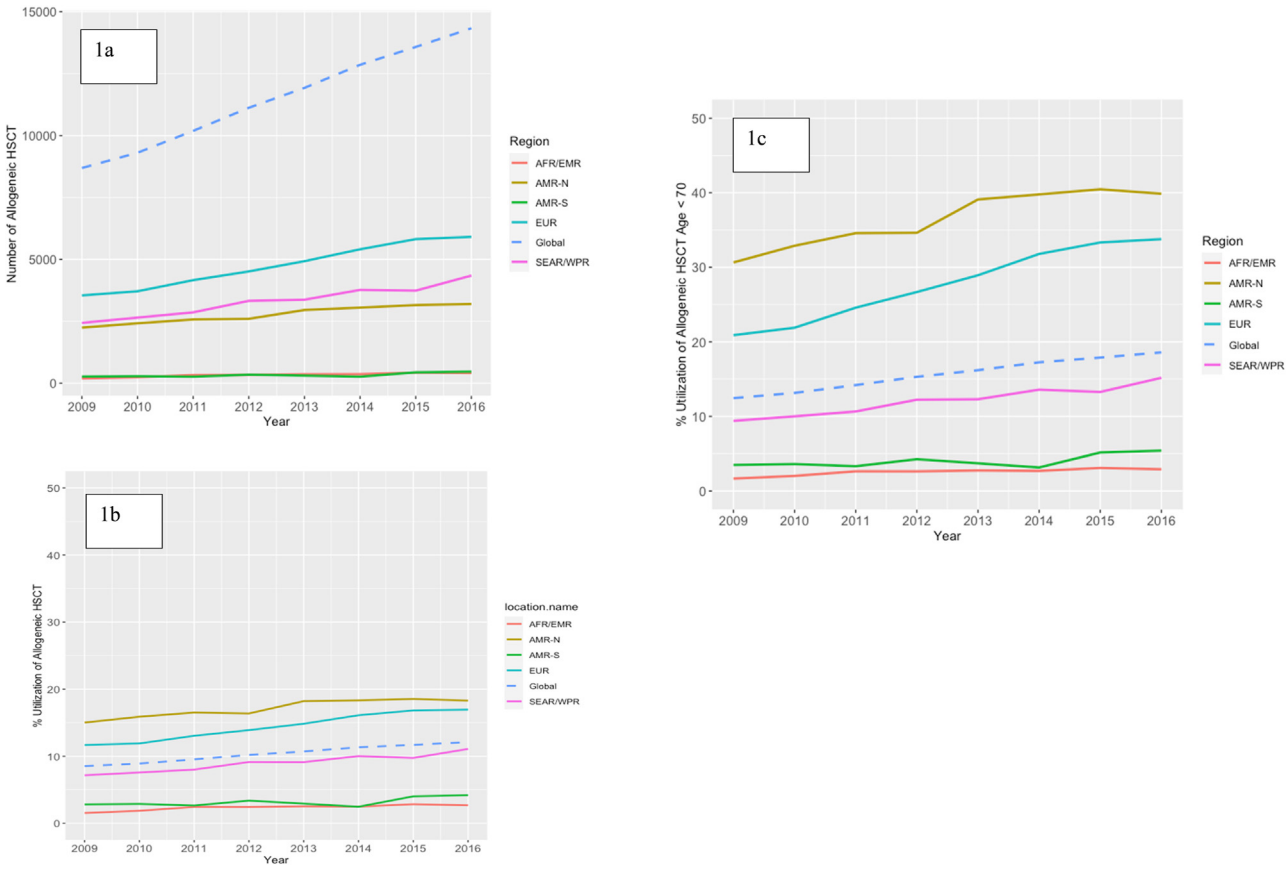

Figure 1. Global trends in number (a) and utilization rate (b) of allogeneic stem cell transplantation for AML, all ages, worldwide by region, 2009 to 2016; and global trends in utilization rate of allogeneic stem cell transplantation for AML, age ≤70 (c), worldwide by region, 2009 to 2016.

donor sources reflected a combination of both HLA-identical and non-HLA-identical (or haploidentical) family donors. Although overall the majority of these allogeneic HSCT were from HLA-identical family members, there was a steady increase in the proportion of related HSCT using non-HLA-identical donors from 2009 to 2016 (percent change 28.7% for HLA-identical versus 342.1% for non-HLA-identical).

HSCT stem cell sources included PBSC, BM, and umbilical cord (UCB). Allogeneic donor cell sources globally in 2009 included 67.9% from PBSC, 21.6% from BM, and 10.5% from UCB. More recently, this distribution shifted toward PBSC (PBSC 78.6%, BM 14.4%, UCB 7.0% in 2016) (Supplemental Table S1). The greatest percent increase in PBSC usage globally was seen in nonidentical sibling HSCT (from 532 to 2543 [378.0%] 2009 to 2016 globally) (Table 2).

DISCUSSION

Although the highest incidence of AML and HSCT utilization were reported by world regions dominated by high resource countries, the greatest growth was represented by world regions with lower resource economies such as AFR/EMR and AMR-S. The gross numbers of HSCT continued to be almost 10-fold smaller in AFR/EMR than AMR-N (430 versus 3223 in 2016); however, the growth of 94.6% in AFR/EMR from 2009 to 2016 demonstrate that this will continue to be a region of increasing import when considering the future trends in HSCT uptake globally. This regional trend of increasing HSCT use has been described across disease types; for example, though AFR/EMR represents only 2.7% of global HSCT, it had an 80% increase in HSCT rates across multiple disease indications from 2006 to 2016 [12].

However, despite these increasing numbers of HSCT, global utilization remains low. Even in younger patients (<70) who have higher utilization rates overall, the maximal utilization of allogeneic HSCT remained at 39.9% in AMR-N and 33.8% in EUR in 2016, with far lower uptake in all other regions. This level of utilization remains unfortunately low as compared to reported utilization rates in Germany for younger patients ranging from 46.6% for patients in CR1 to 69.6% for patients with refractory disease [3]. This gap in allogeneic HSCT utilization is most pronounced in the lower-resource regions of AFR/EMR and AMR-S (with maximum of 3% to 4% utilization across all ages from 2009 to 2016), reflecting a disproportionately low uptake in these countries marked by younger populations where we would expect higher utilization rates [29]. In low-resource countries, the median age of the population is very young (18.4 to 19 years, World Bank regions 2015 to 2020); with the percentage of the population 70+ years representing less than 2% of the total population [30]. Augmenting the stark under-utilization in these regions is the reality that AML incidence is likely underestimated in low-resource settings because of underdiagnosis for a variety of reasons (i.e., early mortality before centralized referral, limited availability of appropriate diagnostics, and paucity of robust reporting registries). To this extent, true utilization rates are likely lower than the <5% that is reported in our article.

The lower utilization rate reflected in these low-resource regions despite the younger age at diagnosis further underlines the disparity in HSCT uptake, likely based on regional

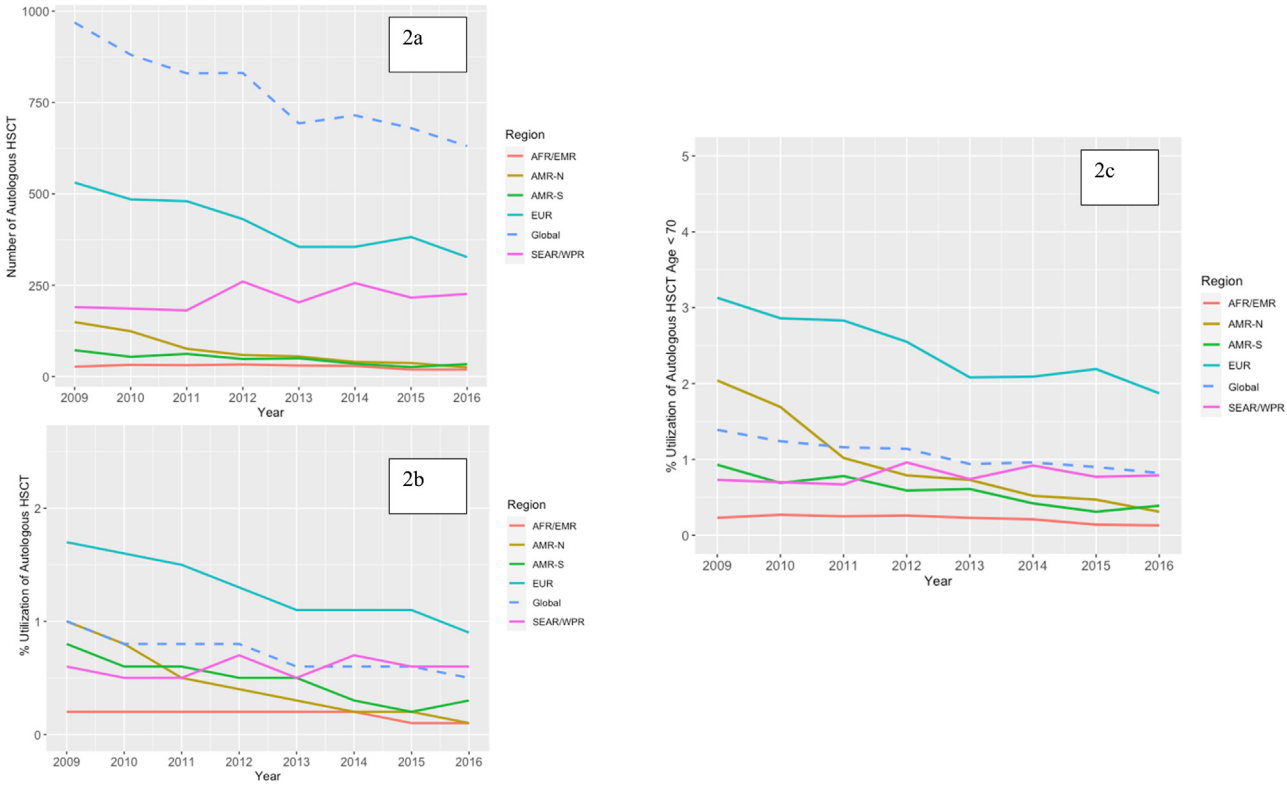

Figure 2. Global trends in number (a) and utilization rate (b) of autologous stem cell transplantation for AML, all ages, worldwide by region, 2009 to 2016; and global trends in utilization rate of autologous stem cell transplantation for AML, age ≤70 (c), worldwide by region, 2009 to 2016.

resource factors. Differing utilization patterns for allogeneic HSCT uptake for AML likely reflect the regional capability, both financially and logistically, of achieving CR through induction chemotherapy, limited access to cytogenetic and molecular testing for ELN risk stratification to guide prioritization for HSCT, differences in aggressive therapy available, and the supportive care structures necessary to allow for survival from induction to transplant [31]. In resource-constrained settings, inducing CR1 through aggressive chemotherapy regimens presents institutional and financial challenges independent of the HSCT itself that contribute to low utilization of HSCT in these regions. In considering how to increase HSCT uptake in these areas, it will be important to also consider supportive care measures that can improve outcomes with induction therapy to allow for later HSCT candidacy.

We observed great variability in the use of donor type for allogeneic HSCT globally; EUR and AMR-N primarily use unrelated donor sources whereas the rest of the world relies largely on related donor sources. The influences behind the variations in donor source are likely multifactorial. In many low- and middle-resource countries with larger family units and higher birth rates, the likelihood of matched related donor availability

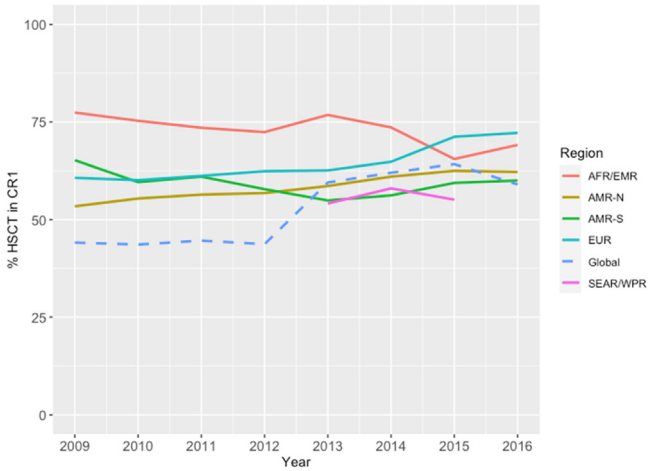

Figure 3. Global trends in transplant timing of HSCT by rate of total HSCT (autologous + allogeneic) occurring in CR1 for AML, all ages, worldwide by region, 2009 to 2016.

reaches >50%, with reported likelihoods as high as 63.5% in Saudi Arabia and 70% in Pakistan as compared to 30% in the United States [31,32]. Our study reflected a steady increase in matched related donor HSCT from 2009 to 2016 in AMR-S, AFR/EMR and SEAR/WPR, increasing 1.2 (AMR-S) to 2.2 (AFR/EMR) fold for PBSC HSCT; however, this growth was compounded by even greater increases in mismatched related donor sources in these same regions for PBSC (SEAR/WPR 304 to 1455; AFR/EMR 1 to 49; AMR-S 5 to 85), although with smaller absolute numbers in AMR-S and AFR/EMR. This increased availability of familial donors (matched and mismatched) in low- and middle-resource countries coupled with geographic proximity make related donor HSCT a more accessible and expeditious stem cell source [12,31]. Conversely, the identification process for a matched URD through international registries is laborious, time-consuming, and often futile given under-representation of many racial and ethnic minorities in donor registries. The probability of finding a URD match is racially and ethnically dependent, ranging from 44% for Hispanics and 16% for Blacks of South or Central American descent versus 75% to 79% for Whites of European Descent [33,34]. Even if a URD is located, the logistics of transporting the stem cell product and the increased financial burden of URD transplants often present insurmountable cost barriers in resource constrained settings [35]. Future studies should focus on elucidating factors affecting donor source selection given the implication of donor source on conditioning, graft success, immunosuppressive regimens, and future risk of transplant related complications.

In addition to donor type, stem cell source is an important logistical and clinical consideration globally. Peripheral blood represents the preferred stem cell source worldwide for both related and unrelated donor HSCT. In fact, the percent change in nonidentical sibling PBSC across all regions, including regions with higher resource countries, surpasses the growth seen in URD in these higher resource regions. This global predilection for PBSC, which represents a logistically simpler mode of collection, is important to examine given studies demonstrating decreased rates of chronic GVHD and improved work productivity for patients receiving BM HSCT instead of PBSC [36] endpoints that might be particularly salient in lower-resource regions.

Finally, our study demonstrates a general global trend toward reduction in autologous HSCT for AML in favor of allogeneic HSCT, which itself has implications on program capacity in regions given the logistical challenge of allogeneic versus autologous program initiation. Although a full exploration of the reasons for this shift toward allogeneic HSCT is out of the scope of this article, likely the trend is due to the lack of convincing evidence to demonstrate autologous HSCT superiority over other treatment modalities for AML (such as allogeneic HSCT or intensive consolidative chemotherapy) [21,37–39]. At the same time, multiple advances in allogeneic HSCT such as advances in GVHD prophylaxis and treatment [40,41], improving infectious diagnostics and therapeutics [42–45], and the introduction of reduced intensity conditioning [46–49] have expanded patient eligibility and improved outcomes in many regions of the world. However, further inquiry needs to focus on whether these advancements favoring allogeneic HSCT feasibility and success for AML are equivalent across regions with differing financial and technical landscapes.

The singular exception to this global autologous HSCT trend was found in SEAR/WPR, where rates of autologous HSCT for AML remained largely stable from 2009 to 2016 (from 190 to 226 or 5% to 7% of total transplants). One explanation for this consistent autologous utilization could be the rapid increase in total HSCT in SEAR/WPR (from 2626 to 4572), especially in countries such as China and India, which outpaces the ability to synchronously increase allogeneic HSCT infrastructure. Additionally, in Japan, autologous HSCT is commonly used for APL in second CR, and from 2004 to 2016, this indication accounted for over 70% of autologous HSCT for AML, accounting for stable autologous utilization in Japan over this time period [50,51]. Further inquiry into outcomes from SEAR/WPR could help delineate areas in which autologous HSCT could remain advantageous in disparate global practice settings.

Further outcome studies of HSCT globally would be a useful next step to complement this analysis. Because HSCT (both allogeneic and autologous) is both technically challenging to develop and administer and requires high resource utilization, comparative studies into the cost-effectiveness of various aspects of HSCT across diverse settings would be valuable. A future study could evaluate the impact of HSCT on outcomes by comparing the number needed to treat as a measure against the economic costs in different international settings. Such cost estimates would need to assess regional barriers including out of pocket expenditures, government support structures, local referral systems, and other considerations that reflect patient-specific burdens. Recognizing that HSCT is a resource intensive treatment option, the establishment of HSCT programs might not be the priority for many LMICs where resources are needed to expand baseline diagnostics and upfront treatment availability. Considerations of creative global structures utilizing referral centers to share capacity could be an interesting future area of study.

Further limitations of our article reflect the global patterns of data reporting available for HSCT. As noted in Supplemental Table 2, regional reporting for the WBMT is limited by the number of centers performing HSCT in given areas of the world. Specifically, with the AFR/EMR region, there are limited numbers of centers in Sub-Saharan Africa performing and thus reporting HSCT outcomes, skewing data toward the eastern Mediterranean regional results. In AMR-S, under-registration continues to be a challenge; in some countries (Brazil, Chile, Colombia, and Panama) less than 50% of the centers performing HSCT reported their activity to the WBMT, skewing AMR-S transplantation activity to appear lower than expected [52,53]. Thus, although WBMT represents the most extensive international data reporting for global HSCT patterns, gaps in reporting infrastructure should be recognized as a possible source of regional HSCT under-reporting or underestimation. Additionally, this study reports numbers of transplantation instead of rates by population, which could over-represent use in more densely populated countries. Finally, GBD estimates of AML incidence also are limited by data availability and highlight the need for continued efforts to increase the global coverage of population-based cancer registries. These registries will be crucial for more accurate, inclusive reporting globally, and will require consistent disease specific norms for delineating relevant subtypes (i.e., the separation of leukemia into lymphoid and myeloid [AML] subtypes).

CONCLUSION

HSCT remains a central curative treatment modality in AML and an understanding of global access, practices, and unmet needs is important. Allogeneic HSCT for AML is rising globally, but there are marked variations in regional utilization and practices, including types of graft source and autologous use in SEAR/WPR. Resource-constrained regions have the largest growth in HSCT use, but utilization rates remain low with a

Table 2
Global Number of Allogeneic HSCT by Donor Type and Stem Cell Source for AML, as Well as Percentage of Related and Unrelated Allogeneic HSCT for All Ages, Worldwide and by Region, 2009 and 2016

WBMT Regional Designation	Related										Unrelated					Total Allogeneic HSCT
	HLA - Id Sibling			Non - Id			Twin		Total	Percent Related	BM	PBSC	Cord	Total	Percentage Unrelated	
	BM	PBSC	Cord	BM	PBSC	Cord	BM	PBSC								
North America (AMR-N)																
2009	114	688	3	45	68	4	—	5	**927**	**41.3%**	227	849	241	**1317**	**58.7%**	2244
2016	115	746	3	148	362	17	—	3	**1394**	**43.6%**	304	1,281	219	**1804**	**56.4%**	3198
South-East Asian & Western Pacific (SEAR/WPR)																
2009	179	610	2	57	307	13	—	8	**1176**	**48.3%**	506	347	407	**1260**	**51.7%**	2436
2016	101	1104	—	44	1,455	—	—	3	**2707**	**62.3%**	364	634	641	**1639**	**37.7%**	4346
Africa & Eastern Mediterranean (AFR/EMR)																
2009	45	142	—	3	1	—	—	—	**191**	**98.5%**	—	1	2	**3**	**1.5%**	194
2016	21	314	—	10	49	—	—	—	**394**	**95.9%**	2	13	2	**17**	**4.1%**	411
Latin America (AMR-S)																
2009	69	145	2	5	5	—	—	—	**226**	**83.7%**	13	10	21	**44**	**16.3%**	270
2016	70	173	1	42	85	—	1	2	**374**	**79.9%**	37	51	6	**94**	**20.1%**	468
Europe (EUR)																
2009	284	1170	7	31	151	3	3	5	**1654**	**46.6%**	296	1388	208	**1892**	**53.4%**	3546
2016	248	1556	1	258	592	2	—	5	**2662**	**45.0%**	301	2834	114	**3249**	**55.0%**	5911
Global																
2009	691	2755	14	141	532	20	3	18	**4174**	**48.0%**	1042	2595	879	**4516**	**52.0%**	8690
2016	555	3893	5	502	2543	19	1	13	**7531**	**52.5%**	1008	4813	982	**6803**	**47.5%**	14,334

predilection for familial related donor sources, in younger patients and typically offered in CR1. Further studies are necessary to elucidate the reasons, including economic factors, to understand and address these health inequalities and improve discrepancies in use of HSCT as a potentially curative treatment globally.

Our study provides the first comprehensive evaluation of global HSCT utilization for AML by region, as well as HSCT patterns by donor type, transplantation timing, and stem cell source. Globally, efforts in the coming years should concentrate on increasing HSCT utilization and availability globally for appropriate patients with AML with a focus on increasing capacity particularly in lower-resource regions with increasing incidence. It will be important to balance the expansion of HSCT availability with resource utilization globally and other cancer control priorities, as part of comprehensive efforts to improve outcomes for patients with AML.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.12.013.

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