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The Global State of Hematopoietic Cell Transplantation for Multiple Myeloma: An Analysis of the Worldwide Network of Blood and Marrow Transplantation Database and the Global Burden of Disease Study

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A B S T R A C T

Multiple myeloma (MM) is a plasma cell neoplasm characterized by destructive bony lesions, anemia, and renal impairment. Access to effective therapy is limited globally. We report the rates and utilization of hematopoietic cell transplantation (HCT) globally from 2006-2015 to better characterize access to HCT for patients with MM.

This was an analysis of a retrospective survey of Worldwide Network of Blood and Marrow Transplant sites, conducted annually between 2006-2015. Incidence estimates were from the Global Burden of Disease study. Outcome measures included total number of autologous and allogeneic HCTs by world regions, and percentage of newly diagnosed MM patients who underwent HCT, calculated by the number of transplants per region in calendar year/gross annual incidence of MM per region.

From 2006 to 2015, the number of autologous HCT performed worldwide for MM increased by 107%. Utilization of autologous HCT was highest in Northern America and European regions, increasing from 13% to 24% in Northern America, and an increase from 15% to 22% in Europe. In contrast, the utilization of autologous HCT was lower in the Africa/Mediterranean region, with utilization only changing from 1.8% in 2006 to 4% in 2015. The number of first allogeneic HCT performed globally for MM declined after a peak in 2012 by -3% since 2006.

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Autologous HCT utilization for MM has increased worldwide in high-income regions but remains poorly utilized in Africa and the East Mediterranean. More work is needed to improve access to HCT for MM patients, especially in low to middle income countries.

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INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy with substantial morbidity and mortality, characterized by the presence of abnormal clonal plasma cells and end-organ destruction with renal failure, osteolytic bone lesions, and anemia. Although less common on a global level compared to lung cancer or breast cancer, MM is a global disease; in 2016, there were an estimated 138 509 incident cases, with an age-standardized incidence rate of 2.1 cases per 100 000 persons, and MM incident cases have increased globally by 126% from 1990 to 2016, largely attributable to an aging world population [1]. There are heterogeneities with respect to the burden of MM, possibly due in part to underascertainment in certain world regions.

Although MM is considered an incurable disease, modern treatments have dramatically improved the long-term outcomes for patients. Starting with the introduction of autologous hematopoietic cell transplantation (HCT) in the 1990s and continuing more recently with the introduction of proteasome inhibitors (PIs) and immunomodulatory agents (IMiDs)—particularly lenalidomide and bortezomib—survival has improved dramatically for patients with MM [2-5]. Recent Food and Drug Administration and European Medicines Association approvals of the CD38 antibody daratumumab and the SLAMF7 antibody elotuzumab also have expanded the options for patients and are being studied in the new diagnosis setting [6-12].

Autologous HCT with melphalan conditioning was one of the first therapeutic options to improve outcomes for patients with MM. Pioneered in the 1980s, and with dramatically expanded use in the 1990s and 2000s, autologous HCT results in durable remissions in many patients [2-4]. Transplantation eligibility is largely determined by several factors, including comorbidities, physiological health, and, in some cases, chronologic age. The most recently reported randomized clinical trial to examine the effect of autologous HCT in the novel agent era is the IFM-2009 trial, a randomized study of lenalidomide, bortezomib, and dexamethasone (RVd) induction and consolidation followed by lenalidomide maintenance compared with RVd induction, autologous HCT, RVd consolidation, and lenalidomide maintenance [4]. Although there was no difference in overall survival between the 2 groups, the autologous HCT arm had better progression-free survival (50 months versus 36 months). This trial and others continue to support autologous HCT as a standard of care for eligible patients.

Although autologous HCT is effective in treating MM, the availability and utilization of HCT in general are limited outside of high-income regions of the world. A landmark publication by the Worldwide Network of Blood and Marrow Transplantation (WBMT) published in 2010 [13] assessed the global use of HCT and explored associations with macroeconomic factors associated with HCT utilization [14]. There was significant variability between regions with respect to use of HCT; this was associated with government health expenditures, number of transplantation teams per 1 million people, and gross national income. A follow-up report with longer follow-up described similar findings of higher transplantation rates in countries with more resources, more transplantation teams, and an unrelated donor infrastructure [15].

Given the central importance of autologous HCT for MM, and data showing global disparities in the utilization of HCT in general, we sought to determine the numbers and utilization of autologous and allogeneic HCT for MM both globally and regionally.

METHODS

Study Design

This retrospective survey of all the HCT teams was organized by the WBMT through well-established international and regional organizations and, where no organizations were in place, directly from the transplantation centers. Informed consent from the individual patients was waived because no individualized data were transferred to the investigators.

The main outcome measures were ascertainment of numbers of first autologous and allogeneic HCT for plasma cell disorders (PCDs) by region type on a global level. Secondary outcomes included determination of first autologous and allogeneic HCT utilization, for all ages, and a subset of patients age <70 years. We determined HCT utilization by dividing the number of transplantations per region, divided by the gross incidence of MM per region per year (first HCT for MM/MM incidence in a given year).

Participating Groups, Continents, Countries, and Teams

Organizations providing information to the WBMT included the Australasian Bone Marrow Transplant Recipient Registry, Asia-Pacific Blood and Marrow Transplantation Group, Bone Marrow Donors Worldwide, Canadian Blood and Marrow Transplantation Group, Center for International Blood and Marrow Transplant Research, European Society for Blood and Marrow Transplantation, Eastern Mediterranean Blood and Marrow Transplantation Group, Latin American Blood and Marrow Transplantation Group, and World Marrow Donor Association.

Data Collection

Global transplantation numbers for PCDs by country of origin, year, and donor type (autologous versus allogeneic) were searched for using the reporting member organization. The WBMT registry includes all HCTs for PCDs, the majority of which were for MM. In our calculations and reporting, we worked under the assumption that the majority of HCTs were performed for MM. In the European region only, first allogeneic HCT included both tandem auto-allo HCT and first allogeneic HCT; all other regions reported first allogeneic HCT only.

Global raw incidence data, unadjusted for MM by year and World Bank region, were obtained from the Global Burden of Disease (GBD) Study 2017, using the GBD source tool [16]. Separate data were obtained for patients of all ages and for those age <70 years.

Definitions

We reported the number of HCTs per year by region and by donor type from 2006 to 2015. We did not adjust for patients who crossed a border to undergo HCT in a different country. Given that some regions and teams do not routinely use a strict age cutoff for HCT in MM, 2 analyses were performed: for all ages and for age <70 years. We calculated utilization of HCT by donor type, determined by the number of HCTs per calendar year, divided by the gross annual incidence of MM for a given region.

RESULTS

Transplantation Activity

From 2006 to 2015, there was a 100% increase in the use of HCT for MM worldwide, increasing from 11,446 transplantations in 2006 to 22,896 transplantations in 2015 (Figure 1). Autologous HCT activity outnumbered allogeneic donor HCT in all the years reported, and autologous HCT activity increased from 10,673 to 22,144 transplantations globally from 2006 to 2015 (a 107% increase). In contrast, globally, the number of first allogeneic HCTs for MM remained largely stable (Table 1).

All regions studied reported an increasing frequency of HCT for MM. The regions with the largest increases in autol-

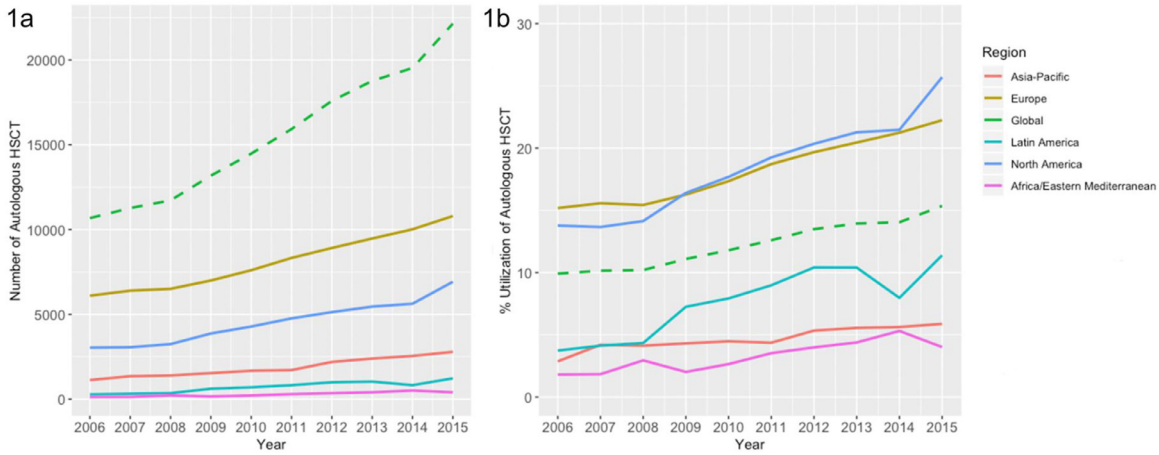

Figure 1. Number (A) and utilization rate (B) of autologous HCT, all ages, worldwide by region, 2006 to 2015.

Table 1
HCT Utilization by Region

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	% Change, 2006-2015
North America											
Autologous	3038	3062	3245	3872	4282	4763	5132	5458	5627	6922	128%
Allogeneic	204	238	213	228	172	211	184	186	221	105	-49%
Incidence, Gross, All Ages	22050.76	22418.30	22952.77	23610.29	24209.06	24742.40	25224.68	25663.29	26212.15	26937.22	22%
Incidence, Gross, Age < 70	10843.45	11093.57	11431.86	11807.79	12107.55	12337.44	12568.47	12696.61	12902.74	13268.20	22%
Utilization auto / allo HSCT, all ages	13.78/0.93	13.66/1.06	14.14/0.93	16.40/0.97	17.69/0.71	19.25/0.85	20.35/0.73	21.27/0.72	21.47/0.84	25.70/0.39	+87% / -58%
Utilization auto / allo HSCT, age < 70	28.02/1.88	27.60/2.15	28.39/1.86	32.79/1.93	35.37/1.42	38.61/1.71	40.83/1.46	42.99/1.46	43.61/1.71	52.17/0.79	+86% / -58%
Asia Pacific											
Autologous	1127	1352	1398	1535	1676	1712	2195	2394	2548	2790	148%
Allogeneic	53	67	63	77	65	77	93	90	95	70	32%
Incidence, Gross	30709.17	32202.62	33897.37	35604.72	37443.57	39231.98	41120.69	43094.63	45312.55	47447.92	55%
Incidence, Gross, Age < 70	18631.45	19508.90	20535.75	21631.75	22783.67	23927.04	25190.52	26556.55	28067.64	29537.14	59%
Utilization auto / allo HSCT, all ages	3.67/0.17	4.20/0.21	4.12/0.19	4.31/0.22	4.48/0.17	4.36/0.20	5.34/0.23	5.56/0.21	5.62/0.21	5.88/0.15	+60% / -15%
Utilization auto / allo HSCT, age < 70	6.05/0.28	6.93/0.34	6.81/0.31	7.10/0.36	7.36/0.29	7.16/0.32	8.71/0.37	9.01/0.34	9.08/0.34	9.45/0.24	+56% / -17%
Africa and East Mediterranean											
Autologous	125	132	220	157	215	298	352	404	512	406	225%
Allogeneic	2	12	17	6	15	28	22	17	24	26	1200%
Incidence, Gross	6931.16	7192.70	7470.27	7785.06	8125.95	8456.45	8824.53	9214.89	9645.25	10111.78	46%
Incidence, Gross, Age < 70	4729.58	4907.72	5101.99	5322.56	5558.37	5799.91	6073.47	6363.84	6686.38	7037.35	49%
Utilization auto / allo HSCT, all ages	1.80/0.03	1.84/0.17	2.95/0.23	2.02/0.08	2.65/0.18	3.52/0.33	3.99/0.25	4.38/0.18	5.31/0.25	4.02/0.26	+123% / +791%
Utilization auto / allo HSCT, age < 70	2.64/0.04	2.69/0.24	4.31/0.33	2.95/0.11	3.87/0.27	5.14/0.48	5.80/0.36	6.35/0.27	7.66/0.36	5.77/0.37	+118% / +774%
Latin America											
Autologous	282	323	354	617	701	825	996	1037	825	1228	335%
Allogeneic	11	8	11	2	4	8	6	14	10	9	-18%
Incidence, Gross	7551.52	7826.32	8152.86	8509.68	8847.85	9189.38	9567.46	9968.37	10353.19	10784.06	43%
Incidence, Gross, Age < 70	4908.45	5078.10	5297.63	5526.58	5729.29	5942.42	6191.24	6452.62	6697.50	6973.91	42%
Utilization auto / allo HSCT, all ages	3.73/0.15	4.13/0.10	4.34/0.13	7.25/0.02	7.92/0.05	8.98/0.09	104.1/0.06	10.40/0.14	7.97/0.10	11.39/0.08	+205% / -43%
Utilization auto / allo HSCT, age < 70	5.75/0.22	6.36/0.16	6.68/0.21	11.16/0.04	12.24/0.07	13.88/0.13	16.09/0.1	16.07/0.22	12.32/0.15	17.61/0.13	+206% / -42%
Europe											
Autologous	6101	6398	6506	6998	7604	8328	8915	9473	10017	10798	77%
Allogeneic	503	503	515	552	552	583	658	588	562	542	8%
Incidence, Gross	40177.92	41091.70	42166.11	43024.01	43844.04	44503.89	45316.02	46330.43	47165.95	48549.73	21%
Incidence, Gross, Age < 70	19773.47	20067.16	20430.98	20658.60	20917.67	21058.37	21389.82	21916.59	22362.32	23130.78	17%
Utilization auto / allo HSCT, all ages	15.18/1.25	15.57/1.22	15.43/1.22	16.27/1.28	17.34/1.26	18.71/1.31	19.67/1.45	20.45/1.27	21.24/1.19	22.24/1.12	+46% / -11%
Utilization auto / allo HSCT, age < 70	30.85/2.54	31.88/2.51	31.84/2.52	33.87/2.67	36.35/2.64	39.55/2.77	41.68/3.08	43.22/2.68	44.79/2.51	46.68/2.34	+51% / -8%
Global Total											
Autologous	10673	11267	11723	13179	14478	15926	17590	18766	19529	22144	107%
Allogeneic	773	828	819	865	808	907	963	895	912	752	-3%
Incidence, Gross	107420.54	110731.64	114639.38	118533.76	122470.47	126124.10	130053.38	134271.60	138689.09	143830.71	34%
Incidence, Gross, Age < 70	58886.39	60655.46	62798.21	64947.28	67096.54	69065.18	71413.51	73986.21	76716.59	79947.38	36%
Utilization auto / allo HSCT, all ages	9.94/0.72	10.18/0.75	10.23/0.71	11.12/0.73	11.82/0.66	12.63/0.72	13.53/0.74	13.98/0.67	14.08/0.66	15.40/0.52	+55% / -27%
Utilization auto / allo HSCT, age < 70	18.12/1.31	18.58/1.37	18.67/1.30	20.29/1.33	21.58/1.20	23.06/1.31	24.63/1.35	25.36/1.21	25.46/1.19	27.70/0.94	+53% / -28%
Total HSCT	11446	12095	12542	14044	15286	16833	18553	19661	20441	22896	100%

ogous HCTs were Latin America and Africa/Eastern Mediterranean, increasing by 335% and 225%, respectively, from 2006 to 2015. For the Africa/Eastern Mediterranean region, this corresponded to an absolute increase of 281 transplantations. The Asia-Pacific region also had large increase in activity, by 148%. In contrast, most regions had relatively stable numbers of first allogeneic HCTs from 2006 to 2015, with some regions, notably North America, reporting declines in allogeneic HCT frequency.

Transplantation Utilization for All Age Groups

We first analyzed the utilization of HCT by donor type, among patients of all ages with MM, using data from the GBD study for 2006 to 2015 (Table 1). Globally, there was a 55% increase in the use of autologous HCT for MM, from 9.9% in 2006 to 15.4% in 2015. The North American and European regions had among the highest utilization at baseline and modest increases over 2006 to 2015. In 2015, the utilization of autologous HCT for all patients with MM was 25.7% in North America, a 87% increase from 2006,

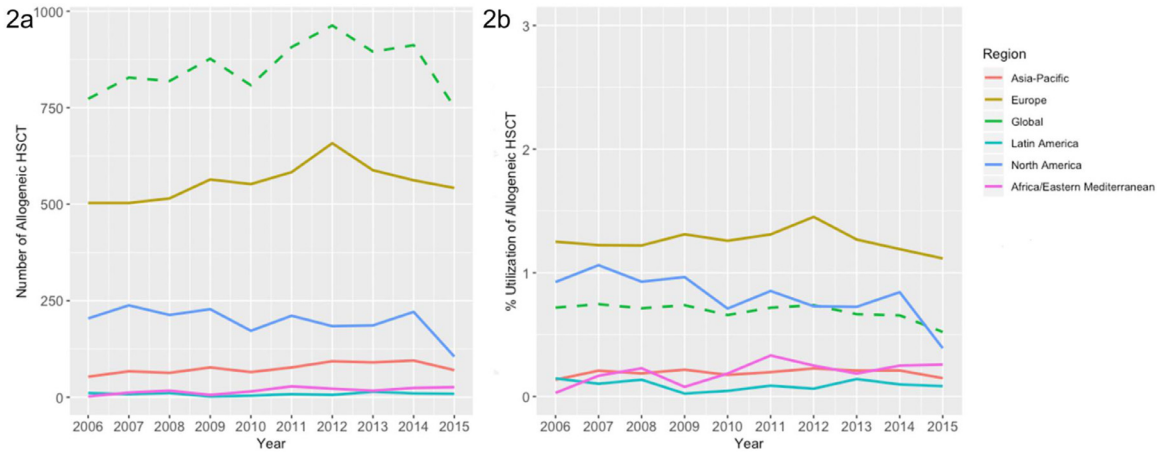

Figure 2. Number (A) and utilization rate (B) of allogeneic HCT, all ages, worldwide by region, 2006 to 2015.

and 22.2% in Europe, a 46% increase from 2006. In contrast, all other reporting regions had much lower baseline utilization of autologous HCT but had among the largest increases from 2006 to 2015. The use of autologous HCT for MM increased from 1.8% to 4.02% by 2015 in Africa and the eastern Mediterranean region, a 123% increase, and from 3.7% to 11.4% by 2015 in Latin American, a 205% increase.

Although the use of autologous HCT increased globally, in contrast, there was a 27% decreased use of first allogeneic HCT for MM, declining from .7% to .5% from 2006 to 2015 (Figure 2). The North American region saw the largest decline, from .93% in 2006 to .4% in 2015, a 58% decrease. The European region had the smallest decline over time, with first allogeneic HCT performed for MM in 1.3% of patients in 2006 and in 1.1% of patients in 2015, a 11% decrease.

HCT in Patients Age <70 Years

Given that many healthcare systems restrict the use of autologous and allogeneic HCT for MM in patients younger than 65 to 70 years, we then examined the utilization of HCT in MM in the age <70 population using data from the GBD source tool for data. Globally, the utilization of autologous HCT was 27.7% in 2015, representing a 53% increase since 2006, whereas the utilization of allogeneic HCT was only .94%, a 28% decline since 2006 (Figure 3). Both North American and European regions reported the highest use of autologous HCT among patients with MM age <70 years, at 52.2% in North America and 46.7% in Europe in 2015.

Allogeneic HCT in Europe

As discussed previously, the reporting of allogeneic HCT in Europe includes both tandem auto-allo HCT and first allogeneic HCT in the total numbers of allogeneic HCTs reported to the WBMT. Including only first allogeneic HCT and excluding auto-allo HCT, the absolute number of allogeneic HCTs was 270 in 2006 and 250 in 2015.

DISCUSSION

Autologous HCT for eligible patients with newly diagnosed MM remains a standard of care globally, despite the introduction of effective drugs such as PIs, IMiDs, and monoclonal antibodies. In our analysis of the global state of HCT for MM, autologous HCT gross numbers have increased globally by 107% from 2006 to 2015 in all studied world regions. The utilization rate of autologous HCT has also increased globally by 66%, from 9.9% to 15.4% in 2015. Particularly encouraging is the findings that autologous HCT activity has increased among world regions with predominantly lower middle-income countries, such as Latin America, where autologous HCT utilization has increased from 3% to >10% over this 9-year period (an absolute increase from 282 to 1228 HCTs

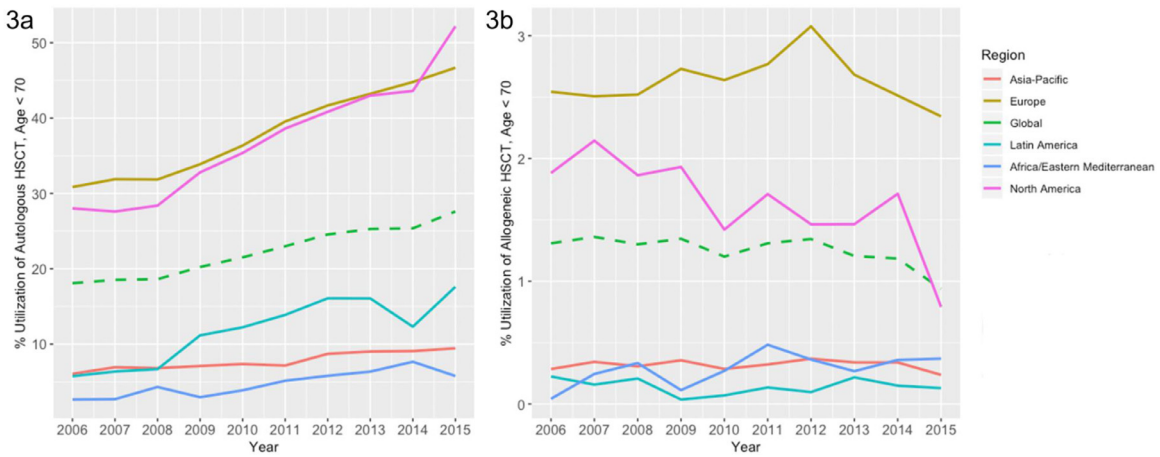

Figure 3. Utilization of autologous (A) and allogeneic (B) HCT in patients age <70 years, worldwide by region, 2006 to 2015.

per year). Notably, autologous HCT utilization in North America and Europe in the <70 age group has increased dramatically, exceeding 50% in North America and 45% in Europe. It is encouraging that an effective therapy such as autologous HCT is being widely used for eligible patients in these high-income regions.

Nevertheless, there are disparities in HCT activity in general when comparing high-income regions such as North America and Europe with all other world regions, particularly the Asia-Pacific and Africa/Eastern Mediterranean regions. This is likely due to a combination of factors, including fewer active transplantation teams per 10 million inhabitants, differences in healthcare infrastructure, and possibly poor awareness of the effectiveness of autologous HCT for MM. One potential reason for the lower frequency of HCT usage in Asia-Pacific may be that HCT for curable diseases such as aplastic anemia, acute leukemia, and hemoglobinopathy tends to take priority over autologous HCT [17]. Previous work by the WBMT has established a clear relationship between transplant activity and economic factors such as gross national income and health expenditures, and it is likely that the same factors are involved with autologous HCT for MM in these data [14,15]. Potential remedies for this imbalance include efforts by nonprofit (eg, WBMT) and government agencies alike to increase the number of functioning transplantation teams in low-utilization countries and to improve education and awareness of HCT through teaching and training programs that partner with high-volume transplantation centers. Such activities are currently operative in a few pilot centers using telemedicine supervision.

In contrast to the marked gains seen globally with autologous HCT for MM, the pattern of use for allogeneic HCT is dramatically different. Throughout the 9-year study period, allogeneic HCT was much less widely utilized in all regions worldwide except Africa and Asia-Pacific. The region that saw the greatest utilization, Europe, also had the most stable rates of use. In contrast, North America has seen a decline in utilization of allogeneic HCT from a peak of >2% in 2007 for those under 70, currently, in 2015, at much less than 1%. There are likely several reasons for the global decline in allogeneic HCT. Although some studies have demonstrated improvement in outcomes with and over autologous HCT alone, other large randomized trials have failed to reproduce these findings [18-20]. It is very likely that the results of these conflicting trials have led to decreased use globally. Moreover, with the addition of several new agents for treatment of relapsed and newly diagnosed MM, the indication for allogeneic HCT may have changed to second-line or after autologous HCT [6-8,11]. Despite these factors, allogeneic HCT utilization has remained at a steady but low rate in Europe. We note that these numbers represent only the first allogeneic HCT, and that trends over the last decade have increasingly leaned toward allogeneic HCT in the relapsed MM setting in Europe [21].

With respect to allogeneic HCT in Europe, there may be differences in reporting here compared with other world regions. The European data include both first allogeneic HCT and tandem auto-allo HCT in the data for allogeneic HCT for MM. However, the differences between the absolute numbers and the utilization rate do not change the overall picture in Europe—that allogeneic HCT is not commonly utilized. Although there may be some discrepancies in reporting methods among different world regions, it is clear that allogeneic HCT remains utilized at a consistent but low level.

With respect to pre-autologous HCT utilization of novel agents—PIs, IMiDs, and monoclonal antibodies—we did not have the ability to assess for this, given the data collected by the WBMT survey. For a full picture of global therapeutic utilization for MM, future research should investigate the utilization of and access to novel agent therapy before autologous HCT. The limited published data show that as of 2017, global regulatory approval of lenalidomide, a commonly used IMiD, and bortezomib, a PI, were widely approved, but some regions still lacked regulatory approval, such as Central Asia and sub-Saharan Africa [1].

Our study has some important limitations. We used data from the GBD study to determine gross incidence of MM globally, but because these statistics themselves may have inherent flaws (such as under ascertainment, as acknowledged specifically in the recent publication on the global burden of MM [1]), these data should be taken as rough estimates. In addition, the population burden of MM may vary significantly among countries, especially those with a different age structure, adding to the uncertainty about the true utilization of HCT across different regions. However, we note that it is difficult to adjust for these factors and conclude that although this study may have limitations, it is also useful as a benchmark for understanding trends and disparities in how HCT is used on global level. Owing to the nature of the data from the WBMT and the GBD, we lack long-term outcomes data, which are critical for a complete full evaluation of HCT on a global level. Finally, our WBMT registry data for HCT for PCDs include other diagnoses at low frequencies, such as immunoglobulin light-chain AL amyloidosis, and does not represent a totally clean dataset. Nonetheless, given that the vast majority of HCTs worldwide for PCDs are for MM, we feel confident that the data represent a good assessment of the numbers and utilization of HCT for MM worldwide.

In summary, here we have reported data on the global use of HCT for MM. Although Europe and North America remain heavy utilizers of autologous HCT for MM, the rest of the world is dramatically different. Economic factors play into this finding but cannot be the sole reason. As an example, in the Asia-Pacific region, one of the regions with comparatively lower use of autologous HCT for MM, human development and gross national income have increased rapidly over the past 15 years, yet HCT rates for MM have not kept pace. Thus, other factors may be important, including improved training, education, and awareness of the optimal management of MM pathways that includes autologous HCT. Further efforts need to be focused on building a better healthcare infrastructure globally and on expanding education and training in transplantation, to improve the access of patients with MM to HCT on a global level.

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