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Global Characteristics and Outcomes of Autologous Hematopoietic Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma: A Study of The Worldwide Network for Blood and Marrow Transplantation (WBMT)

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Contribution: LGa, LGr, MA, YA, DN designed the study; LK, LB, AD, NEM, PH, WS, AC, MI, SO, HT, SM, KK, YK, NH, BSK, CL, KWH, ASG, SKT, AME, AB, QNC, RA, MAB, MB, CAFO, ER, SG, FB, HM, AMcC, FRW, LM, MK, JS, SS, DMcL, PH, AS, HG enrolled patients; LGa, LGr, DNe, NH, MA, YA, DN analyzed the data; LGa, LGr, DNe, NH, MA, YA, DN wrote the manuscript.

Declaration of interest

COI: Laurent Garderet declares consulting fees from BMS, Janssen, Sanofi, and Pfizer. Anita D'Souza reports institutional clinical trial support from Abbvie, Caelum, Janssen, Novartis, Prothena, Sanofi, TeneoBio; ad board and consulting fees from BMS/Celgene, Janssen, Kedrion, Pfizer, and Prothena. John Snowden declares consulting fees from Medac, Jazz and Vertex. Hira Mian is supported by an early career award from Hamilton Health Sciences. Ad board and consulting fees: BMS, Janssen, Sanofi, Amgen, Pfizer, and Takeda. Research funding: Janssen and Pfizer. Yoshiko Atsuta reports consulting fees from JCR Pharmaceuticals Co., Ltd. and Kyowa Kirin Co., Ltd.; lecture fees from Otsuka Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd., Novartis Pharma KK, AbbVie GK; and honorarium from Meiji Seika Pharma Co, Ltd. Mickey Koh: received honoraria from Gilead, KiTE and Takeda. Other investigators have no COI.

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki.

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Abstract

Autologous hematopoietic cell transplantation (AHCT) is a commonly used treatment in multiple myeloma (MM). However, real-world global demographic and outcome data are scarce. We collected data on baseline characteristics and outcomes from 61,725 patients with newly diagnosed MM who underwent upfront AHCT between 2013 and 2017 from nine national/international registries. The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS), relapse incidence (RI) and non-relapse mortality (NRM). Median OS amounted to 90.2 months (95%CI 88.2–93.6), median PFS 36.5 months (95%CI 36.1 to 37.0). At 24 months cumulative RI was 33% (95%CI 32.5–33.4%) and NRM was 2.5% (95%CI 2.3–2.6%). In the multivariate analysis, superior outcomes were associated with younger age, IgG subtype, complete hematological response at autoHCT, Karnofsky score of 100%, ISS stage 1, HCT comorbidity index 0, standard cytogenetic risk, autoHCT in recent years, and use of lenalidomide maintenance. There were differences in the baseline characteristics and outcomes between registries. While the NRM was 1–3% at 12 months worldwide, the OS at 36 months was 69–84%, RI at 12 months was 12–24% and PFS at 36 months was 43–63%. The variability in these outcomes is attributable to differences in patient and disease characteristics as well as the use of maintenance and macroeconomic factors. In conclusion, worldwide data indicate that AHCT in MM is a safe and effective therapy with an NRM of 1–3% with considerable regional differences in OS, PFS, RI, and patient characteristics. Maintenance treatment post AHCT had a beneficial effect on OS.

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm characterized by uncontrolled proliferation of mutated plasma cells, leading to specific end-organ damage¹. It was the third

most common hematological malignancy after non-Hodgkin lymphoma and leukemia in 2020, contributing to 176,404 (14%) of the 1,278,362 blood cancers diagnosed worldwide². Although the cause of MM remains largely unknown, the risk factors include male sex, Black race, older age, living in developed countries, family clusters, radiation exposure, and obesity^{1,4}. Two additional studies confirmed a wide variation in the burden of MM, with a higher incidence and mortality observed in men and countries with a higher human development index^{5,6}. Due to the introduction of newly developed targeted therapies and transplantation techniques, five-year overall survival (OS) has doubled over the past decade to approximately 54%³. The utilization of autologous hematopoietic cell transplantation (AHCT) plays an important role in the treatment of MM^{7–11}.

The worldwide network for stem cell transplantation (WBMT) was founded as a federation of several societies working in the field of hematopoietic cell transplantation (HCT), with the aim of improving HCT, stem cell donation, cellular therapy, accreditation, and access to HCT worldwide, especially in countries with low or no activity. To this end, the WBMT has since 2006 regularly published worldwide transplant activity surveys^{13–15}. Previous publications have revealed a variable incidence of MM between countries, which has increased uniformly since 1990, with the largest increase occurring in middle and low-middle socio-demographic index countries. Access to effective MM care is limited in many countries with low socioeconomic development, particularly in sub-Saharan Africa¹. AHCT activity in plasma cell disorders, principally MM, has increased worldwide from 10,675 in 2002 to 23,701 in 2016². Greater utilization has mostly been seen in high-income regions, and it remains poorly utilized in Africa and the Eastern Mediterranean Region. More work is needed to improve access to AHCT in MM patients, especially in low-income to middle-income countries³.

The overall objective of this study was to analyze the outcomes of AHCT in patients with MM from nine registries worldwide. The outcomes of patients with newly diagnosed MM (NDMM) were computed accounting for differences in patient and disease risk factors between countries and country-specific macroeconomic factors.

Patients and methods

Study design and data sources

This retrospective registry study was conducted through the WBMT, utilizing data from their member societies and international or regional registries on HCT for patients with NDMM aged ≥ 18 years between 2013 and 2017. As center-based activity reports do not contain patient-specific information, member societies were asked to provide patient, disease, AHCT characteristics, and outcome information. The need for additional informed consent from patients was waived because the study was performed by the secondary use of registry data, and no personal information was transferred. The primary endpoint was overall survival (OS) and the secondary endpoints were progression-free survival (PFS), cumulative relapse incidence (RI), and non-relapse mortality (NRM).

Outcome data were obtained through requests from the following regional registries:

1. The Center for International Blood and Marrow Transplantation (CIBMTR; www.cibmtr.org), the United States of America (USA),
2. The Canada registry using the Ottawa Blood Disease Center MM Database (OBDCMMD),
3. Latin American Blood and Marrow Transplantation group (LABMT).
4. The European Society for Blood and Marrow Transplantation (EBMT; www.ebmt.org)
5. Australia and New Zealand Transplant & Cellular Therapies Registry (ANZTCTR; www.anztct.org.au)
6. The Asian Pacific Blood and Marrow Transplant Group (APBMT; www.apbmt.org) with reporting registries
 - a. Myeloma Transplant Registry, Ministry of Health, Malaysia (MTRMOHM)
 - b. Japan Society for Transplantation and Cellular Therapy/ Japanese Data Center for Hematopoietic Cell Transplantation (JSTCT/JDCHCT)
 - c. Taiwan Society of Blood and Marrow Transplantation (TBMT)
 - d. Beijing Bone Marrow Transplant registry
7. Eastern Mediterranean Blood and Marrow Transplant Group (EMBM).

Regional contributions

In 2016, 1,662 teams in 86 countries across six WHO regions delivered HCT services. These included the Americas (AMR/PAHO; WHO regions North, Middle, and South America, and Canada); Asia (SEAR/WPR; WHO regions Southeast Asia and the Western Pacific Region, which includes Australia and New Zealand); Europe (EUR, which includes Turkey and Israel); and AFR/EMR [WHO regions Africa (AFR) and Eastern Mediterranean Region (EMR)] (www.who.int/about/regions/en/). A detailed list of organizations providing activity data and the definitions used in the manuscript has been reported in previous publications².

The registries reported all AHCTs without time interval restrictions between diagnosis and AHCT, except for CIBMTR, which provided information on patients who underwent transplantation within 12 months of diagnosis.

Definitions

Deletion 17p and/or t(4:14) and/or t(14:16) were considered high-risk cytogenetic findings, with the remaining being standard risk¹⁶. Hematological responses were defined according to the IMWG criteria¹⁷. OS was defined as the time from AHCT to death from any cause and PFS was defined as survival without relapse or progression. RI was defined as the cumulative incidence of either relapse or progression post-AHCT, and NRM as death without evidence of relapse or progression. Transplant rate (TR) was defined as the number of AHCTs in a country per 10 million inhabitants.

Economic factors

Gross National Income (GNI) is defined as gross domestic product, plus net receipts from abroad of compensation of employees, property income, and net taxes less subsidies on production (<https://data.oecd.org/natincome/gross-national-income.htm>). Current health expenditure (HCE) includes healthcare goods and services consumed each year without capital health expenditure. Both factors are expressed in current international dollars and converted into purchasing power parity (PPP) per capita. Factors were obtained from the World Bank (www.worldbank.org), WHO (www.who.int), and United Nations (<http://hdr.undp.org>) for 2013 – 2017.

Statistical analysis

Clinical, demographic, and AHCT-related characteristics at baseline were tabulated by the year of AHCT, registry, and country. Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as frequencies and proportions. Median follow-up after baseline and 95% confidence intervals (CI) were calculated using the reverse Kaplan-Meier (KM) method. The probabilities of OS and PFS were estimated using the KM method, and the groups were compared using the log-rank test. The cumulative incidence of NRM together with RI was analyzed in a competing risk framework, and Gray's test was used to compare the differences between the groups.

Associations between patient characteristics and outcomes were evaluated by multivariate analysis (MVA) using Cox (cause-specific) proportional hazard models based on complete cases. All models included a random country effect (normally distributed) and the following variables: ISS at diagnosis, cytogenetic risk, age at AHCT, sex, year of AHCT, diagnosis and AHCT time interval, immunoglobulin subtype, Karnofsky score (100 and $\leq 90\%$), stage at diagnosis, preparative regimen (type and dose), HCT-comorbidity index (CI), and lenalidomide maintenance. As there was a high degree of missing information on ISS at diagnosis, cytogenetic risk, and HCT-CI, we analyzed the first model with all variables except ISS, cytogenetic risk, and HCT-CI. A second analysis was performed using a subset of patients with complete information on the three additional aforementioned variables. The association between maintenance therapy (lenalidomide, other, no maintenance) and OS, PFS, and relapse was analyzed using landmark Cox proportional hazards models at 3 months, including the subset of patients with available maintenance data and the same two sets of confounders as described above.

All outcomes in the MVA analyses were artificially censored at 36 months. All tests were two sided. To determine the factors associated with the time-to-event outcomes, the type 1 error rate was fixed at 0.05. No adjustments were made for the multiple comparisons. All analyses were performed in R version 4.2.2 using 'survival', 'cmprsk,' and 'prodlim' packages ¹⁸.

The methods used for the analysis of country-specific macroeconomic factors are described in the supplementary material.

Results

Patient characteristics

A total of 103,847 first AHCTs for MM were reported in the WBMT activity survey between 2013 and 2017⁴. Outcome information was available for 61,725 NDMM patients (59.5%) from 629 transplant centers in five WHO regions. AHCTs/year increased from 11,317 in 2013 (18.3%) to 13,498 in 2017 (21.9%). The mean number of transplantations per year increased in all regions except in EMR (Supplemental Table S1). The transplant rate per 100,000 population in 2017 per region/country is shown in Supplemental Table S4. The patient, disease, and AHCT characteristics are shown in Table 1. The median age at diagnosis was 59.9 years with the lowest median age in the EMR (52.5 years) and Malaysia (54.3 years) and highest in Ottawa, Canada (61.5 years). The median year of diagnosis was 2014, and was well balanced between registries. IgG (54.0%), light chain (24.4%), and IgA (18.6%) were the predominant subtypes; however, there were significant differences between regions. Disease stage at diagnosis was reported in 54.5% of patients (ISS I in 38.0%, ISS II in 34.8%, and ISS III in 27.1%) and cytogenetics in 44.5% of patients (high-risk 30.3%). Median age at AHCT was 60.8 (IQR: 54.6–65.8) years, lowest in EMR (53.6 years) and highest in Canada (62.2 years). Only 5.1% of patients were older than 70 years at AHCT, with the lowest proportions in Malaysia (0%) and EMR (0.6%), and the highest in the USA (9.8%). HCT-CI at AHCT (available in 71.8%) was low in 52%, intermediate in 25% and high in 23%. USA and Latin America reported high-risk HCT-CI scores in 42.2% and 5.5 %, respectively. Karnofsky score at AHCT was $\leq 90\%$ in 72.0%, lowest in Latin America (44.3%) and highest in Ottawa (92.4%). Most patients underwent AHCT in very good partial remission (VGPR, 38.0%) and partial remission (PR, 36.2%). Complete remission (CR) was reported in 19.1% of patients, minimal remission/stable disease (MR/SD) in 4.7%, and relapse/progression in 1.8%. The percentage of patients with VGPR or better ranged from 76% in Latin America to 39% in Australia and New Zealand. The most frequently used conditioning regimen was melphalan at a dose of 200 mg/m² (70% of patients). However, only 60.4% of patients received this dose in Malaysia, as opposed to 89.6% in Ottawa, Canada. Only a minority of patients had tandem AHCTs (6.7%): 10.1% in Europe and 1.3% in the USA. Lenalidomide was used for post-transplant maintenance in 51% of 6,801 patients for whom information was available (11.0% of all patients).

Outcome in the entire population

After a median follow-up of 41 months (IQR 19–60), median OS was 90.2 months (95% CI 88.2–93.6) and OS at 24 months was 88.4% (95% CI 88.1–88.7) and 63.4% (95% CI 62.7–64.0)% 72 months (Figure 1a). The median PFS was 36.5 months (95% CI 36.1 to 37.0), the PFS was 64.6% (95% CI 64.1–65)% at 24 and 28.6% (95% CI 28.0–29.2%) at 72 months (Figure 1b). The cumulative RI increased from 2.4% (95% CI 2.3–2.5) at three months to 33% (95% CI 32.5–33.4%) at 24 months (Figure 1c) and 65.5% (95% CI 64.9–66.1%) at 72 months. In contrast, NRM was 0.6% (95% CI 0.6–0.7%), 2.5% (95% CI 2.3–2.6%) and 5.9% (95% CI 5.6–6.1%) at 3, 24 and 72 months, respectively (Figure 1d).

Outcome according to regions

Three-year OS varied between regions, from 84.3% to 68.6% ($p < 0.001$; Figure 2a and Table S2a). The longest median OS was observed in the USA, and the shortest in Malaysia (Table S2a). The differences observed within 12 months became more pronounced with longer follow-up periods. PFS showed similar patterns (Figure 2b and Table S2a), with the highest PFS at 36 months in Japan (62.5%) and lowest in Malaysia (43.3%). This was reflected in the lowest cumulative 36-month RI observed in patients in Japan (31.7%) and the highest in those from the EMR (52.3%) (Figure 2c and Table S2b). The highest 36-months NRM of 5.8% was observed in patients from Japan and the lowest in patients from the EMR at 2.0% (Figure 2d).

Outcome according to risk factors

Univariate analyses were performed using Karnofsky score, sex, MM subtype, ISS Staging, cytogenetic score, HCT-CI risk score, disease status, conditioning, graft source, age, and maintenance. All these factors were significantly associated with OS, while the interval from diagnosis to transplant, graft source, and tandem AHCT were not. Notably, the 36-month OS increased from 80% (95% CI 79–81%) in 2013 to 84% (95% CI 83–85%) in 2017.

Multivariate analysis (MVA)

The MVA OS model (without ISS, cytogenetic risk, and HCT-CI) included 52,568 patients with complete data (Supplemental Table S3). The most important risk factors for OS and PFS were relapse at AHCT (HR 5.23 for OS and HR 3.44 for PFS), SD/MR at AHCT (HR 1.99 and 1.84), no maintenance (HR 1.79 and 1.72), IgA subtype (HR 1.47 and 1.82), Karnofsky score $\leq 90\%$ (HR 1.33 and 1.10), melphalan 140 mg/m² (HR 1.25 and 1.16), VGPR at AHCT (HR 1.21 and 1.28), light chain MM (1.14 and 1.08), older age (HR 1.1 and 1.03 per 10 years increase, respectively) as compared to baseline (CR at AHCT, maintenance, IgG subtype, Karnofsky score 100%, melphalan 200 mg/m² and younger age). A more recent calendar year of AHCT was associated with better OS, PFS, and RI (Supplemental Table S3). The same factors, except for older age at AHCT (HR 0.95), were also associated with increased RI. Non-CR stage at AHCT (HR 2.5, 2.19, 1.47 for VGPR, PR, SD/MR, and relapse/progression, respectively), melphalan dose 140 mg/m² instead of 200 mg/m² (HR 1.64), Karnofsky score $\leq 90\%$ (HR 1.40), and older age at AHCT (HR 1.36) were strongly associated with NRM. The time interval from diagnosis to AHCT was not significantly associated with OS, PFS, risk of relapse, or NRM.

An additional MVA was performed on a subset of 20,355 patients for whom data on cytogenetic risk, HCT-CI risk scores, and ISS at diagnosis were available (Table 2). A higher HCT-CI (HR 1.30 and 1.15 for high and intermediate) was significantly associated with worse OS, but was not significantly associated with PFS or an increased risk of relapse. High-risk cytogenetics (HR 2.13) and a higher ISS (HR 2.13 and 1.51 for ISS III and II, respectively) were associated with worse OS, PFS, and RI. The point estimates of other variables in these analyses were similar to those presented in Supplemental Table S3.

We then performed a three-month landmark analysis restricting the two datasets to patients with information on post-AHCT maintenance. The characteristics of the patients with and

without maintenance information were similar, except for the year of HCT. Lenalidomide maintenance was associated with improved OS, PFS, and lower RI, but not NRM (Supplemental Figure 1). No treatment or treatment other than lenalidomide maintenance was associated with lower OS (HR 2.09 and 1.36), PFS (HR 1.61 and 1.39), and higher RI (HR 2.09 and 1.36). (Tables 2 and S3).

Transplant activity and outcomes by macroeconomic factors

Country HRs extracted from the model and country-specific health economic variables were correlated. TR correlated strongly with HCE, with higher AHCT activity in countries with higher HCE ($r = 0.67$, $p < 0.01$; Supplemental Figure S2a). Furthermore, a lower risk of death after AHCT was observed in countries with higher HCE ($r = -0.49$, $p < 0.01$; Supplemental Figure S2b) and in countries with higher HCE/GNI ($r = -0.45$, $p < 0.01$; Supplemental Figure S2c). Similarly, the risks of death or relapse ($r = -0.39$, $p < 0.01$; Supplemental Figure S2d) and relapse ($r = -0.37$, $p < 0.01$; Supplemental Figure S2e) were lower in countries with higher HCE/GNI quotients. In contrast, only a trend was found between the HR for death without relapse and HCE/GNI ($r = -0.26$, $p = 0.06$; Supplemental Figure S2f).

Discussion

Information on the outcomes of patients with MM undergoing upfront AHCT between 2013 and 2017 (inclusive) was collected from different regions worldwide. The median OS was 90.2 months and the median PFS 36.5 months. The cumulative RI was 15.7% at 12 months, and the NRM was 1.5% at 12 months and 3.4% at 36 months. This confirms the safety of AHCT worldwide, independent of the country's income. Notably, these were real-world data and were not derived from clinical trials with defined eligibility criteria.

In MVA, older age was associated with inferior OS, primarily due to a higher NRM. Females tended to have a slightly better OS than males as reported previously for other hematological diseases and solid tumors^{19–22}. In recent years, outcomes have improved, most likely due to the availability of numerous novel therapies, such as immunomodulatory drugs (IMiDs), proteasome inhibitors, and CD38 monoclonal antibodies²³. Interestingly, the stage of disease at AHCT was the most important prognostic factor. The risk of death was higher with more advanced disease at AHCT, underscoring the importance of utilizing a highly effective induction regimen at the outset to achieve the best response to AHCT. Achieving at least CR and, currently, a minimal residual disease (MRD) negative status has a clear positive impact on post-transplant outcomes²⁴. With respect to the immunoglobulin subtype, our analysis confirms the detrimental outcomes seen with IgA compared to IgG paraproteins and, to a lesser extent, light chain myeloma compared to IgG subtype, as has also been previously reported^{25, 26}.

The association between lower Karnofsky scores and poorer outcomes was stronger for NRM and OS and weaker for RI. Higher HCT-CI was only associated with worse NRM and OS, whereas poor cytogenetic risk was associated with increased RI, but had no impact on NRM. There was a strong association between the ISS stage and all outcomes.

The observation that patients conditioned with a melphalan dose of 140 mg/m² had poorer outcomes than those receiving 200 mg/m² was at odds with published data. Although we also found that the differences in the risk of adverse outcomes between lower and standard melphalan doses were substantially smaller in models adjusted for cytogenetic risk, ISS at diagnosis, and number of comorbidities, a significantly higher risk of NRM remained in those who had received a lower melphalan dose. This finding may be due to selection bias, as patients receiving a lower dose of melphalan were older, had lower Karnofsky scores, and had more comorbidities. Despite adjusting for these factors, confounding by other factors that were not tested here may be possible. E.g., we could not adjust for differences in renal function as the data was not readily available. In a previous study, outcomes were similar following melphalan 140 mg/m² and melphalan 200 mg/m², with remission status at the time of transplantation being the overriding determinant i.e., AHCT in less than PR favored melphalan 200 mg/m² over 140 mg/m² in terms of OS, PFS, and relapse risk²⁷.

AHCT outcomes were significantly associated with macroeconomic factors. In general, a higher HCE/GNI ratio was associated with a lower risk of death and disease recurrence but not NRM. Unsurprisingly, this finding suggests that investment in healthcare services affects the outcomes. Further health care services and health economics research are required to elucidate the causes of this association, which may be due to a lack of access to maintenance therapy.

Our study has some important limitations. Reporting practices, data collection systems, and quality checks differ between registries, resulting in varying amounts of missing information. Despite a generally low NRM, significant differences in survival and relapse outcomes between registries were observed in univariate analyses. Different factors, including variations in the baseline characteristics, may be responsible for this effect. For example, lower-income regions tend to transplant younger patients and select patients who achieve a good hematological response, while in other registries, a higher percentage of older patients (>70 years) were transplanted, and tandem HCT was used routinely. The percentage of patients with high HCT-CI scores also differed between regions, with the highest percentage among patients from the USA and Malaysia and a lower percentage of high-risk patients in Japan and Latin America. Importantly, there were limitations in data collection for post-HCT consolidation and maintenance treatment. Maintenance therapy has been shown in prior studies to improve PFS and OS²⁸. With the caveat that the data were limited, our analysis showed that patients with post-AHCT lenalidomide maintenance had a lower risk of relapse with improved OS and PFS. Access to lenalidomide varies globally, which may partially explain the different outcomes observed in Malaysia. We have tried to address the important issue of drug access but we found it more difficult than expected. First, within the same region, country approval date varies considerably. Second, there may be an important gap between approval of a drug and its reimbursement. It depends very much on the type of medical coverage whether it is state driven (“social security system”) or through private insurance. Sometimes, within the same country, both type of reimbursement exist and in the end it is difficult to capture for a single patient whether or not the patient actually has access to these new expensive myeloma drugs. Despite these limitations, this study provides important insights into the use of AHCT in NDMM and has generated useful data on its safety and efficacy at the global level.

In conclusion, this exceptionally large study provides a high-level overview of AHCT. Despite the reassuringly low early NRM rate, differences in patient selection, transplant procedures, and outcomes across geographic regions have been identified. To our knowledge, this is the first time that real-world outcome data encompassing almost 60% of the world's transplant activity have been reported in the field of MM. Patients with MM who underwent AHCT outside of clinical trials between 2013 and 2017 had a RI of 15.7% in the first year, a median PFS of three years and a median OS of seven years and the treatment has been increasingly utilized¹². However, the regional differences in relapse and survival outcomes warrant further investigation. Our new transplant registry collaboration provides a framework for evaluating and improving MM outcomes globally. In addition, the experience gained also paves the way for future analyses of novel non-transplant therapies and assessment of relative global access, utilization, and outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing:

data can be obtained upon request to the corresponding author

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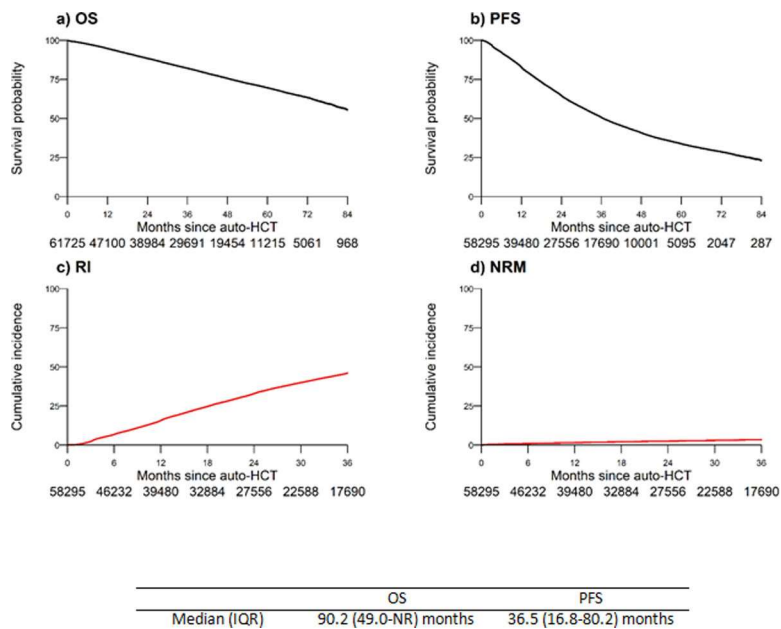


Figure 1: Outcome after auto-HCT: a) probability of overall survival (OS), b) progression free survival (PFS), c) cumulative relapse incidence (RI) and d) cumulative incidence of non-relapse mortality (NRM). Due to the large number of patients, the 95% confidence intervals are very narrow and cannot be distinguished from the point estimates. Numbers below the graphs show the number of patients at risk.

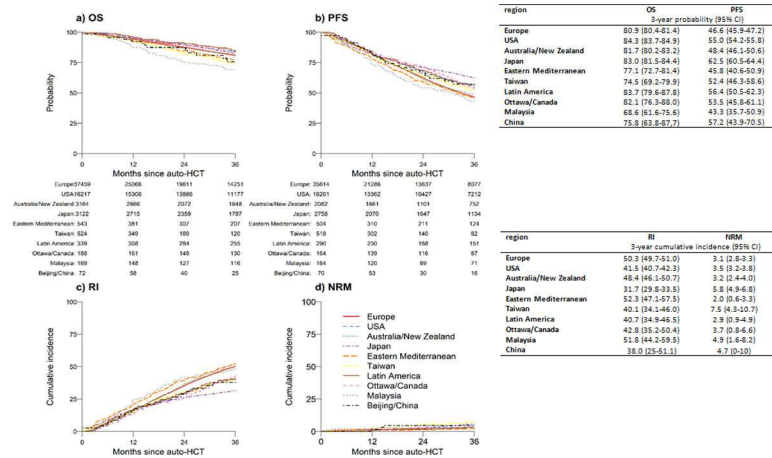


Figure 2: Outcome after auto-HCT by registry / region: a) probability of overall survival (OS), b) progression free survival (PFS), c) cumulative relapse incidence (RI) and d) cumulative incidence of non-relapse mortality (NRM). Numbers below the graphs show the number of patients at risk.

Table 1: A;

Characteristics of patients and diseases of global population and by region.

Characteristics (information available)	Group	Total	Europe	USA	Australia/ New Zealand	Japan	EM region	Taiwan	Latin America	Ottawa, Canada	Malaysia	China
	all patients	61725	37459	16217	3164	3122	543	524	339	188	169	72
		% or median (range) [IQR]										
Age diagnosis (n=61663)	Median years (IQR)	59.9 (17.0– 82.7) [53.6– 64.9]	59.6 (17– 82.7) [53.5– 64.4]	60.9 (19.7– 82.5) [54.5– 66.6]	60.7 (19.7– 78.7) [54.6–65.4]	59 (24– 76) [53– 64]	52.5 (17.5– 81.7) [46–58.1]	57.7 (27.6– 74.3) [51.9– 62.5]	55 (20–73) [48–60]	61.5 (34.2– 72.6) [56.4–65.8]	54.3 (29.4– 68.6) [48.3– 58.9]	58 (34– 73) [50– 64]
Race (n=28023)	Male	58.0	58.1	57.3	62.7	55.4	61.3	53.2	57.2	59.6	60.9	52.8
	Caucasian	73.1	93.4	79.9		0.2			98.3	87.9		
	Asian	15.7	3.1	2.1		99.7		100.0		5.3	100.0	100.0
	Black	10.7	3.2	17.4		0.1				6.1		
	Am. Indian/ Alaska	0.1	0.1	0.2					1.7	0.8		
Ethnicity (n=27653)	Hawaiian/ Other PI	0.3	0.1	0.5								
	No Hispanic	91.8	91.3	92.1		100	100	100	0.3	100	100	100
Year of Diagnosis (n=61663)	Median year (range)	2014 (1976– 2017)	2014 (1976– 2017)	2015 (2012– 2017)	2014 (1990–2017)	2014 (1999– 2017)	2014 (1995– 2017)	2015 (2006– 2017)	2014 (2001– 2017)	2015 (2010– 2017)	2014 (2000– 2017)	2016 (2011– 2016)
	[IQR]	[2013– 2016]	[2013– 2016]	[2013– 2016]	[2013–2016]	[2013– 2015]	[2013– 2015]	[2013– 2016]	[2013– 2015]	[2013– 2016]	[2013– 2015]	[2013– 2016]
MM classification (n=60429)	IgG	54.0	52.1	56.2	61.6	56.7	46.0	51.4	61.7	59.6	73.6	52.4
	Light chain	24.4	27.2	20.7	16.5	19.3	37.8	21.3	16.4	14.4	4.3	17.5
	IgA	18.6	17.6	20.8	18.6	19.4	13.1	23.0	16.4	23.9	20.2	25.4
	Non- secretory	1.7	1.9	11.2	1.9	1.6	1.1	0.4	3.0	1.1		

Characteristics (information available)	Group	Total	Europe	USA	Australia/ New Zealand	Japan	EM region	Taiwan	Latin America	Ottawa, Canada	Malaysia	China
	all patients	61725	37459	16217	3164	3122	543	524	339	188	169	72
		% or median (range) [IQR]										
	Other Ig	1.3	1.1	1.1	1.4	3.0	1.9	3.9	2.4	1.1	1.8	3.2
ISS (n=33640)	I	38.0	38.8	38.9	38.8	35.7	25.3	25.7	30.5	20.6	15.7	27.9
	II	34.8	34.0	34.6	37.5	38.7	36.0	36.4	24.1	47.5	41.3	41.2
	III	27.1	27.2	26.6	23.7	25.7	38.7	37.9	45.4	31.9	43.0	30.9
Cytogenetic risk (n=27468)	High	30.3	31.3	34.8		9.9	5.2	11.8	22.3	61.9	27.4	41.4
Interval Dg – HCT (n=61663)	months	7.1 (0–476) [5.5–9.9]	7.4 (0–476) [5.6–10.9]	6.4 (0–12) [5.2–8.2]	6.9 (0–294) [5.5–9.9]	7.8 (0–173) [5.9– 11.3]	8.6 (2.8–254) [6.3– 13.2]	7.7 (1.8–101) [5.9–10.5]	13 (3–170) [8–20]	6.4 (3–35) [5.6–8.2]	10.8 (5–178) [8.3–15.9]	n.a.

Abbreviations: CR: complete response, VGPR: very good partial response, PR: partial response, R/R: relapse/refractory, PI: Proteasome Inhibitor, PB: peripheral blood, BM: bone marrow, IQR: inter quartile range; HCT: hematopoietic cell transplant; HCT-CI: hematopoietic cell transplant comorbidity index, OS: overall survival, PFS: progression free survival, RI: relapse incidence, NRM: non-relapse mortality, HR: hazard ratio, CI: confidence interval, IMiD: immunomodulatory drug, ISS: International staging scoring, PB, peripheral blood; BM, bone marrow; ANZICT: Australia and New Zealand Transplant & Cellular Therapies Registry, EM: Eastern Mediterranean region,

* European data were provided by EBMT and included also patients from South Africa (n=142), Colombia (n=12), Singapore (n=48), Iraq (n=1), Iran (n=114), India (n=3) and Brazil (n=7).

Table 1: B;

AHCT characteristics of the global population and according to region.

Group	Total	Europe	USA	Australia/ New Zealand	Japan	EM region	Taiwan	Latin America	Ottawa, Canada	Malaysia	China
all patients	61725	37459	16217	3164	3122	543	524	339	188	169	72
Transplant Rate (HCT/10 million population)		138.6	213.7	226.9	53.3	5.9	31.3	22.8	37.2	17.4	3.6
% or median (range) [IQR]											
Year of HCT (n=61725)	2013/14/15	19/20/20	17/18/19	19/18/20	18/20.5/19.5	24/20/17	17/17/21	11/16/17	15/18/21	16/21/22	18/8/8
	2016/17	20/21	22/23	22/21	20/21	16/23	23/23	24/32	27/19	18/22	21/44
Age at HCT (n=61725)	years	60.7 (18.1– 83.2) [55–66]	61.5 (20– 83) (55–67)	61.6 (22.1– 79.5) [55–66]	60 (25–77) [54–64]	53.6 (19– 83) [47–59]	58.5 (28– 75.7) [52–63]	56 (30.5– 69) [50–61]	62 (36.5– 73) [57–66]	56 (30.5– 69) [49–60]	59(34– 74) [51–65]
	<60/60– 65/66–70	47/31/19	43/26.5/20	42/31/22	46/36/17	79/16/4	58/30/10.5	67/23/9	36/35/26	73/20/8	54/28/17
	>70	5.1	3.5	9.8	4.6	0.6	1.9	1.5	3.7		1
HCT-CI risk (n=44319)	Low (0)	51.8	65.2	26.8	77.3	53.0	62.9	71.3	52.8	3.8	
	Intermediate (1–2)	25.0	21.6	31.1	16.9	31.7	28.3	23.2	28.9	63.8	
	High (>= 3)	23.2	13.1	42.2	5.8	15.3	8.7	5.5	18.3	32.4	
Kamofsky at HCT (n=55799)	≤90	72.2	66.9	88.1	78.2	57.9	50.6	44.3	92.4	82.6	
Disease at HCT (n=60367)	CR	19.1	20.5	15.8	12.8	19.0	29.5	40.0	16.3	26.8	40.3
	VGPR	38.0	39.1	39.4	26.1	31.6	41.2	35.8	4.3	27.4	29.0
	PR	36.2	34.2	38.1	49.0	42.8	24.0	21.8	36.5	40.9	21.0
	SD/MR	4.7	3.4	6.7	10.1	4.0	1.8	1.5	12.9		6.5
	R/R	1.8	2.4	0.0	2.0	2.2	3.5	0.9		4.9	3.2
	Untreated	0.2	0.3		0.1	0.4					

Characteristics (information available)	Group	Total	Europe	USA	Australia/New Zealand	Japan	EM region	Taiwan	Latin America	Ottawa, Canada	Malaysia	China
all patients		61725	37459	16217	3164	3122	543	524	339	188	169	72
Transplant Rate (HCT/10 million population)			138.6	213.7	226.9	53.3	5.9	31.3	22.8	37.2	17.4	3.6
% or median (range) [IQR]												
Graft source (n=61725)	PB/BM/ PB+BM	99,8/0,1/0,0	99,7/0,2/0,1	100/0/0	99,9/0,1/0	99,9/0,0/0	99,6/0,2/0,2	99,8/0,2/0	100,0/0,0/0	100/0,0/0	100,0/0,0/0	100/0,0
Non cryopreserved (n=9567)		0.7		1.2	0.0	0.0		0.0	13.6	0.0	0.0	0.0
Conditioning (n=61355)	Mel200	70.1	62.2	81.8	88.5	81.7	71.0	77.8	83.7	88.6	60.4	90.3
	Mel140	12.0	9.8	18.2	10.2	8.4	4.6	20.7	7.7	5.9	29.0	9.7
	unknown dosage/ others	14,8/3,1	23,5/4,5		0,1/1,2	8,0/1,8	11,3/13,1	0,6/1,0	0,0/8,6	1,1/4,3	0,0/10,7	
Tandem (n=61663)	yes	6.7	10.1	1.3	1.1	3.7	1.5	0.6	0.6	0.0	1.2	100,0
Maintenance (n=6789)	Lenalidomide	50.8	58.4	57.9		46.2	61.7	1.2	24.7	44.6	4.2	15.7
	none	11.0		20.9		36.9			17.0	55.4	67.3	24.3
	Other(s)	10.6	19.2	2.9		1.9	10.0	0.2	1.1			
	Thalidomide	9.4	9.9	0.2			15.0	30.5	38.7		21.4	44.3
	Bortezomib	9.3	11.5	8.6		3.8	13.3		15.9		6.0	2.9
	IMiD/PI	7.9	0.1	7.9		11.2		67.7	2.6		1.2	
	Carfilzomib	1.0	0.9	1.6				0.4				

Abbreviations: CR: complete response, VGPR: very good partial response, PR: partial response, R/R: relapse/refractory, PI: Proteasome Inhibitor, PB: peripheral blood, BM: bone marrow, IQR: inter quartile range; HCT: hematopoietic cell transplant; HCT-CI: hematopoietic cell transplant comorbidity index, OS: overall survival, PFS: progression free survival, RI: relapse incidence, NRM: non-relapse mortality, HR: hazard ratio, CI: confidence interval, IMiD: immunomodulatory drug, ISS: International staging scoring, PB, peripheral blood; BM, bone marrow; ANZTCT: Australia and New Zealand Transplant & Cellular Therapies Registry, EM: Eastern Mediterranean region,

* European data were provided by EBMT and included also patients from South Africa (n=142), Colombia (n=12), Singapore (n=48), Iraq (n=1), Iran (n=114), India (n=3) and Brazil (n=7).

Multivariable analysis on outcome of patients according to characteristics at diagnosis. The OS model included 20355, the PFS, relapse and NRM 19873 patients.

Table 2: A;

Clinical characteristics		OS		PFS		Relapse		NRM	
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Gender	Male	1.00		1.00		1.00		1.00	
	Female	0.93 (0.87–1.01)	0.08	0.94 (0.90–0.98)	0.005	0.94 (0.90–0.99)	0.01	0.94 (0.80–1.10)	0.45
MM classification	IgG	1.00		1.00		1.00		1.00	
	IgA	1.42 (1.30–1.56)	<0.0001	1.26 (1.19–1.34)	<0.0001	1.24 (1.17–1.31)	<0.0001	1.56 (1.28–1.90)	<0.0001
Cytogenetic risk	Light chain	1.10 (1.00–1.22)	0.06	1.12 (1.05–1.19)	0.0004	1.12 (1.05–1.19)	0.0003	1.04 (0.84–1.31)	0.61
	Standard	1.00		1.00		1.00		1.00	
ISS at diagnosis	High	2.13 (1.96–2.30)	<0.0001	1.62 (1.55–1.70)	<0.0001	1.65 (1.57–1.73)	<0.0001	1.32 (1.11–1.58)	0.002
	I	1.00		1.00		1.00		1.00	
	II	1.51 (1.37–1.67)	<0.0001	1.23 (1.16–1.30)	<0.0001	1.22 (1.15–1.29)	<0.0001	1.46 (1.19–1.79)	0.0003
	III	2.16 (1.96–2.39)	<0.0001	1.49 (1.41–1.58)	<0.0001	1.46 (1.38–1.55)	<0.0001	2.02 (1.64–2.49)	<0.0001
Interval diagnosis-HCT (per 6 months more)		1.02 (0.99–1.04)	0.14	1.00 (0.99–1.01)	0.99	1.00 (0.98–1.01)	0.54	1.04 (1.00–1.08)	0.04

Abbreviations: HR >1 is associated with an increased risk for the endpoint. OS: overall survival, PFS: progression free survival, NRM: non-relapse mortality, HR: hazard ratio, CI: confidence interval, MM: multiple myeloma, CR: complete response, VGPR: very good partial response, PR: partial response, SD: stable disease, MR: minor response.

*The association of lenalidomide was investigated in a separate landmark model including only patients without event at 3 months and with data on maintenance therapy available (n= 2904 for OS and 2753 for PFS and relapse) but including the variables listed in this table and a random country effect

Table 2: B;

Multivariable analysis on outcome of patients according to characteristics at HCT. The OS model included 20355, the PFS, relapse and NRM 19873 patients.

Clinical characteristics		OS		PFS		Relapse		NRM	
		HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Age at HCT	(per 10 year increase)	1.07 (1.02–1.12)	0.005	0.98 (0.96–1.01)	0.23	0.96 (0.94–0.99)	0.01	1.29 (1.16–1.44)	0.0004
Year of HCT	(per year later)	0.92 (0.89–0.95)	<0.0001	0.92 (0.90–0.93)	<0.0001	0.91 (0.90–0.93)	<0.0001	0.95 (0.89–1.01)	0.12
Karnofsky score at HCT	100	1.00		1.00		1.00		1.00	
	≤90	1.29 (1.17–1.44)	<0.0001	1.10 (1.05–1.15)	<0.0001	1.08 (1.01–1.15)	0.02	1.31 (1.04–1.64)	0.02
HCT-CI risk score	Low (0)	1.00		1.00		1.00		1.00	
	Intermediate (1–2)	1.15 (1.04–1.27)	0.006	1.01 (0.96–1.08)	0.65	0.99 (0.93–1.05)	0.69	1.44 (1.15–1.80)	0.001
	High (≥3)	1.30 (1.17–1.45)	<0.0001	1.05 (0.98–1.12)	0.15	1.00 (0.94–1.07)	0.93	1.92 (1.52–2.43)	<0.0001
Disease stage at HCT	CR	1.00		1.00		1.00		1.00	
	VGPR	1.17 (1.04–1.32)	0.01	1.25 (1.16–1.34)	<0.0001	1.26 (1.17–1.36)	<0.0001	1.09 (0.84–1.40)	0.53
	PR	1.44 (1.28–1.63)	<0.0001	1.55 (1.44–1.67)	<0.0001	1.54 (1.43–1.67)	<0.0001	1.58 (1.22–2.03)	0.0004
	SD/MR	2.20 (1.84–2.62)	<0.0001	1.88 (1.68–2.11)	<0.0001	1.81 (1.61–2.04)	<0.0001	2.52 (1.77–3.59)	<0.0001
	Relapse/progression	5.55 (4.36–7.06)	<0.0001	3.07 (2.52–3.73)	<0.0001	2.98 (2.42–3.67)	<0.0001	3.83 (2.06–7.12)	<0.0001
Conditioning	Melphalan 200	1.00		1.00		1.00		1.00	
	Melphalan 140	1.07 (0.96–1.19)	0.21	1.09 (1.02–1.16)	0.01	1.06 (0.99–1.14)	0.09	1.36 (1.11–1.67)	0.003
Maintenance*	Lenalidomide	1.00		1.00		1.00			
	Other	1.36 (1.04–1.78)	0.03	1.39 (1.20–1.60)	<0.0001	1.36 (1.04–1.78)	0.03		
	None	2.09 (1.53–2.87)	<0.0001	1.61 (1.33–1.96)	<0.0001	2.09 (1.53–2.87)	<0.0001		

Abbreviations: HR >1 is associated with an increased risk for the endpoint. OS: overall survival, PFS: progression free survival, NRM: non-relapse mortality, HR: hazard ratio, CI: confidence interval, MM: multiple myeloma, CR: complete response, VGPR: very good partial response, PR: partial response, SD: stable disease, MR: minor response.

* The association of lenalidomide was investigated in a separate landmark model including only patients without event at 3 months and with data on maintenance therapy available (n= 2904 for OS and 2753 for PFS and relapse) but including the variables listed in this table and a random country effect