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ARTICLE

Providing both autologous and allogeneic hematopoietic stem cell transplants (HSCT) may have a stronger impact on the outcome of autologous HSCT in adult patients than activity levels or implementation of JACIE at Belgian transplant centres

Hélène A. Poirel[1] · Marijke Vanspauwen[1] · Gilles Macq[1] · Anke De Geyndt[1] · Johan Maertens[2] · Evelyne Willems[3] · Dominik Selleslag[4] · Xavier Poiré[5] · Koen Theunissen[6] · Carlos Graux[7] · Tessa Kerre[8,9] · Pierre Zachée[10,11] · Nathalie Meuleman[12] · Ann De Becker[13] · Anke Verlinden[14] · Florence Van Obbergh[15] · Christine Schuermans[16] · Virginie De Wilde[17] · Aurélie Jaspers[18] · Delphine Pranger[19] · Dries Deeren[20] · Ivan Van Riet[13,21] · Evelien Vaes[1] · Yves Beguin[3,9,11,18] · On behalf of the Belgian Transplant Registry and the Belgian Haematological Society's Transplant committee

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Abstract

While performance since the introduction of the JACIE quality management system has been shown to be improved for allogeneic hematopoietic stem cell transplants (HSCT), impact on autologous-HSCT remains unclear in Europe. Our study on 2697 autologous-HSCT performed in adults in 17 Belgian centres (2007–2013) aims at comparing the adjusted 1 and 3-yr survival between the different centres & investigating the impact of 3 centre-related factors on performance (time between JACIE accreditation achievement by the centre and the considered transplant, centre activity volume and type of HSCT performed by centres: exclusively autologous vs both autologous & allogeneic). We showed a relatively homogeneous performance between Belgian centres before national completeness of JACIE implementation. The 3 centre-related factors had a significant impact on the 1-yr survival, while activity volume and type of HSCT impacted the 3-yr survival of autologous-HSCT patients in univariable analyses. Only activity volume (impact on 1-yr survival only) and type of HSCT (impact on 1 and 3-yr survivals) remained significant in multivariable analysis. This is explained by the strong relationship between these 3 variables. An extended transplantation experience, i.e., performing both auto & allo-HSCT, appears to be a newly informative quality indicator potentially conveying a multitude of underlying complex factors.

Introduction

Hematopoietic stem cell transplantation (HSCT) following high-dose chemotherapy with or without radiotherapy is widely used for the treatment of malignant and non-malignant diseases [1–4]. Over the years, a better control of the different transplant-related toxicities reduced post-transplant morbidity and mortality. Given the balance between pros and cons, autologous-HSCT (auto-HSCT) are mostly performed for the treatment of lymphomas, plasma cell disorders and certain solid tumours, and allogeneic transplants (allo-HSCT) mainly for acute leukemias, myelodysplastic syndromes and myeloproliferative neoplasms, as well as a number of non-malignant disorders [5–9]. The advantages of autologous over allogeneic transplants (allo-HSCT) are the lower risk of life-threatening complications, such as graft-versus-host disease, graft failure and infections. Moreover, treatment-related mortality (TRM) is lower and auto-HSCT are relatively well tolerated by elderly patients [10–13]. However, the use of a patient's own stem cells has certain disadvantages. The autograft may be contaminated with tumour cells and patients do not benefit

These authors contributed equally: Hélène A. Poirel, Marijke Vanspauwen

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✉ Hélène A. Poirel
helene.antoine-poirel@registreducancer.org

Extended author information available on the last page of the article

from the potent immune-mediated graft-versus-tumour effect as observed after allo-HSCT, explaining the higher relapse rate after auto-compared to allo-HSCT [6, 10, 11, 14].

Quality management organizations were launched end of the 1990's, FACT (Foundation for the Accreditation of Cell Therapy) in the USA followed by JACIE (Joint Accreditation Committee-ISCT [International Society for Cellular Therapy] & the EBMT [European Society for Blood and Marrow Transplantation]) in Europe (https://www.ebmt.org/jacie-accreditation) to improve the quality of HSCT [15]. While increasing evidence suggests that patient outcome has been improved for allo-HSCT since the introduction of the JACIE quality management system (QMS) [16–18], results remain contradictory for auto-HSCT in Europe. A preliminary retrospective observational study showed a significant improvement in relapse-free survival when the centre was further along in the JACIE accreditation process [16]. However, these findings were no longer observed with 5 more follow-up years of the same EBMT cohort (66 281 auto-HSCT between 1999 and 2007) [1].

In Belgium, all centres performing HSCT needed to achieve JACIE accreditation by the end of 2017 to get reimbursement [19]. The Belgian Cancer Registry (BCR) has a lot of expertise in collecting, handling, quality controlling, coding, analysing and reporting on cancer-related public health data [20]. Thanks to collaboration between the BCR and the Belgian Haematology Society (BHS), it was decided in 2012 to maintain a Belgian Transplant Registry (BTR) at the BCR. The initial data are downloaded from the EBMT-ProMISe database and handled by the joint effort BCR-BHS. The BTR is a good starting point for reporting transplant centre-specific survival rates after HSCT as already required in other countries, such as the USA, in the frame of QMS.

The present study aims at comparing adjusted survival between the different auto-HSCT centres and investigating the impact of 3 centre-related factors on the performance in Belgium.

Patients and methods

Data collection

Data on all HSCT performed in Belgium between 2007 and 2013 were obtained through a download of the full Minimal Essential Data (MED-A) which are directly introduced by each participating Belgian centre into the ProMISe database. The downloaded file was checked and centres were asked to correct contradictory results and to fill out missing variables. The national social security identity number for each patient was requested to obtain the vital status for outcome analysis. If needed, a data-manager collected the data on-site.

Vital status and date of death/censoring

As the BCR is enabled by law to retrieve vital statuses by coupling its database to the national Crossroads Bank for Social Security, vital statuses were obtained for the BTR database entries. Follow-up was collected until 31 December 2015. Patients alive at the follow-up end are censored at the end of follow-up and patients who are lost to follow-up are censored at earlier dates. The unit of analysis in the study was the transplant, therefore patients could participate more than once if they received several transplants. For those cases, the vital status of the patient was only used for the last transplant. Other transplants are censored at the date the next transplant takes place. In total, 15% of patients in the complete database (both auto and allo-HSCT) have more than one transplant.

Exclusion criteria

A total of 2979 auto-HSCT from 22 Belgian centres were registered over the 2007-2013 period. Our target population for all survival analysis was adult patients undergoing auto-HSCT for hematological disorders. Patients younger than 16 years ($n = 121$) and transplants for solid tumours were excluded ($n = 77$). Centres that performed less than 5 auto-HSCT per year on average were excluded ($n = 79$ transplants from 3 centres), according to the FACT-JACIE standards [15]. Finally, 5 records had a missing vital status, resulting in a total of 2697 auto-HSCT records for outcome analyses from 17 Belgian centres.

Observed survival

The observed survival rates are reported at one year and 3 years after transplant with a minimal follow-up of at least 2 years. Observed survival was calculated with the Kaplan–Meier method using a semi-complete cohort analysis approach.

Adjusted survival

Variables used in the multivariable models

- Transplant year over the 2007–2013 period.
- Age of the patient at transplant divided into 4 categories: 16–19 years, 20–39 years, 40-59 years and ≥60 years.
- Gender of the patient: male versus female.
- Performance status before transplant assessed with the Karnosfky scale: 2 main categories were considered,

90–100 (well performing patients) versus 0–80 (less well performing patients).
- Disease risk index (DRI) adapted from [21], which is a 4-level grouping scheme (low, intermediate, high and very high) combining three major prognostic factors for HSCT outcome: diagnosis, disease status and genetic aberrations. The genetic risk groups are only defined for patients with the diagnosis of acute myeloid leukemia (adapted from the ELN stratification [22, 23]) and myelodysplastic syndrome (adapted from the IPSS score [24]).
- Transplant number: all transplants of patients who received multiple HSCT (autologous and/or allogeneic) were ordered in time and given a transplant number accordingly.
- Time between diagnosis of the disease and auto-HSCT: 2 categories were considered, <18 and ≥18 months.

Generalized linear regression model (GRp model)

In order to fairly compare survival estimates across the different Belgian transplant centres, the overall survival rates were adjusted for the different confounders as mentioned above. This was done by applying a fixed effects censored data generalized linear regression model [25, 26] [Supplementary Data]. Separate models were applied to 1 and 3-year survivals. All relevant covariables were entered into the GRp model and a backward elimination procedure based on Akaike's information criterion (AICc) [27] was used to define the list of covariables that most strongly predicted 1 or 3-year survival. Transplant year, Karnofsky performance status, DRI and the total number of performed transplants were retained for 1-year survival by the AICc selection. In addition to these 4 variables, age of the patient at transplant and time between diagnosis and transplant were selected for the endpoint of 3-year survival.

Once the models were built, accurate predicted survival rates based on the centres' case-mix were obtained. The centre was not included as a confounder in the analysis but the centre effect was indirectly assessed. As such it assumes that the Belgian transplant recipients are dying at the same uniform rate across all transplant centres, after adjusting for the main prognostic covariables (i.e., the case-mix). Subsequently, confidence limits for the centre-specific predicted survival estimate are calculated by a bootstrapping methodology [28]. We state that when the observed survival lies outside of the bootstrap-predicted 95% intervals, the centre 7is over or under-performing the overall network of centres [28]. These results are summarized by forest plots (Figs. 1a, b) for all centres.

Odds ratio

Another goal of this study was to assess the impact of three centre-related factors on the performance of the auto-HSCT centres:

- Centre activity volume: annual number of auto-HSCT performed by each centre (continuous variable).
- Type of transplant performed by each centre: centres that exclusively perform auto-HSCT, vs centres that perform both auto and allo-HSCT. Centres performing at least 35 allo-transplants over the whole period were defined as 'both auto and allo-HSCT', while those providing less than 5 allo-HSCT per year on average were labelled 'only auto-HSCT' centres.
- JACIE accreditation time during the 2007–2013 period: modelled as a continuous variable corresponding to the time between JACIE accreditation achievement by the centre and the considered transplant. The value of a transplant which is performed in an unaccredited centre at the time of transplant is 0. Ten centres achieved JACIE accreditation during the period (2008: 1, 2009: 1, 2010: 1, 2011: 1, 2012: 4 & 2013: 2).

These centre-related variables were added to the GRp models. This enabled us to explore their effect while adjusting for the other, patient and transplant-related confounders that were already found to influence survival. As the continuous centre activity volume and JACIE accreditation time were found to have a linear relationship with 1 and 3-yr survival, centre volume was divided by 50 and JACIE time by 365.241 so that every unit increase would actually correspond to an increase of 50 transplants (volume) and 1 year (JACIE). No interactions were included in the final model because no interactions for a selection of variables (backward type) remained in the 1-yr survival model, and only interaction between the centre activity volume and the centre type in the 3-yr survival model. However, the interpretation of this interaction is difficult as the centre activity volume variable is not significant.

Results

Diagnostic indications for transplant

Diagnostic indications are listed in Table 1 for the 2,858 auto-HSCT performed in adult patients. As expected, the most frequent indications are plasma cell disorders, mainly multiple myelomas (46.5%), and non-Hodgkin's lymphomas (40.2%). No trend modification appears over the 2007–2013 period.

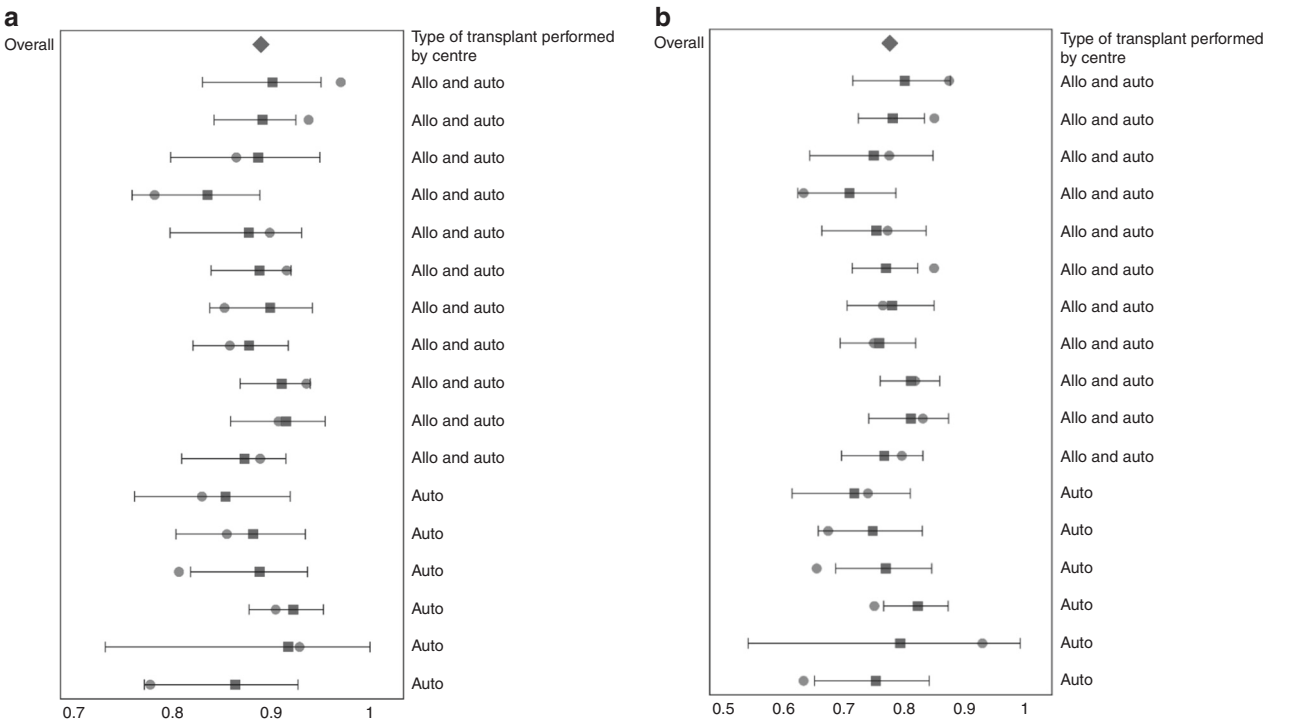

Fig. 1 Forest plot of the survival at 1 year (**a**) and 3 years (**b**) for autologous transplants in Belgium (2007-2013), as predicted by the multivariable model for all centres. Survival at 1 year was adjusted for transplant year, performance status, disease risk index and transplant number. Survival at 3 years was adjusted for transplant year, age, performance status, time between diagnosis and transplant, disease risk index and transplant number. Centres are represented by a blue square that indicates the 1-year (or 3-year) survival for that centre as predicted by the multivariable model (adjusted for case-mix). 95% confidence limits for predicted survival are indicated by black lines. The observed survival for that centre is represented on the forest plot by a dot. The overall result of predicted survival is indicated by a diamond on the top of the forest plot. If the actual observed survival of the centre, as represented by the dot, is higher or lower than the upper or lower limit of the confidence interval, there is evidence of the centre over-performing or under-performing, respectively, the overall network of Belgian centres. Note that centres are not displayed in a particular order (e.g., by centre activity volume) in order to preserve anonymity

Outcome analysis

Descriptive analysis

Table 2 shows the variables selected for the multivariable analysis on the 2697 auto-HSCT. Most transplants were performed in patients between 40 and 59 years of age (49.2%) and within 18 months after diagnosis (71.6%). In 66.6% of the transplants, the patients had an intermediate DRI index. Nearly 90% were first auto-HSCT and 9.6% were second transplants.

Adjusted survival

Observed survival was 88 and 77% at 1 and 3 years, respectively. The overall adjusted survival for the whole of Belgium was 89% at 1 year and 78% at 3 years. For 1-yr survival, 2 out of the 17 centres were found to be over-performing the general network of Belgian auto-transplant centres versus 3 underperforming centre (Fig. 1a). For 3-yr survival, 2 centres were overperforming and 1 under-performing (Fig. 1b).

Impact of centre-related indicators

The impact of three additional factors on the 1-yr and 3-yr survival was investigated (Fig. 2): the JACIE accreditation time of the transplant, the type of transplant performed by the centre and the centre activity volume. Univariable analysis showed that each of the 3 variables had a significant impact on 1-yr and centre volume and type of transplant on 3-yr survival (only a trend for JACIE accreditation time). However, when the 3 variables were added simultaneously in the adjusted model, (i) the JACIE accreditation time of centres had no significant impact on 1-yr or 3-yr adjusted survivals; (ii) increasing centre activity volume significantly improved survival at 1 year ($p = 0.0022$) but not at 3 year ($p = 0.5341$); (iii) performing both auto- and allo-HSCT had a significant positive impact on both 1-year ($p = 0.0349$) and 3-year survival ($p < 0.0001$) (Fig. 2).

The 3 centre-related indicators are related when taken 2 by 2. The Spearman correlation confirmed the positive relationship between the centre activity volume and JACIE accreditation time (0.20199, $p < 0.0001$). Centres that

Table 1 Diagnostic indications of the total Belgian adult (≥16 yr-old) population per transplant year

	2007		2008		2009		2010		2011		2012		2013		2007-2013	
Year of transplant	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Overall	395		382		355		393		464		435		434		2858	
Diagnostic indications																
Plasma cell disorders	211	53.4	178	46.6	154	43.4	204	51.9	236	50.9	222	51.0	231	53.2	1436	50.2
Multiple myeloma	195		165		148		190		220		201		211		1330	46.5
Primary amyloidosis	8		4		3		3		3		11		10		42	1.5
Other plasma cell disorders[a]	8		9		3		11		13		10		10		64	2.2
Lymphoma	152	38.5	161	42.1	169	47.6	167	42.5	196	42.2	176	40.5	165	380	1186	41.5
Non-Hodgkin lymphoma	116		129		141		144		174		139		132		984	34.4
Hodgkin lymphoma	35		32		28		23		21		36		33		210	7.3
Lymphoma, NOS	1		0		0		0		1		1		0		3	0.1
Acute leukaemia	18	4.6	31	8.1	13	3.7	11	2.8	16	3.4	8	1.8	9	2.1	106	3.7
Others	12	3.0	12	3.2	19	5.3	11	2.8	16	3.5	29		30	6.7	129	4.5
Solid tumour	6		8		12		8		7		19		21		81	2.8
Auto-immune disease	3		1		3		1		4		9		7		28	1.0
MDS/MPN	3		1		0		1		2		1		1		9	0.3
Chronic leukaemia	0		2		2		0		3		0		1		8	0.3
Histiocytic disorders	0		0		2		0		0		0		0		2	0.1
Bone marrow failure	0		0		0		1		0		0		0		1	0.0
Missing	2	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.01

For further analysis, 161 transplants were excluded as described in the exclusion criteria of the Patients and Methods section

[a]other plasma cell disorders include plasmacytoma (solitary plasmacytoma of bone, multiple plasmocytoma), plasma cell leukemia and POEMS syndrome

perform both autologous and allo-HSCT tend to have a higher activity volume than centres that exclusively perform auto-HSCT (median number of transplants: 158 versus 104, $p = 0.072$). Finally, only one out of 6 centres that exclusively perform auto-HSCT achieved JACIE accreditation compared to 9 out of 11 centres that perform both autologous and allo-HSCT.

Discussion

The aim of this study was to describe patient- and transplant-related covariables influencing short (1-year) and longer term (3-year) survival of auto-HSCT recipients in Belgium. Survival within the first year is considered as a better measure of the toxicity of the transplant procedure itself thereby evaluating the specific transplant performance of each centre, whereas survival beyond the first year may be more severely impacted by disease relapse (which depends on the disease status at transplantation and the time from diagnosis to transplant) [28]. In the FACT-JACIE standards, the 1-yr survival outcome is used to compare the performance of the centre to (inter)national outcome data and JACIE standard B4.7.5 states that 'If expected 1-year survival outcome is not met, the Clinical Program shall submit a corrective action plan' [15]. Our study gives the opportunity for centres to meet this standard and, if necessary, to implement a corrective action plan to improve outcomes. In our study, the 2 additional covariables retained for survival at 3 years by the backward selection procedure, i.e., age at transplantation and time between diagnosis and transplant, confirm the arguments of Logan et al. [28]. Our multicentre study had several limitations, i.e., exclusion of small centres, transplant as the unit of the study instead of the patient, incomplete case-mix, not including comorbidities, conditioning regimens…). Despite a relatively homogeneous performance between centres, two of them were found to be over-performing and three (only one at 3 years) under-performing. We further examined some centre characteristics potentially contributing to these differences.

QMS, such as JACIE, have been developed to increase harmonization and standardization of HSCT with the final aim to improve patient care and outcome. The aim of the JACIE accreditation time variable is to measure the impact of being in an accreditation process, which results from a prolonged preparatory work starting several months before accreditation achievement. JACIE accreditation time throughout the study period had no effect on short term or longer term survival. As Belgian centres implemented this QMS with different timings from 2008, the impact of

Table 2 Case mix of the total Belgian autologous transplant population (2007–2013): variables considered in the multivariable model for adjusted survival

Characteristics	*N*	%
Overall	2697	100.0
Sex		
Female	987	36.6
Male	1,710	63.4
Transplant year		
2007	388	14.4
2008	370	13.7
2009	338	12.5
2010	372	13.8
2011	437	16.2
2012	399	14.8
2013	393	14.6
Age groups		
16–19	26	1.0
20–39	291	10.8
40–59	1328	49.2
≥60	1052	39.0
Performance status		
0–80	885	32.8
90–100	1567	58.1
Missing	245	9.1
Time between diagnosis & transplant		
<18 months	1932	71.6
≥18 months	765	28.4
DRI by Armand		
Low	464	17.2
Intermediate	1797	66.6
High	316	11.7
Very high	63	2.3
Missing	57	2.1
Transplant number		
First	2402	89.1
Second	260	9.6
Third	28	1.0
Fourth	4	0.1
Missing	3	0.1

JACIE implementation may be underestimated by the short periods of accreditation. Gratwohl et al. [16]. did not show a significant impact of JACIE accreditation on long-term outcome of auto-HSCT (as observed for allografts [16, 29, 30]), but a stepwise improvement in outcome depending on the particular phase of the accreditation process at the time of transplant [17]. However, JACIE accreditation status significantly influenced outcome of auto-HSCT in specific indications, such as autoimmune diseases [31].

Several studies showed that overall survival, treatment failure and TRM were influenced by centre activity volume for allo-HSCT, with thresholds for high volume centre varying from 3 to 45 transplants per year [32–38]. Data on auto-HSCT remain limited [28, 38]. Our study showed that transplant centre activity volume had a significant impact on survival of auto-transplant patients at 1-year, even after exclusion of very low volume centres. We excluded such centres that did not meet a minimal threshold of activity for statistical reasons. However, this number is also in line with JACIE standards that require a minimum of 5 auto-transplant patients on average per year [15].

We also identified an influence of the type of transplants centres perform. Patients transplanted in centres that performed both allo and auto-HSCT had significantly higher 1 and 3-year survivals than in centres only performing auto-HSCT. The three additional centre-related factors, JACIE accreditation time, type of transplant and activity volume, are strongly related. It is noteworthy that over-performing centres had all a mixed allo- and auto-HSCT activity while under-performing centres were all among centres performing only auto-HSCT. The JACIE accreditation process may have 'forced' centres to structure and optimize care, which is easier from a logistic point of view for large centres with more expertise. So, we believe that any of these three related factors can be seen as a proxy for centre 'expertise'. It is not clear which factor of the three is more important than the others. The stronger impact of the type of transplant centre and to a lesser extent of the centre activity volume compared to achieving JACIE accreditation may be explained by the fact that the impact of quality management may be efficient long before accreditation. The type of transplant centre variable appears to be a newly identified and informative indicator which conveys a multitude of underlying complex factors: it may indicate the usefulness of a large centre mastering different HSCT techniques and engaged in a quality system.

A GRp model on pseudo values was applied [25]. This model has several advantages: instead of modelling the hazards (e.g., the Cox model), the survival probability is directly modelled. A direct link between certain factors and their influence on survival time can thus be drawn and easily communicated. Moreover, this method can also be applied when the proportional hazards assumption does not hold, which was the case for some of the covariables under study. Since 'centre' is not added to the model, we are applying an indirect way of standardizing centres. In a large simulation exercise (data not shown) in which we compared direct to indirect standardization of centres using the GRp model, we have found that both have advantages and disadvantages. A patient may have received several auto-HSCT or a combination of both auto- and allo-HSCT during the period in which transplants were registered into

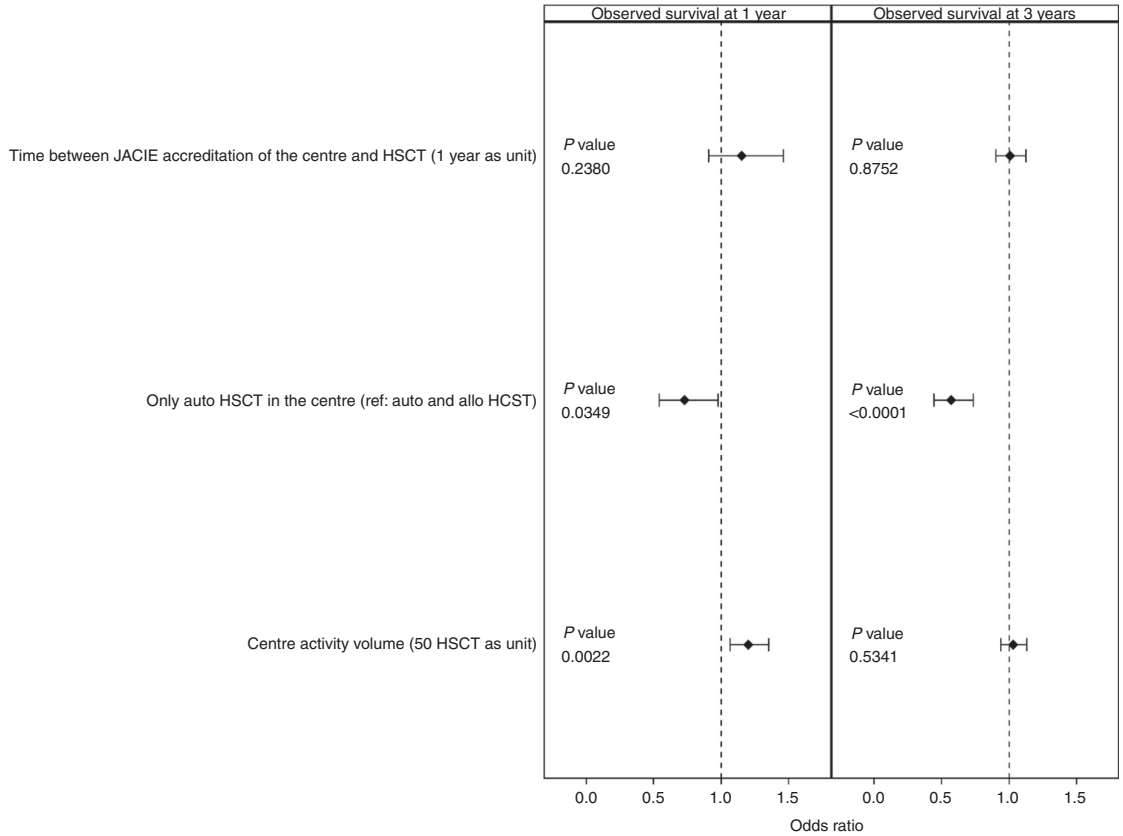

Fig. 2 Comparison of the 1-year and 3-year adjusted survival between centres with JACIE accreditation vs no, between centres with only an autologous transplant unit vs both an autologous and allogeneic transplant unit, and for centre activity volume that was modelled as a continuous variable

ProMISe (2007-2013), thereby introducing a bias. To investigate this bias, we repeated all statistical models only on the patients that contributed one transplant in the BTR. The final results showed little to no difference globally and on the level of the individual centres. Given these conclusions and the fact that only 15% of patients contribute more than one transplant, we believe the bias to be minimal.

In conclusion, the results presented here are the first on the Belgian transplant level and the first to identify centre activity as predictor of survival after auto-HSCT. This study shows relatively homogeneous performance between Belgian centres before complete JACIE accreditation implementation at the national level. Feedback reports for each centre with comparison to national and even international activities may stimulate continuous quality improvement in the field of HSCT [15]. Further studies with a longer period of accreditation to better assess the survival improvements of the implementation of a QMS in auto-HSCT are however, warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Spivak JL. Myeloproliferative neoplasms. N Engl J Med. 2017;376:2168–81.
2. Zahid U, Akbar F, Amaraneni A, Husnain M, Chan O, Bin Rias I, et al. A review of autologous stem cell transplantation in lymphoma. Curr Hematol Malig Rep. 2017;12:217–26.
3. Kipps TJ, Stevenson FK, Wu CJ, Croce CM, Packham G, Wierda WG, et al. Chronic lymphocytic leukaemia. Nat Rev Dis Prim. 2017;3:17008.
4. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med. 2006;354:1813–26.
5. Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, Dufour C, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant. 2017;52:811–7.
6. Saba N, Abraham R, Keating A. Overview of autologous stem cell transplantation. Crit Rev Oncol Hematol. 2000;36:27–48.
7. Ljungman P, Bregni M, Brune M, de Witte T, Dini G, Einsele H, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009. Bone Marrow Transplant. 2010;45:219–34.
8. Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, et al. Indications for autologous and allogeneic

hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015;21:1863–9.
9. Sureda A, Bader P, Cesaro S, Dreger P, Duarte RF, Dufour C, et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. Bone Marrow Transplant. 2015;50:1037–56.
10. Peters WP, Dansey R, Baynes RD. Autologous bone marrow and stem cell transplantation. In: Kufe DW, Pollock RE, Weichselbaum RR et al., editors. Holland-Frei Cancer Medicine. B.C. Decker; 2003.
11. Champlin R. Hematopoietic cellular transplantation. In: Kufe DW, Pollock RE, Weichselbaum RR et al., editors. Holland-Frei Cancer Medicine. B.C. Decker; 2003.
12. Kusnierz-Glaz CR, Schlegel PG, Wong RM, Schriber JR, Chao NJ, Amylon MD, et al. Influence of age on the outcome of 500 autologous bone marrow transplant procedures for hematologic malignancies. J Clin Oncol. 1997;15:18–25.
13. Miller CB, Piantadosi S, Vogelsang GB, Marcellus DC, Grochow L, Kennedy MJ, et al. Impact of age on outcome of patients with cancer undergoing autologous bone marrow transplant. J Clin Oncol. 1996;14:1327–32.
14. Blume KG, Thomas ED. A review of autologous hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2000;6:1–12.
15. Snowden JA, McGrath E, Duarte RF, Saccardi R, Orchard K, Worel N, et al. JACIE accreditation for blood and marrow transplantation: past, present and future directions of an international model for healthcare quality improvement. Bone Marrow Transplant. 2017;52:1367–71.
16. Gratwohl A, Brand R, Niederwieser D, Baldomero H, Chabannon C, Cornelissen J, et al. Introduction of a quality management system and outcome after hematopoietic stem-cell transplantation. J Clin Oncol. 2011;29:1980–6.
17. Gratwohl A, Brand R, McGrath E, van Biezen A, Sureda A, Ljungman P, et al. Use of the quality management system 'JACIE' and outcome after hematopoietic stem cell transplantation. Haematologica. 2014;99:908–15.
18. Schetelig J, de Wreede LC, Andersen NS, Moreno C, van Gelder M, Vitek A, et al. CLL subcommittee, Chronic Malignancies Working Party. Centre characteristics and procedure-related factors have an impact on outcomes of allogeneic transplantation for patients with CLL: a retrospective analysis from the European Society for Blood and Marrow Transplantation (EBMT). Br J Haematol. 2017;178:521–33.
19. Royal Decree amending article 20, § 1, a), of the annex to the Royal Decree of 14 September 1984 establishing the nomenclature of health care benefits, on compulsory insurance for health care and allowances. Belgisch Staatsblad / Moniteur Belge; 2012-12-06/09.
20. Haematological malignancies in Belgium, Belgian Cancer Registry, Brussels 2015.
21. Armand P, Kim HT, Logan BR, Wang Z, Alyea EP, Kalaycio ME, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood. 2014;123:3664–71.
22. Dohner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood. 2010;115:453–74.
23. Deeg HJ, Scott BL, Fang M, Shulman HM, Gyurkocza B, Myerson D, et al. Five-group cytogenetic risk classification, monosomal karyotype, and outcome after hematopoietic cell transplantation for MDS or acute leukemia evolving from MDS. Blood. 2012;120:1398–408.
24. Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079–88.
25. Andersen PK, Klein JP, Rosthøj S. Generalised linear models for correlated pseudo-observations, with applications to multi-state models. Biometrika. 2003;90:15–27.
26. Logan BR. Review of multistate models in hematopoietic cell transplantation studies. Biol Blood Marrow Transplant. 2013;19: S84–S87.
27. Hurvich CM, Tasi C-L. Regression and time series model selection in small samples. Biometrika. 1989;ume 76(Issue 2):297–330.
28. Logan BR, Nelson GO, Klein JP. Analyzing center specific outcomes in hematopoietic cell transplantation. Lifetime Data Anal. 2008;14:389–404.
29. Anthias C, Ethell ME, Potter MN, Madrigal A, Shaw BE. The impact of improved JACIE standards on the care of related BM and PBSC donors. Bone Marrow Transplant. 2015;50:244–7.
30. Anthias C, O'Donnell PV, Kiefer DM, Yared J, Norkin M, Anderlini P, et al. European Group for Blood and Marrow Transplantation Centers with FACT-JACIE accreditation have significantly better compliance with related donor care standards. Biol Blood Marrow Transplant. 2016;22:514–9.
31. Snowden JA, Badoglio M, Labopin M, Giebel S, McGrath E, Marjanovic Z, et al. European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP); EBMT Paediatric Working Party (PWP); Joint Accreditation Committee of the International Society for Cellular Therapy (ISCT); EBMT (JACIE). Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. Blood Adv. 2017;1:2742–55.
32. Horowitz MM, Przepiorka D, Champlin RE, Gale RP, Gratwohl A, Herzig RH, et al. Should HLA-identical sibling bone marrow transplants for leukemia be restricted to large centers? Blood. 1992;79:2771–4.
33. Hows J, Bradley BA, Gore S, Downie T, Howard M, Gluckman E. Prospective evaluation of unrelated donor bone marrow transplantation. The International Marrow Unrelated Search and Transplant (IMUST) Study. Bone Marrow Transplant. 1993;12:371–80.
34. Matsuo K, Hamajima N, Morishima Y, Harada M. Hospital capacity and post-transplant survival after allogeneic bone marrow transplantation: analysis of data from the Japan Society for hematopoietic cell transplantation. Bone Marrow Transplant. 2000;26:1061–7.
35. Frassoni F, Labopin M, Powles R, Mary JY, Arcese W, Bacigalupo A, et al. Effect of centre on outcome of bone-marrow transplantation for acute myeloid leukaemia. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation. Lancet. 2000;355:1393–8.
36. Loberiza FR Jr., Serna DS, Horowitz MM, Rizzo JD. Transplant center characteristics and clinical outcomes after hematopoietic stem cell transplantation: what do we know? Bone Marrow Transplant. 2003;31:417–21.
37. LeMaistre CF, Loberiza FR Jr. What is quality in a transplant program? Biol Blood Marrow Transplant. 2005;11:241–6.
38. Gratwohl A, Sureda A, Baldomero H, Gratwohl M, Dreger P, Kröger N, et al. Joint Accreditation Committee (JACIE) of the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) and the European Leukemia Net (ELN). Economics and outcome after hematopoietic stem cell transplantation: a retrospective cohort study. EBioMedicine. 2015;2:2101–9.

Affiliations

Hélène A. Poirel[1] · Marijke Vanspauwen[1] · Gilles Macq[1] · Anke De Geyndt[1] · Johan Maertens[2] · Evelyne Willems[3] · Dominik Selleslag[4] · Xavier Poiré[5] · Koen Theunissen[6] · Carlos Graux[7] · Tessa Kerre[8,9] · Pierre Zachée[10,11] · Nathalie Meuleman[12] · Ann De Becker[13] · Anke Verlinden[14] · Florence Van Obbergh[15] · Christine Schuermans[16] · Virginie De Wilde[17] · Aurélie Jaspers[18] · Delphine Pranger[19] · Dries Deeren[20] · Ivan Van Riet[13,21] · Evelien Vaes[1] · Yves Beguin[3,9,11,18] · On behalf of the Belgian Transplant Registry and the Belgian Haematological Society's Transplant committee

1 Belgian Cancer Registry, Brussels, Belgium

2 UZ Gasthuisberg Leuven, Leuven, Belgium

3 CHU de Liège, Liège, Belgium

4 AZ Sint Jan Brugge-Oostende, Brugge, Belgium

5 UCL St-Luc, Brussels, Belgium

6 Jessa Ziekenhuis, Hasselt, Belgium

7 CHU UCL Namur (Godinne site), Yvoir, Belgium

8 UZ Gent, Gent, Belgium

9 Belgian Hematological Society—Transplant Committee, Brussels, Belgium

10 ZNA Antwerpen, Antwerpen, Belgium

11 Co-chair of the Belgian Transplant Registry, Brussels, Belgium

12 Institut Jules Bordet, Brussels, Belgium

13 UZ Brussel, Brussels, Belgium

14 Antwerp University Hospital, Edegem, Belgium

15 Hopital de Jolimont, La Louvière, Belgium

16 GZA Sint-Augustinus, Wilrijk, Belgium

17 Erasmus Brussel, Brussels, Belgium

18 CHR Citadelle, Liège, Belgium

19 Grand Hôpital de Charleroi, Charleroi, Belgium

20 AZ Delta, Roeselare, Belgium

21 Chair of the Belgian Hematological Society – JACIE Committee, Brussels, Belgium