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Allogeneic stem cell transplantation in adults 2015–21

ORIGINAL ARTICLE

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BACKGROUND

Allogeneic stem cell transplantation is the only curative treatment for several malignant and non-malignant haematological diseases, and is associated with a risk of serious complications. In recent years, several changes have been

introduced with the aim of reducing treatment-related complications. This retrospective study reviews quality indicators for patients who underwent transplantation in the period 2015–21.

MATERIAL AND METHOD

The study included 589 adult patients who were treated with allogeneic stem cell transplantation for the first time at Oslo University Hospital in the period May 2015 to May 2021. Three two-year periods are compared using descriptive methods.

RESULTS

In the period 2015–2021, the number of first-time transplant patients per year increased from 85 to 113. One-year survival increased from 68 % in the first two-year period to 74 % in the second period and 82 % in the last period. Both acute and chronic GVHD were reduced, and one-year GVHD-free and relapse-free survival increased from 42 % to 60 % during the study period.

INTERPRETATION

Since 2015, the number of transplants has increased, while survival has improved and the risk of complications is lower.

Main findings

In the period 2015–21, the number of allogeneic stem cell transplants per year increased from 85 to 113. The most common indication for transplantation was acute leukaemia.

One-year survival increased in the same period from 68 % to 82 %, while one-year GVHD-free and relapse-free survival increased from 42 % to 60 %. The median age at transplantation was 56 years in the first two-year period and 58 years in the last two-year period.

Allogeneic stem cell transplantation is the only curative treatment for a number of malignant haematological diseases and congenital or acquired immunodeficiencies. In allogeneic stem cell transplantation, the patient's own bone marrow is destroyed following pre-transplant treatment with high-dose chemotherapy with or without total body irradiation before infusion of haematopoietic stem cells from a healthy donor. The main effect is the introduction of a new immune system with an antileukemic effect (1). Stem cells are harvested directly via aspiration of bone marrow from the iliac crest, from blood cells via leukapheresis after pre-transplant treatment with granulocyte colony-stimulating factor, or from umbilical cord blood drawn from the placenta after the umbilical cord is severed. Patients are initially treated with immunosuppressive drugs to prevent graft-versus-host disease

(GVHD). The aim is to develop tolerance between the patient's and the donor's immune systems, enabling immunosuppressive treatment to be gradually phased out after three to six months.

Treatment with allogeneic stem cell transplantation is associated with a considerable risk of death due to acute and chronic GVHD, infections or multi-organ failure. In a retrospective analysis of patients treated in Norway between 1985 and 2012, the risk of death 100 days post-transplant was 18 %, with a five-year survival rate of 54 %, while 46.5 % developed GVHD (2). The criteria for selecting patients for treatment had therefore been strict. When the treatment was introduced in Norway in 1985, the upper age limit was 40. At the start of the 2000s, this was increased to 60 (3). Better knowledge about immunosuppressive treatment, new drugs in the pre-transplant treatment and better access to donors have meant that more patients can be offered transplants with a lower risk of serious complications and no upper age limit. Several modifications have been made to the transplant programme with a view to reducing the risk of treatment-related death and GVHD, whilst also ensuring a sufficient antileukemic effect. We aimed to investigate changes in transplant activity and the quality of the service for patients treated with allogeneic stem cell transplantation in the period 2015–21.

Material and method

The study was retrospective and included all adult patients who were treated with allogeneic stem cell transplantation for the first time at the Department of Haematology, Oslo University Hospital, in the period 24 May 2015 to 23 May 2021. The study period was divided into three two-year periods: 24 May 2015–23 May 2017 (period 1), 24 May 2017–23 May 2019 (period 2) and 24 May 2019–23 May 2021 (period 3). The date of data retrieval and analysis was 27 September 2022.

Quality indicators recorded included one-year survival, treatment-related death 100 days post-transplant, treatment-related death one year post-transplant, relapse of primary disease one year post-transplant, and acute and chronic GVHD. Treatment-related death was defined as all deaths that were not due to relapse of the primary disease. Subcategories of acute GVHD included cases requiring systemic immunosuppression (grades II–IV) and severe disease (grades III–IV). Survival without GVHD or relapse of primary disease was recorded, as were invasive fungal infection, cytomegalovirus infection and Epstein-Barr virus infection.

The data were obtained from the Department of Haematology's quality register, which is linked to the National Population Register. The quality register was approved by the data protection officer at the hospital, and the Regional Committee for Medical and Health Research Ethics (REK) has approved publication.

Statistical analyses

Categorical variables are presented as percentages and continuous variables as median values with the lowest and highest observed value. Survival was defined as time from transplantation to death or date of analysis. Survival was estimated using the Kaplan-Meier method. Treatment-related death was defined as death from causes other than relapse. The cumulative incidence of treatment-related death, GVHD and relapse was estimated using the Fine-Gray model, which is a non-parametric estimator that factors in competing events. Analyses were performed using Statistica version 13.5 (TIBCO, Palo Alto, CA, USA) and EZR version 1.38 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Patients

In each two-year period, the median observation time was 6.0 years (5.0–7.0), 3.8 years (3.0–4.9) and 2.0 years (1.0–3.0), respectively. The number of transplants was 186 in period 1, 177 in period 2 and 225 in period 3. The median age at transplantation was 56 years in period 1 and 59 years in period 3. The most common indications for allogeneic stem cell transplantation were acute leukaemia (51.1 %), myelodysplastic syndrome and myeloproliferative disorders (27.3 %) and lymphoproliferative disorders (15.6 %). Non-malignant conditions accounted for 4.1 %. During the study period, the number of transplants for patients with acute leukaemia and myelodysplastic syndrome and myeloproliferative disorders increased slightly, while a fall was observed in the absolute and relative proportion of transplants for patients with lymphoma (see Table 1).

Table 1

Patient and donor characteristics for adult patients treated with allogeneic stem cell transplantation at the Department of Haematology, Oslo University Hospital, in the period 24 May 2015 to 23 May 2021.

Variable	Full period 24.5.2015–23.5.2021 (2192 days)	Period 1 24.5.2015–23.5.2017 (731 days)	Period 2 24.5.2017–23.5.2019 (730 days)	Period 3 24.5.2019–23.5.2021 (731 days)
Number of patients	589	186	177	226
Age at transplantation, years, median (range)	57 (15–74)	56 (16–71)	55 (15–74)	58 (16–74)
Gender				
Female	225	67	61	97
Male	364	119	116	129

Variable	Full period 24.5.2015–23.5.2021 (2192 days)	Period 1 24.5.2015–23.5.2017 (731 days)	Period 2 24.5.2017–23.5.2019 (730 days)	Period 3 24.5.2019–23.5.2021 (731 days)
Primary disease, number (%)				
Acute leukaemia	291 (49,4)	93 (50,0)	89 (50,3)	119 (52,7)
Myelodysplastic syndrome/ myeloproliferative disorders	161 (27,3)	47 (25,3)	53 (29,9)	61 (27,0)
Lymphoma/chronic lymphocytic leukaemia	91 (15.4)	39 (21.0)	24 (13.6)	28 (12.4)
Chronic myelogenous leukaemia	11 (1.9)	3 (1.6)	2 (1.1)	6 (2.7)
Non-malignant conditions	24 (4.1)	4 (2.2)	8 (4.5)	12 (5.3)
Donor type, number (%)				
Family donor with identical tissue type	95 (16.1)	39 (21.0)	31 (17.5)	25 (11.1)
HLA-haploidentical donor	29 (4.9)	11 (5.9)	9 (5.1)	9 (4.0)
Unrelated donor	465 (78.9)	136 (73.1)	137 (77.4)	192 (85.0)
Donor's age, years, median (range)				
All	28 (0–74)	30 (17–74)	27 (0–69)	28 (17–64)
Related	54 (17–74)	57 (17–74)	52 (18–69)	43 (17–64)
Unrelated	26 (0–58)	27 (19–57)	24 (0–58)	27 (18–54)
Stem cell source, number (%)				
Bone marrow	120 (20.4)	62 (33.3)	35 (19.8)	23 (10.2)
Blood stem cells	468 (79.5)	124 (66.7)	141 (79.7)	203 (89.8)
Umbilical cord blood	1 (0.2)	0 (0)	1 (0.4)	0 (0)

Donor, stem cell sources, pre-transplant treatment and prophylaxis

Characteristics of the donor and stem cell source are shown in Table 1. The proportion of transplant patients with a family donor with identical tissue type was 21 % in period 1 and 11 % in period 3. The proportion of transplants with an

HLA-haploidentical donor was 5.9 % in period 1 and 4 % in period 3. An unrelated donor was used in 85 % of the transplants in period 3. The median age of sibling donors was 54 years in period 1 and 39 years in period 3.

Bone marrow as a stem cell source accounted for 33.3 % in period 1 and 10.2 % in period 3, and stem cells from peripheral blood were used in 89.8 % of the transplants in period 3. Umbilical cord blood as a stem cell source was used for one patient, for whom no suitable family donors or unrelated donors were found.

The proportion of transplants with bone marrow-depleting pre-transplant treatment was 58 % in period 1 and 76 % in period 3 (Figure 1a).

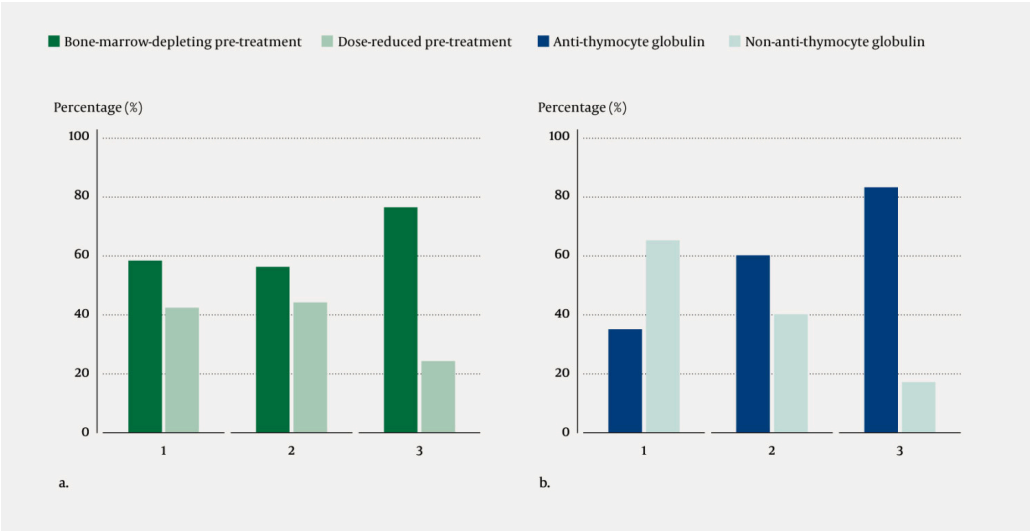

Figure 1 Pre-treatment and prophylaxis prior to allogeneic stem cell transplantation in 2015–21. Use of bone marrow-depleting and dose-reduced pre-treatment (a) and anti-thymocyte globulin as prophylaxis for GVHD (b) in 589 patients in three two-year periods (periods 1, 2 and 3).

Methotrexate and cyclosporine were given prophylactically for GVHD. From 2016, anti-thymocyte globulin was given in addition when the donor was unrelated or when blood was used as a stem cell source (Figure 1b). Patients with an HLA-haploidentical donor received cyclosporine, mycophenolate mofetil and cyclophosphamide post-transplant.

Survival and relapse

For the three two-year periods, one-year survival was 68 %, 74 % and 82 %, respectively (Figure 2a). Treatment-related mortality was 12 %, 11 % and 8 % after 100 days, and 20 %, 14 % and 10 % after one year (Figure 2b). Relapse after one year was 21 %, 19 % and 15 %, respectively (Figure 2c).

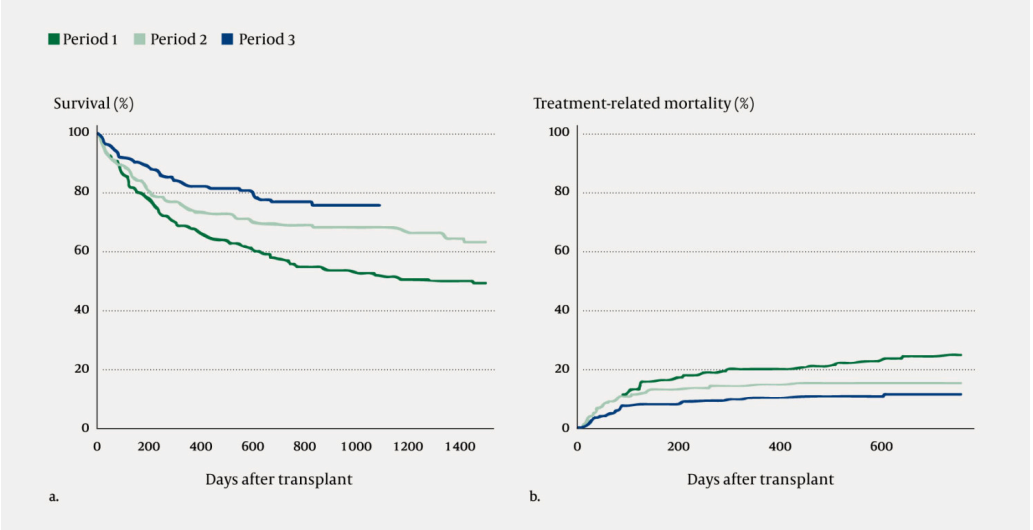

Figure 2A, 2B Clinical results after allogeneic stem cell transplantation in 2015–21. Results for a) survival and b) treatment-related mortality. The dark green line indicates period 1 (n = 186), the light green line period 2 (n = 177) and the blue line period 3 (n = 226). Period 3 in Figure 2a has a shorter observation time than periods 1 and 2.

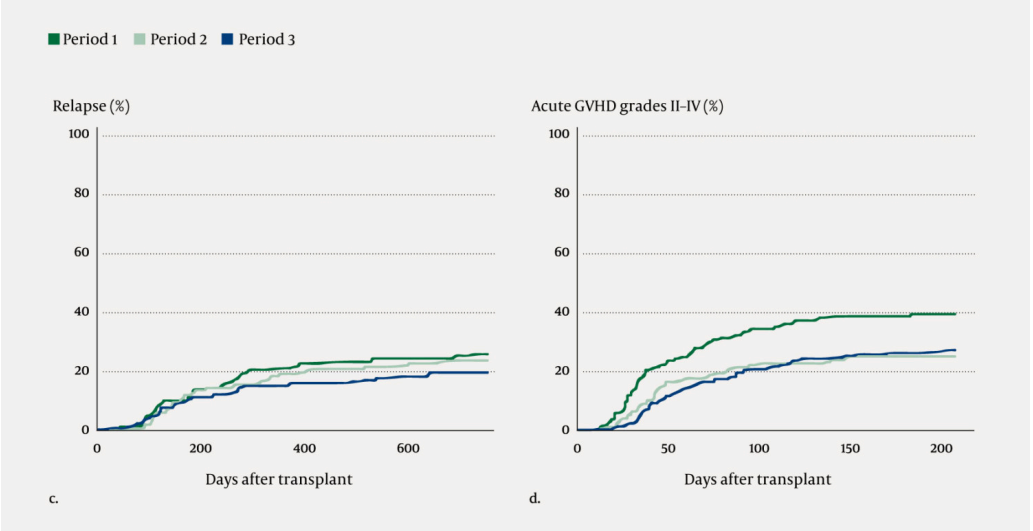

Figure 2C, 2D Clinical results after allogeneic stem cell transplantation in 2015–21. Results for c) relapse and d) acute GVHD grades II–IV. The dark green line indicates period 1 (n = 186), the light green line period 2 (n = 177) and the blue line period 3 (n = 226).

Acute and chronic GVHD

The incidence of acute GVHD grades II–IV within 100 days was 34 %, 23 % and 21 % for periods 1, 2 and 3, respectively (Figure 2d). The incidence of grades III–IV was 13 %, 6 % and 7 %, respectively.

Chronic GVHD occurred in 45 % of patients in period 1, 42 % in period 2 and 26 % in period 3. The incidence of pronounced chronic GVHD after one year was 20 % in period 1 and 15 % in period 3 (Figure 2e). One-year GVHD-free and relapse-free survival was 42 %, 54 % and 60 % for the three periods respectively (Figure 2f).

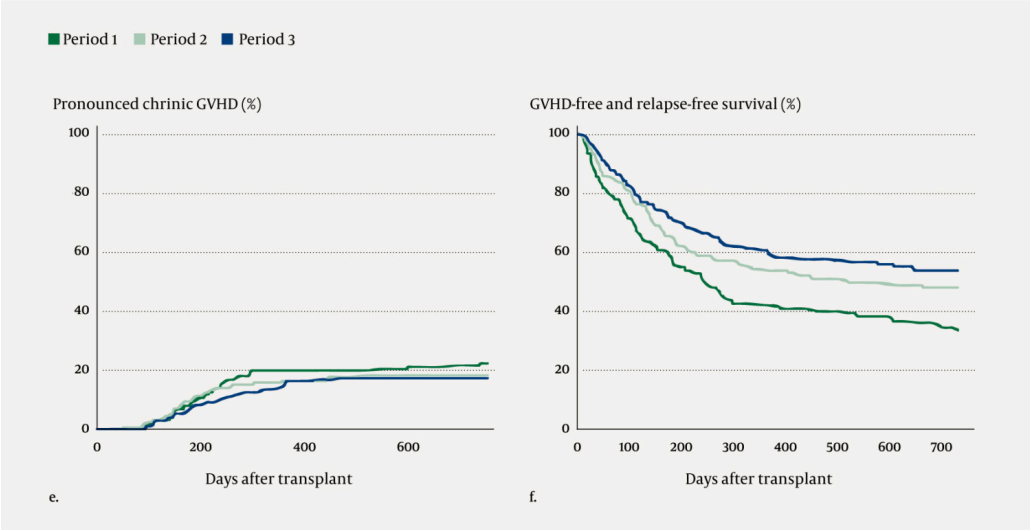

Figure 2E, 2F Clinical results after allogeneic stem cell transplantation in 2015–21. Results for e) pronounced chronic GVHD and f) GVHD-free and relapse-free survival. The dark green line indicates period 1 (n = 186), the light green line period 2 (n = 177) and the blue line period 3 (n = 226). When calculating the incidence of chronic GVHD, only patients who were alive 100 days post-transplant were included.

Infectious complications

The proportion of patients with cytomegalovirus reactivation requiring treatment was 40 % in period 1, 41 % in period 2 and 42 % in period 3. The proportion with Epstein-Barr virus reactivation requiring treatment increased from 3 % in period 1 and 4 % in period 2 to 8 % in period 3. The incidence of invasive fungal infection was reduced from 29 % in period 1 to 20 % in period 2 and 14 % in period 3.

The proportion of patients requiring treatment in the intensive care unit was 23 % in period 1, 20 % in period 2 and 15 % in period 3. The median number of days spent in intensive care in the three periods was 8, 9 and 5, respectively.

Death within one year of transplantation

The proportion who died within one year was 60/186 (32.3 %) in period 1, 46/177 (26.0 %) in period 2 and 40/226 (17.7 %) in period 3. The most common causes of death in the first year after the transplant were relapse of the primary disease (38.3–43.5 %) and multiorgan failure (21.7–28.3 %). Death due to GVHD was 16.7 % in the first period and 7.5 % in the last period. Infection was the cause of death in 7.5–15.2 % of patients. Up to 5 % died as a result of haemorrhage in the first year after the transplant.

Discussion

The main finding in the study was that the number of patients being treated with allogeneic stem cell transplantation has increased, whilst one-year survival has improved and relapse-free and GVHD-free survival is more common.

The increase in transplants is a result of several factors. The main reasons are probably the ageing population, with leukaemia mainly affecting older patients, and the removal of the upper age limit for transplantation. The number of transplants in Norway was previously lower than in other European countries. While Norway carried out 15 to 20 transplants per 1 million inhabitants in 2013–14, the corresponding figure for Sweden, Finland and Denmark was 20 to 30 transplants (4). Activity in Norway is now on a par with other Nordic countries (5). The extent to which new forms of treatment can replace transplantation will determine the need for the service going forward. For lymphoma and B-lymphoblastic leukaemia, treatment with chimeric antigen receptor T-cell therapy is an option for some patients, but this treatment is not yet available for other haematological diseases.

An important prerequisite for more patients being offered a transplant was a reduction in treatment-related mortality. Mortality after 100 days decreased from 20 % in the period 1985–2012 (2) to 8 % in period 3 of the study. The most likely reason for this is the changes in pre-transplant treatment, with increased use of treosulfan. Compared with busulfan, treosulfan causes less organ toxicity, and several studies demonstrate better tolerance and at least as good an antileukemic effect in people over the age of 60 (6, 7).

The reduction in acute GVHD and severe chronic GVHD has probably also contributed to the improvement in survival from period 1 to period 3. Reduction of chronic GVHD is particularly important for quality of life and long-term survival (8). Treatment with anti-thymocyte globulin was introduced as prophylaxis for GVHD in period 1. Anti-thymocyte globulin induces a dose-dependent reduction of T cells. A balanced reduction of donor T cells is necessary to maintain the antileukemic effect whilst also preventing GVHD (9). A total dose of 4–6 mg/kg has been shown to effectively reduce GVHD without simultaneously increasing the risk of relapse (10, 11). Although the frequency of chronic GVHD has been reduced and is on par with other studies, a further reduction is desirable because of the reduced quality of life associated with the disease.

An expected side effect after the introduction of anti-thymocyte globulin treatment was several cases of Epstein-Barr virus reactivation. However, increased use of anti-thymocyte globulin does not appear to have impacted on the risk of cytomegalovirus reactivation. The proportion of invasive fungal infections was reduced, which was presumably a result of milder pre-transplant treatment and the introduction of prophylaxis for mould infections (12).

Both GVHD and treatment-related mortality are impacted by the choice of donor. What constitutes an optimum donor and stem cell source is open to debate. An HLA-identical sibling donor has been considered better than a matched unrelated donor, but new data suggest that young matched unrelated donors yield better outcomes (13, 14). An unrelated donor is now used for the majority of patients. Since the siblings of older patients are older too, the ageing population will also influence the choice of donor.

One of the weaknesses of the study was the short observation time, particularly for the last two-year period. Relapses mainly occurred in the first year after the transplant. The estimate for both chronic GVHD and relapse would be rather

different if the observation time was longer. Another possible bias in the study is the change in the practice for reporting cases of chronic GVHD during the COVID-19 pandemic (in period 3). All patients need to be evaluated at least every three months at the transplant centre. This ensures consistent reporting, particularly for chronic GVHD, where it can be difficult to differentiate between mild, moderate and severe cases. During the pandemic, some patients preferred to have their check-ups at a local hospital rather than Oslo University Hospital in order to avoid using public transport.

The Unit for Allogeneic Stem Cell Transplantation at Oslo University Hospital is accredited under the European Society for Blood and Bone Marrow Transplantation (EBMT) quality system, and reports data to their quality register on an ongoing basis. The findings in this study are comparable to the results at other centres (15, 16). This review of data from an internal quality register showed that the number of allogeneic stem cell transplants has increased over the past six years, while survival has improved and the risk of complications has been reduced.

The article has been peer-reviewed.

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