

Long-term follow-up of patients treated at home during the pancytopenic phase after allogeneic haematopoietic stem cell transplantation

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Summary:

To prevent neutropenic infections, patients are kept in isolation rooms after allogeneic haematopoietic stem cell transplantation (ASCT). Patients living within one hours' driving distance from our unit were given the opportunity of treatment at home after ASCT during the pancytopenic phase. We compared 36 patients treated at home during March 1998 until December 2000, with 54 controls treated in the hospital during September 1995 and September 2001. The incidence of grades II–IV acute graft-versus-host disease (GVHD) was lower in the home care group compared to the controls, that is, 17 vs 44% ($P < 0.01$). The cumulative incidence of chronic GVHD was 52% in the home care group, compared to 57% in the controls. Transplant-related mortality (TRM) was 13% in the home care patients vs 44% in the controls ($P = 0.002$). The probability of relapse was similar in the two groups. The 4-year survival was 63% in the home care patients compared to 44% in the controls ($P = 0.04$). Home care after ASCT is a novel approach that resulted in less TRM, similar incidence of chronic GVHD and relapse, and improved long-term survival compared to controls treated in the hospital.

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Neutropenia and immunosuppression often result in infections that cause death after allogeneic haematopoietic stem cell transplantation (ASCT).^{1–6} To prevent infections, patients are kept in a protected environment, such as laminar airflow rooms (LAF) and reversed isolation.^{7–11}

We tried a new approach after ASCT: home care during the pancytopenic phase because the bacterial flora at home may be safer than that in the hospital.^{12,13} After condition-

ing and transplantation in the hospital, patients were treated at home.

On multivariate analysis, the home care patients were discharged earlier, had fewer days on total parenteral nutrition, less acute graft-versus-host disease (GVHD) grades II–IV, lower transplant-related mortality (TRM), and lower costs compared with controls treated in the hospital. However, acute and especially chronic GVHD is associated with a graft-versus-leukaemia effect and decreases the risk of relapse.^{14–16} Therefore, the best long-term leukaemia-free survival is seen in patients with mild acute and mild chronic GVHD. Since patients treated at home had a decreased risk of acute GVHD compared to patients treated in the hospital, we feared that these patients might have an increased risk of relapse compared to patients treated in the hospital. In addition, there is a close correlation between acute and chronic GVHD.^{17–19} Therefore, the lower risk of acute GVHD may have resulted in a lower risk of chronic GVHD and subsequently an increased risk of relapse and similar or decreased leukaemia-free survival. The analysis compares home care with hospital care after ASCT regarding long-term outcome, especially chronic GVHD, relapse, and survival.

Methods

Patients and patient selection for home care

From 1 March 1998 until 31 December 2000, 60 patients who lived within one hours' driving distance from Huddinge University Hospital underwent ASCT. Six of the 60 patients who lived in the Stockholm area were not asked to participate because they did not speak Swedish, were addicted to narcotics, or were considered medically and psychologically unfit.¹³ Of the 54 patients who were asked, 36 preferred to stay at home and they fulfilled the following requirements: a care giver (relative or friend) was willing to stay at home and help, and approval of the home by the Head of the Department of Infection Control.¹³ These criteria could not be fulfilled by 18 patients, who either had no caregiver ($n = 15$), had pets in the home ($n = 2$), or would not feel safe at home ($n = 1$). These patients served as controls. To avoid the bias that more fit and determined patients chose to stay at home than those treated in the hospital, we also selected a control group of

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patients who resided outside the Stockholm area and matched them for as many variables as possible, including diagnosis, stage of disease, age, sex, type of donor (related, unrelated), source of stem cells, bone marrow (BM) or peripheral blood stem cells (PBSC), and conditioning (Table 1). Thus, the 36 home care patients were compared with 54 controls treated in the hospital during September 1995 and September 2001. Of the 54 control patients, 41 were treated during the same time as the home care group, between March 1998 and December 2000. Further details of this study have been previously published.^{1,3} There were

two patients in the home care group who could not go home as planned after transplantation because of their poor clinical condition. One was almost blind from retinitis, and the other patient had respiratory insufficiency and multiorgan failure. Both patients were included in the home care group to avoid bias and because we had planned to treat them at home. Of the 34 patients who went home, 21 were readmitted to the ward on 33 occasions, median 1 day (range, 0–25 days), because of fever ($n=24$), no caregiver at home ($n=2$), diarrhoea and/or fever and/or pain ($n=3$), pain ($n=1$), GVHD ($n=1$), nausea and vomiting ($n=1$), and mucositis ($n=1$). The Ethics Committee at Huddinge University Hospital, Karolinska Institute approved the study. Informed consent was provided according to the declaration of Helsinki.

Table 1 Patient and donor characteristics, conditioning, and immunosuppression

	Home care	Controls	P-value
Number of patients	36	54	
<i>Diagnosis</i>			NS
Acute myeloid leukaemia	11 (31%)	18 (33%)	
Acute lymphoblastic leukaemia	9 (25%)	13 (24%)	
Chronic myeloid leukaemia	7 (19%)	11 (20%)	
Myelodysplastic syndrome	4 (11%)	4 (7%)	
Lymphoma	3 (8%)	4 (7%)	
Chronic lymphoid leukaemia	2	2	
Myelofibrosis	0	1	
Adrenoleukodystrophy	0	1	
<i>Remission</i>			NS
CR1/CP1	19 (53%)	29 (54%)	
CR2/CP2	6	9	
CR > 2	2	3	
PR	2	4	
Relapse	3	2	
Disease stage, early/late ^a	19/17	31/23	NS
Recipient sex (M/F)	25/11	29/25	NS
Recipient age	42 (14–58)	40 (15–64)	NS
<i>Donor type</i>			NS
Identical twin	1	0	
HLA-identical sibling	10 (28%)	19 (35%)	
Matched unrelated donor	25 (69%)	35 (65%)	
Donor sex (M/F)	25/11	29/25	NS
Donor age	38 (19–56)	36 (10–61)	NS
BM/PBSC	13/23	22/32	NS
NC dose	8.7 (1–27.6)	6.7 (0.7–16.8)	NS
G-CSF after HSCT	36 (100%)	47 (87%)	0.04
Female donor to male recipient	5 (10%)	11 (20%)	NS
<i>Conditioning</i>			NS
Cy + TBI	19 (53%)	29 (54%)	
Bu + Cy	11 (31%)	18 (33%)	
Flu + Bu/ATG	5 (14%)	6 (11%)	
Replantation	1	1	
<i>GVHD prophylaxis</i>			NS
No	2	1	
CyA + MTX	33 (92%)	50 (93%)	
CyA + Pred	0	3	
CyA + MMF	1	0	
Follow-up, months (range)	48 (37.7–68.3)	54.6 (35.9–95.2)	0.07

CR = complete remission; Cy = cyclophosphamide; TBI = total body irradiation; Bu = busulfan; Flu = fludarabine; ATG = antithymoglobuline; CyA = cyclosporine; MTX = methotrexate; Pred = prednisolone; MMF = mycophenolate mofetil; NS = nonsignificant.

^aEarly: 1st CR, 1st chronic phase; late: beyond these stages.

Conditioning and information

Conditioning consisted of 60 mg/kg cyclophosphamide (Cy) for 2 days, combined with 10 Gy of total body irradiation (TBI) with the lungs shielded, single fraction, or fractionated 3 Gy daily for 4 days.²⁰ Alternatively, 4 mg/kg/day busulfan (Bu), divided into four doses given for 4 days (total dose 16 mg/kg), adjusted to the Bu levels.^{21,22} Bu was combined with 60 mg/kg Cy for 2 days. A total of 11 patients were given reduced intensity conditioning, including 30 mg/m² per day fludarabine for 6 days, combined with 4 mg/kg/day Bu for 2 days (total dose 8 mg/kg), combined with 2 mg/kg/day thymoglobulin (SangStat-IMTIX, Lyon, France) for 4 days.²³ Patients who received unrelated grafts were given 2 mg/kg/day thymoglobulin for 2–4 days before ASCT.²⁴ Conditioning was given in the hospital. The patients and caregiver received information during this time. During this time, the caregiver stayed with the patient in the hospital to learn about the procedure and to get to know the staff. At home, it was important for the caregiver to be friendly with the patient (providing the patient with companionship), to make food if needed, and to telephone the hospital if help was necessary. The patients were always welcome to the hospital if they or the caregiver preferred it.

Home care

After infusion of the graft, the patient could go home. An experienced nurse from the ward visited the patient once or twice daily, depending on the needs of the patient. The nurse checked vital signs, temperature, blood pressure, and examined the patient for GVHD or other lesions. In the morning, the nurse took blood samples and gave medication intravenously if needed. Erythrocyte transfusions were given if the patient had a haemoglobin level less than 80 g/l and platelet transfusions when the platelet count fell below $30 \times 10^9/l$ or if there were signs of haemorrhage.^{13,20} The patients received parenteral nutrition when the caloric intake was below 70% of the total need. Patients treated at home were as carefully followed as the patients in hospital and they got parenteral nutrition at the same level. If the nurse needed any advice, she called the physician on the ward. At the hospital, the nurse and the physician went through the clinical and laboratory data. The physician then called the patient to tell him about the chemistry

results, to check the patient's status, and to change medications if needed. Criteria for readmission to the ward were (1) deterioration of the patient's condition, (2) if the patient's temperature rose above 38.5°C at least twice, (3) if the patient needed i.v. injections more than twice daily, and (4) if the care giver was unable to stay at home and support the patient. When the patient received a check-up in the hospital for an infection and felt well, he could go home even with a fever; intravenous antibiotics were continued at home.

Hospital care

Patients being treated at the hospital were treated in conventional single rooms with reversed isolation and a relative or friend could stay with them.²⁰ They could take a walk outside the hospital after 18:00 h on weekdays and during weekends.^{12,13} This is possible because after 'office hours' there are less staff, patients and relatives moving around in the corridors at the hospital who could infect the patient. The same is applicable also for the area around the hospital. After trying home care for some months while we let the patients take a walk in the forest or in other non-traffic areas close to the home, we found several benefits for the patient and implemented similar routines at the hospital. For example, with more exercise they may be motivated to eat better.

Infection prophylaxis was the same for all patients. During conditioning, the patients started with gut decontamination consisting of 500 mg oral ciprofloxacin twice a day and 250 mg amphotericin B once a day until neutrophils were more than $0.5 \times 10^9/l$. Co-trimoxazol was given as prophylaxis against *Pneumocystis carinii*. Patients with a herpes simplex virus immunoglobulin G (IgG) titer of more than 10 000 (determined by enzyme-linked immunosorbant assay (ELISA)), received oral or intravenous acyclovir prophylaxis until the ANC was more than $0.5 \times 10^9/l$.²⁵ Granulocyte colony-stimulating factor at 5 µg/kg/day was given from day +10 after ASCT until the ANC was more than $0.5 \times 10^9/l$ for two consecutive days.

Immunosuppression and donors

Cyclosporine (CyA) combined with four doses of methotrexate was given as prophylaxis against GVHD.²⁶ One patient with a twin donor and two patients undergoing retransplantation did not receive any prophylaxis. Two-thirds (67%) of the patients received grafts from HLA-A, -B, and -DRβ1 compatible unrelated donors. HLA-matching criteria were similar in the home care group and controls. Monitoring and chemistry was the same for all patients. Details regarding treatment have been reported elsewhere in detail.^{13,20,21,24}

Statistics

The probability of GVHD, TRM, relapse, leukaemia-free survival (LFS) and survival rates were compared using the Kaplan–Meier method with the log-rank test (Mantel–Haenszel). The Cox regression model was used for the multivariate analysis. Factors with $P \leq 0.1$ on univariate analysis were included in the multivariate analysis. The

following factors were analysed: home care or hospital care, type of donor (siblings/unrelated), source of stem cells (BM vs PBSC), diagnosis, stage of disease (early was defined as 1st remission or chronic phase; late was defined as more advanced), sex, age, cytomegalovirus (CMV) serology, bacteraemia, acute GVHD grades 0–I vs grades II–IV, nucleated cell dose, donor age, donor sex, and female donor to male recipient. Home care was the main factor tested, whereas all the other factors were included to control for differences between the groups. The home care patients were compared to the two control groups taken together to improve statistical analysis.

Results

Graft-versus-host disease

Grades of acute GVHD and affected organs in the two groups are given in Table 2. The incidence of grades II–IV acute GVHD in the home care group was 17%, which was significantly lower than 44% in the control groups ($P < 0.01$).¹³ Home care vs hospital care was also significant on multivariate analysis (RR 0.25, $P = 0.01$). Patients receiving PBSC had an increased risk of acute GVHD vs those receiving BM (RR 3.73, $P = 0.02$). No other factor was significant for acute GVHD. Chronic GVHD occurred in 52% of the home care group vs 57% in the controls (NS, Figure 1).

Transplant-related mortality

TRM was 13% in the home care patients vs 44% in the controls (Figure 2, $P = 0.002$). On multivariate analysis, TRM was significantly associated with acute GVHD grades II–IV and home care (Table 3). In patients with no risk-factor for TRM (patients treated at home and with grades 0–I acute GVHD, $n = 30$), the probability of TRM was 8%. In patients with one risk-factor ($n = 35$), the cumulative proportion of TRM was 26% ($P = 0.04$ vs no risk-factor). However, in those with two risk-factors, the risk for TRM was 63% ($n = 23$, $P = 0.017$ vs no risk-factor).

Relapse

The cumulative proportion of relapse was 39% in the home care patients compared to 29% in the controls.

Table 2 Grade of acute GVHD and organs affected in patients treated at home or in the hospital

	Home care	Controls	P-value
<i>Acute GVHD</i>			
No	11 (31%)	8 (15%)	0.11
Grade I	19 (53%)	21 (39%)	0.28
Grade II	5 (14%)	14 (26%)	0.19
Grade III–IV	1 (3%)	9 (17%)	0.08
Day of acute GVHD	21 (8–134)	19 (9–60)	0.21
<i>Organs affected by GVHD</i>			
Skin	25 (100%)	44 (100%)	
Liver	3 (12%)	15 (34%)	NS
Gastrointestinal tract	4 (16%)	14 (32%)	NS

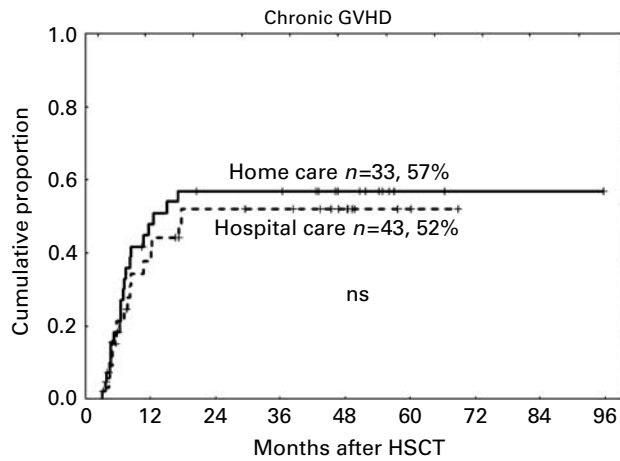


Figure 1 Time to and cumulative incidence of chronic GVHD in home care patients and controls.

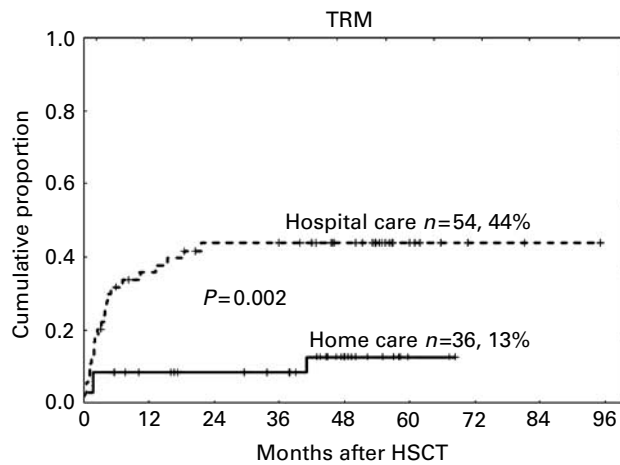


Figure 2 Time to and cumulative incidence of TRM in home care patients and controls.

Survival and leukaemia-free survival

In the home care patients, 4-year survival was 63% vs 44% in the controls (Figure 3a, $P=0.04$). On multivariate analysis, the only factor significant for poor survival was acute GVHD grades II–IV; relative hazard (RH) 2.41, confidence interval (CI) 1.32–4.39, $P=0.005$. If GVHD was not included, home care was associated with better survival (Table 3). The 4-year relapse-free survival was 52% in the home care patients compared to 37% in the controls (Figure 3b, $P=0.07$).

Discussion

A significant finding in this trial comparing home care with hospital care was that the home care patients had a lower probability of grades II–IV acute GVHD. The home care group and hospital care group were comparable for all prognostic factors except for G-CSF prophylaxis. G-CSF was given to all patients in the home care group compared to 87% in the two control groups ($P=0.04$). G-CSF is

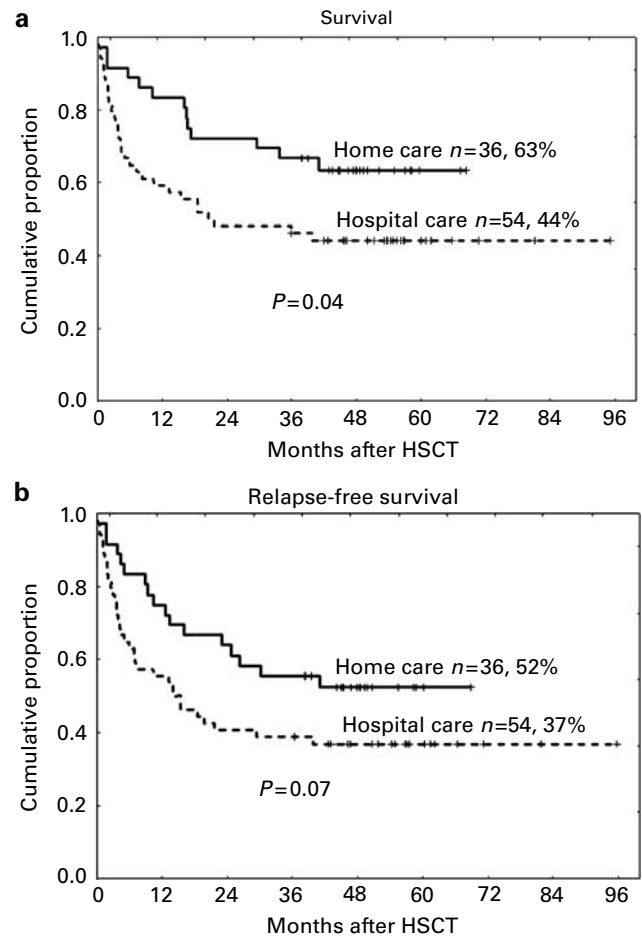


Figure 3 (a) Cumulative proportion of surviving patients in the home care group and in the controls. (b) Cumulative proportion of relapse-free survival in the home care group and in the controls.

Table 3 Multivariate analysis for outcome in patients treated at home or in the hospital regarding TRM and survival

Factor	RH	CI	P-value
TRM			
Acute GVHD II–IV	3.46	1.49–8.00	0.004
Home care	0.23	0.07–0.78	0.019
Survival			
Acute GVHD 0–I	2.41	1.32–4.39	0.005
Without GVHD			
Home Care	1.93	1.01–3.71	<0.05

associated with acute, chronic GVHD and death after ASCT.^{27,28} Despite this, the home care group had less acute GVHD and TRM vs the hospital care group. A possible reason for this may be that there are fewer bacteria found in the home compared to the hospital. It is known that GVHD may be triggered by infections from bacteria and virus. For instance, gnotobiotic mice have a lower risk of developing GVHD.^{29,30} Furthermore, patients who are seropositive for 3–4 herpesviruses more often developed

acute GVHD compared to those who are seropositive for 0–2 herpesviruses.³¹ Storb *et al*³² report that patients treated in LAF rooms were less likely to develop acute GVHD than those treated in regular hospital rooms. Another probability may be that there is more stress in the hospital than at home, which may result in the release of cytokines, triggering acute GVHD. We will test this hypothesis by studying cytokine levels in patients treated at home compared to patients treated in the hospital after ASCT. In this context, inflammatory cytokines like interferon- γ , TNF- α , IL-2, IL-12, and IL-18 are of interest. It may be difficult to evaluate this, because many factors influence stress, such as GVHD, inflammation and infections, all of which are common problems after ASCT. It may therefore also be informative to study MIC-A gene polymorphism, which is a genetic marker for stress.

A concern was that patients treated at home, who could take a walk outside whenever they wanted to, would have an increased risk of *Aspergillus* infection. However, no patient acquired *Aspergillus* infection. *Aspergillus* infections are relatively rare in our ASCT patients.⁴ This may be because of our cold climate. It has been reported that strict isolation after ASCT reduces the risk of *Aspergillus* infection.¹² Regarding the risk of *Aspergillus* infection, home care may therefore be more suitable in a colder climate. Incidences of bacteremia and CMV infections tended to be lower in the home care group (25% and 5%) compared to the control group (41% and 26%) (NS). Indeed, ASCT without protective isolation was also used successfully by Russell *et al*³³ in Canada. To take walks outside may have several positive effects, such as exercise and good appetite. Eating and keeping the gastrointestinal tract working may decrease the risk of gut inflammation, infections, cytokine release, and in the end GVHD.³⁴

Acute GVHD is a major cause of morbidity and mortality after ASCT. Grades III–IV acute GVHD are particularly associated with high mortality.³⁵ Therefore, TRM and grades II–IV acute GVHD are highly correlated. In keeping with this, the home care group had a lower TRM than the controls in the hospital. The controls had a TRM of 44%, which may seem high. This is due to the greater age, median 42 years (only one child was included); 25/54 had advanced disease, and follow-up is long. However, the best long-term survival in patients with leukaemia was observed in patients with grade I acute GVHD rather than no acute GVHD.^{35,36} This is due to the lower relapse risk associated with GVHD.

Despite the low incidence of acute GVHD, we saw the same risk for chronic GVHD in the home care patients and the controls. This may be surprising because there is a strong correlation between acute GVHD and chronic GVHD.^{17,19} Concern was that because of the lower risk of acute GVHD in the home care patients, this could result in an increased risk of relapse. Chronic GVHD has a stronger antileukaemia effect compared to acute GVHD.^{14–16} Thus, no difference in relapse was seen in the home care patients compared to those treated in the hospital. Other factors than acute GVHD may be more important for the subsequent development of chronic GVHD. For instance, a shorter duration of immunosuppression to induce chronic GVHD and also a graft-versus-leukaemia effect may be

valid in this context.³⁷ This could explain why home care, while reducing acute GVHD, did not result in an increased relapse risk. This is in contrast to more effective immunosuppression, using for instance T-cell depletion or CyA combined with four doses of methotrexate, which decreased acute and chronic GVHD compared to monotherapy but resulted in an increased risk of relapse.^{38,39}

The long-term follow-up of this home care project is very encouraging. In addition to a reduced risk of acute GVHD and TRM, several early beneficial effects were seen in the home care patients. Thus, on multivariate analysis, home care patients were discharged earlier to the outpatient clinic, and they required fewer days on total parenteral nutrition, which made home care cheaper compared to hospital care.¹³ Several other advantages with home care include keeping patients with their family, so they can go to their own kitchen and eat whatever and whenever they like. Furthermore, the patients can be more active with more things to do at home compared to being in an isolation room in the hospital, and they can also take a walk whenever they want to.

To confirm these results using home care after ASCT, a randomized multicentre study is necessary. We have encouraged other centres to join us. Awaiting this and based on the successful outcome of this study, we continue to offer home care to patients living in the Stockholm area.

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