

Allogeneic haematopoietic cell transplantation with nonmyeloablative conditioning in Denmark

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ABSTRACT

INTRODUCTION: Haematopoietic cell transplantation with nonmyeloablative conditioning (NMC-HCT) is used in the treatment of haematological malignancies.

MATERIAL AND METHODS: Use of NMC-HCT in Denmark from 2000-07 was examined.

RESULTS: Unrelated donor searches resulted in a suitable donor in 75% of cases of which 36% were transplanted. Among 244 patients referred for NMC-HCT, 72% were transplanted. There was a significant difference in the number of NMC-HCTs between national regions. Increasing waiting time resulted in 22% of the referred patients being taken off the waiting list without NMC-HCT.

CONCLUSION: Some patients may have had a chance of cure if they had been transplanted without delay.

In the 1990's, allogeneic haematopoietic cell transplantation with nonmyeloablative conditioning (NMC-HCT) was introduced as a treatment option for both haematological malignancies and some non-malignant disorders [1]. In the malignant diseases, the graft-versus-tumor (GVT) effect was exploited as the curative principle [2, 3]. Use of NMC-HCT accelerated in the late 1990's and early 2000's as more disease indications were established, especially for older patients and patients with comorbidities [4]. NMC-HCT is now a well-established treatment modality [5, 6]. As less than 30% of the potential recipients of an allogeneic HCT have a human leukocyte antigen (HLA) identical sibling, the use of alternative stem cell sources, including matched unrelated donors (MUD), is essential [5]. The use of MUD as a stem cell source has increased, especially within the last decade [7, 8].

In this study, we report on the development in searches for MUD and the pattern of referrals, waiting time and outcome of NMC-HCT in Denmark from 2000-07. The results showed that Danish health care was slow in adapting to the demands for NMC-HCT. This led to prolonged waiting times and suboptimal treatment results.

MATERIAL AND METHODS

Donor searches and referred patients

From February 2000 to December 2007, 219 MUD

searches were performed for patients with haematological diseases in preparation for a potential NMC-HCT at Rigshospitalet. The searches were performed by the Departments of Clinical Immunology at Rigshospitalet and Aarhus University Hospital. MUD was primarily searched for in the German "Zentrales Knochenmarkspender-Register Deutschland" and in the American "National Marrow Donor Program" registries. In the same period, 244 patients were referred to NMC-HCT at the Allo-HCT Unit, Department of Hematology, Rigshospitalet. The group of patients referred to NMC-HCT included both potential NMC-HCT with matched, related donors (MRD) (n = 130) and MUD (n = 114). Data were retrospectively analyzed as of 1 May 2008.

The subcommittee for allogeneic HCT of The Danish Society of Hematology writes and updates disease-specific recommendations for referral of patients for NMC-HCT in Denmark. Patients referred for HCT were approved according to these recommendations at weekly patient care conferences at the Allo-HCT Unit, Rigshospitalet. Because of insufficient capacity for NMC-HCT resulting in long waiting times, all patients accepted for HCT were, as from May 2006, classified as 1) "Urgent" (to be transplanted within 4-6 weeks), 2) "As soon as possible" (to be transplanted within 2-3 months), or 3) "Can wait" (to be transplanted within 3-4 months). HCTs were scheduled accordingly. Categories 1 and 2 primarily included patients with higher-risk diseases such as acute myeloid leukaemias (AML) and myelodysplastic syndrome (MDS), while category 3 were mainly patients with indolent lymphomas and chronic lymphocytic leukemia (CLL). As the number of patients on the waiting list increased, it was not always possible to transplant patients within the scheduled time limits.

Treatment regimen for haematopoietic cell transplantation with nonmyeloablative conditioning

HLA genotyping, conditioning regimen, and leukapheresis procedures were performed as previously described [9].

Transplantation capacity

From 2000 to 2003, the Allo-HCT Unit at Rigshospitalet had 10-12 beds available for allogeneic and autologous

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HCTs of both adults and children. In 2003 the capacity was increased to 16 beds. Autologous HCTs and child HCTs were performed elsewhere.

Statistics

Continuous variables were compared using the Wilcoxon two-sample test while categorical variables were compared using Fisher's exact test.

Survival analysis was performed as previously described using the Kaplan-Meier method, and comparisons were made with the log-rank test [9]. P values ≤ 0.05 were considered significant.

RESULTS

MUD searches

Among the 219 MUD searches performed, a suitable HLA-matched donor was found in 164 (75%) cases, no MUD was available in 34 (15%) cases, and the search was cancelled prematurely in 21 (10%) cases. A total of 114 patients (52%) were referred for NMC-HCT and among these 78 cases (36%) were transplanted at Rigshospitalet. Transplants were performed with MUDs from Germany (n = 64), Denmark (n = 8), England (n = 4), USA (n = 4), Italy (n = 1), and Sweden (n = 1). An increase in the number of MUD searches was observed from 2000 to 2007, reaching a maximum in 2006 and 2007 with 53 and 43 MUD searches, respectively. In 2007, the median time from a MUD search was initiated until a suitable donor was found was 60 days (range 16-127 days).

In 2007, the cost of MUD searches in the donor registries, of tissue typing, donor apheresis, and transportation of the graft from donor centers to Rigshospitalet was 210,000 € or approximately 11,500 € per patient.

Referrals, transplantation and waiting times for transplantation

Among the 244 patients referred for NMC-HCT at Rigshospitalet, 175 (72%) were transplanted, 97 (55%) with an MRD, and 78 (45%) with a MUD. An increase in the number of referrals, particularly with MUD, was observed between 2000 and 2007. A borderline significant increase in referrals of patients with AML (p = 0.053) and CLL (p = 0.049) was found when comparing the second half of the referral period (2004-2007) with the first half of the period (2000-2003) (data not shown). A non-significant decrease was observed in referrals of patients with multiple myeloma (MM) and Hodgkin's disease.

There was a significant increase in the number of patients waiting for an NMC-HCT in the 2006-2007 period (median 18, range 11-28) compared with 2000-2005 (median 6, range 1-14) (p < 0.001) (Figure 1A). Although the number of NMC-HCTs performed annually

increased from eight to over 30, the amount of referrals increased even more. This resulted in the waiting list peaking in 2006-2007. The number of patients taken off the waiting list without transplantation varied with the number of patients on the waiting list. It reached its maximum in 2007 when as many as 30 patients were transplanted while 18 patients were taken off the waiting list without transplantation.

The increase in patients referred to and waiting for NMC-HCT was reflected in the waiting time from referral to transplantation (Figure 1B). The time required for the necessary pre-transplantation assessment of patients amounts to 1-4 weeks, depending on the urgency of the transplantation. Very few grafts were infused within the minimal possible waiting time. The lowest median waiting time was about three months. It was obtained in 2004. The median waiting time for the whole period 2000-2007 was 110 days (range 9-443 days) with a significant increase from 99 (range 9-443) days in the 2000-2005 period to 148 (range 24-326) days in the 2006-2007 period (p < 0.001).

National regions

The Capital Region referred 5.6 patients and performed 3.7 NMC-HCTs per 100,000 inhabitants from 2000 to 2007. The corresponding figures were 7.7 and 6.3 for The Zealand Region, 2.8 and 1.6 for North Denmark, 2.7 and 2.0 for Central Denmark, and 3.4 and 2.5 for Southern Denmark.

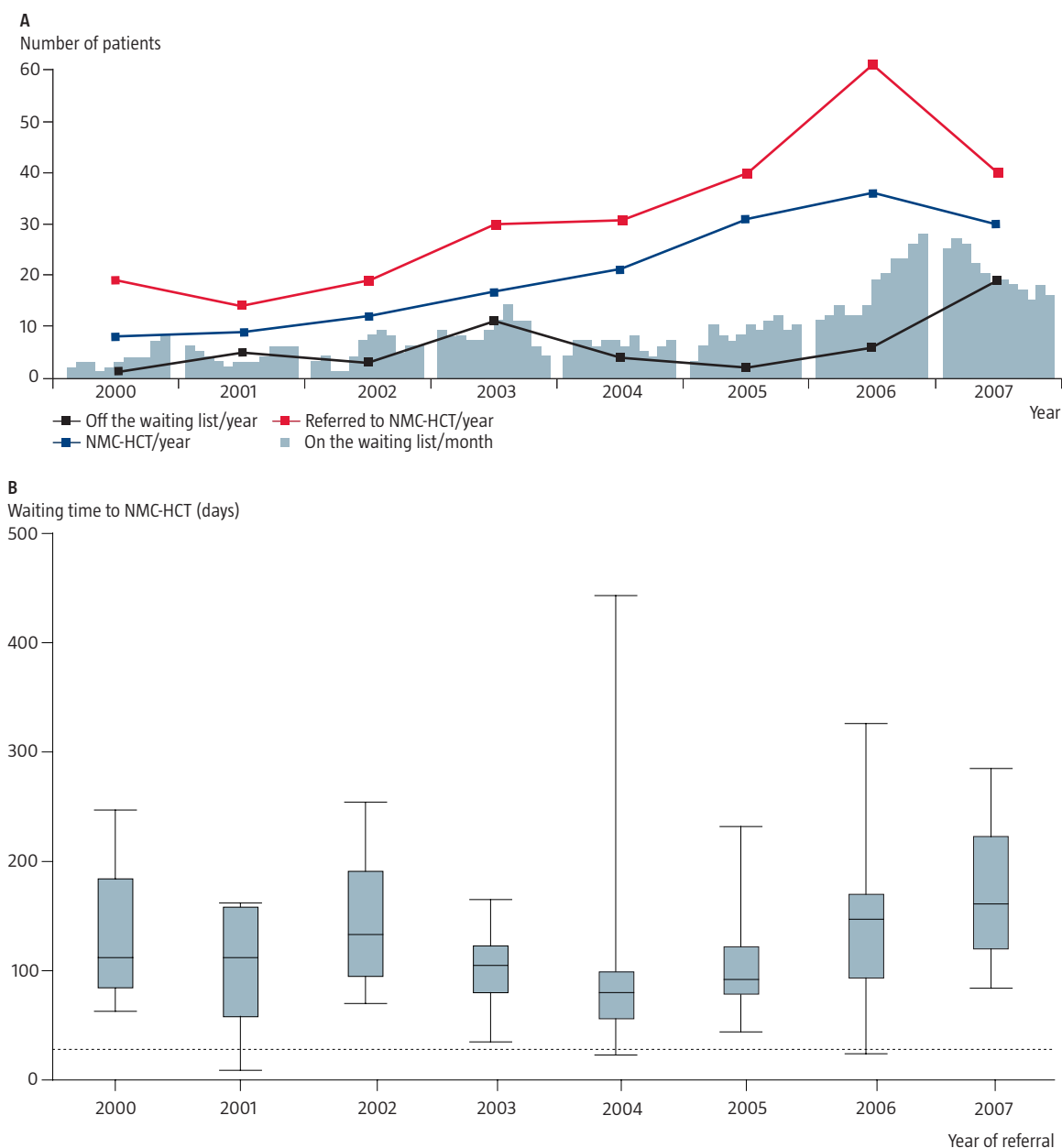
The difference in referrals as well as performed NMC-HCTs between the Capital Region along with the bordering Region Sealand and the rest of regions was significant (p < 0.001). This indicates a clear tendency towards fewer referrals and fewer performed NMC-HCTs the further away from the capital the referring region was located.

Treatment outcome

Among the 244 patients referred for NMC-HCT, four (2%) were not accepted for NMC-HCT by the patient care conference, 175 (72%) patients underwent NMC-HCT at Rigshospitalet, five (2%) patients underwent NMC-HCT in neighboring Sweden, three (1%) patients underwent myeloablative-conditioning HCT, and four (2%) patients were still on the waiting list at the end of follow-up. A total of 53 (22%) patients were accepted for NMC-HCT, but were taken off the waiting list without HCT. Twenty-nine (12%) of these were taken off the waiting list due to relapse or progression of the malignant disease, and 24 (10%) were taken off due to other complications (infections (n = 6), patient wish (n = 5), other cancers (n = 3), poor performance status (n = 3), reduced pulmonary function tests (n = 2), donor withdrawal (n = 1), or others (n = 4)). Twenty-three of

 FIGURE 1

A. Number of monthly patients on the waiting list for NMC-HCT from February 2000 to December 2007 together with number of patients referred for NMC-HCT, number of performed NMC-HCTs, and number of patients taken off the waiting list annually without transplantation. **B.** Waiting time to NMC-HCT. Box showing the median and the 25th and 75th percentiles. The whiskers of the graph indicate the range. The dotted line corresponds to a waiting time of four weeks. NMC-HCT = haematopoietic cell transplantation with nonmyeloablative conditioning.



the 29 patients taken off the waiting list due to relapse or progression died, while half of the patients taken off the list due to other complications died.

Table 1 shows a comparison of patients transplanted and patients taken off the waiting list without transplantation. There were significantly more CLL patients who did not reach transplantation, which may be a result of postponing patients with CLL in favor of early HCT in patients with AML and MDS. The waiting time was not significantly different in the two groups (110 versus 106 days). Significantly more patients did not ob-

tain complete remission (CR) in the group not reaching transplantation than in the group which did reach transplantation (85% versus 61%, $p = 0.001$). Patients taken off the waiting list due to relapse or progression had a significantly shorter waiting time than patients who received transplants (110 versus 91 days) ($p = 0.007$) (**Table 2**). In an intention-to-treat analysis, the overall survival (OS) and progression-free survival (six years) of all referred patients were 44% and 33%, calculated from time of referral (**Figure 2AB**). A significantly lower OS was observed in patients taken off the waiting list than

TABLE 1

Comparison of variables at referral between patients receiving NMC-HCT and patients taken off the waiting list without NMC-HCT.

Parameter	Patients receiving NMC-HCT (n = 175)	Patients taken off the waiting list without receiving NMC-HCT (n = 53)	p values
Sex, male/female, n (%)	109 (62)/66 (38)	34 (64)/19 (36)	0.872
Age, median years (range)	53 (20-69)	56 (18-69)	0.188
<i>Diagnosis, n (%)</i>			
AML	53 (30)	9 (17)	0.080
MDS	14 (8)	4 (8)	1.000
NHL	46 (26)	12 (23)	0.719
CLL	25 (14)	16 (30)	0.013
HD	16 (9)	4 (8)	1.000
MM	15 (9)	6 (11)	0.589
Other	6 (3)	2 (4)	1.000
Waiting time ^a , median days (range)	110 (9-443)	106 (4-308)	0.375
<i>Remission status^b no. patients (%)</i>			
CR	69 (39)	8 (15)	
Not in CR	106 (61)	45 (85)	0.001

AML = acute myeloid leukaemia; CLL = chronic lymphocytic leukaemia; CR = complete remission; HD = Hodgkin's disease; MDS = myelodysplastic syndrome; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; NMC-HCT = haematopoietic cell transplantation with nonmyeloablative conditioning.

a) Waiting time was calculated from day of referral to day of transplantation or cancellation of transplantation. b) Remission status at time of referral for haematopoietic cell transplantation with non-myeloablative conditioning.

TABLE 2

Comparison of waiting times between patients receiving NMC-HCT and patients taken off the waiting list without HCT because of relapse or progression of malignant disease.

Parameter	Waiting time to NMC-HCT, median days (range) (n = 175)	Waiting time to relapse or progression, median days (range) (n = 29)	p values
<i>Diagnosis, n (%)</i>			
AML	87 (9-443)	77 (6-127)	0.452
MDS	94 (38-148)	77 (45-112)	0.659
NHL	139 (35-285)	92 (27-127)	0.005
CLL	161 (65-326)	118 (4-236)	0.111
HD	111 (35-200)	172 (58-107)	0.867
MM	110 (59-147)	106 (77-146)	0.813
Other	209 (105-245)	–	–
Total	110 (9-443)	91 (4-236)	0.007

AML = acute myeloid leukaemia; CLL = chronic lymphocytic leukaemia; HD = Hodgkin's disease; MDS = myelodysplastic syndrome; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; NMC-HCT = haematopoietic cell transplantation with nonmyeloablative conditioning.

among patients transplanted in all disease categories, except for MM (Figure 2C-F).

DISCUSSION

NMC-HCT with MRD was established in Denmark in 2000. NMC-HCT with MUD was initiated in 2002, but the number of referrals for HCT with MUD exceeded that of HCT with MRD as early as 2003, clearly indicating the

need for alternative donor transplants. The number of actually performed NMC-HCTs with MUD exceeded sibling transplants as from 2006. A suitable HLA-matched donor was found in 75% of MUD searches. The median search time was two months. Half of the patients for whom a donor was identified were referred for transplantation, but only 36% actually underwent NMC-HCT at Rigshospitalet. This was mainly due to relapse/progression of the malignant disease or comorbidity. Our findings are similar to data reported by Copelan [5] where a MUD was identified for more than 50% of patients requiring a HCT. Because donor identification and graft procurement took more than three months, less than half of the identified MUD were used.

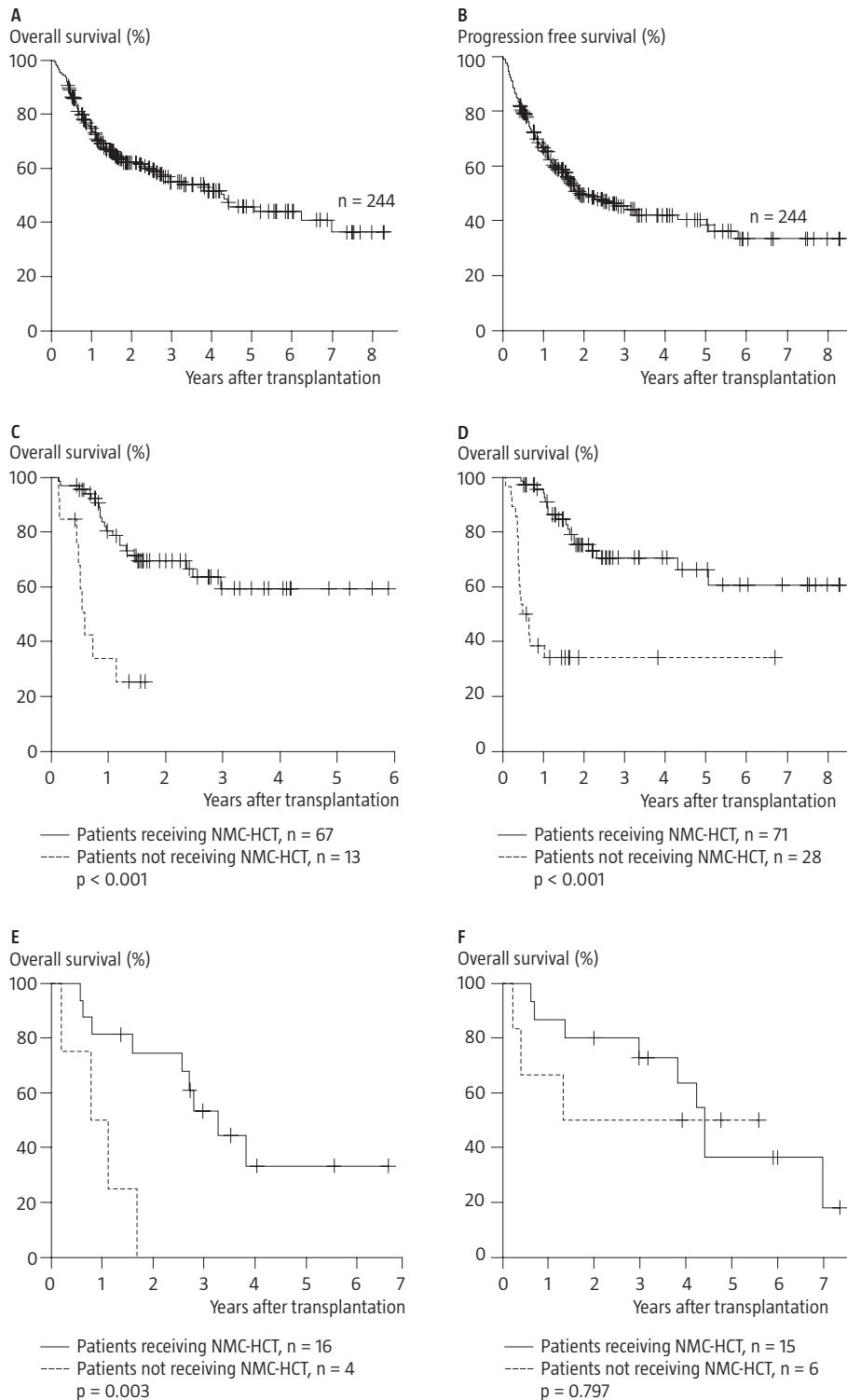
The increase in MUD searches and NMC-HCTs performed with MUD at our centre reflects the increased interest in performing allogeneic HCTs with MUD worldwide [7, 8]. The cost of MUD graft procurement in our study was 11,500 € per patient transplanted. This amounts to approximately 5% of the average total cost of an NMC-HCT, which we have estimated to 208,000 € [9]. The cost of MUD graft procurement is increasing [10]. The fact that 78% of all MUD identified were from the German registry primarily reflects the search strategy and the relatively small sizes of the Danish MUD registries.

The majority of all referrals for NMC-HCT came from the Capital and Zealand regions. This may reflect a delay in dissemination of information to haematologists and patients in other parts of the country on the positive effects of this new treatment modality. It may also reflect that the travel distance to the transplant centre constitutes a referral barrier.

The number of NMC-HCTs increased during the observation period, and a tendency towards more NMC-HCTs among patients with AML and CLL was also detected. The European Cooperative Group for Bone Marrow Transplantation (EBMT) data also shows a clear increase in the number of reduced intensity conditioning transplants and a change in disease indications towards more allogeneic HCTs for leukaemias [6, 11]. The capacity for NMC-HCT increased at our centre to more than 30 HCTs a year, but referrals increased even more (Figure 1A). This resulted in median waiting times peaking at approx. six months and in patients being taken off the waiting list without HCT due to relapse/progression of the malignant disease or other complications (Figure 1B). The intention to treat analysis showed overall and progression-free survival at six years of only 44% and 33%, respectively (Figure 2). The emerging picture revealed significantly inferior survival in patients – with all diagnoses except MM – who were taken off the waiting list without transplantation compared with patients re-

FIGURE 2

A. Overall survival of all referred patients. **B.** Progression-free survival of all referred patients. **C.** Overall survival of patients with AML/MDS receiving NMC-HCT compared with patients taken off the waiting list due to relapse or progression of malignant disease or other complications. **D.** Overall survival of patients with NHL/CLL receiving NMC-HCT compared with patients taken off the waiting list due to relapse or progression of malignant disease or other complications. **E.** Overall survival of patients with HD receiving NMC-HCT compared with patients taken off the waiting list due to relapse or progression of malignant disease or other complications. **F.** Overall survival of patients with MM receiving NMC-HCT compared with patients taken off the waiting list due to relapse or progression of malignant disease or other complications. AML = acute myeloid leukaemia; CLL = chronic lymphocytic leukaemia; HD = Hodgkin's disease; MDS = myelodysplastic syndrome; MM multiple myeloma; NHL = non-Hodgkin's lymphoma; NMC-HCT = haematopoietic cell transplantation with nonmyeloablative conditioning.



ceiving NMC-HCT. Not surprisingly, the proportion of patients not in CR pretransplant was higher in the group taken off the waiting list. They did, however, wait a median of three months before relapse/progression. In a

recent study, Baron et al [2] reported that out of 221 patients with haematological malignancies who were not in remission at the time of NMC-HCT, 44% achieved a CR a median of 176 days after HCT. This finding indicates

that a powerful GVT effect may be present after three months which supports the notion that some of our patients may have had a chance of cure if they had been transplanted without delay.

The waiting time from a suitable donor is identified to infusion of the graft should ideally not exceed 4-6 weeks for patients with haematological malignancy. The present nationwide survey has shown that in our publicly funded health care system, with competition for limited resources, adaptation to a rapidly increasing demand for a new expensive treatment modality is slow and insufficient. In 2008 and 2009, we have tried to solve the capacity problem by having some patients transplanted in Germany and by opening a new transplant centre in Aarhus. Transplantation capacity has also been further increased at Rigshospitalet.

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