Leukemia & Lymphoma, 2003 Vol. 44 (6), pp. 983–987

Taylor & Francis
healthsciences

Analysis of 127 Stem Cell Donations of the Regional Bone Marrow Donor Bank Europdonor Nijmegen, The Netherlands

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(Received 4 November 2002)

In December 2000, the Bone Marrow Donor Bank Europdonor Nijmegen in the Netherlands celebrated its tenth anniversary. We describe the organisation and activities in the first 10 years of this regional bone marrow donor bank. A concise inquiry was sent to all transplant centres who had received a graft from our donors. Response rate was 88% and data were available from 127 recipients. Three donors donated twice to different patients. Median age of the 124 donors (42 females and 82 males) was 37 years and 30 years for the 127 recipients (48 females and 79 males).

Time interval between first request of a blood sample and collection of bone marrow varied from 13 to 695 days (median, 113 days).

All but two donors received general anaesthesia for 25–120 min (median; 60 min). Hospital stay has been reduced to 24 h. Most donors experienced pain from the collection sites for 3–5 days. However, 9 donors (7%) suffered from pain for 2–3 weeks. All but two donors (98%) were willing to donate a second time for the same patient and 119 (96%) donors wished to remain in the register.

The number of nucleated cells (NC) in the collected marrow varied from 0.2 to 8.3×10^8/kg body weight of the recipient (median, 3.5×10^8/kg) with $6.4–470.0 \times 10^4$ CFU-GM/kg body weight of the recipient (median, 18.0×10^4/kg body weight).

The 3-year projected probability of survival of the 127 recipients transplanted with marrow from donors provided by Bone Marrow Donor Bank Europdonor Nijmegen was 27 ± 9% (± 95% CI).

Keywords: SCT; Voluntary unrelated donors; Bone Marrow Donor Bank Europdonor Nijmegen; Confirmatory typing

INTRODUCTION

Stem cell transplantation is a curative treatment option for several malignant and non-malignant haematological diseases, especially leukaemias [1,2]. However, only 30% of patients have a suitable family donor. If no family donor is available, stem cell transplantation can be performed with stem cells from a voluntary unrelated donor (VUD) or with stem cells obtained from cord blood. Worldwide, several stem cell donor banks and cord blood banks have been erected [3,4].

The Bone Marrow Donor Bank Europdonor Nijmegen was founded in December 20, 1990 by the Blood Bank Nijmegen, the Department of Hematology and the Department of Blood Transfusion and Transplantation Immunology of the University Medical Centre Nijmegen. The Bone Marrow Donor Bank Europdonor Nijmegen has a close cooperation with the Europdonor Foundation in Leiden that acts as the "hub" centre for The Netherlands [5]. The activities of Bone Marrow Donor Bank Europdonor Nijmegen are recruitment of volunteer unrelated stem cell donors in the region, the organisation of HLA typing (performed by the Department of Blood Transfusion and Transplantation Immunology), the organisation of confirmatory typing (CT) samples, and donor counselling at various stages of the work-up to the ultimate harvest. Bone Marrow Donor Bank Europdonor Nijmegen has contracted the NMDP-accredited Department of Hematology and the Central Laboratory of Hematology of the University Medical Centre Nijmegen for medical examination, actual harvest and processing of the bone marrow, and medical follow-up of the donor.

In October 1991, the first donor was admitted to our hospital for a stem cell harvest and in a period of 10 years,

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ISSN 1042-8194 print/ISSN 1029-2403 online © 2003 Taylor & Francis Ltd
DOI: 10.1080/1042819031000067701

124 donors donated marrow to 127 patients. To mark the tenth anniversary of the Bone Marrow Donor Bank Europdonor Nijmegen, we sent a concise inquiry to all centres that had performed a transplantation with marrow from a donor of our Bone Marrow Donor Bank. This overview describes the organisation and activities in the first 10 years of the Bone Marrow Donor Bank Europdonor Nijmegen and the results of the 127 recipients.

MATERIALS AND METHODS

Donors

The Bone Marrow Donor Bank Europdonor Nijmegen recruits its donors from the southeastern part of the Netherlands with a population of about 4.0 million people. Donors are mainly recruited amongst the blood donors of the seven Blood Banks in this region. This approach is facilitated by the good organisation of the Dutch Blood Bank Organisation Sanguin and the motivation of blood donors for donation. Moreover, all blood donors receive a periodical medical check-up including testing for infectious diseases. The overall recruitment strategy of Bone Marrow Donor Bank Europdonor Nijmegen is strategic and economical. Written information about bone marrow donation is available at all locations of the Blood Banks. An essential part of our recruitment drives are information gatherings in the region. In such meetings detailed information about the organisation, the HLA-typing, the physical examination, the stem cell harvest procedure is given. Usually, a donor who actually donated marrow is present to share the experience of the procedure.

A second source of bone marrow donors consists of family members of patients who are HLA-typed as part of the search for a family donor. They are asked by the Department of Hematology if they are willing to become a donor for the Bone Marrow Donor Bank Europdonor Nijmegen.

The file of typed donors consists of 3728 females and 3192 males with a median age of 41 years (range, 18–55 years). Each year, about 500 newly recruited donors are added to the file. Each year, an average of 104 donors leaves the register due to a variety of reasons like moving house, medical reasons or reaching the upper age limit. Only 10% of the donors were not willing anymore because they lost interest or were afraid of anaesthesia.

Ninety-six percent of the donors are HLA-typed for A,B and DR. From 1998 onwards donors are typed for HLA, -A, -B, DRB and DQB. Recently serological A and B typing has been replaced by DNA typing techniques using polymerase chain reaction (PCR)-based typing with sequence specific oligonucleotide probes (SSOP) [6]. For HLA-C typing PCR-based typing with sequence-specific primers (SSP) is used [7].

In the Netherlands stem cells from unrelated donors are aspirated by multiple punctures from the iliac crests. Peripheral stem cell harvesting after mobilisation with G-CSF is awaiting for approval by insurance companies.

As a part of the preparation of the donor, one or two units of autologous blood were taken pre-harvest. According to the NMDP standards [8,9], the number of autologous units depends upon the amount of marrow requested, as well as donor related factors determined by the collection centre physician. If less than 20×10^9 NC were required, one unit of autologous blood was drawn. Between 20×10^9 and 25×10^9 NC, one or two units of autologous blood were taken and if more than 25×10^9 NC were asked, two units of autologous blood were drawn.

RESULTS

Donors

Seven out of 768 (1%) donors withdrew at the time of request for high-resolution typing and 23 of 1360 (2%) withdrew at the time of request for confirmatory testing.

A work-up was initiated for 157 donors but this was cancelled in 30 cases. Cancellation was due to patient-related factors (deterioration, $N = 10$; alternative donor, $N = 4$; death $N = 3$; and one case each of patient's withdrawal, alternative therapy and for unknown reason). In 10 cases work-up was cancelled due to donor-related factors such as rejection on medical grounds ($N = 6$) or unwillingness to donate ($N = 4$). In three donors work-up was done twice since these donors donated for two different patients. Two donors donated twice for the same patient and one donor donated three times for the same patient.

Ultimately, 124 donors actually donated marrow to 127 patients. Median age of the donors (42 females and 82 males) was 37 years (range, 22–53 years).

Median interval between first request and stem cell collection was 113 days (range, 13–695 days) and median interval between start of work-up and SCT was 50 days (range, 1–240 days).

Additional examination pre-harvest was performed in 11 donors (9%): in 6 cases, a cardiologist was consulted and in 4 cases other medical specialists were asked. One donor underwent additional infectious disease marker tests because of a tattoo and several piercings. All donors were found suitable for donation.

All but two donors received general anaesthesia. The median duration of anaesthesia was 60 min (range, 25–120 min). No complications occurred during anaesthesia. Since no donor had complications, hospitalisation duration of the donors was short. Ninety donors (74%) were admitted for 24 h or less.

The number of nucleated cells that was collected per kg body weight of the recipient varied from 0.2 to 8.3×10^8/kg (median, 3.5×10^8/kg body weight) with $6.4–470.0 \times 10^4$ CFU-GM/kg body weight of the recipient (median, 18.0×10^4/kg body weight). The total number of nucleated cells that was requested by the transplant centres varied from 0.3 to 4.0×10^8/kg (median, 0.3×10^8/kg body weight). The amount of nucleated cells requested by the transplant centre could not be collected

in 45 of 111 evaluable cases (41%). In 17 of these 45 cases (38%), the transplant centre asked for more nucleated cells than the estimated maximum number of nucleated cells as recommended by the NMDP standards (20 ml × donor weight [in kg] × 0.22×10^8) [8]. The volume aspirated varied from 256 to 1670 ml (median, 1078 ml).

Donor Experience

Ninety-eight donors (77%) experienced some pain and stiffness from the puncture sites for 1–3 days. They did not require analgesic drugs. The other 26 donors had more complaints during an interval of 4–20 days and used analgesic drugs like acetaminophen. No major complications occurred.

Only 6 of 124 (5%) donors did not wish to be informed about transplantation outcome. Of the 124 donors, 122 (98%) were willing to donate a second time for the same patient. Three donors were approached for a second donation, two donors actually donated a second time and another donor even donated twice additionally for the same patient.

Hundred and nineteen donors (96%) wished to remain in the donor file. This means that these donors become available for donation after one year, according to the policy of being temporarily unavailable after marrow donation.

Nine donors were asked for lymphocytapheresis for the treatment of relapse after transplantation [10]. One request was postponed because the donor was pregnant. One request was cancelled because the patient deteriorated rapidly.

Patients

Forty-eight patients (38%) who received a graft from a donor of the Bone Marrow Donor Bank Europdonor Nijmegen were female and 79 (62%) were male. Median age was 30 years (range, 0.5–60 years). Of the 48 female recipients, 29 (60%) received a graft from a male donor and in 58 of 79 male recipients (73%) the donor was a male.

Indication for transplantation were CML ($N = 39$), ALL ($N = 30$), AML ($N = 21$), MDS ($N = 10$), SAA ($N = 9$), NHL ($N = 6$) and others ($N = 12$).

Fifty-five requests came from centres within the USA and Canada, 68 requests came from centres within Europe of which 21 came from the Netherlands, and 4 requests came from Australia. We did not ask for information about conditioning, T cell depletion and immunoprophylaxis post-transplant since these conditions vary in the different centres. Taking into consideration the limited number of patients transplanted we did not find it appropriate to draw conclusions regarding these variables and the outcome of the transplantation.

Eighty-five patients (67%) died. Principal causes of death were GVHD in 22 cases (26%), infections in 22 (26%), and relapse in 19 patients (22%). Nine patients (11%) died from multi-organ failure (MOF) and 13 patients died from other causes. At the end of follow-up (December 15, 2000) 42 patients (33%) were alive with a follow-up between 0.5 and 110 months (median, 33 months) after stem cell transplantation. The 3-year projected probability of survival is 27 ± 9% (±95% CI) and is given in Fig. 1.

DISCUSSION

The Bone Marrow Donor Bank Europdonor Nijmegen is a relatively small but active regional bone marrow donor bank considering the number of requests that were received. It is remarkable that most requests came from

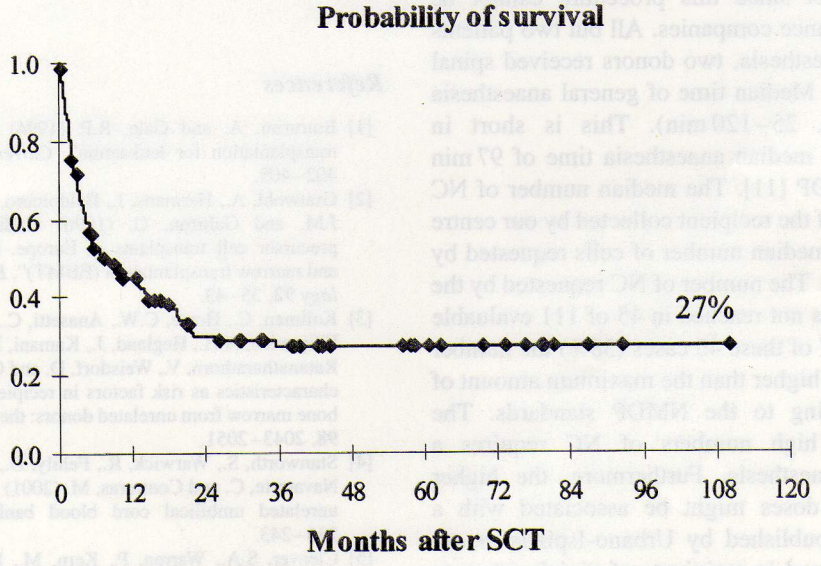

FIGURE 1 Probability of survival projected at 3 years in recipients of marrow from the Regional Bone Marrow Donor Bank Europdonor Nijmegen (BEN), The Netherlands.

outside the Netherlands, despite the fact that countries like the USA have much larger registries. A provable explanation for this is the high number of A-B-DR typed donors in the Dutch donor file.

The Bone Marrow Donor Bank Europdonor Nijmegen has a very close relationship to the Blood Banks and the University Medical Centre that acts as collection facility. The communication lines are short and that is beneficial for the daily practise. Efficiency is also high when looking at the relatively low median time interval between first request and collection of stem cells. This was 113 days with a range of 13–695 days. The upper limit of the range was influenced by postponing the harvest on request of the transplant centre due to the medical condition of the patients, especially relapses. A better indicator of efficiency is the median interval between start of work-up and SCT. This was only 50 days. Median time interval between first request and collection of stem cells of the Bone Marrow Donor Bank Europdonor Nijmegen is comparable with the median time of 4 months from formal search to transplant for NMDP donors initiated in 1999–2000 [11]. The relatively short time interval is also the result of the high percentage of donors that is matched for HLA-A, -B and -DR antigens (96% of all our donors) in comparison with 61% of the total NMDP donor pool that has been fully typed for HLA-A, -B and -DRB [11]. Furthermore, the time interval is relatively short because distances in the Netherlands are easily covered by public transport or by car. More important is the motivation of our donors, who seem to make it a priority to schedule an appointment as soon as possible once they are called for CT. High motivation may also be concluded from the low percentage of donors that withdrew over the years. For CT, it is only 2% and for work-up, only 2.5%. Also looking at the willingness of almost all donors to donate a second time we can conclude that motivation is high.

In contrast to NMDP policy, collection of G-CSF mobilised stem cells from unrelated donors is not performed by us yet since this procedure cannot be covered yet by insurance companies. All but two patients received general anaesthesia, two donors received spinal epidural anaesthesia. Median time of general anaesthesia was 60 min (range, 25–120 min). This is short in comparison with the median anaesthesia time of 97 min reported by the NMDP [11]. The median number of NC per kg body weight of the recipient collected by our centre was higher than the median number of cells requested by the transplant centres. The number of NC requested by the transplant centres was not reached in 45 of 111 evaluable harvests (41%). In 17 of these 45 cases (38%) the number of requested NC was higher than the maximum amount of NC allowed according to the NMDP standards. The collection of such high numbers of NC requires a relatively longer anaesthesia. Furthermore, the higher CD34 positive cell doses might be associated with a poorer outcome as published by Urbano-Ispizua *et al.*, although this was found in recipients of peripheral stern cells from HLA-identical siblings [12]. In our transplant centre we have the policy to count the NC after collection of the first 450 ml. If these first 450 ml contain more than 12.5×10^9 nucleated cells, and the recipient is an adult sibling, another 450 ml is aspirated. If the first 450 ml contains less than 12.5×10^9 nucleated cells, we aspirate in the second bag at least 650 ml bone marrow. This procedure can be performed within one hour and the total number of cells is enough for an allogeneic sibling transplantation even performing a T cell depletion procedure [13].

Our inquiry was very concise concerning patient details. We have given only the probability of survival projected at 3 years after transplantation. Age was the only donor trait significantly associated with overall survival. Five-year overall survival rates were 33, 29 and 25%, respectively, with donors aged 18–30 years, 31–45 years and more than 45 years [3]. Median age of our donors was 37 years and we found a probability of survival that can be compared with that published by others [3].

In summary we conclude that our regional bone marrow donor bank is very efficient. First of all this can be ascribed to a high number of A-B-DR typed donor. This is of great interest for those countries who initially made a choice to build their registry in a different way. Furthermore our recruitment strategy is strategic and economical, the donor population is highly motivated and the structure of the organisation is set up with short communication lines. All this resulted in many workup requests that were handled quickly and efficiently. Through the years we provided bone marrow of our donors for many patients around the world to give them a probability of survival.

Acknowledgements

The authors would like to thank all transplant centres for responding to our inquiry and their contribution to this article.

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