Donors’ Health State the Year after Peripheral Haematopoietic Progenitor Cell Collection: A Prospective Follow-Up Study in Related and Unrelated Donors Compared to First-Time Platelet Donors

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Granulocyte colony-stimulating factor (G-CSF) mobilized peripheral haematopoietic progenitor cells collected by apheresis (HPC-A) are the most common source used for allogeneic hematopoietic stem cell transplantation (HSCT). Retrospective short and long-term donor follow-up studies show very low risks of serious complications and do not report compelling evidence of increased cancer occurrence. Some studies reported a prolonged period of leucopenia without an obvious association with infectious complications. However, beyond the first few weeks after the procedure a relationship between events is elusive. We therefore evaluated medical service utilization by prospectively recruited HPC-A donors and first-time platelet apheresis donors for comparison for 1 year after donation. Data were prospectively collected using questionnaires and by medical record review. A total of 215 HPC-A donors (111 unrelated donors and 104 related donors) and 96 first-time platelet donors consented to participate in the study. Follow-up was available for 202 (96%): questionnaires were returned by 74% and records from nonstudy contacts were available for 94% of donors. During the 1-year follow-up, 94 of the donors who returned questionnaires sought medical attention for diagnostic evaluation and/or treatment: 41% of HPC-A donors and 40% of platelet donors. Medical service utilization the first year after HPC-A donation is similar to that after first-time platelet donation. The occurrence of serious medical conditions in both related and unrelated HPC-A donors underscores the importance of participation in long-term follow-up in large cohorts. The findings in this relatively small cohort contribute to evidence on the safety of G-CSF mobilization and HPC-A. J. Clin. Apheresis 31:523–528, 2016. © 2016 Wiley Periodicals, Inc.

INTRODUCTION

Peripheral haematopoietic progenitor cell collection by apheresis (HPC-A) is currently the most used source of allogeneic hematopoietic stem cells for transplantation in patients with various diagnoses. Information about safety and donors burden is therefore of pivotal importance [1]. Information regarding serious adverse events (SAEs) around the donation procedure and regarding malignant and auto-immune disorders in long-term follow-up reports, in particular in unrelated donors, is regularly published [2,3]. The World Marrow Donor Association (WMDA) maintains a registry of serious adverse events (SAEs) and reactions (SARs) associated with HPC-A and HPC-BM donation. A recent review of haematological abnormalities after HPC-A donation concluded that there is “a reassuring lack of evidence for development of haematological malignancy” [4]. In this survey it was remarked that the minor decrease of neutrophils, lymphocytes, monocytes, and/or NK cells observed post-donation, and in a minority of donors persisting beyond a year,
was not associated with reported infectious complications. In the case of (minor) events occurring more than 2 weeks after donation however, a causal relationship may not be suspected. There are data showing that G-CSF could induce a hypercoagulable state, placing patients with coronary artery disease or vascular disease at increased risk [5]. In particular venous thromboembolic disease has been reported during or shortly after using G-CSF [6].

While uniform international standards are followed for unrelated donors, a survey showed that Dutch centers performing related HPC-A donation procedures differ in their policies concerning age, potential risk factors, and follow-up procedures of the related donors [7]. Previously we retrospectively collected data on a Dutch cohort of related HPC-A donors (1996 till May 2006) and observed that related donors not fulfilling the health requirements for unrelated donors showed a higher incidence of cardiovascular and malignant complications at long-term follow-up as compared to related donors complying with eligibility criteria for unrelated donations [8]. Obviously causality was not be established and the incidence of events remained within the range expected for an age and gender matched population. This study was conducted to register all medical events occurring during the collection procedure and the first year after donation in prospectively recruited related and unrelated HPC-A donors compared to first-time platelet donors.

MATERIALS AND METHODS

Procedures for Acceptance, Donation, and Follow-Up (HPC-a Donation)

In The Netherlands all unrelated HPC-A donations are performed in two university medical centers, in Leiden and in Nijmegen; both collection and apheresis centers are JACIE-accredited. The national blood supply organisation Sanquin and the Dutch stem cell donor registry, Eurodonor, are responsible for the eligibility criteria for donation and coordination of follow-up of unrelated donors. All related donors asked for participation in this study were managed at Leiden University Medical Center. All donors who underwent G-CSF mobilization and HPC-A harvesting from May 2006 until April 2012 were eligible for inclusion in this prospective study (Fig. 1). Donors were approached for participation in this study by staff of the hemapheresis centers on the day of their first G-CSF injection. Donors with insufficient knowledge of the Dutch language were excluded.

The unrelated donors met the criteria for donation as recommended by the National Marrow Donor Program (NMDP). Additionally, in accordance with Dutch guidelines, they were aged <56 years and had to be classified as level 1 status according to the scale of the American Society of Anesthesiologists (ASA). Clearance of unrelated donors was performed by medical staff of the collection centers. The related donors were examined and accepted for HPC-A procedure by medical staff of the Leiden collection center who were not involved in the care of the recipient. If these donors did not fulfil the NMDP criteria, in some cases they could however still be accepted after discussion within the team of donor physicians and with specific donor consent. The procedures and the reference criteria for this subgroup have been previously described [8].

Donors were treated with G-CSF (Filgrastim, Amgen, Thousand Oaks, CA) in a dose of 10 μg per kilogram body weight once daily for three days and twice on the fourth day in Leiden. In Nijmegen a dose of 5 μg per kilogram twice daily was given for 4 days, while on the fifth day a dose of 10 μg per kilogram once daily was administered. If necessary the dose was adjusted according to the leucocyte count on the fourth day according to a local protocol. During the course of the study, for related donors only the possibility of treatment with Plerixafor (Mozobil, Genzyme Europe) was added to the protocol for use in the case of inadequate mobilization using G-CSF.

Apheresis of HPC-A was performed using a Cobe® Spectra Apheresis system (Terumo, Germany) according to local standard operating procedures which included the use of oral or intravenous calcium supplementation as necessary for relief of symptoms due to hypocalcaemia. Donors were instructed to contact the apheresis department in the event of particular symptoms occurring within 2 weeks of the donation.

Laboratory parameters (complete blood count, serum creatinine, bilirubin, lactate dehydrogenase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, calcium) were tested at baseline, during mobilization, before and directly after harvest and at follow-up visits in all unrelated donors. Routine follow-up visits and blood tests of unrelated donors were scheduled at approximately 2–4 weeks, 6 months, 1 year after donation, and thereafter yearly. In related donors these laboratory analyses were performed at similar times before and immediately after harvest, as well during follow-up at ~3 and 11 months after harvest.

Procedures for First-Time Platelet Donors

Platelet apheresis donors are recruited among regular whole blood and plasma donors. In The Netherlands regular whole blood donors are asked consent for HLA typing with the purpose of platelet donation, stem cell donation or both. All donations are voluntary and non-remunerated. Donors are screened according to the national guideline for donor health examination (Sanquin Blood Supply Foundation), which endorses all
criteria laid down in European legislation. In contrast to unrelated HPC-A donors, they may donate up to and including the age of 69 years; antihypertensive medication and obesity do not constitute deferral reasons. Platelet donors are not checked on a regular basis, only prior to any upcoming donation. The platelet donors were invited to participate by the staff of the blood bank apheresis centers in the Southwestern region of The Netherlands when attending for their first platelet donation.

Study Data Collection

Approval was obtained from the hospital as well as Sanquin Blood Supply medical ethics committees. Donor consent provided at the time of inclusion authorised the receipt of a questionnaire and the use of routinely collected data up to 1 year after donation by extracting parameters from medical records and computerised laboratory results. The data of donations of platelet donors were collected from the blood bank computer system eProgesa (MAKsystems, Paris, France). All events requiring unscheduled medical examination or treatment from the start of mobilization until the end of the follow-up year were recorded. The definition for serious adverse event (SAE), in accordance with international criteria (FDA, Clinical Trials legislation) was met if any of the following occurred: death, life-threatening event, unplanned or prolonged inpatient hospitalization, chronic morbidity.

The questionnaire included a checklist to ascertain medical consultations, diagnostic procedures, diagnosis, and treatment during the follow-up period. The questionnaire included questions on occurrence of venous and arterial (cardio)vascular events, neoplastic diseases, auto-immune diseases, infections treated with antibiotics, pulmonary diseases, diabetes mellitus, joint and/or muscular problems, skin and thyroid diseases. The investigators contacted donors by telephone or e-mail to clarify answers if necessary. A panel of physicians (TN, IB, JW, MF) reviewed all (S)AE.

The follow-up period was defined as the period starting 2 weeks after peripheral haematopoietic progenitor cell collection or the first platelet apheresis to the latest contact with the last included donor until the end of the study period (June 2013). Participants who did not respond during follow-up were contacted by telephone or e-mail by the investigators. If a donor declined filling in of further questionnaires, or was lost to follow-up for other reasons, that donor’s data were included up to the point where participation ceased.

RESULTS

A total of 311 donors gave informed consent (Fig. 1). The characteristics of these donors are summarised in Table I. The majority (231, 74%) returned the questionnaire. In all groups over half the donors were male. Related HPC-A donors were 10 years older on average than unrelated donors, whereas the age of platelet donors was in-between.

Mobilization Phase

All except one of the donors were adequately mobilised with the initially calculated dose of Filgrastim. One related donor received additional Plerixafor.
leading to an adequate harvest of CD34+ cells. During the mobilization period the most frequent symptoms were muscular aches and bone pain. This was documented in 51% of the related, and in 63% of the unrelated HPC-A donors. One related donor suffered modest dyspnea after the first dose of G-CSF which resolved following inhalation of Salbutamol. Mobilization was continued without complications and HPC-A collection was uneventful. Five donors needed unscheduled medical evaluation during the period of mobilization and the week after HPC-A harvesting. Two of the five, who were related donors, were analyzed for chest pain. It was concluded that symptoms were best explained as bone pain caused by G-CSF and they were able to continue the donation procedure. Three unrelated donors were evaluated in the hospital because of symptoms suggestive of possible splenic infarction or threat of rupture. In no case was pathology of the spleen (rupture or infarction) demonstrated by ultrasound. All five donors continued the procedure; these events were not classified as SAE.

Collection of PBSCs and Platelets and 2-Week Follow up

Although HPC-A harvest was completed in one day in the majority of the donors, 36% of related donors and 8% of unrelated donors needed a second day of collection in order to meet the requested target. This difference can be explained by the higher target number of HPC-A cells requested for the related transplantation (overall 14.7 CD34+ cells per kg of the related recipient’s weight vs. 7.1 cells/kg for unrelated collections); moreover in general female donors were more likely to require two days, and females were over-represented among the related donors. Serious technical problems did not occur in any of the procedures. Venous access problems were resolved in ten procedures by the use of central venous catheters. In one case CVC placement led to a local hematoma. Three donors showed signs of tetany; one of them, an unrelated donor, was admitted overnight for observation although the carpopedal spasm had fully resolved. This event was therefore classified as an SAE. Transient vasovagal symptoms occurred in two donors but did not lead to premature termination of the collection.

Within 2 weeks following donation one related donor developed symptoms of thrombophlebitis in the right arm. One unrelated donor experienced unilateral sensory symptoms ten days after donation for which he was hospitalized for 3 days. The complaints persisted for 48 h and no substrate could be found despite neurological analysis including CT and MRI. In the next 12 months he did not have recurrent symptoms.

None of the platelet donors suffered from medical disorders requiring in-patient medical care. In one of the donors a modest hematoma occurred directly after donation.

Follow-Up Beyond 2 Weeks

Follow-up data were available for 74% of HPC-A participants from returned questionnaires and for an additional 22% because of subsequent donations (screening and donation procedures) or through scheduled follow-up visits. Eighty-eight percent of the related donors completed the 12 month follow-up as compared to 99% of the unrelated donors. One unrelated donor was lost to follow-up as from two months after harvest. Twelve related donors did not answer any means of contact, also not for the last scheduled follow-up.

Fifty-seven related donors subsequently donated lymphocytes during the study follow-up period, and two underwent a second stem cell donation (one time bone marrow, one time HPC-A). Of the unrelated donors, eight donors donated lymphocytes during follow-up to 1 year and one donor donated HPC-A again. All the participating first-time platelet donors completed follow-up. They donated on average three times (median 2, range 0–17) during the follow-up period (a total of 292 donations of whole blood, plasma, or platelets).

Medical Service Utilization by Donors

Among those who returned questionnaires, 94 participants needed medical consultations and/or treatment during follow up: 37 unrelated and 28 related HPC-A donors (41% of the HPC-A donors) and 29 platelet donors (40%).

The most frequent consultations during the year after donation were for nonspecific joint and muscle symptoms as well as for miscellaneous infections. The episodes are summarized in Table II. One unrelated male, 44 years of age, was diagnosed with Wallenberg’s
syndrome due to an ischemic stroke 6 months after donation. This donor had no known (cardio)vascular risk factors. In a female unrelated HPC-A donor the first symptoms of multiple sclerosis occurred ten months after donation. One related donor was diagnosed with Type 2 diabetes mellitus during the follow-up period and started on oral antidiabetic treatment. The only known predisposing factor for this donor was obesity. One platelet donor had been diagnosed with a vestibular schwannoma and another with polymyalgia rheumatica. The laboratory analyses performed at follow-up revealed no abnormalities of clinical relevance. In particular no white blood count abnormalities were observed.

**DISCUSSION**

Post-donation medical service utilization by related and unrelated Dutch HPC-A donors was compared to first-time platelet apheresis donors because the Dutch platelet and stem cell donors are mainly recruited from the same blood donor population and—apart from G-CSF—they undergo a similar apheresis procedure. This study is the first to compare these two types of donations prospectively. It is also the first report describing health status of first-time platelet donors followed up for 1 year after their index donation.

Miscellaneous medical problems were reported by a surprisingly high proportion of donors during the follow-up to one year, in both HPC-A and platelet donors. Incidences of health care use for musculoskeletal complaints, infections requiring antibiotic treatment and other complaints were similar between the three cohorts of donors. We found no indication that HPC-A donation was associated with increased susceptibility for infections or other nonsevere morbidities.

During the follow-up period there were also a number of serious events: one donor suffered a cerebral infarction, two donors were treated for malignancies and two others were diagnosed with polymyalgia rheumatica (a platelet donor) and multiple sclerosis, respectively. The rates of malignancies seem high and call for comparison with similar groups of healthy people in the light of previous publications which raised concern that stem cell mobilization with G-CSF might trigger the development of malignancies or auto-immune disorders [9]. Reported rate of malignancies in recent large studies varies between 0.1 and 0.3% per donor year [10,11]. In a large registry-based study the rate was 0.1% for both PBSC and bone marrow donors, actually lower than population rate for age and gender matched subjects [2]. We compared the rate with Dutch population age- and sex-specific incidence rates for all invasive malignancies (available on the searchable national cancer web database, www.cijfersoverkanker.nl). The standardized morbidity ratio (i.e., taking account of the age and sex) of our cohort for malignancies in comparison to the general population was 2.5 with a 95% confidence interval of 0.03–8.9 signifying no significant difference in incidence rate. However, our small study is not suitable for such rare events and large sample sizes are required. Similarly, possible causality of vascular and auto-immune events cannot be interpreted from our study.

This is a small descriptive study and a number of limitations need to be noted. First, only a total of 215 HPC-A donors consented to participation in the study protocol out of a potential total of 274. The incomplete inclusion of 79% is a result of donors not being invited to participate by the collection center staff because of heavy workload, hence it is unlikely to have caused bias. Age and sex of the nonparticipating donors were similar to those of included donors, diminishing the likelihood of bias (data not shown). Another limitation is the incomplete response to the 1-year questionnaires (~75% in all subgroups), however the frequent regular follow-up contacts during the first year and screening for subsequent donations should have elicited data on

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**TABLE II. Reasons for Medical Consultations During the 1 Year After Donation**

<table>
<thead>
<tr>
<th>Reason</th>
<th>HPC-A donors</th>
<th>Platelet donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint and muscle</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Infectious</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Ear and respiratory tract infections</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Skin</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Urinary</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Auto-immune disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Polymyalgia rheumatica</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Neurological</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Migraine</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Gynecological</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Surgical</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Dermatological</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Eczema</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Various</td>
<td>23</td>
<td>9</td>
</tr>
</tbody>
</table>

*a*One related HPC-A donor (37 years of age) developed gastric carcinoma 8 months after donation; in one 48 years old unrelated HPC-A donor breast cancer was diagnosed 9 months after donation.

*b*One donor with an unexplained transient neurological disorder (see Results).
the serious outcomes. The questionnaire was not a previously validated tool such as those which exist for quality of life evaluations; however, it elicited a rate of \( \sim 40\% \) positive responses and broad range of conditions.

Some donors were lost to follow-up. This problem is not unique, with similar follow-up rates of 70% to 94% in other donor studies [12,13]. This occurred predominantly in related donors. In a recently published Italian cohort it was also observed that relatives are more often lost to follow-up than unrelated donors [14]. This issue might be of great relevance if there were medical reasons for the donors’ failure to participate in follow-up. The age and sex of the donors without follow-up were similar in distribution to the group which remained in contact; however, we were unable to ascertain any further detail. Efforts to document and publish follow-up information in all settings are needed in order to inform care of future cohorts of donors [15]. Furthermore, reporting should not be limited to cases where causation by the procedure is deemed likely.

The follow-up period was only 12 months. This interval was chosen because of reported decreased white blood cell counts up to one year and because donor-reported events from two weeks after donation onwards could occur simply by chance or could have a relationship with the procedure. In conclusion, this cohort of related and unrelated Dutch HPC-A donors reported similar incidences and reasons for medical service utilization as compared to platelet donors in the year following their index donation. The study was not designed to, and thus cannot, conclude on possible increased risks of cancer, autoimmune illness or vascular disease during this period of observation. Although this study concerns a relatively small cohort, the results contribute to information on the donors’ general health and safety of HPC-A donation.

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REFERENCES

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