Focus on the donor

Anne-Marie van Walraven, PhD MPA

http://focusonthedonor.nl

A donor

What is the first word that comes to your mind?

Donor

Altruism

Healthy

Consent

Suitable

Volunteer

Deferred

Consent

Compatible

On Time

Family

Available

Match

Sibling

Mismatch

???
**Donation in historical perspective**

**Blood donation**
- 1492 – Pope Innocentius VIII
- Three children as donor
- Each promised a ducat
- ‘Transfusion’ – through a tube in the stomach
- No survivors

Source: Stefano Infessura

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**First attempts**

- 1939 Osgood et al.
  - F, 19 yr. hypoplastic marrow; infusion of 18 ml bone marrow; died of infection.
- 1940 Morrison & Samwick
  - M, 42 yr. aplastic anemia; infusion of 13 ml bone marrow; developed leukemia.

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**1950-60’s**

- McFarland et al.*
  - 37 patients: SAA
  - 20 bone marrow therapy, 17 controls
  - Conditioning: high dose prednisone (100-150 mg/daily)
  - Bone marrow procurement:

  every effort was made to obtain marrow from a close relative; however, in 9 instances this was not possible, and professional donors had to be used.

Bone Marrow Therapy

The dose of bone marrow administered ranged between 1,000,000,000 and 40,000,000,000 nucleated cells. Some patients received multiple infusions from several donors, while others received only one infusion from a single donor. The marrow was generally administered intravenously, but in 7 cases it was injected directly into the medullary cavity (Table 2). The donor's blood was crossmatched with the recipient's in the usual manner.


Outcome

| Outcome | Thomas & Storb, Blood, 1970;36:507-515 |

Harvesting bone marrow

| Harvesting bone marrow | Thomas & Storb, Blood, 1970;36:507-515 |
The start of bone marrow registries

What was the main reason?

In an atomic age, with reactor accidents not to mention stupidities with bombs, somebody is going to get more radiation than is good for him. If infusions of marrow can induce recovery in a mouse or monkey after lethal radiation, one had best be prepared with this form of treatment in mind. The leukemic patient who needs radiation and bone marrow, and the acute patient who needs a spare kidney, are people who deserve immediate consideration. From helping them one will be preparing for the atomic disaster of tomorrow and it is high time one did.


International collaboration

- 1989 – Start Bone Marrow Donors Worldwide
- MDP Belgium is one of the founding registries, together with
- United Kingdom, Netherlands, USA, France, Germany, Italy, Austria
Principles of Donor Care Management

• First do no harm: stem cell donation is not in the physical interest of the donor
  – Donor information and examination by an independent physician\(^1\)
  – Estimation of risk\(^2\)
  – Sometimes: protect the donor for themselves
• The assumption that parents never refuse to donate is not a reason to use them as means to an end.\(^3\)

1. Van Walraven et al., 2010, BMT;45:1269-1273
2. Shaw et al., 2010, BMT;45:832-838
3. Stelling F Focus on the Donor

Freedom of choice

• Respect for autonomy
• Information
  – Risk of the donation
  – Alternative treatments
• Informed consent

Safety

• Donation is accepted in society and must be a safe procedure
  – Severe events and adverse reactions registry
  – Short and long term effects
  – Follow up
    • Unrelated donors up till 10 years post donation

Shaw et al., 2010, BMT;45:832-838
Anonymity

- Legislation (local and international)
- Safeguard privacy donor/recipient
- Protect safety of donor/recipient
- Objective decision making donor
- Positive donation experience

The importance of donor care

- Donation is established in legislation
  - National level:
    - Organ legislation
  - European level: Tissues and Cells directive
  - International level: WHO guiding principles

Donor care – more specific

- Guidelines/Standards
  - JACIE (http://www.jacie.org/)
    - B6: allogeneic and autologous donor selection, evaluation, and management
  - FACT (http://www.factwebsite.org/)
  - WMDA (https://www.wmda.info/)
Donor vigilance

- Registry of
  - Severe reactions/events
  - Complications
- WMDA S(P)EAR registry
  - Inventory
  - Analyse
  - Rapid alert
- A global registry for any donor’s serious events and adverse reactions is the only way to prove safety of stem cell donation.

2. AAP, 2010, Pediatrics; 125:392-404

What went wrong in 1492?

- Three children acting as donor
- Patient: Pope Innocentius VIII
- Remuneration: 1 ducat
- Transfusion – through tube into stomach
- No survivors

Issue 1: child as a donor

- Donors < 18 jaar
  - Donation is only allowed to sibling
  - no alternative adult donor available
  - donation is potentially ‘life saving’
  - Parents give proxy consent
  - Donor gives assent for procedure
  - Positive emotional relationship with recipient
  - A risk (clinical, emotional, psychological) must be minimized

2. AAP, 2010, Pediatrics; 125:392-404
Issue 2: Voluntary and anonymous

- The family donor
  - 0-80 Jr
  - Confrontation with donation: free choice?
  - Chance to help a loved one
  - Lifelong relationship (sometimes: broken)
- The unrelated donor
  - Aged 18 – 55 year (16-60 year)
  - No relationship recipient: anonymous donation
  - Altruism

Issue 3: Financial reward

- Donation is voluntary and unpaid
- Altruism as basic principle
  - WHO guiding principle 5
  - WMDA Standard 3.03
- Safety
- Dignity
- Donor altruism as motivation to donate must not be confused with ‘carte blanche’.

1. WHO Guiding principles, 2008
4. Stelling. Focus on the Donor

Issue 4: Consent

- No informed consent
- No proxy consent
- Assent?
- Experimental treatment!
A lot happened since….

- Invention of the cardiovascular system (1628, Harvey)
- Invention of ABO bloodgroups (1901, Landsteiner)
- Start unravelling HLA system (1953, van Rood, Payne, Thomas, Dausset)

What do we know about donors?

- Donor research
  - Motivation
  - Safety (also retrospective studies)
  - Attrition
- Donation experiences:
  - (un)related donors (bone marrow/stem cells):
    - parents
    - children

2. Shaw et al. 2010
3. Switzer et al. 2004
5. Van Walraven et al. 2013

Advancing insight

- Worldwide Network for Blood and Marrow Transplantation
  - Donor Outcome Workshops
    - Bern (2009); Leiden (2011); Vienna (2013)
- European Group for Blood and Marrow Transplantation (EBMT)
  - Donor Outcome Committee
    - Establishment donor database
The missing link….

- Education

A European Master

- DoHeCa (http://www.donorhealthcare.org/)
  - European master in Donor Health Care
  - Funding Erasmusfund Life Long Learning
  - Blood, tissues, cells, organs
  - Physicians and nurses (BSN)
  - University of Amsterdam in collaboration with Sanquin
  - Start 2017??

WMDA SCCP

- World Marrow Donor Association
- Search Coordinator Certification Program
  - Basic level (start 2015)
  - Advanced level (pilot phase, start 2016)
- Search coordinators of Registries and transplant centers
- http://www.worldmarrow.info
Conclusions I

- Donors deserve a respectful treatment
- Donor care management is presently getting more attention
- International collaboration helps to establish global donor safety
- Specific educational programs are being developed

Let's look at the other side

From experiment to regular treatment

- 1968 – 1st successful BMTs (1st child donor)
- 1987 – 1st unrelated bone marrow donation
- 1988 – 1st cord blood transplantation
- 1994 – G-CSF in family donors
- 1996 – G-CSF in unrelated donors
- 2006 – double cord blood
- 2014 – renewed interest in haplo-identical donors
Present facts

• Allogeneic haematopoietic stem cell transplantation (SCT) is an effective curative option for a variety of haematological disorders (leukaemia’s and bone marrow failure syndromes)

• Approximately 70% of eligible patients lack an HLA identical sibling

• Stem cells provided by extended family members, unrelated donors or derived from cord blood are an acceptable alternative

Transplant activity


Volunteer stem cell donations worldwide

Source: WMDA annual reports
However...

- Mainstream of donors have North Western European background
- HLA diversity in donor pool is limited
- A number of patients does not reach transplantation
  - Range in Europe: 53% (range 7-78%)

Faster is better than more?

- The Worldwide donor pool (Bone Marrow Donor Worldwide) increased from a few hundred thousand donors in the late eighties to 8 million in the year 2000 and now reached over 26 million.
- The answer to “How to increase the donor pool” is the answer to “how increase the chance on a successful unrelated donor search”*

*Heemskerk et al. Bone Marrow Transplantation;2005;36(7):645-652
Reasons for not reaching trx

Patient related
- Untimely start of donor search
- Clinical deterioration

Donor related
- HLA
- Donor availability
- Length of donor search

Patient related factors

- Start of search / HLA typing
  - At time of diagnosis?
  - At 1\textsuperscript{st} remission?

- Clinical deterioration
  - Refractory disease
  - Early relapse
  - Refractory infections

HLA

- Polymorphism
  - 14,015 HLA alleles discovered
Increase of number of HLA-alleles

**HLA**

- **Polymorphism**
  - 14,015 HLA alleles discovered
  - Rare alleles -> negative predictor
- **Associations**
  - HLA-B/C, HLA-DRB1/DQB1
  - Unknown association?
- **Haplotype frequency**
  - A1-B8-DR3
  - Frequent haplotype -> positive predictor

**Countless combinations?**

- HLA-A*, -B*, DRB1* phenotypes
- The number of possible combinations?
  - >3,000,000,000,000,000
  - Estimation total number of humans ever lived: 100-115,000,000,000

*Curtin, Scientific American, 2007;297(3):126*
Keep in mind

• Rare HLA alleles and/or unknown HLA associations should ring a bell
• For a number of patients, a (partially) compatible donor or cord blood cannot be found.

The optimal donor pool

• Young – better outcome
  – 10% of all donors < 26 yr.
  – Recruiting younger donors: different approach
• Male – better grafts
  – Globally: 19% male & < 36 yr.
• Diverse – to serve as much patients
• Available – how to prevent attrition?
  – Information and motivation

Donor availability

• At verification typing stage
  – Donor temporary unavailable (TU)
  – Availability donors in EU MS: 74% (range 27-100%)
  – Ethnic minority donors
• At work up stage
  – Donor deferred for medical reason (8%)*
  – Donor no longer available for personal reason (2%)**
  – No show

*Lown, Bone Marrow Transplantation, 2014;49(4):525-531.
Effects of donor attrition*

- Patient
  - Perceptions about numbers of donors
  - Disappointment to loss of potential donors
- Donor
  - Guilt, negative self-perceptions
- Donor registries
  - Monetary costs
  - Loss of credibility
- Societal
  - Creation of ‘non-volunteers’

NMDP: An increase of 5% unavailability would offset 2 years of recruitment

Solutions?

- Recruitment strategies
  - Select the best candidates
  - ‘Tailor-made’ for different groups
  - Which factors are associated with commitment?
- Prevent donor retention
  - At recruitment: information
  - Analyse risks for opt-out at typing stage

Length of Donor Search

- Time from diagnose to transplantation
- Time needed to identify a donor
- How long does it take to identify a donor?
Factors of influence

- Urgency
- Level of knowledge and skills
  - HLA, search tools
  - International rules and regulations
- Efficient search strategy
  - Network
  - Back up donor
- Level of HLA typing of donors
  - 5 loci (HLA-A, -B, -C, -DRB1, -DQB1)
  - Low versus high resolution

Donor search: the Dutch experience

- 1987 – start unrelated donor searches
  - 3 transplant centers
- 2000 – 100 new Dutch searches per year
  - 6 transplant centers
- 2015 – appr. 600 searches per year
  - 10 transplant centers

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Median age in yr (range)</th>
<th>% of all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>adults</td>
<td>male/female (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987-1995</td>
<td>65/35</td>
<td>27.4 (16.1-52.3)</td>
<td></td>
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<tr>
<td>1996-2000</td>
<td>60/40</td>
<td>33.2 (16.4-53.6)</td>
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<tr>
<td>2001-2006</td>
<td>64/36</td>
<td>43.5 (16.9-67.3)</td>
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<tr>
<td>2007-2012</td>
<td>59/41</td>
<td>52.3 (17.1-79.7)</td>
<td></td>
</tr>
<tr>
<td>children</td>
<td>Med age in yr (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987-1995</td>
<td>5.0 (0.3-15.7)</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>1996-2000</td>
<td>6.5 (0.1-15.0)</td>
<td>51</td>
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</tr>
<tr>
<td>2001-2006</td>
<td>6.9 (0.0-15.9)</td>
<td>30</td>
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<tr>
<td>2007-2012</td>
<td>8.3 (0.1-16.0)</td>
<td>17</td>
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Donor found vs reaching trx

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients (Caucasian descent)</th>
<th>Patients (non-Caucasian descent)</th>
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<tbody>
<tr>
<td>1987-1995</td>
<td>51%</td>
<td>33%</td>
</tr>
<tr>
<td>1996-2000</td>
<td>69%</td>
<td>42%</td>
</tr>
<tr>
<td>2001-2006</td>
<td>91%</td>
<td>65%</td>
</tr>
<tr>
<td>2007-2012</td>
<td>95%</td>
<td>82%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients (Caucasian descent)</th>
<th>Patients (non-Caucasian descent)</th>
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<tbody>
<tr>
<td>1987-1995</td>
<td>48%</td>
<td>23%</td>
</tr>
<tr>
<td>1996-2000</td>
<td>59%</td>
<td>31%</td>
</tr>
<tr>
<td>2001-2006</td>
<td>76%</td>
<td>52%</td>
</tr>
<tr>
<td>2007-2012</td>
<td>82%</td>
<td>69%</td>
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</table>

Stem cell source

<table>
<thead>
<tr>
<th>Year</th>
<th>BM/PBSC (CAU)</th>
<th>BM/PBSC (non-CAU)</th>
<th>Cord blood (CAU)</th>
<th>Cord blood (non-CAU)</th>
<th>Alternative donor (CAU)</th>
<th>Alternative donor (non-CAU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001-2006</td>
<td>93.8</td>
<td>64.2</td>
<td>4.6</td>
<td>28.4</td>
<td>1.6</td>
<td>7.4</td>
</tr>
<tr>
<td>2007-2012</td>
<td>87.6</td>
<td>54.3</td>
<td>11.6</td>
<td>41.1</td>
<td>0.8</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Conclusions II

- HLA, length of search, donor availability, but also timely start of search are crucial for reaching transplantation
- Cord blood has become an important stem cell source
- Not all patients find a donor
Thank you for your attention!