BLOOD DONORS AND THALASSEMI A

Dr. Giancarlo Ferrazza, M.D.
U.O.C. di Immunoematologia e Medicina Trasfusionale
Policlinico Umberto I - “Sapienza” Università di Roma
EVOLVING ROLE OF TRANSFUSION MEDICINE

In the last 20 years Transfusion Medicine has evolved:

- From an activity mainly focused on laboratory and on serological blood aspects
- Also to a discipline clinically oriented to patient care and safety
TRANSFUSION THERAPY

- It’s a replacement therapy having temporary effects
- It’s a limited therapeutic resource
- Has limited and measurable risks
- Therefore it’s to be used according to precise requirements and using selectively the specific blood component necessary to cure the disease
QUALITY IN BLOOD TRANSFUSION: DEFINITION

In clinical use the quality of blood components involves administration of:

- “right” quantity
- “right” blood component
- in the “right” way
- at the “right” time
- to the “right” patient

and the appropriate documentation of the entire process and possible consequences
Incidence and Severity of Cancer-Related Anemia by Tumour Type (ECAS)

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Patients (%)</th>
<th>Hb &lt; 12 g/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>3,123</td>
<td>30.4%</td>
</tr>
<tr>
<td>Lung</td>
<td>2,002</td>
<td>37.6%</td>
</tr>
<tr>
<td>GI-Colorectal</td>
<td>2,402</td>
<td>38.9%</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>684</td>
<td>24.9%</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>1,675</td>
<td>49.1%</td>
</tr>
<tr>
<td>Lymphoma/Myeloma</td>
<td>2,260</td>
<td>52.5%</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>624</td>
<td>53.0%</td>
</tr>
<tr>
<td>Urogenital</td>
<td>894</td>
<td>29.2%</td>
</tr>
</tbody>
</table>

ECAS = European Cancer Anaemia Survey;

Anemia is a frequent complication of chemotherapy

Hb<12 g/dl at least once during a period of 6 months


Patients with anemia (%)
Transfusion of Red Blood Cell Concentrates

Fast correction of anemia
Transfusion of Red Blood Cell Concentrates: problems

- Not easy to plan: avoid very low Hb levels
- Limited availability of blood
- Side effects and risks
**TRANSFUSION REQUIREMENTS OF SEVERAL SURGERY OPERATIONS**

- Esophagectomy: 4 RBC
- Gastrectomy: 2 RBC
- Hepatectomy: 4 RBC
- Small bowel or colon resection: 2-4 RBC
- Pancreasectomy: 4 RBC
- Lobectomy: 2 RBC
- A.A.A.: 4 RBC
- T.A.A.: 6 RBC
- By-pass: 2-4 RBC
- Removal of brain tumours: 2 RBC
- Prostatectomy: 4 RBC
- Hip or knee prothesis: 2 RBC
TRANSFUSION REQUIREMENTS FOR SEVERAL SURGERY OPERATIONS

ORGAN TRANSPLANTATION:

- Heart: 4 RBC
- Kidney: 2 RBC
- Liver: 5-10 RBC
- Both lungs: 10-20 RBC
TRANSFUSION REQUIREMENTS IN SEVERAL BLOOD DISEASES

- Bone marrow aplasias  ~ 1 RBC a week
- Major Thalassemias  ~ 40 RBC per year
- Leukemia pts  ~ 80-100 RBC during treatment
- Bone marrow transplant  ~ 100 RBC

More than any surgical request!!!
Transfusion is still the cornerstone therapy in the treatment of all forms of thalassemia. Its aim is to correct anemia and to suppress the bone marrow’s intense activity.
TRANSFUSION THERAPY

Blood transfusions performed on a regular basis have allowed to improve the quality of life and life expectancy of these patients. It has been nominated since 1960.

GOLD STANDARD

since 1960
CURRENT TRANSFUSION REGIME IN THALASSEMIA

Pre-transfusional Hb  9.5 +/- 0.4 g/dl

In fact, when Hb < 9 g/dl, intestinal iron absorption and bone marrow erythropoiesis both increase, thus causing skeleton alterations.
Consequences of repeated transfusions

- Hb fluctuation
- Increased need for transfusion
- Inhibition of endogenous EPO
Red blood cells must be:

- Fresh (not more than 7 days old)
- Free of white blood cells
- Free of platelets
- Free of micro-aggregates
- Free of plasma residues
ASPECTS OF TRANSFUSION THERAPY THAT CAN BE IMPROVED BY CAREFUL PLANNING

- **Prevention of alloimmunization**

  The mean immunization value in the population of transfused thalassemic patients ranges from 10% to 45%
  
  Most cases, 80-95 %, concern the Rh and Kell systems

  **At least Rh and Kell typing**
TRANSFUSION THERAPY

Transfusion therapy must be:
- safe
- quantitatively and qualitatively adequate

The best practice would consist in programming and planning of transfusion therapy taking into account the clinical and social needs of the patient.
ROLE OF THE TRANSFUSION CENTRE

- Collection, processing, validation and storage of blood components (from whole blood or from apheresis)
- Distribution of blood components and blood safeguarding
- Solutions for immuno-haematologic problems
- Monitoring of transfusion therapy efficacy
- Collection, handling and storage of peripheral blood stem cells for autografting and allografting
- Umbilical cord bank
- Bone marrow donor bank
Our Transfusion Center is not self-sufficient in terms of support to the various and numerous requests of our Highly Specialized University Hospital Departments and for this reason, historically, we used, together with the units collected in our fixed center, also whole blood units collected by mobile modules.
ASPECTS OF TRANSFUSION THERAPY THAT CAN BE IMPROVED BY CAREFUL PLANNING

- Keeping Hb at constant levels with lower number of hospital accesses/year

This can be obtained via the quality and appropriateness of the transfused blood component.

The recommendation is to transfuse concentrated red blood cells with a hemoglobin content > 56 g/unit.
The best transfusion practice envisages the lowest consumption of blood without compromising any vital functions.
HISTORICAL NOTES

• ’70s:
  Introduction of multiple plastic bags

• ’80s:
  Additive solutions

• ’90s:
  Apheresis donation
The advent of blood donation by apheresis is an indispensable tool for the production of blood components intended for “ideal selective transfusion” purposes.
RED CELLS COLLECTION PROTOCOLS USED:

1. RBCP (red cells and plasma collection)
2. LDPRBC (red cells and platelets)
3. SDR (single donor double unit of red cells)
MCC vs Whole Blood

Donors Recruitment

Donors Selection

Whole Blood Donation

Fractionating & Testing

Patients

1 plt
1 RBC 1 pl
1 plt

Plasmapheresis

3 pl

Plateletapheresis

6 plt

Erithroapheresis

2 RBC
Whole Blood Donation

450 cc ± 10%
- 250 cc RBC
- 150 cc Plasma
- 50 cc Platelets

Donor 1
- Hb 13.50 gr/dl
- 200 cc RBC

Donor 2
- Hb 16.50 gr/dl or more
- 250 cc RBC

Same clinical efficacy?
Careful donor selection is a key factor for improving transfusion therapy.
### Apheresis Donor Selection

**Donor Requirements (D.M. 3/3/2005)**

<table>
<thead>
<tr>
<th></th>
<th>Whole Blood</th>
<th>Plasma</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>≥18 and ≤ 65 years</td>
<td>≥18 and ≤ 60 years</td>
<td>≥18 and ≤ 65 years</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>≥ 50 kg</td>
<td>≥ 50 kg</td>
<td>≥ 50 kg</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td><strong>Systolic:</strong> ≥ 110 and ≤ 180 mmHg, <strong>Dyastolic:</strong> ≥ 60 and ≤ 100 mmHg</td>
<td><strong>Systolic:</strong> ≥ 110 and ≤ 180 mmHg, <strong>Dyastolic:</strong> ≥ 60 and ≤ 100 mmHg</td>
<td><strong>Systolic:</strong> ≥ 110 and ≤ 180 mmHg, <strong>Dyastolic:</strong> ≥ 60 and ≤ 100 mmHg</td>
</tr>
<tr>
<td><strong>Hearth Freq.</strong></td>
<td>50-100 heartbeats/ min</td>
<td>50-100 heartbeats/ min</td>
<td>50-100 heartbeats/ min</td>
</tr>
<tr>
<td><strong>Hb</strong></td>
<td>♂ ≥ 13,5 g/ dl, ♀ ≥ 12,5 g/ dl</td>
<td>♂ ≥ 12,5 g/ dl, ♀ ≥ 11,5 g/ dl</td>
<td>♂ ≥ 13,5 g/ dl, ♀ ≥ 12,5 g/ dl</td>
</tr>
<tr>
<td><strong>Total serum protein</strong></td>
<td>−</td>
<td>≥ 6 g/ dl</td>
<td>−</td>
</tr>
<tr>
<td><strong>PLT</strong></td>
<td>−</td>
<td>−</td>
<td>≥ 150,000/ mmc</td>
</tr>
<tr>
<td><strong>PT, PTT</strong></td>
<td>−</td>
<td>−</td>
<td>Normal values</td>
</tr>
</tbody>
</table>
## Donor Requirements in Multi-Component Collection (MCC)

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Requirement Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WEIGHT</strong></td>
<td>( \geq 60 \text{ kg} )</td>
</tr>
<tr>
<td><strong>PLT</strong></td>
<td>( \geq 150.000/ \text{ mm}^3 )</td>
</tr>
<tr>
<td><strong>MAXIMUM VOLUME COLLECTED WITH MCC</strong></td>
<td>( \leq 650 \text{ ml} )</td>
</tr>
<tr>
<td><strong>Hb POST- DONATION</strong></td>
<td>( \text{♂} &gt; 12.5 \text{ g/dl} )</td>
</tr>
<tr>
<td></td>
<td>( \text{♀} &gt; 11.5 \text{ g/dl} )</td>
</tr>
<tr>
<td><strong>PLT POST- DONATION</strong></td>
<td>( \geq 120.000/ \text{ mm}^3 )</td>
</tr>
<tr>
<td></td>
<td>RBC/WhB</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
</tr>
<tr>
<td>RBC/WhB</td>
<td>90</td>
</tr>
<tr>
<td>RBC+PLS</td>
<td>90</td>
</tr>
<tr>
<td>RBC+PLT</td>
<td>90</td>
</tr>
<tr>
<td>PLS+PLT</td>
<td>30</td>
</tr>
<tr>
<td>2 PLT</td>
<td>30</td>
</tr>
<tr>
<td>PLS</td>
<td>30</td>
</tr>
<tr>
<td>2 RBC</td>
<td>90</td>
</tr>
</tbody>
</table>

Initial donation

WhB: Whole Blood
RBC: Red Blood Cell
PLS: Plasma
PLT: Platelets
Not the same donation for everyone but taylor-made for donor, depending on the his/her characteristics

THE RIGHT DONATION FOR EACH DONOR!!!
EXAMPLE

- Donor values:
  - 14.5 g/dl < Hb < 16 g/dl

Which is the best donation?

- Whole Blood
- RBC+Plasma Apheresis
Female Donor (childbearing potential):
- 12.5 g/dl < Hb < 13.5 g/dl

Which is the best donation?
- Plasma
- Plasma+PLT
- Whole Blood
- PLT
Male Donor:
- PLT > 200,000/mmc
- Ht > 45%

Which is the best donation?

- Plasma?
- RBC + plasma
- Whole Blood
- PLT + RBC
Male Donor:
- Hb > 15.5 g/dl
- Ht > 45.5%

Which is the best donation?

- Double Red Cell
- Plasma ?
- PLT + RBC
- Whole Blood ?
- Plasma + RBC ?
Donor: AB Group

Which is the best donation?

Plasma

if: Ht < 47%
The production of a double unit of concentrated red cells (Single Donor Red cell, SDR) from a habitual blood donor and its subsequent transfusion to the thalassemic patient is how we propose to achieve the ideal of this “selective” transfusion.
APHERESIS DOUBLE UNIT RED CELL COLLECTION

PHYSICAL REQUIREMENTS OF PERIODICAL DONORS ENROLLED IN THE STUDY

- Male
- Weight $\geq 70 \text{ kg}$
- Hb $\geq 15.5 \text{ g/dl}$
- Ht $\geq 45.5 \%$
- Normal ferritin
- Normal cardiovascular functionality
**APHERESIS DOUBLE UNIT RED CELL COLLECTION**

**PHYSICAL CHARACTERISTICS AND BLOOD PARAMETERS OF DONORS ENROLLED IN THE STUDY**

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>39.6</td>
<td>20 - 58</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>80.5</td>
<td>62 - 103</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>177.1</td>
<td>165 - 191</td>
</tr>
<tr>
<td><strong>Hb g/dl</strong></td>
<td>16.6</td>
<td>15.5 - 18.3</td>
</tr>
<tr>
<td><strong>Ht %</strong></td>
<td>49.8</td>
<td>45.6 - 55.7</td>
</tr>
</tbody>
</table>
### PROTEIN IRON BALANCE OF DONORS ENROLLED IN STUDY

Initial mean values of serum iron, ferritin

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum iron mcg/dl</strong></td>
<td>88.4</td>
<td>47.5 - 144.5</td>
</tr>
<tr>
<td>(norm: 50-150)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ferritin ng/ml</strong></td>
<td>52</td>
<td>15 - 208</td>
</tr>
<tr>
<td>(norm: 28-300)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total protein g/dl</strong></td>
<td>7.6</td>
<td>5.6-7.9</td>
</tr>
<tr>
<td>(norm: 6-8.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Physical characteristics and blood parameters of donors enrolled in study.
APHERESIS DOUBLE UNIT RED CELL COLLECTION

RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb g/dl</td>
<td>13.2</td>
<td>11.5 - 15.7</td>
</tr>
<tr>
<td>Ht %</td>
<td>39.1</td>
<td>33.1 - 47.1</td>
</tr>
</tbody>
</table>

Mean values of Hb and of Ht of donors post donation.

<table>
<thead>
<tr>
<th></th>
<th>After 30 days</th>
<th>Range</th>
<th>After 90 days</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb g/dl</td>
<td>15.5</td>
<td>14.6 - 16.4</td>
<td>16.2</td>
<td>15.2 - 18</td>
</tr>
<tr>
<td>Ht %</td>
<td>45.6</td>
<td>43.2 - 48</td>
<td>47.4</td>
<td>44.8 - 50</td>
</tr>
</tbody>
</table>

Mean values of Hb and Ht of donors 30 and 90 days after donation.
## APHERESIS DOUBLE UNIT RED CELL COLLECTION

<table>
<thead>
<tr>
<th></th>
<th>MEAN after 30 days</th>
<th>Range</th>
<th>MEAN after 90 days</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron mcg/dl</td>
<td>59.7</td>
<td>52 - 67.4</td>
<td>87.7</td>
<td>55.8 - 144</td>
</tr>
<tr>
<td>(norm: 50-150)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin ng/ml</td>
<td>21</td>
<td>9 - 34</td>
<td>34.1</td>
<td>26 - 42.2</td>
</tr>
<tr>
<td>(norm: 28-300)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serum iron and ferritin values 30 and 90 days post-donation
**APHERESIS DOUBLE UNIT RED CELL COLLECTION**

**RETICULOCYTE COUNT IN DONORS ENROLLED IN STUDY**

<table>
<thead>
<tr>
<th></th>
<th>Reticulocytes (norm: 30,000-130,000)</th>
<th>CHr (norm &gt; 26 pg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean after 30 days</td>
<td>95,750</td>
<td>33.15</td>
</tr>
<tr>
<td>Mean after 90 days</td>
<td>119,225</td>
<td>34.1</td>
</tr>
</tbody>
</table>

Mean value of reticulocytes and of CHr 30 and 90 days post donation

**CHr** → **Reticulocyte Hemoglobin Content**
The SDR procedure was performed using a Haemonetics MCS Plus device, with the 948F disposable equipped with Pall filter RCH2 that allows pre-storage filtering of concentrated red cells. During this procedure, the red cells are rinsed in saline.
APHERESIS DOUBLE UNIT RED CELL COLLECTION

PRODUCT FEATURES

At the end of the procedure, the red cells are not reconstituted in 140 ml of SAG-M medium, resulting in a product with the following features:

Values relating to the sum of the two units ($U_2$)

<table>
<thead>
<tr>
<th>Mean volume ml</th>
<th>Range</th>
<th>Mean Ht %</th>
<th>Mean Hb/$U_2$</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>379</td>
<td>366-413</td>
<td>90.5</td>
<td>120</td>
<td>98-140</td>
</tr>
</tbody>
</table>
# Apheresis Double Unit Red Cell Collection

Quality parameters of the blood component, pre versus post filtration

<table>
<thead>
<tr>
<th>Filtration</th>
<th>Volume ml</th>
<th>Ht %</th>
<th>Hb g/U₂</th>
<th>WBC/U₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE</td>
<td>404</td>
<td>71.4</td>
<td>120.4</td>
<td>2x10⁹</td>
</tr>
<tr>
<td>POST</td>
<td>379</td>
<td>90.5</td>
<td>114.5</td>
<td>3.6x10⁵</td>
</tr>
</tbody>
</table>
The resulting SDR unit has undergone less handling and has a high Ht already at end of donation.

Reduction in transfusion product preparation time and in SIT workload.
COMPARING APHERESIS AND WHOLE BLOOD DONATION

Standardization

1. Apheresis RBC

2. Whole Blood RBC

 +/- 6 % Range Variation

 +/- 12 % Range Variation

High quality product

Reduced storage lesion from initial AC/cell ratio

Provides proper amount of AC to any dose collected

G. Matthes - The potential of multicomponent blood donation - La trasfusione del sangue 2000;45:173-183
COMPARING APHERESIS AND WHOLE BLOOD DONATION

- Relative Changes
  - Rigidity (RCC)
  - Rigidity
  - Sedim. Index
  - Blood Viscosity

- Manual collected RCC
- Apherased RCC

Storage Time at 4 °C (days)

- Apherased red cell concentrate (RCCa)
- Red cell concentrate (RCC)
- Aggregation Index
- Deformability

- Plasma viscosity
  - (PV)p
  - (PV)n

- Haematocrit

- Haemorheological Risk after 42 days of storage at 4 °C
  - RCCa Increase to 107 %
  - RCC Increase to 133 %
FRACTIONATION BY DONOR SIDE

TIME DELAY (COLLECTION → FRACTIONATION → STORAGE) - NULL

CONSTANT PROCESS TEMPERATURE

MANUAL DONATION

COLLECTION IN BAGS OF WHOLE BLOOD
CENTRIFUGATION
SEPARATION
CENTRIFUGATION
FINISHED PRODUCT

MULTICOMPONENT DONATION

COLLECTION BY APERHERESIS
FRACTIONATION BY CENTRIFUGATION
LEUKODEPLETION
FINISHED PRODUCT
All of the enrolled habitual donors enthusiastically accepted enrollment in the study on single-donor double red cell collection by apheresis.

Collection was well tolerated and a slight adverse reaction was observed in only one donor who was treated with calcium gluconate and that resulted in immediate recovery.

No significant alterations in control electrocardiographic recordings were observed.

High donation rate kept by the donors participating in this protocol (two SDR procedures/year = four whole blood donations).
The SDR blood component proved to be a uniform and standardized transfusion product compared to the conventional concentrated red cell unit, showing quality parameters in compliance with those imposed by European guidelines (EC Recommendation R (33) 15).

The mean hemoglobin content (120 g/U) of the SDR product proved to be higher than that of standard concentrated red cell units subjected to leukodepletion (minimum content: 45 g/U).

The mean hematocrit value of the SDR unit was 90.5%, i.e. higher than that required for red cell concentrates obtained using standard methods (65-75%).
The Pall RCH2 filter allowed for good leukodepletion efficiency, with a mean leukocyte residue of $3.6 \times 10^5 / U$.

The mean content of free hemoglobin was 0.09 g/dl, in perfect compliance with the requested quality standards.
The double unit of red cells, obtained from a single donor by apheresis, is the ideal transfusion product for the clinical treatment of patients subjected to chronic transfusion regimes, due to its quality characteristics and to the chance it gives of reducing the patient’s risk of infections and immune reactions.
MAIN ADVANTAGES FROM USING BLOOD COMPONENTS OBTAINED WITH CELL SEPARATOR IN THE THERAPY OF HEMOGLOBINOPATHIES

• One or two concentrated red blood cell units can be collected from each single donor, thus improving collection quality

• The final product is filtered prior to storage

• RBCs have standardized mass and volume

• Lower risk of infection and of alloimmunization
Several categories of patients undergoing hyper-transfusion regimes, such as those affected by thalassemia, are benefited by receiving a double unit of single-donor red blood cells both in terms of transfusional safety and of extension of interval between transfusion sessions.
DOUBLE RED CELL UNITS FROM APHERESIS FOR THALASSEMIC PATIENTS

Our study involved 15 patients, of which 13 affected by β-thalassemia major and 2 by intermediate thalassemia, with an average number of 6 consecutive transfusions per patient.

The mean Hb value of the 15 patients prior to transfusion was 9.4 g/dl (range: 8.7-9.6); the post transfusion value, assayed 24 hours later, was 13 g/dl (range: 12-13.8).
RESULTS

The systematic use of this blood component in this group of patients resulted in an extension of the interval between transfusions from:

15 to 21 days in 12 pts       15 to 30 days in 3 pts
ADVANTAGES FROM USING DOUBLE RED CELL APHERESIS UNITS

DONOR
- Customized protocols
- Volemic compensation
- Minor side effects versus whole blood donation
- Good compliance
- Motivation

PATIENT
- Standardized blood components
- Better yield
- Lower transfusion risk:
  - Infections
  - Alloimmunization
- Optimization of transfusion regime

TRANSFUSION CENTER
- High donation rates
- Greater availability of dedicated donors
- Better use of donors with rare phenotypes
- Easier and faster unit preparation for freezing
CONCLUSIONS

The double unit of red blood cells, obtained from a single donor by apheresis, is the ideal transfusion product for the clinical treatment of chronically transfused patients.