

Spanish Donor Registry. Follow-Up Data

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Introduction

- G-CSF mobilized peripheral blood is the main source of stem cells for hematopoietic transplantation.
- In the allogeneic setting the routine use of mobilized PBSC must be based not only on clinical results, but also on the safety of donors.
- Specific data about short- and long-term biological and clinical effects of G-CSF in normal donors is still needed.
- This task will be more easily approached by the development of national or international donor registries that allow the inclusion of higher number of donors.

Introduction

“High-quality, safe and efficacious procedures are essential for donors and recipients alike. **The long-term outcomes** of cell, tissue and organ donation... **should be assessed for the living donor**... in order to document benefit and harm. **The level of safety, efficacy** and quality of human cells, tissues and organs for transplantation... **must be maintained and optimized on an ongoing basis**. This requires implementation of quality systems including traceability and **vigilance, with adverse events and reactions reported, both nationally**...”

But... This need has not yet been addressed by other regulatory bodies (FACT-JACIE)!

Spanish Donor Registry

- Created in 1998.
- 27 centers.
- Prospective and standardized data collection.
- Aims:
 - ✓ To know the efficacy of G-CSF administration to healthy donors for PBSC collection.
 - ✓ To have a better knowledge of the incidence and nature of side effects.
 - ✓ Long-term follow-up to monitor the possible appearance of delayed side-effects in this population (incidence and type of malignancies and autoimmune disorders).

Spanish Donor Registry

- Initial (baseline) assessment.
- General information: Age, sex, grade of HLA matching.
- Laboratory data: CBC and serum biochemistry before and after G-CSF administration.
- Mobilization and collection
 - ✓ Dose and type of G-CSF administered.
 - ✓ Number of aphereses; CD34+ cell collected.
- Procedure-related side effects.
- Long-term follow-up
 - ✓ The first control performed within 4-6 weeks after mobilization.
 - ✓ Five additional controls (annually for 5 consecutive years).
 - ✓ Mail or phone calls not accepted as FU controls.

Registro de Donantes Movilizados con G-CSF Hoja de Recogida de Datos a la Movilización

Registro de Donantes Movilizados con G-CSF
Hoja de Recogida de Datos a la Movilización

Personal **Nº Registro**

Datos Personales

Nombre

Inicial D. Inicial E. Sexo Donante

Edad Nº Hb en base: Sexo Sexo receptor

Análisis Pre-movilización

Fecha de extracción

Hb p/dl **Bilirrubina** mg/dl

Seres Neg. **Virias** **CMV** **Igucosa** x 10⁹ /l **GOT** U/L

VEB **Igucosa** x 10⁹ /l **GPT** U/L

VEC **Creatinina** mg/dl **LDE** U/L

VEB **Ac. Úrico** mg/dl **F. Alcalina** U/L

Movilización

Ciclo de Movilización **F. de Inicio** **F. de Fin**

G-CSF Tipo **Dosis** (1000/día) **Duración** **Número de días**

Via **APÉNDICE** **Nº de APéndice** **Valencia**

F. de Inicio **F. de Fin**

Si No Central, Describir Método:

Resultados A Brea (En valores absolutos)

Manipulación

Volúmenes procesados

Vol. de la recolección ml

Leucocitos: baba de recolección x 10¹¹

CDS+ x 10⁹

CDS-4 x 10⁹

F. 1º APéndice **F. 2º APéndice** **F. 3º APéndice**

Volúmenes procesados

CDS+ x 10⁹

CDS-4 x 10⁹

Análisis Post-movilización

Leucocitos: Músculos x 10⁹ /l **Glicosa** mg/dl **GOT** U/L

Igucosa: Músculos x 10⁹ /l **Creatinina** mg/dl **GPT** U/L

Hb Músculos p/dl **Ac. Úrico** mg/dl **GGT** U/L

F. Alcalina U/L **Bilirrubina** mg/dl **LDE** U/L

Complicaciones

El suceso advierte:

Descripción:

Fiebre **F. de Inicio** **F. de Fin**

Cefalea **F. de Inicio** **F. de Fin**

Mialgia/Akralgia **F. de Inicio** **F. de Fin**

Sinosis/Venosis **F. de Inicio** **F. de Fin**

Otro:

Comentarios

Donor Characteristics

- Number of Registries: 1855.
- Number of Donors: 1976.

Characteristic	No. (%)	Median (range)
Sex		
Men / Women	839 (45) / 1008 (54)	
Age (years)		38 (1-75)
<14 / >60	113 (6) / 137 (7,4)	
Type of G-CSF		
Filgr / Lenogr	1551 (79) / 357 (18)	
Dose ($\mu\text{g}/\text{kg}$)		10 (4-23)
PBSC collections		1 (1-5)

Stem Cell Collection

Characteristic	Lenograstim (307)	Filgrastim (1378)
Body weight (kg)*	70 (11-119)	70 (8.5-135)
CD34+ (x10 ⁶ /kg)		
Total	5.7 (0.87 - 35.22)	6 (0.12 - 63.63)
1 st apheresis	4.58 (0.41 – 35.22)	5 (0.06 - 36.1)
CD34+ < 4	78 (25)	319 (23.1)
CD34+ < 2	17 (5.5)	45 (3.26)

*According to receptors' body weight: 77 (6-144) and 68 (10-118) kg.

Low PBPC Collection

- CD34+: $< 4 \times 10^6/\text{kg}$

TABLE 1. Main donor characteristics

Characteristic	
Number of donors*	261
Age (years)†	38 (2-72)
Sex*	
Men	142 (54)
Women	119 (46)
Body weight (kg)†	69 (14-125)
WBC count ($\times 10^9/\text{L}$)†	6.8 (3.5-14.5)
Hb (g/dL)†	14.4 (9.1-17.7)
Platelet count ($\times 10^9/\text{L}$)†	235 (93-535)
Maximum WBC count ($\times 10^9/\text{L}$)†	49 (12.2-95.2)
Form of rHuG-CSF*	
Filgrastim	165 (63)
Lenograstim	96 (37)
Dose of rHuG-CSF ($\mu\text{g}/\text{kg}/\text{day}$)†	10 (5-20)
Daily doses of rHuG-CSF*	
One	102 (39)
Two	159 (61)

* Values expressed as number of donors (%).

† Values expressed as numbers (%).

TABLE 2. Univariate analysis of association with CD34+ cell yield

Characteristic	Number of CD34+ cells collected		p value
	$\geq 4 \times 10^6$ per kg	$< 4 \times 10^6$ per kg	
Number of donors	158	103	
Sex			
Men	85 (60)	57 (40)	
Women	73 (61)	46 (39)	
Age (years)			0.008
<18	10 (59)	7 (41)	
18-37	77 (71)	32 (29)	
38-60	66 (55.5)	53 (44.5)	
>60	5 (31)	11 (69)	
Weight (kg)			
<69	83 (64)	46 (36)	
≥ 69	75 (57)	57 (43)	
WBC ($\times 10^9/\text{L}$)			
<7	80 (58)	58 (42)	
≥ 7	75 (64)	43 (36)	
Hb (g/dL)			
<14	69 (63)	40 (37)	
≥ 14	86 (58.5)	61 (41.5)	
Platelets ($\times 10^9/\text{L}$)			
<241	78 (57)	59 (43)	
≥ 241	77 (65)	42 (35)	
Form of rHuG-CSF			
Filgrastim	105 (64)	60 (36)	
Lenograstim	53 (55)	43 (45)	
rHuG-CSF dose ($\mu\text{g}/\text{kg}/\text{day}$)			
<10	5 (56)	4 (44)	
10-12	140 (59)	96 (41)	
>12	13 (81)	3 (19)	
≤ 12	145 (59)	100 (41)	0.08
Daily doses of rHuG-CSF			0.01
One	52 (51)	50 (49)	
Two	106 (67)	53 (33)	
Maximum WBC ($\times 10^9/\text{L}$)			0.004
<50	71 (52)	65 (48)	
≥ 50	87 (70)	38 (30)	

Values expressed as number of donors (%).

Low PBPC Collection

- CD34+: < 4 x10⁶/kg

TABLE 3. Multivariate analysis of association with CD34+ cell yield

Unfavorable category	Regression coefficient	95% CI	p value
Age ≥38 years	0.52	0.31-0.88	0.014
One daily dose of rHuG-CSF	0.47	0.27-0.79	0.005
Age (continuous)	0.96	0.94-0.98	0.0003
One daily dose of rHuG-CSF	0.41	0.23-0.70	0.0015

Results of Second PBPC Collection

Characteristic	Mobilization	
	First	Second
Age (years)	35 (7-69)	37 (8-70)
Sex (M/F)	22/24	22/24
WBC ($\times 10^9/L$)	6 (4.05-12.5)	6.6 (4.6-16)
Hb (g/dL)	14.7 (11.3-17.5)	14.7 (12.1-16)
Platelets ($\times 10^9/L$)	230 (158-365)	238 (154-332)
G-CSF		
Fil/Leno	33/12	30/15
Dose (mcg/kg/d)	10 (10-12)	10 (9-12.5)

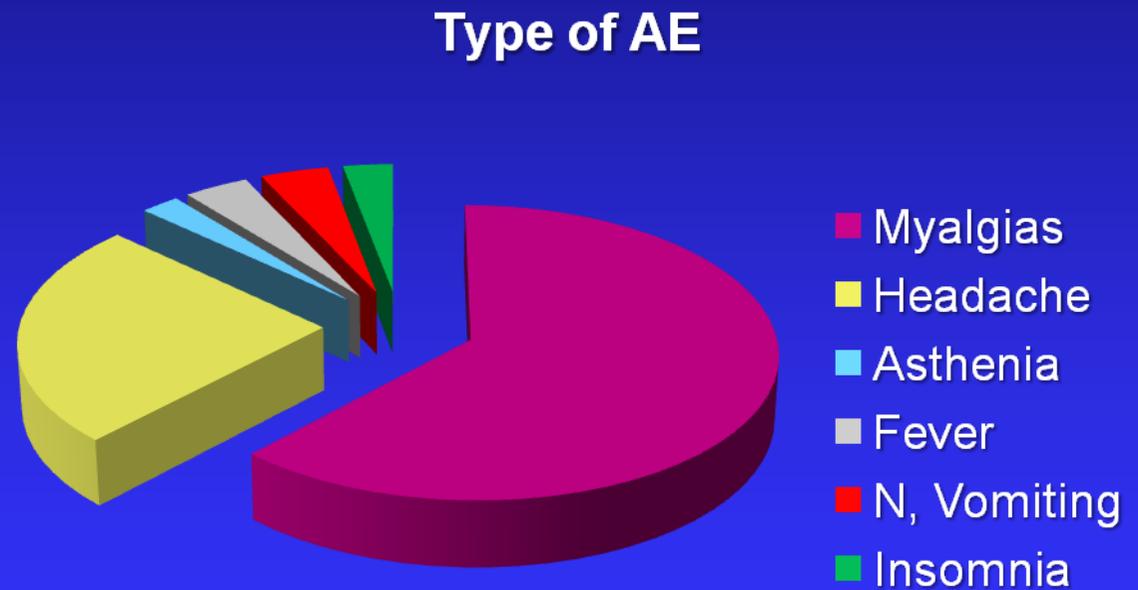
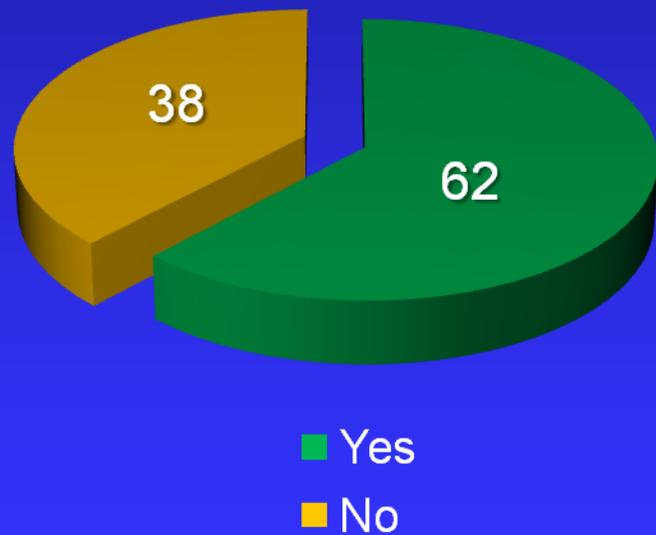
Median time between mobilizations: 187 (7-1428) days.

Results of Second PBPC Collection

CD34+ cell collection (x10 ⁶ /kg)	Mobilization	
	First (%)	Second (%)
<2	2 (4)	4 (9)*
2-4	9 (20)	18 (39)
>4	35 (76)	24 (52)
Mean ± SD	5.72 ± 2.86	4.8 ± 2.094
Median	5.15	3.16†
Range	1.52-15.77	0.35-19.09

*P = 0.057; †P = 0.05; 29 (63%) donors yielded lower values after second mobilization; P = 0.018.

Adverse Events



Adverse Events (cont.)

- Severe adverse events:

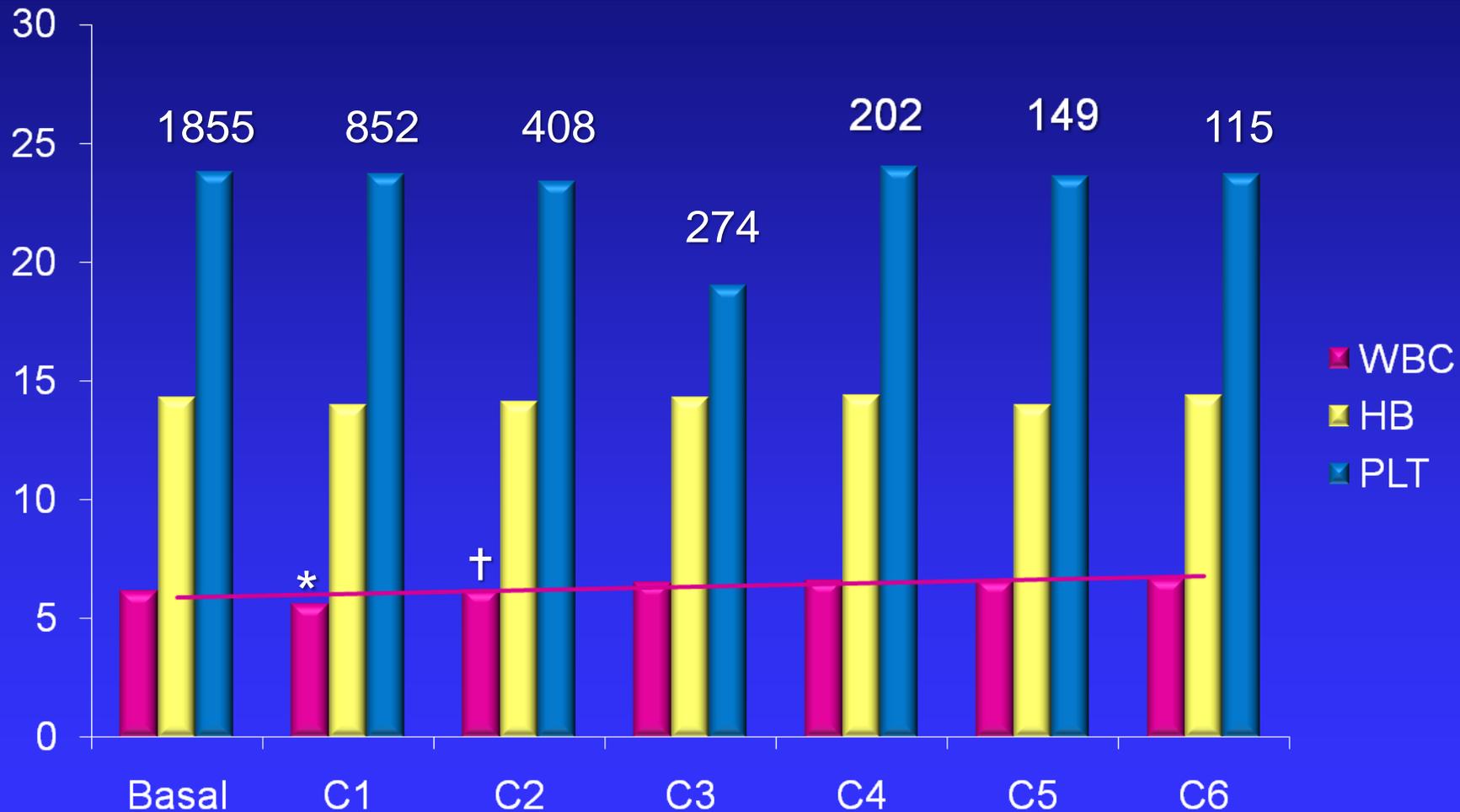
Type of SAE	Age/Sex	Type of Donor	Type/Dose of G-CSF
Splenic rupture	51/M	HLA-id sib	Fil/5 mcg/12 h/d x5
Allergic reaction	46/F	HLA-id sib	Fil/5 mcg/12 h/d x2

Follow-Up. Blood Counts

	Baseline (1855)	C #1 (852)	C #2 (408)	C #3 (274)	C #4 (202)	C #5 (149)	C #6 (115)
WBC (x10 ⁹ /L)	6.15 (3.04-18)	5.6* (2.2- 16.4)	6.2† (2.7- 15.5)	6.5 (3.09- 18.5)	6.6 (3.38- 15.3)	6.6 (2.93- 15.8)	6.7 (3.2- 14.2)
Hb (g/dL)	14.3 (9-18.9)	14 (9.4- 17.6)	14.1 (11.1- 18)	14.3 (10.8- 17.1)	14.4 (11.3- 18.7)	14 (11- 17.3)	14.4 (11- 17.5)
Platelet (x10 ⁹ /L)	238 (72-636)	237 (76-631)	234 (95-570)	190 (82-409)	240 (130- 447)	236 (147- 498)	237 (163- 413)

* P < 0.0001; †P = 0.025.

Follow-Up. Blood Counts



* P < 0.0001; † P = 0.025.

Updated from de la Rubia J, et al. Haematologica 2008.

Follow-Up. Second Neoplasms

Donor #	Age	Sex	Dose of G-CSF	Neoplasm	Months after G-CSF
229	23	Female	5	Choroid melanoma*	64
964†	45	Male	12	Colon cancer	61
1385	47	Female	12	Lung cancer	39
1722	25	Female	10	Thiroid carcinoma	12
1806	49	Male	15	Lung cancer	10
2083	74	Male	10	B-NHL	24

*Left eye; †Previous history of Hodgkin's disease .

Conclusions

- Standard dose of G-CSF is associated with an enough CD34+ cell collection in the majority of donors.
- Preliminary data suggest a trend to a lower stem cell collection in donors undergoing a second mobilization.
- Mild bone pain the most commonly observed side effect.
- Severe adverse events have been rarely detected.
 - ✓ The rate of solid tumors is consistent with the age-adjusted Spanish incidence of cancer in adults.
 - ✓ Low incidence of hematological malignancies

Conclusions

- Number of donors with follow-up is still too low.
 - ✓ Poor adherence (personal or psychological reasons).
 - ✓ Lack of motivation of transplant physicians (mobilization is a low-risk, short-term technique).
- Establishment for a standardized follow-up will enable a better monitoring of the short- and long-term safety profiles of PBSC donation and form a solid basis for future donor selection and counseling.
- Progress can only be achieved by large international cooperation.