Principios básicos del trasplante de progenitores hematopoyéticos (TPH). Un proyecto en marcha en el CHGUV

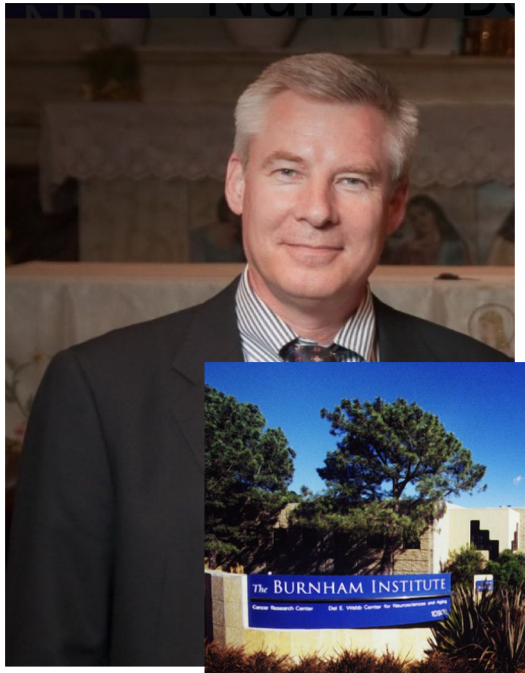
ARMANDO MENA
Servicio de Hematología
CHGUV

No sirve de nada retroceder hasta ayer porque yo era una persona diferente entonces

Un Poco de Historia

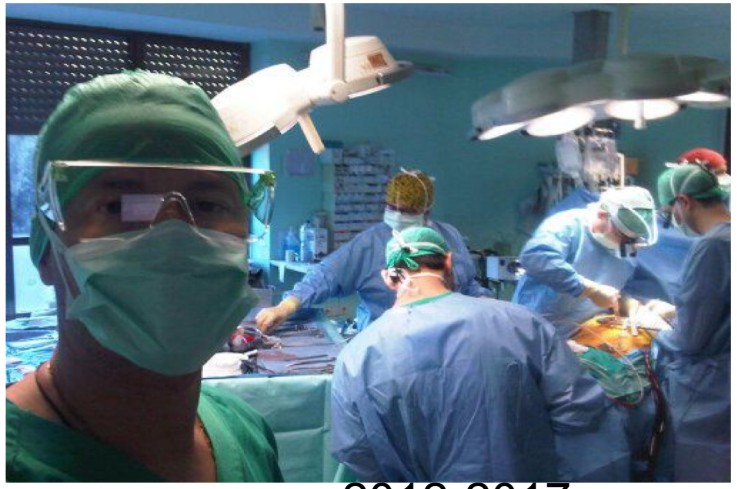
RESIDENCIA HEMATOLOGÍA HCGUV

BECA LA FE



2003-2005

RESIDENCIA HEMATOLOGÍA HCGUV



2012-2017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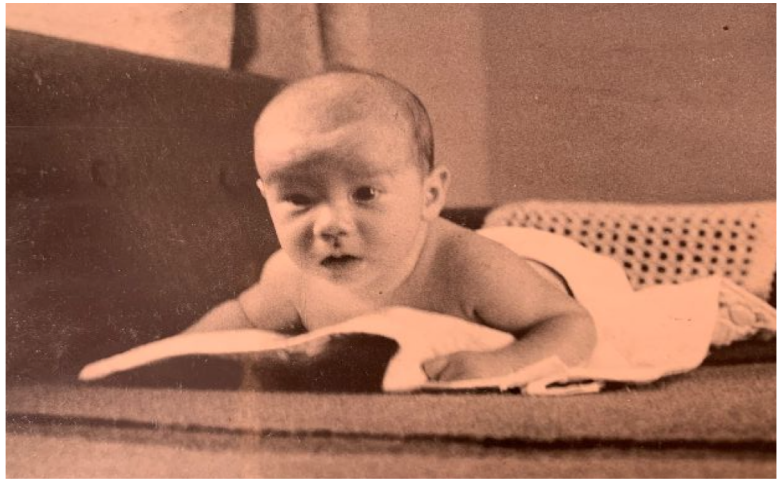
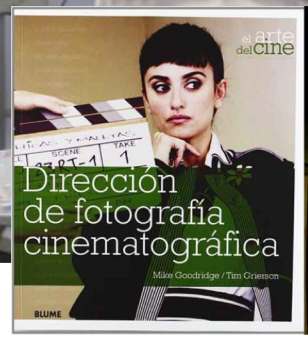



CANNON


el arte del cine
Dirección de fotografía cinematográfica
Mike Goodridge / Tim Grierson
BLUME


José Patricio Pérez Rufí
100 PELÍCULAS
IMPRESCINDIBLES PARA VER ANTES
DE LOS TREINTA
...Y así convertirte en un joven cinéfilo

Principios básicos del trasplante de progenitores hematopoyéticos (TPH). Un proyecto en marcha en el CHGUV

Armando V. Mena Durán

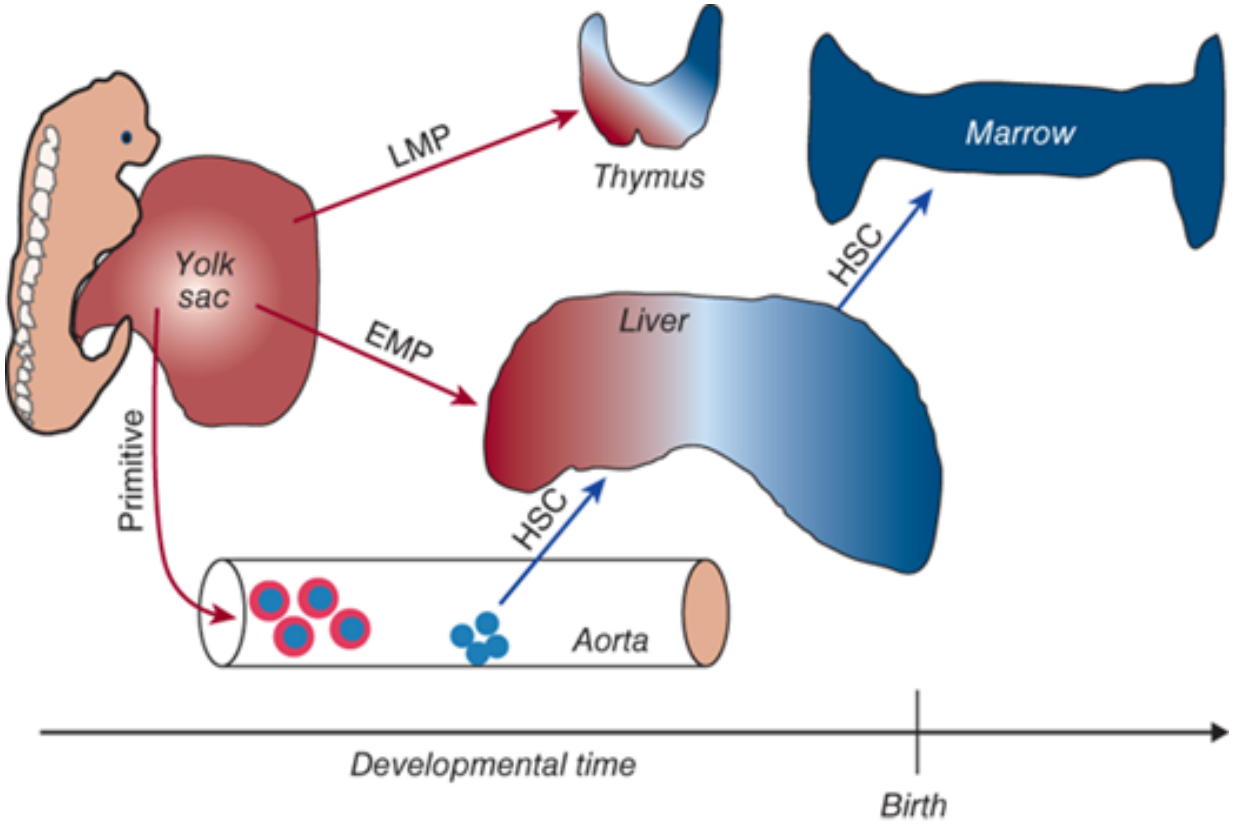
Servicio de Hematología y Hemoterapia

- Un poco de historia…
- Hematopoyesis. Circulación entre médula y sangre periférica
- Bases terapéuticas del TPH
- Fuentes de progenitores hematopoyéticos
- Indicaciones del TPH
- Selección de donantes
- Acondicionamiento y infusión de progenitores
- Resultados en patologías más prevalentes
- Complicaciones del TPH
- AutoTPH: un proyecto en marcha en el CHGUV.

Un poco de historia…

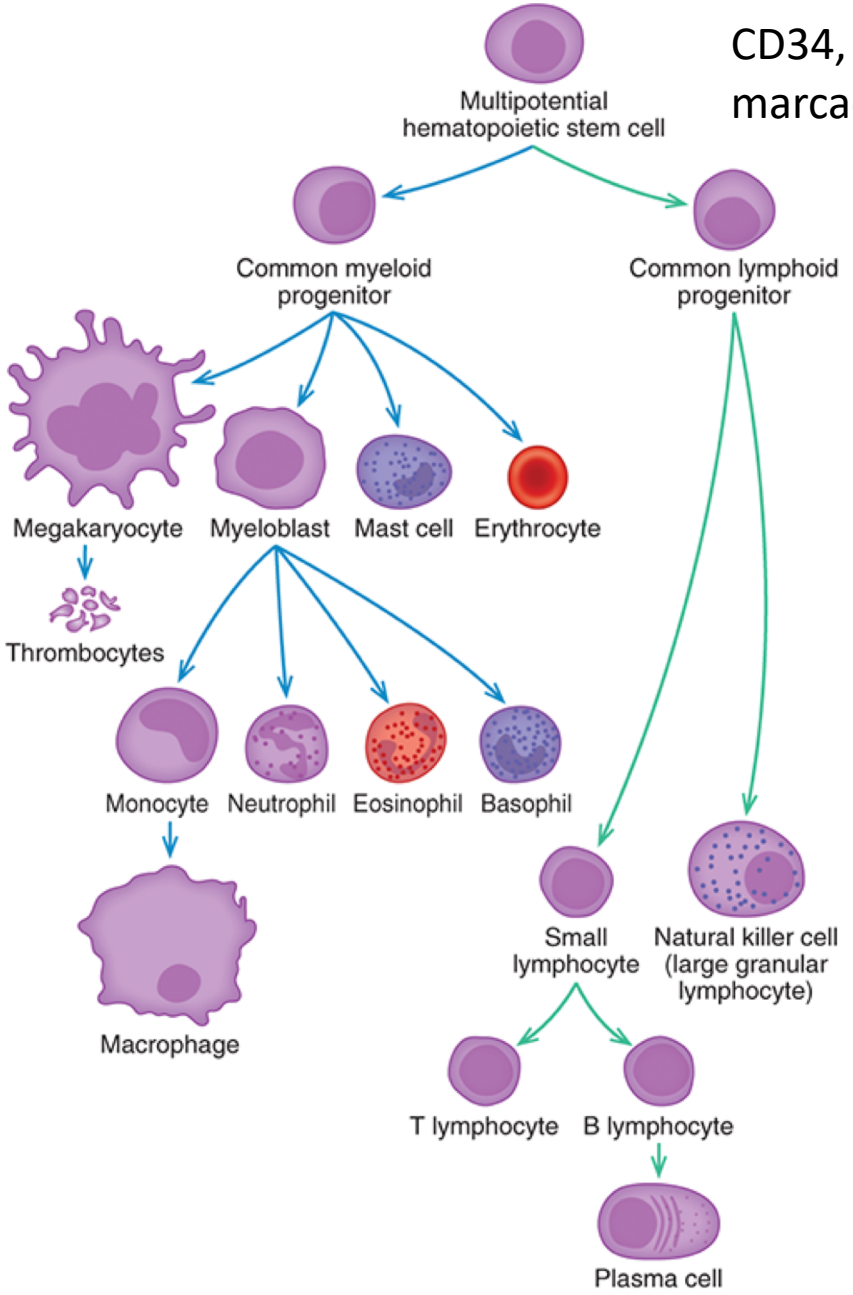
Years	Event
1868–1906	Discovery that marrow was the source of the various blood cell types
1896–1900	Discovery of ABO system making blood transfusions possible
1939	First documented clinical marrow transplantation
1949–1954	Development of preclinical models of marrow and organ transplantation
1956–1959	Early efforts of marrow grafting to treat human diseases
1960–1965	Development of the hierarchical stem/progenitor cell model of hematopoiesis
1960s	Period of pessimism for the clinical application of marrow grafting for the treatment of human diseases
1968–1969	First successful allogeneic HCT in patients with SCID
1975	First successful series of allogeneic HCT for leukemia
1978	First successful series of autologous HCT for leukemia
1988	Isolation of the murine HSC
1990	Nobel Prize in Physiology or Medicine awarded to Dr. E.D. Thomas for establishing bone marrow transplantation as a successful treatment for leukemia and other blood conditions
2008	Since 1968, more than 700,000 patients worldwide transplanted, and more than 125,000 of those patients survived 5 years or longer after transplantation
2018	By 2018, more than 26,000 transplantations were being performed annually

Hematopoyesis



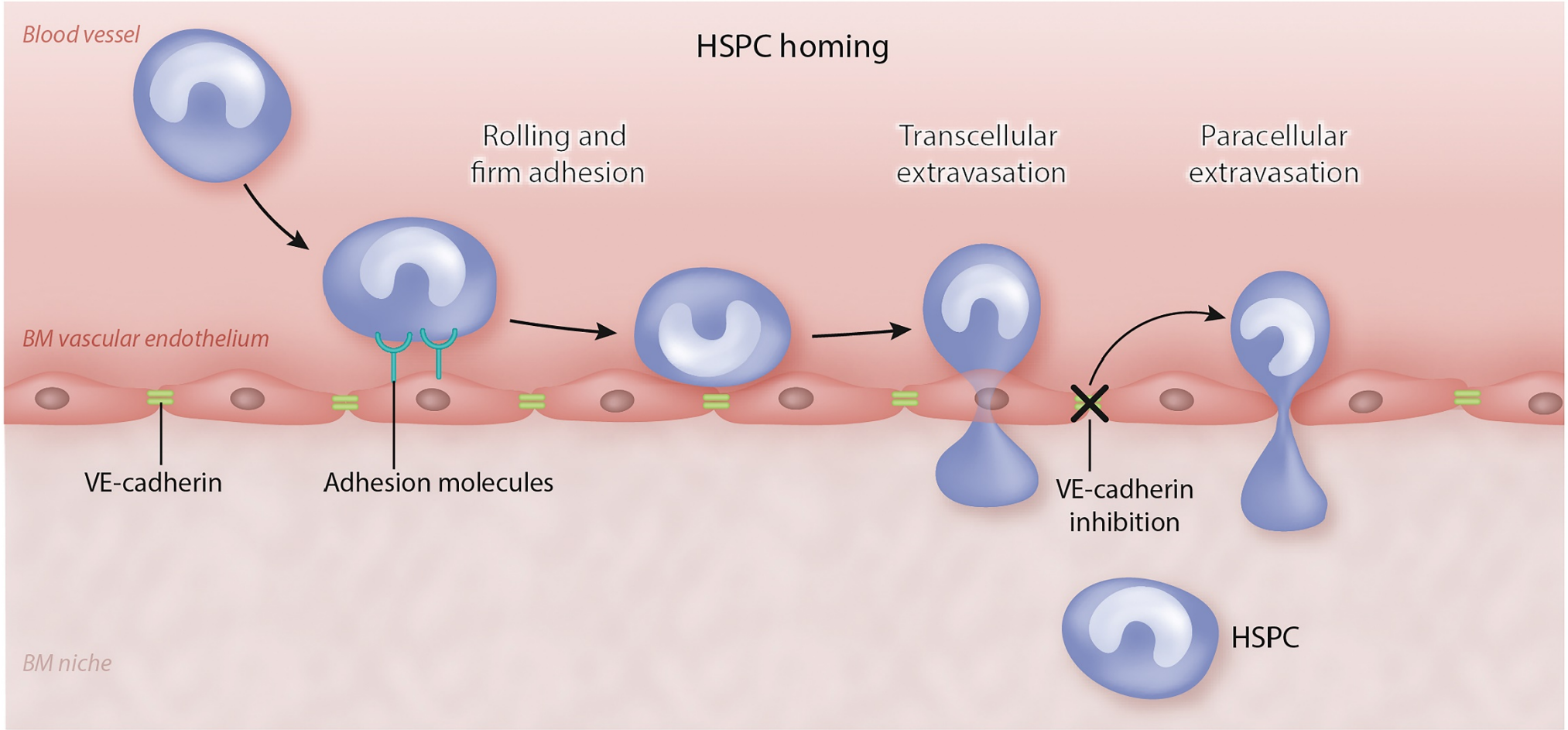
Source: Kenneth Kaushansky, Josef T. Prchal, Linda J. Burns, Marshall A. Lichtman, Marcel Levi, David C. Linch: Williams Hematology, 10e

CD34, Thy-1, (-)
marcadores línea

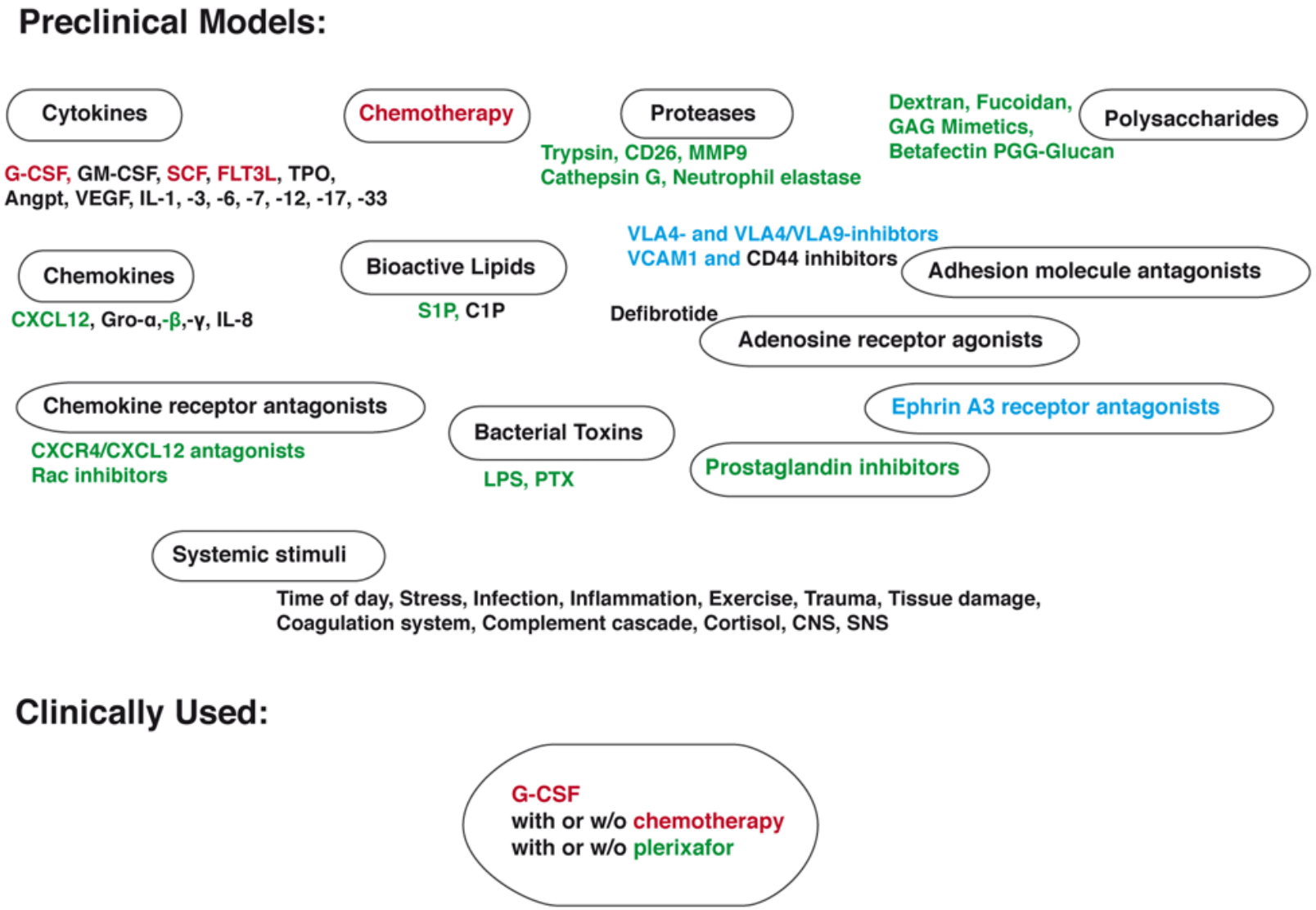


Source: Laura A. Huppert, Timothy G. Dyster: *Huppert's Notes: Pathophysiology and Clinical Pearls for Internal Medicine*

Progenitores hematopoyéticos: circulación y anidamiento en la médula ósea



Progenitores hematopoyéticos: circulación y anidamiento en la médula ósea



Karpova D, Rettig MP and DiPersio JF. Mobilized peripheral blood: an updated perspective [version 1]. F1000Research 2019, 8(F1000 Faculty Rev):2125 (doi: 10.12688/f1000research.21129.1)

F1000Research

Bases terapéuticas del TPH

Why do we want Stem Cells

- Restoration of patient's own hematopoetic tissue in the....

  autologous setting (The correction of HDC-induced aplasia)

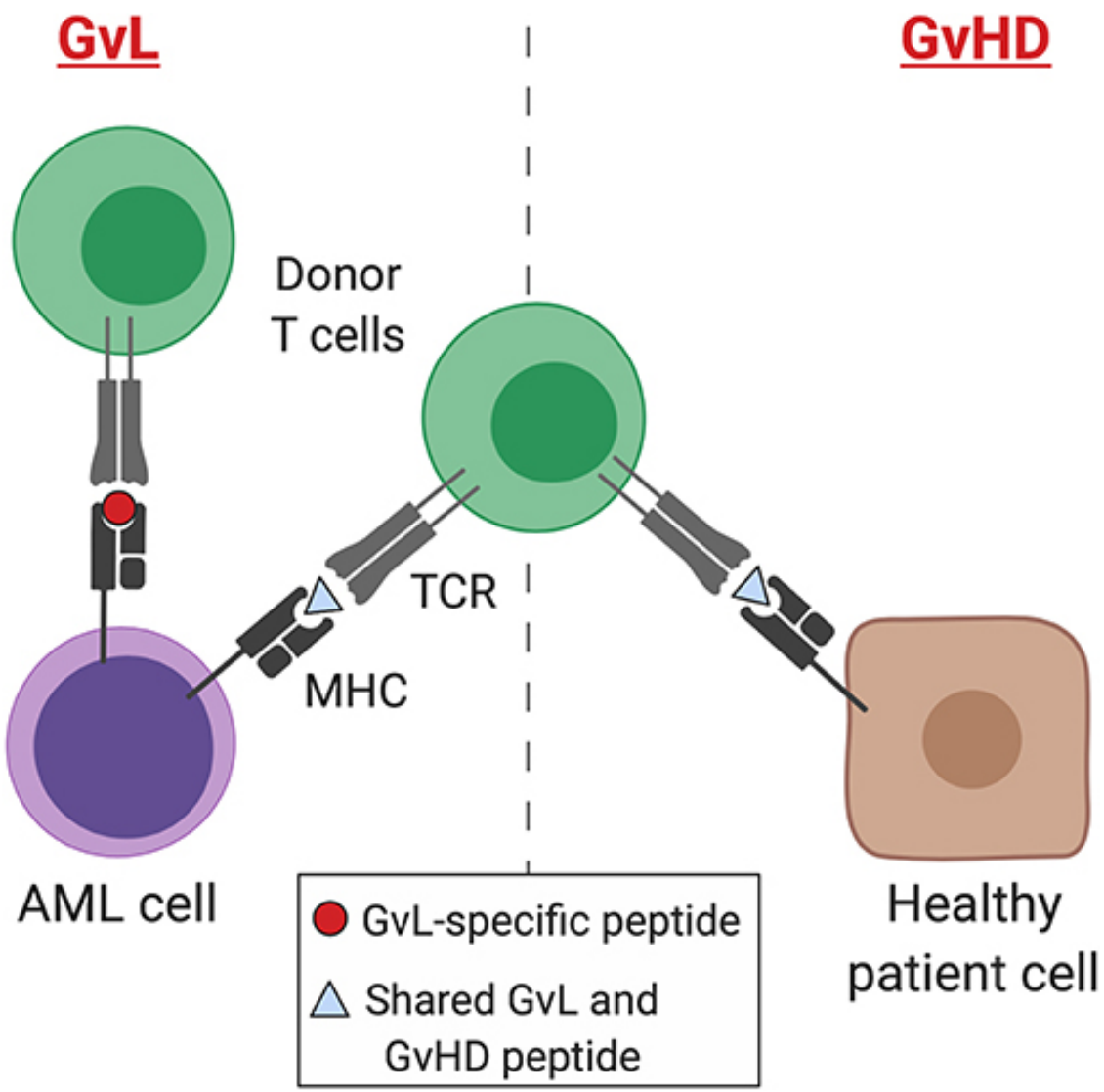
  - to eradicate chemosensitive tumor

- Installation of new hematopoietic tissue in the....

  allogeneic setting (chimerism)

  - to develop alloreactivity (GVL) against malignant disorders
  - to correct functional defects observed in inherited or acquired non- malignant disorders

Bases terapéuticas del TPH

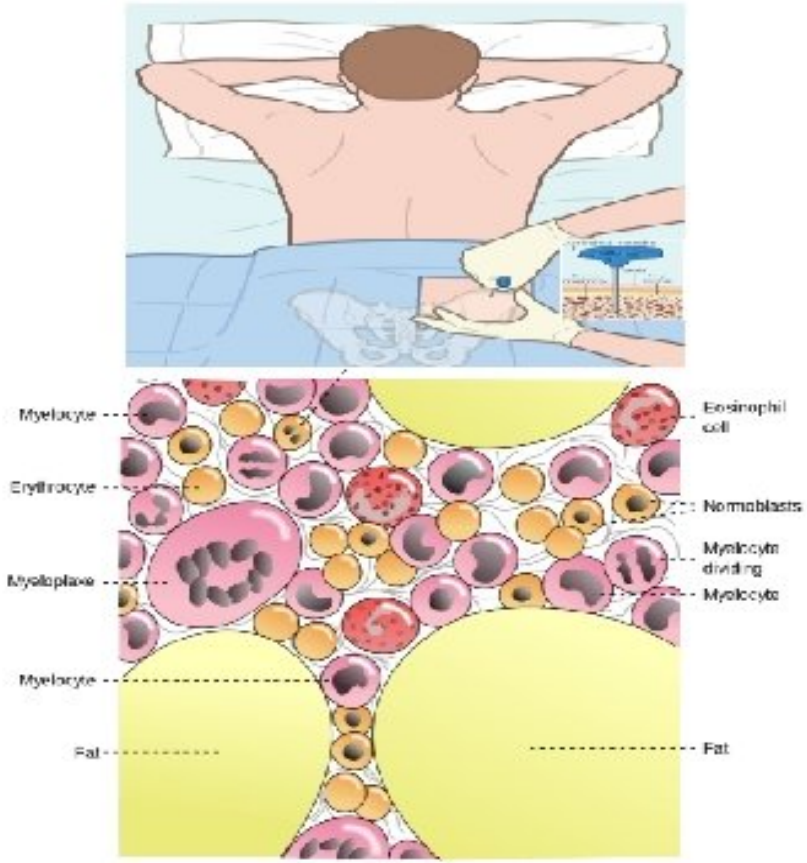


Sweeney C, Vyas P. The Graft-Versus-Leukemia Effect in AML.
Front. Oncol., 19 November 2019 | https://doi.org/10.3389/fonc.2019.01217

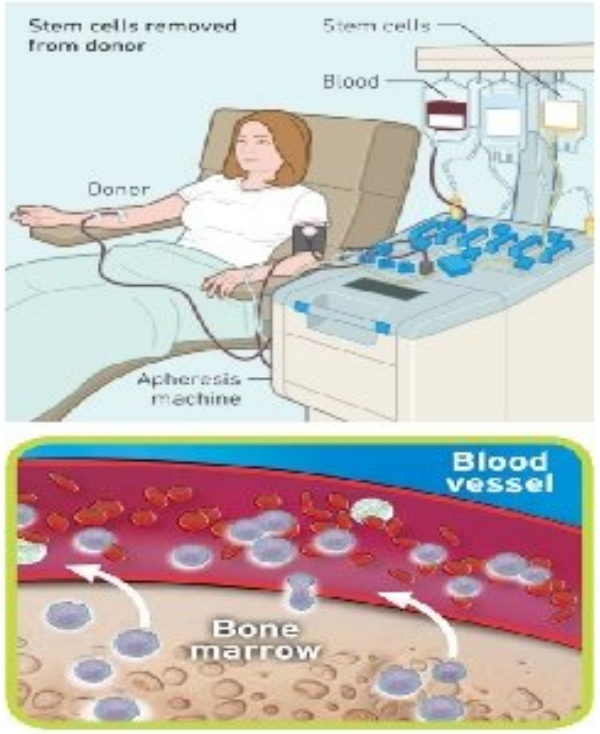
Fuentes de progenitores hematopoyéticos

❷ Sources of Stem Cells

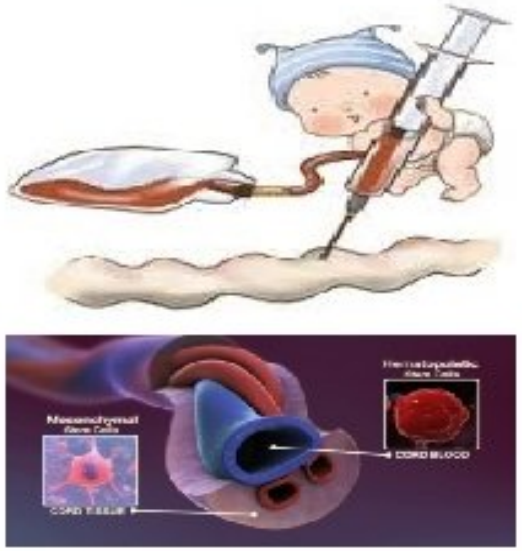
Bone Marrow



Peripheral Blood



Cord Blood



Fuentes de progenitores hematopoyéticos

❷ Sources of Stem Cells

*Cell contents according to source

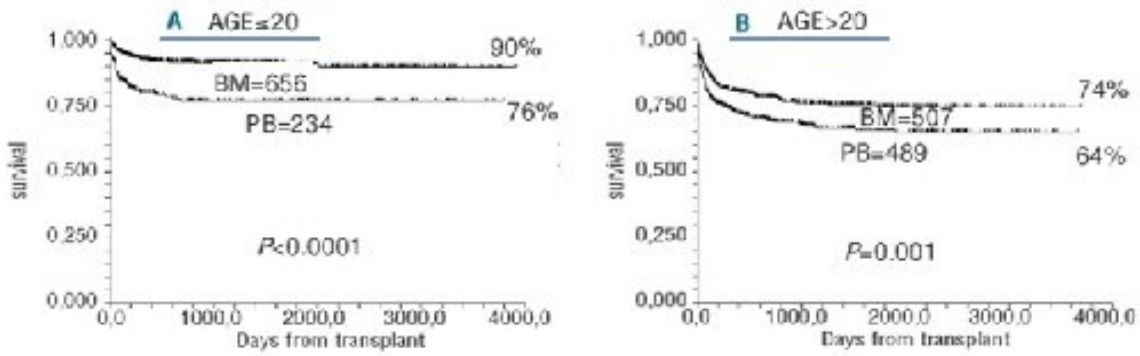
HSC	volume collected	med. CD34+ content	med. CD3+ content	target cell-dose
bone marrow	10-20 ml/kg	2-3x10⁶/kg	25x10⁶/kg	2x10⁸ TNC/kg
peripheral blood	150-400 ml	8x10⁶/kg	250x10⁶/kg	2-5x10⁶ CD34+/kg
umbilical cord blood	80-160 ml	0.2x10⁶/kg	0.5-2x10⁶/kg	> 3x10⁷ TNC/kg

Fuentes de progenitores hematopoyéticos

❷ Sources of Stem Cells

*Cell contents according to source

Survival Advantage for Acquired Aplastic Anemia



Bone marrow *versus* peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups, Andrea Bacigalupo, Haematologica 2012 Aug; 97(8):1142–1148

Fuentes de progenitores hematopoyéticos

❷ Sources of Stem Cells

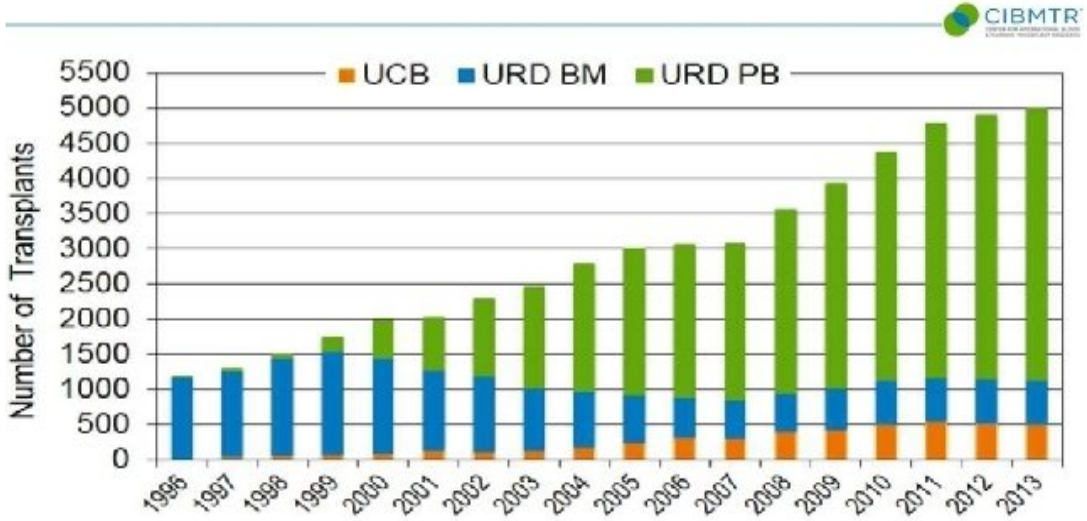
CIBMTR : Stem Cell Sources

Unrelated Donor Allogeneic
Transplants in Patients ≤20 Years

❷ Sources of Stem Cells

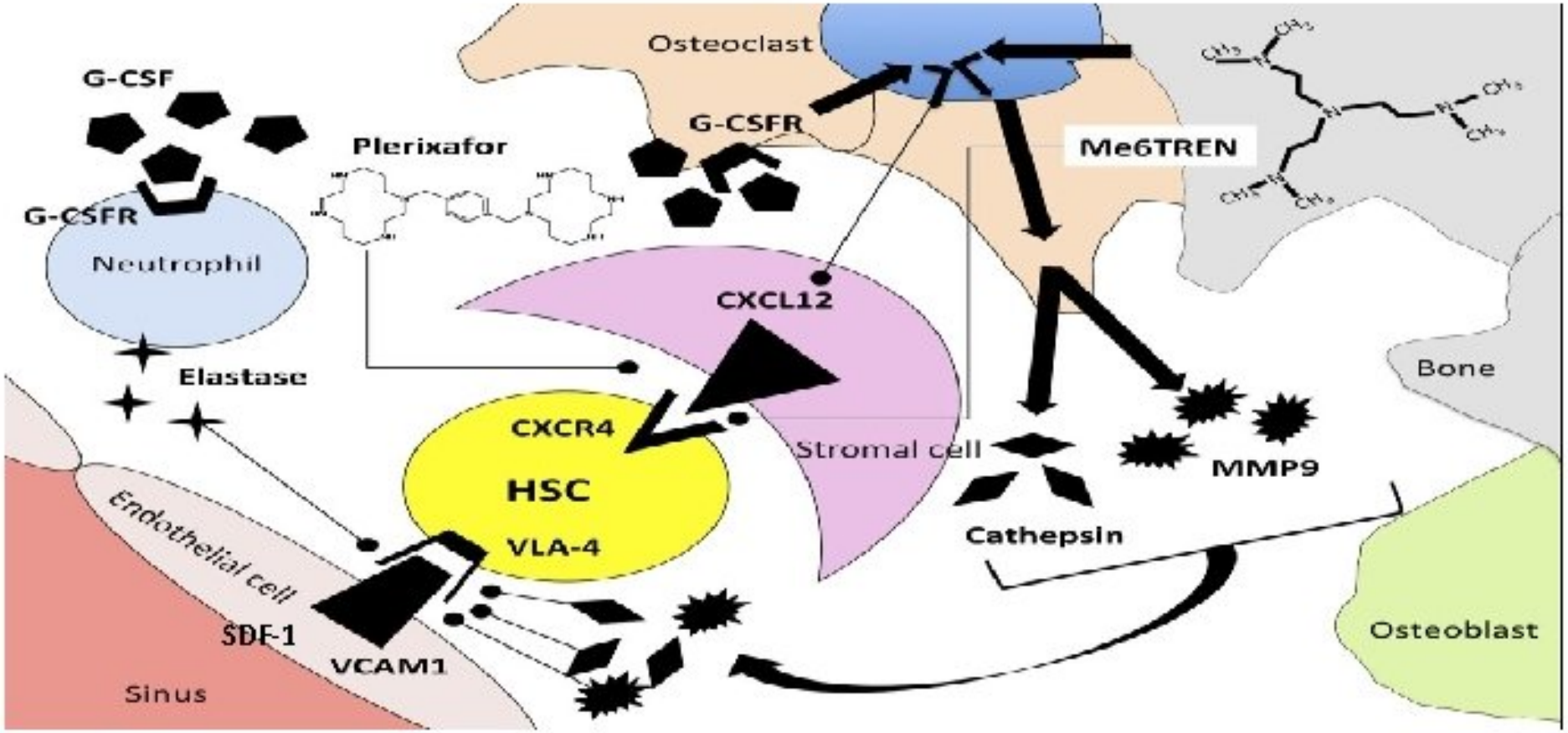
CIBMTR : Stem Cell Sources

Unrelated Donor Allogeneic
Transplants in Patients Age >20 years



Fuentes de progenitores hematopoyéticos

Mobilization: Agents & Mechanisms



Fuentes de progenitores hematopoyéticos

Stem Cell Mobilization & Collection

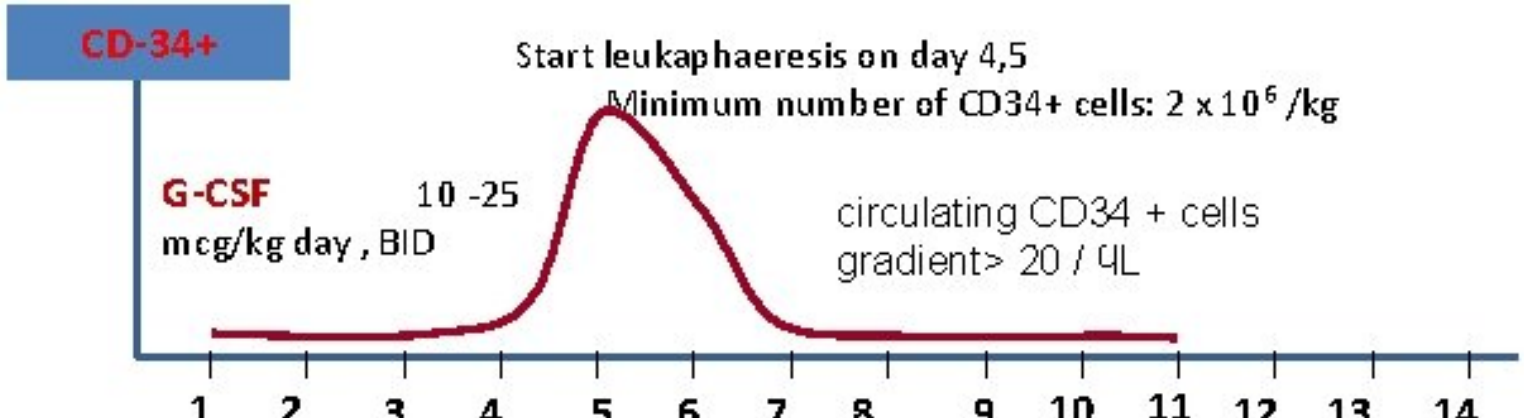
Stem cell mobilization / G-CSF

Filgrastim (G-CSF) (Success rate: 70-95%)

Multi-step interactions in the marrow microenvironment lead to stem cell mobilization

Pain, headaches, arthralgias, malaise, fatigue, insomnia, and nause, Transient increase in ALP, ALT, LDH, Na and transient decrease in potasium, spontaneous splenic rupture

Increased spleen size in length (in 95% of pts) (mean increase,13%) but 10 days after G-CSF administration, spleen size returns to baseline.



Fuentes de progenitores hematopoyéticos

Stem Cell Mobilization & Collection

Stem cell mobilization / Prelixafor

Plerixafor (**Success rate:** 70-80%) after any failure

Reversible inhibitor of the CXCR4/CXCL12 axis

0.24 mg/kg body weight by subcutaneous (SC) injection.
Approximately 11 hours prior to initiation of apheresis session (for up to 4 consecutive/ d) 6- to 10-fold increase in CD34⁺ cell, Typically administered in conjunction with filgrastim

Side effects include abdominal discomfort, leukocytosis, potential for splenic rupture (rare)

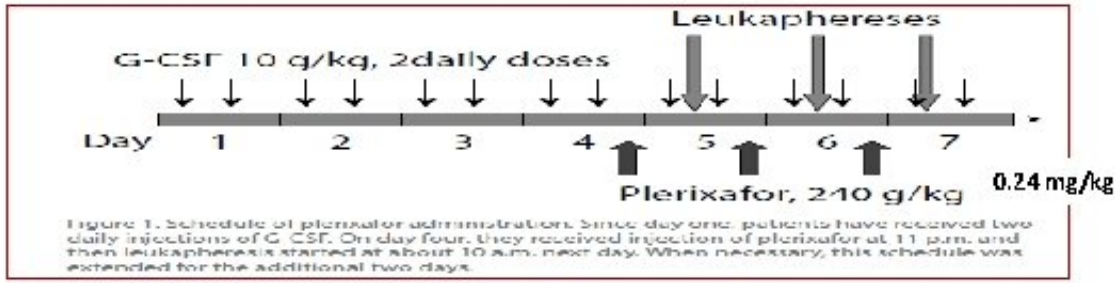


Figure 1. Schedule of plerixafor administration. Since day one, patients have received two daily injections of G-CSF. On day four, they received injection of plerixafor at 11 p.m. and then leukapheresis started at about 10 a.m. next day. When necessary, this schedule was extended for the additional two days.

De Clercq E. The bicyclam AMD3100 story. Nat Rev Drug Discov 2003; 2: 581–587 MP Rettig, G Ansstas and JF DiPersio. Leukemia. 2011 Sep 2. doi: 10.1038/leu.2011.197

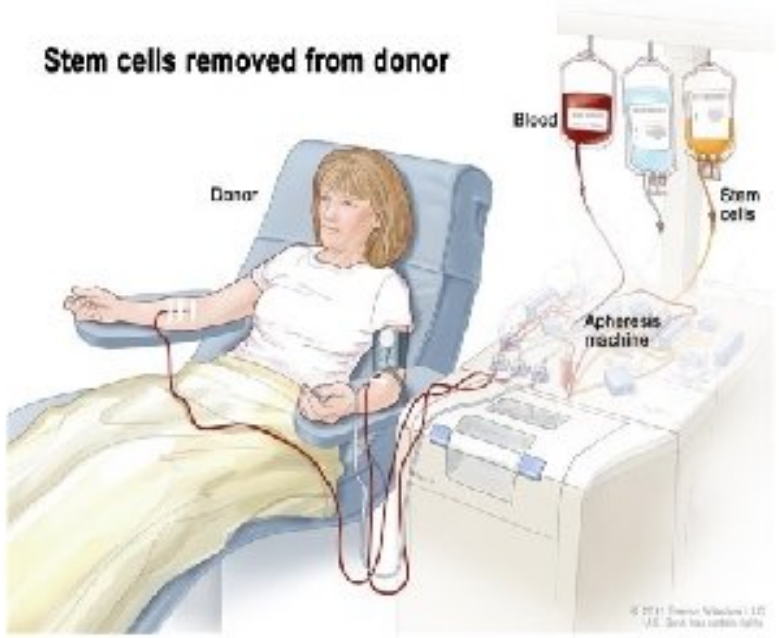
Fuentes de progenitores hematopoyéticos

Stem Cell Mobilization & Collection

Stem Cell Collection Procedures

PBSC Apheresis Procedure

Mobilised Autologous Stem Cells
Removed from patients

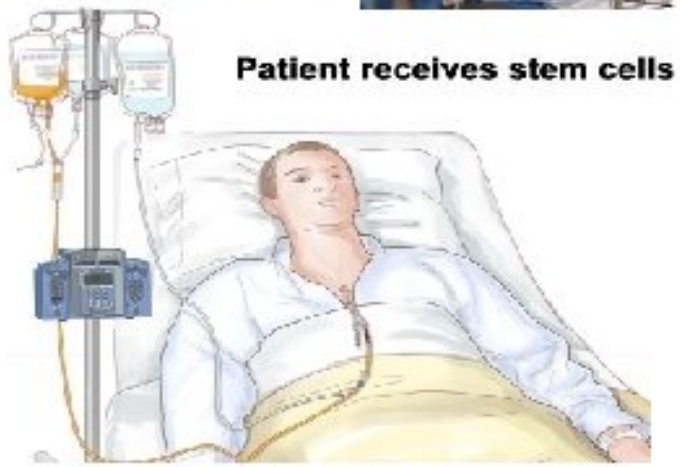


BM Harvesting Procedure

BM Aspiration

BM collection

BM Fitration



Fuentes de progenitores hematopoyéticos

Stem Cell Mobilization & Collection

HSC Storage

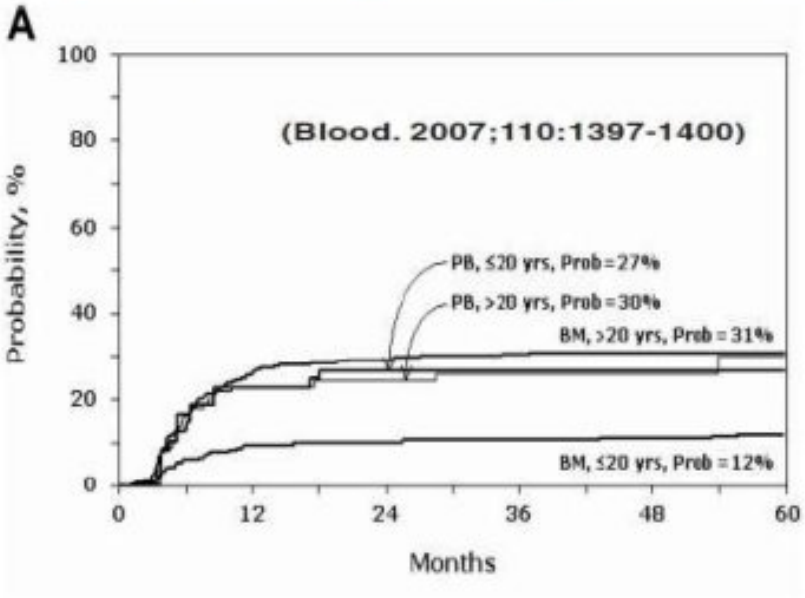
- storage in liquid nitrogen at a temperature of
  - -156ºC (vapor phase)
  - -196ºC (liquid phase)
- container should be temperature-monitored 24h/24h to avoid transient warming during storage
- no use-by date
  - BM autologous SCT after 21 years of cryopreservation
    - Holter J et al, 2011
  - Recovery of functional UCB progenitor after 15 years
    - Broxmeyer HE et al, 2003

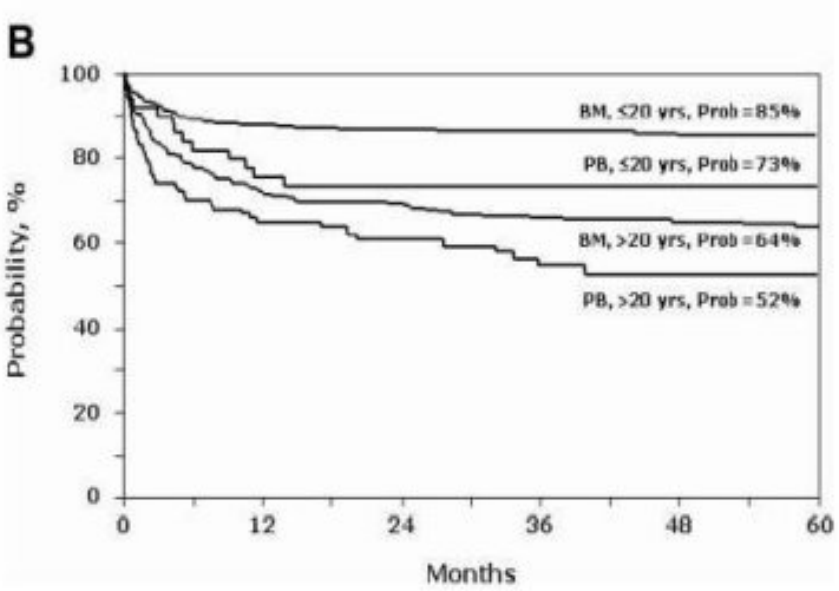
Fuentes de progenitores hematopoyéticos

Stem Cell Mobilization & Collection

Cell Dose and Source: effect on outcomes

Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young patients with severe acquired aplastic anemia





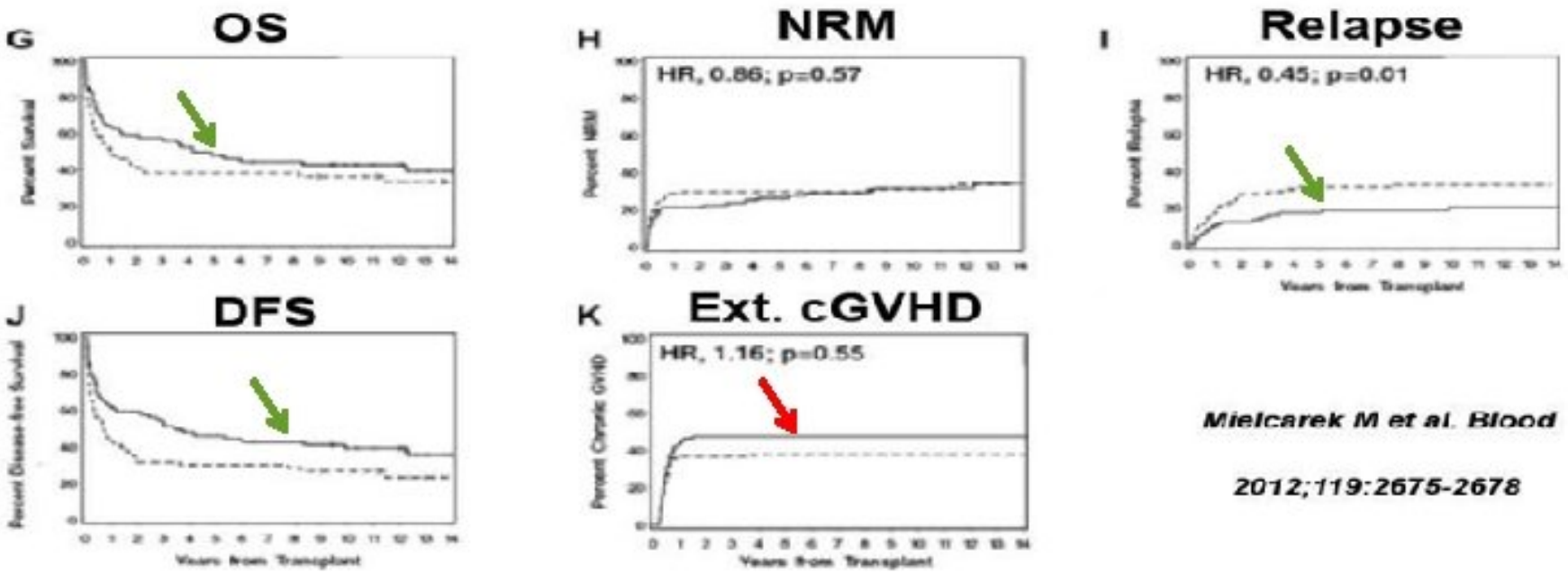
Fuentes de progenitores hematopoyéticos

● Stem Cell Mobilization & Collection

Cell Dose and Source: effect on outcomes

Long-term outcomes after transplantation of HLA-identical related G-CSF–mobilized peripheral blood mononuclear cells versus bone marrow

Marco Mielcarek,[1,2] Barry Storer,[1,2] Paul J. Martin,[1,2] Stephen J. Forman,[3] Robert S. Negrin,[4] Mary E. Flowers,[1,2] Yoshihiro Inamoto,[1] Thomas R. Chauncey,[1,2] Rainer Storb,[1,2] Frederick R. Appelbaum,[1,2] and William I. Bensinger[1,2]



Mielcarek M et al. Blood 2012;119:2675-2678

Indicaciones de TPH o SCT

Bone Marrow Transplantation (2019) 54:1525–1552
https://doi.org/10.1038/s41409-019-0516-2

FEATURE

Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019

Rafael F. Duarte[1] · Myriam Labopin[2] · Peter Bader[3] · Grzegorz W. Basak[4] · Chiara Bonini[5] · Christian Chabannon[6] · Selim Corbacioglu[7] · Peter Dreger[8] · Carlo Dufour[9] · Andrew R. Gennery[10] · Jürgen Kuball[11] · Arjan C. Lankester[12] · Francesco Lanza[13] · Silvia Montoto[14] · Arnon Nagler[15] · Régis Peffault de Latour[16] · John A. Snowden[17] · Jan Styczynski[18] · Ibrahim Yakoub-Agha[19] · Nicolaus Kröger[20] · Mohamad Mohty[21] · for the European Society for Blood and Marrow Transplantation (EBMT)

Received: 19 February 2019 / Revised: 5 March 2019 / Accepted: 7 March 2019 / Published online: 5 April 2019

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
Leukaemias					
AML	CR1 (favourable risk and MRD−)[a]	GNR/II	GNR/II	GNR/II	CO/I
	CR1 (favourable risk and MRD+)[a]	CO/II	CO/II	CO/II	GNR/II
	CR1 (intermediate risk)[a]	S/II	CO/II	CO/II	CO/I
	CR1 (adverse risk)[a]	S/II	S/II	S/II	GNR/I
	CR2	S/II	S/II	S/II	CO/II
	APL molecular CR2	S/II	CO/II	GNR/III	S/II
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III
ALL	Ph (−), CR1 (standard risk and MRD−)[a]	GNR/II	GNR/II	GNR/III	CO/III
	Ph (−), CR1 (standard risk and MRD+)[a]	CO/II	CO/II	CO/II	GNR/II
	Ph (−), CR1 (high risk)[a]	S/II	S/II	CO/II	GNR/III
	Ph (+), CR1 (MRD−)	S/II	S/II	CO/II	CO/III
	Ph (+), CR1 (MRD+)	S/II	S/II	S/II	GNR/II
	CR2	S/II	S/II	S/II	GNR/II
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III
CML	First CP, failing second- or third-line TKI	S/II	S/II	CO/III	GNR/II
	Accelerated phase, blast crisis or >first CP	S/II	S/II	CO/II	GNR/III
Myelofibrosis	Primary or secondary with an intermediate or high DIPSS score	S/II	S/II	S/III	GNR/III
MDS	RA, RCMD, RAEB I and II	S/II	S/II	S/II	GNR/III
	sAML in CR1 or CR2	S/II	S/II	S/II	CO/II
	More advanced stages	S/II	S/II	S/II	GNR/III
CLL	Poor risk disease, not transformed	S/II	S/II	CO/III	GNR/III
	Richter's transformation	S/III	S/III	CO/III	CO/III
Lymphoid malignancies					
DLBCL	CR1 (Intermediate/high IPI at dx)	GNR/III	GNR/III	GNR/III	CO/I
	Chemosensitive relapse, ≥CR2	CO/II	CO/II	D/III	S/I

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
DLBCL	CR1 (Intermediate/high IPI at dx)	GNR/III	GNR/III	GNR/III	CO/I
	Chemosensitive relapse, ≥CR2	CO/II	CO/II	D/III	S/I
	Chemosensitive relapse after auto-HSCT failure	S/II	S/II	CO/III	GNR/III
	Refractory disease	CO/II	CO/II	CO/III	CO/II
	Primary CNS lymphoma	GNR/III	GNR/III	GNR/III	S/I
FL	CR1, untransformed	GNR/III	GNR/III	GNR/III	GNR/II
	CR1, transformed to high-grade lymphoma	GNR/III	GNR/III	GNR/III	CO/III
	Chemosensitive relapse, ≥CR2	CO/III	CO/III	GNR/III	S/II
	≥CR2 after auto-HSCT failure	S/II	S/II	D/III	GNR/III
	Refractory	CO/II	CO/II	CO/III	GNR/III
MCL	CR1	GNR/III	GNR/III	GNR/III	S/I
	CR/PR > 1, no prior auto-HSCT	CO/III	CO/III	D/III	S/II
	CR/PR > 1, after prior auto-HSCT	S/II	S/II	CO/III	GNR/II
	Refractory	CO/II	CO/II	D/III	GNR/II
WM	CR1	GNR/III	GNR/III	GNR/III	GNR/III
	Chemosensitive relapse, ≥CR2	GNR/III	GNR/III	GNR/III	CO/II
	Poor risk disease	CO/II	CO/II	D/III	GNR/III

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
PTCL	CR1	CO/II	CO/II	GNR/III	CO/II
	Chemosensitive relapse, ≥CR2	S/II	S/II	CO/III	CO/II
	Refractory	CO/II	CO/II	CO/III	GNR/II
Primary CTCL	EORTC/ISCL stages I–IIA (Early)	GNR/III	GNR/III	GNR/III	GNR/III
	EORTC/ISCL stages IIB–IV (Advanced)	CO/III	CO/III	D/III	GNR/III
HL	CR1	GNR/III	GNR/III	GNR/III	GNR/I
	Chemosensitive relapse, no prior auto-HSCT	D/III	D/III	GNR/III	S/I
	Chemosensitive relapse, after prior auto-HSCT	S/II	S/II	CO/III	CO/III
	Refractory	D/II	D/II	D/III	CO/III
MM	Upfront standard risk	CO/II	CO/II	GNR/III	S/I
	Upfront high risk	S/III	S/III	CO/II	S/I
	Chemosensitive relapse, prior auto-HSCT	CO/II	CO/II	CO/II	S/II
AL		CO/III	CO/III	GNR/III	CO/II
Other diseases					
Acquired SAA and	Newly diagnosed	S/II	CO/II	GNR/III	NA
AA/PNH	Relapsed/refractory	S/II	S/II	CO/II	NA
Haemolytic PNH		GNR/II	GNR/II	GNR/II	NA
Constitutional SAA[b]		S/II	S/II	CO/II	NA
Breast Ca	Adjuvant high risk, HER2 negative	GNR/III	GNR/III	GNR/III	CO/II
	Metastatic, chemosensitive	D/II	D/II	GNR/III	D/CO/II
Germ Cell Tumours	Second line, high risk	GNR/III	GNR/III	GNR/III	CO/II
	Primary refractory, second and further relapse	GNR/III	GNR/III	GNR/III	S/II
Ovarian Ca	High risk/recurrent	D/II	GNR/III	GNR/III	GNR/I
Medulloblastoma	Post-surgery, high risk	GNR/III	GNR/III	GNR/III	CO/III
Small cell lung Ca	Limited	GNR/III	GNR/III	GNR/III	D/II
Soft tissue Sa	Metastatic	D/III	GNR/III	GNR/III	GNR/II
Ewing's Sa	Locally advanced/metastatic, chemosensitive	D/III	GNR/III	GNR/III	CO/III
Renal cell Ca	Metastatic, cytokine-refractory	D/II	D/II	GNR/III	GNR/III
Pancreatic Ca	Advanced	D/III	GNR/III	GNR/III	GNR/III
Colorectal Ca	Metastatic	D/III	GNR/III	GNR/III	GNR/III
Multiple Sclerosis	Highly active RR-MS failing DMT	D/III	GNR/III	GNR/III	S/I
	Progressive MS with AIC, and aggressive MS[c]	D/III	GNR/III	GNR/III	CO/II
Systemic sclerosis		D/III	GNR/III	GNR/III	S/I
SLE		D/III	GNR/III	GNR/III	CO/II
Crohn's disease		D/III	D/III	D/III	CO/II
Rheumatoid arthritis		D/III	GNR/III	GNR/III	CO/II
JIA		CO/II	CO/II	CO/III	CO/II
Monogenic AD		CO/II	CO/II	CO/III	GNR/II
Vasculitis		GNR/III	GNR/III	GNR/III	CO/II
PM-DM		GNR/III	GNR/III	GNR/III	CO/II

Disease	Disease status	MSD Allo	MUD Allo	MMAD Allo	Auto
Autoimmune cytopenias		CO/II	CO/II	CO/III	CO/II
Neuromyelitis Optica		D/III	D/III	D/III	CO/II
CIDP, MG and SPS		GNR/III	GNR/III	GNR/III	CO/II
Type 1 diabetes		GNR/III	GNR/III	GNR/III	D/II
RCD type II		GNR/III	GNR/III	GNR/III	CO/II
Primary ID		CO/II	CO/II	CO/II	NA

Selección de donantes

- ATSP:
  - Quimiosensibilidad
  - Edad: 70 años
  - Comorbilidades: cardíacas, pulmonares, hepáticas, renales (razón: quimioterapia intensiva)
  - Escalas de morbilidad: EBMT, Pretransplant Assesment mortality score (PAM), HCT-specific comorbidity Index (HCT-CI)

Selección de donantes

Hematopoietic cell transplantation

❶ Donor Selection

EBMT ri

Table 2. European Grou
Transplantation Risk Sc

Risk Factor
Age of the patient, y
<20
20-40
>40
Disease stage*
Early
Intermediate
Late
Time interval from diagn
<12
>12
Donor type
HLA-identical sibling don
Unrelated donor
Donor-recipient sex com
All other
Donor female, male recip

HLA indicates human leukocyte antigen.
*See text for the definitions according to main disease category; does not apply for patients with severe aplastic anemia (score 0).
†Does not apply for patients transplanted in first complete remission

MHC

The Major Histocompatibility Complex & Antigen recognition

HLA, present peptides to T cells, thus allowing elimination of foreign particles and recognition of self or non-self

SO, **If** donor proteins are presented to the host T CELL, (HVG,Rejection)

If host proteins are presented Donor T CELL (GVHD, GVT effect)

(TRM) (*Bottom*) of 56,605 patients with an allogeneic hematopoietic stem cell transplantation (HSCT) for an acquired hematological disorder is shown by risk score. Graphs reflect probability of survival (*Top*) and transplant-related mortality (*Bottom*) over the first 5 years after HSCT.

Selección de donantes

- Alogénico:

❶ Donor Selection

Stem Cell Donor	AVAILABILITY
• HLA-identical sibling - First choice	• 1/3 patients in population
• Unrelated donor	• >29 million donors worldwide
• Cord blood	• ~700 000 cords
• Other related donor - Haploidentical	• Inevitable ?





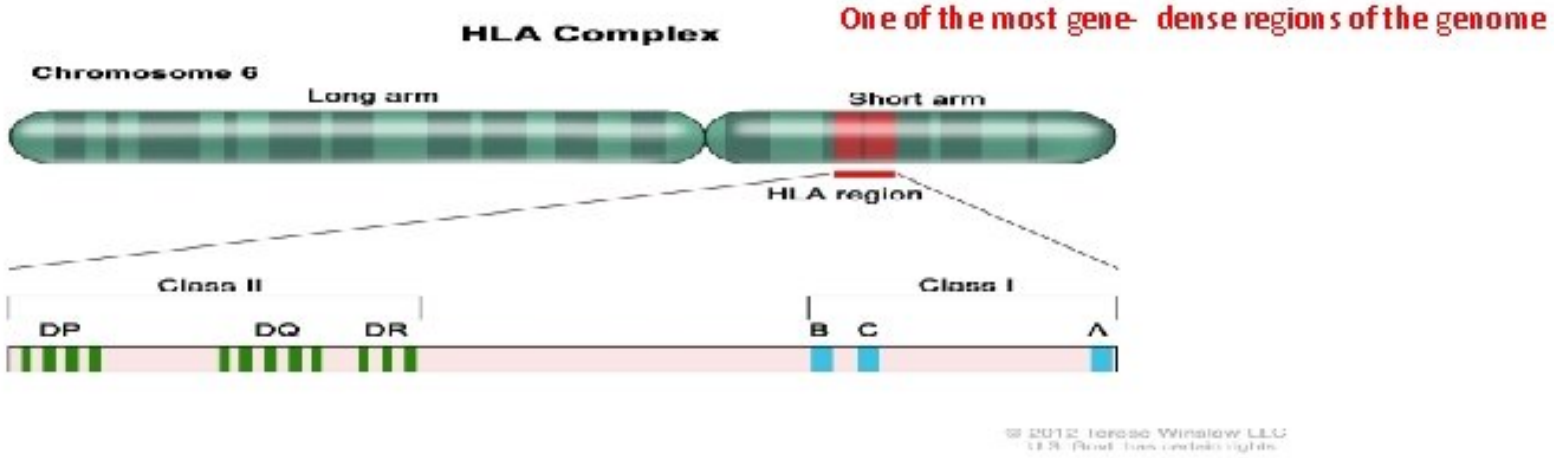


Selección de donantes

❶ Donor Selection

Why is HLA so important?

Human Leukocyte Antigen



- Discovered: in mice (1937), humans (1954)
- HLA is in the MHC on Chr6:
- **HLA is a protein – or marker – found on most cells in your body.**

Selección de donantes

❶ Donor Selection

MHC

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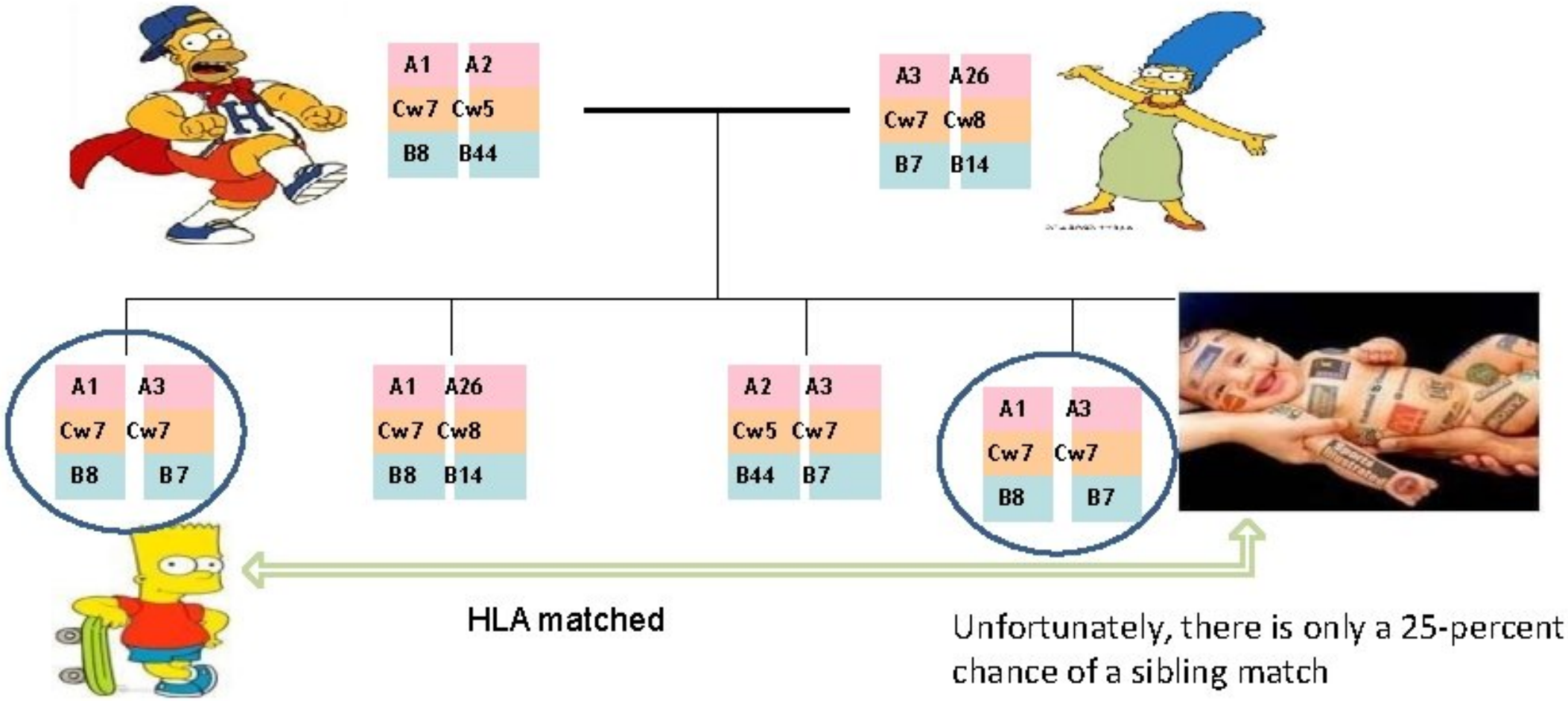
SO, **If** donor proteins are presented to the host T CELL, (HVG,Rejection)

If host proteins are presented Donor T CELL (GVHD, GVT effect)

Selección de donantes

❶ Donor Selection

The HLA Family



Unfortunately, there is only a 25-percent chance of a sibling match

Selección de donantes

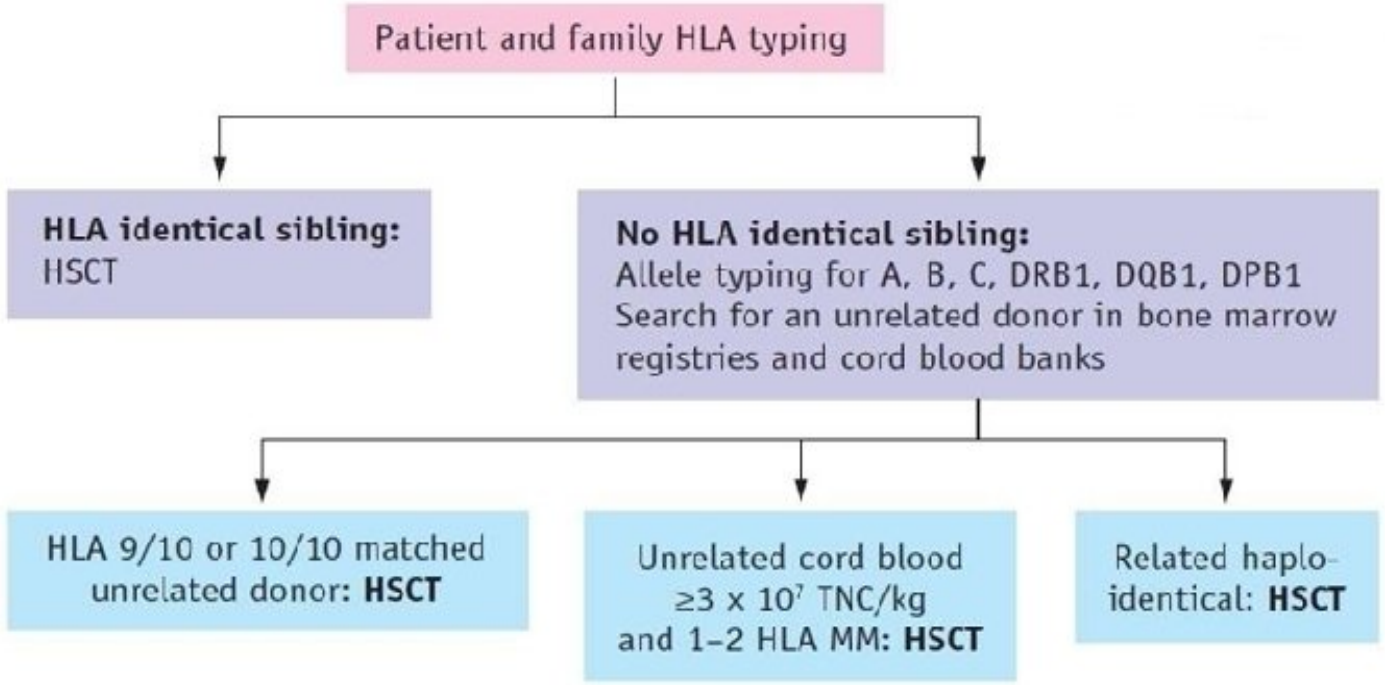
❶ Donor Selection

Requirements for the ideal graft/donor

- Fast and stable engraftment → HAPLO and SIB
- No / Low GvHD → TWIN / SIB
- Early immune reconstitution → SIB
- Strong and lasting GvT effect → HAPLO>CB>SIB
- Chances for immunotherapy → SIB >HAPLO >, CML- DLI
- Quick availability → SIB>HAPLO>CB>URD
- No/Low infectious risks → TWIN/SIB
- Safe for patient, low TRM → SIB
- Cheapest procedure → SIB

Selección de donantes

❶ Donor Selection



- If transplant urgent: prefer related haploidentical transplant or cord blood
- Consider other factors: indication of the transplant, ABO, CMV, donor sex
- Expertise of the centres is very important for donor selection for HLA mismatched transplants
- If not enough cells in a single cord blood unit: consider double cord

Selección de donantes

❶ Donor Selection

UNRELATED donor selection criteria

- HLA matched and permissive mismatches (DP)
- Sex mismatch D/R
- ABO compatibility
- CMV serological status D/R
- Donor: age and gender
- HLA antibodies in the patient

Selección de donantes

❶ Donor Selection

HAPLOIDENTICAL donor selection criteria

REVIEW

T-cell replete haploidentical donor transplantation using post-transplant CY: an emerging standard-of-care option for patients who lack an HLA-identical sibling donor

A Bashey and SR Solomon

1.- No anti-HLA antibodies (patient)

2.- Higher HLA mismatch

3.- KIR alo-reactive donor

4.- Younger donor

5.- Male ☐Male (avoid mothers)

Bone Marrow Transplantation (2014) **49,** 999–1008

Table 3. Donor selection for haploidentical transplantation using post-transplant CY

1. Screen recipient for antibodies targeting mismatched donor HLAs (donor-specific antibodies, DSA)

- Screen all potential donors using solid-phase immunoassay (SPI) and cross-match of recipient serum against donor T and B lymphocytes
- Select donors with negative spi screen or low-level positivity (< 1000 mean fluorescence intensity, MFI); if no negative donors available, and a negative anti-donor cross-match
- Donors with a negative cross-match and positive SPI screen may potentially be desensitized[44] but such donors should only be used if the anti-donor cross-match is negative following desensitization and is safer when using non-myeloablative conditioning

2. Choose a HLA-haploidentical donor with the greatest number of mismatches with the recipient on the non-shared haplotype

- 4 of 8 HLA-A, B, C and DRB1 matched donors appear to have a lower relapse rate and no increase in GVHD or graft rejection when compared to 5 of 8 and 6 of 8 matched donors.[71] Thus, choose a haploidentical donor with the greatest number of HLA mismatches with the recipient on the non-shared haplotype

3. Killer immunoglobulin-like receptor (KIR) mismatch between donor and recipient may facilitate natural killer cell alloreactivity

- Donors mismatched for inhibitory KIR receptors may produce lower relapse risk[45]
- Patients homozygous for KIR 'group A' may have improved outcomes if the donor has at least one KIR 'group B' haplotype[45]
- Additional study of KIR mismatching is necessary before KIR groups can routinely be used in donor selection

4. Younger donors preferred

- e.g. choose a young adult over a sibling or parent donor if other factors are equal[46]

5. Male donors preferable particularly for male patients

- Avoid mother as a donor unless no other choices[46]

Selección de donantes

❶ Donor Selection

UCB Donor selection criteria

UK consensus: WHICH UNIT OR UNITS?

Search step	Search criteria	Comments
1st	Cell Dose	Same cell dose required for RIC and MAC $\geq 3.0 \times 10^7$ NC/kg and/or $\geq 1 \times 10^6$ CD34+/kg
2nd	HLA match	0-1 MM better than 2 - avoid 3-4 MM Avoid ≤4/8 units Prefer class I mismatches to class II Avoid C MM
3rd	Transplant indication	Malignant diseases: cell dose ($\geq 3.0 \times 10^7$ NC/kg) HLA is the best prognostic factor because HLA differences reduce relapse (GVL) Non malignant diseases: increase cell dose ($\geq 5.0 \times 10^7$ NC/kg) and find the best HLA match (avoid CB ≤4/8 units)
4th	Other considerations (if several options available)	ABO important only in RIC setting Cord bank accreditation and location

Notes: Where a single unit meeting these criteria cannot be identified, a double unit may be used

Acondicionamiento e infusión de progenitores

❹ Conditioning Therapy

Dose & Response Curve with Cytotoxic Chemothrapy

- The first stage of the transplant.
- May be given in one dose or over several days.

- Necessary for:
  - Destroying remaining cancer cells
  - Creating room in the bone marrow for the transplanted stem cells
  - Supressing the patients immune system to prevent of graft rejection

- Conditioning regimen is dependent on the type of disease, the type of transplant, co-morbidities and age.

Acondicionamiento e infusión de progenitores

Conditioning Therapy

Regimen Intensity

Low Intensity — High Intensity

Flu / Cy — BEAM — Cy / TBI

- Less regimen related toxicity
- Rely on later GVL effect

- Increase in regimen related toxicities
- Increased level of disease control

Acondicionamiento e infusión de progenitores

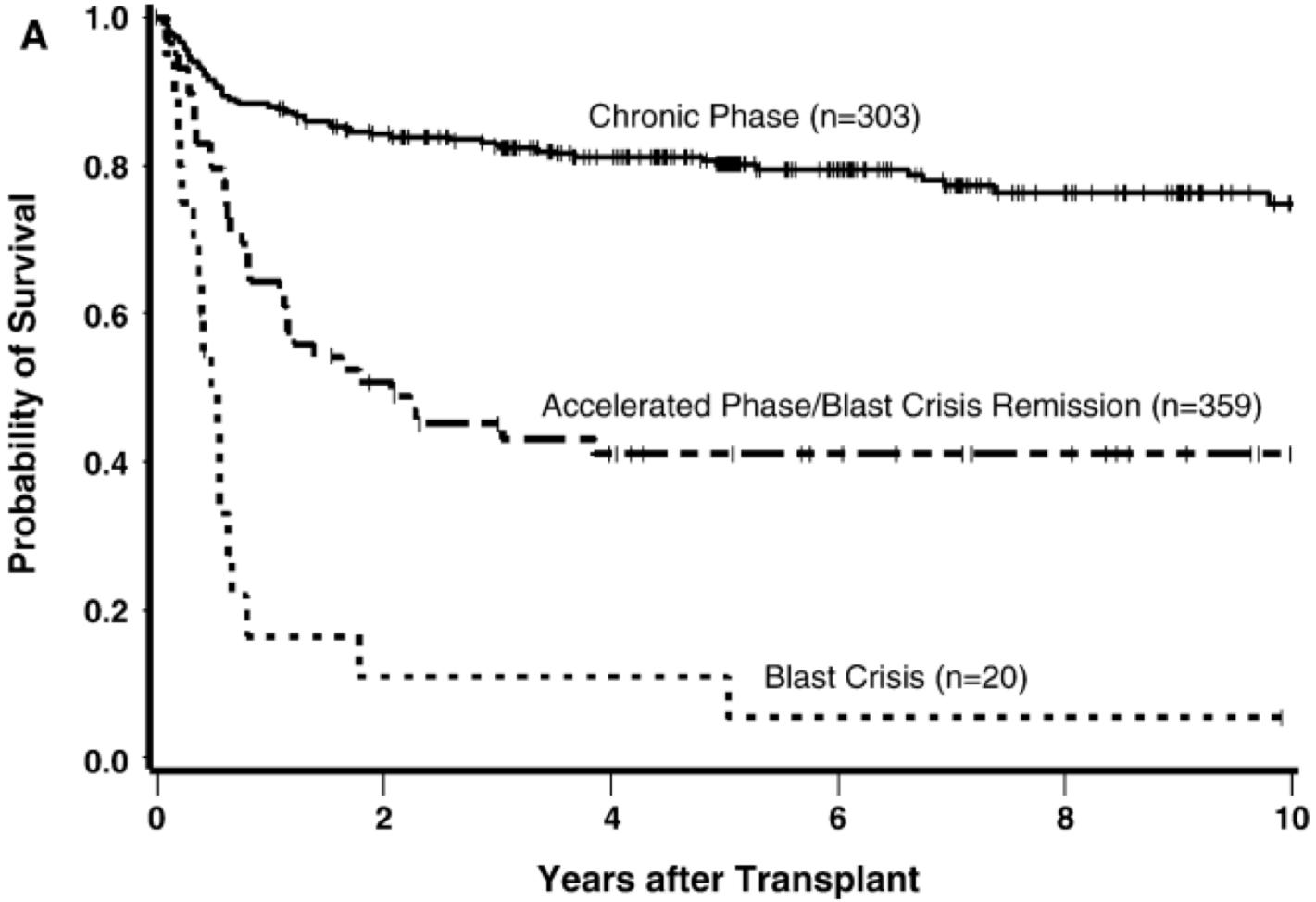
❶ Conditioning Therapy

Regimen Intensity

- **Myeolablative conditioning**
  - Irreversibly destroys the haemopoietic function of the BM with high doses of CT ±TBI.
  - Higher level of disease control
  - Younger patients with a good performance status
  - Quicker engraftment of donor cells
  - Higher toxicities associated with higher transplant related mortality

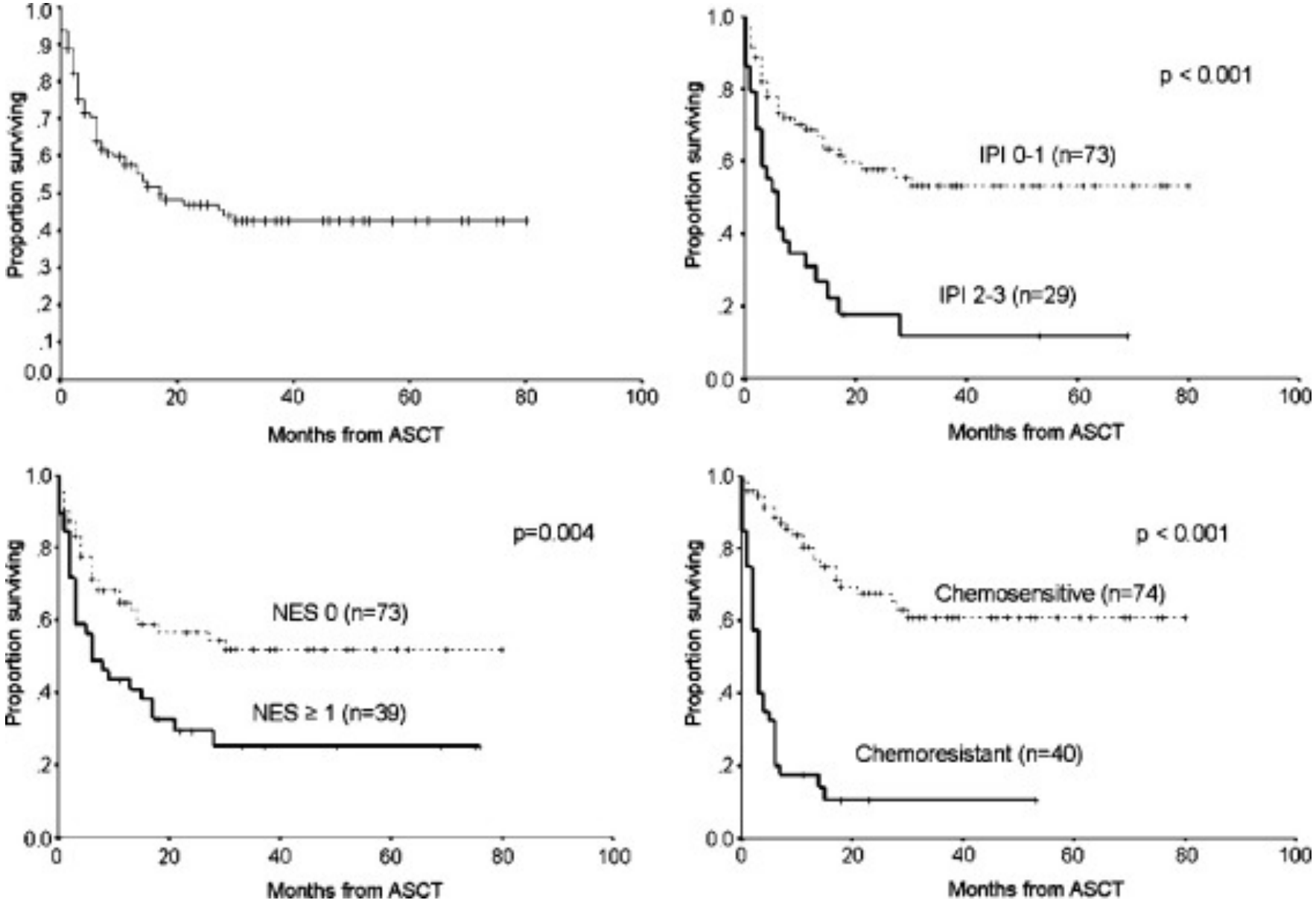
- **Reduced intensity conditioning**
  - It aims to use enough immunosuppression to allow donor cells homing
  - RIC can allow to homing without completely eradicating the recipients bone marrow.
  - Regimens that have been developed to reduce the morbidity and mortality of Allo-HSCT
  - Because of less regimen related toxicities, Can be given to older patients
  - Reduction in morbidity and transplant related mortality

Resultados en patologías hematológicas seleccionadas



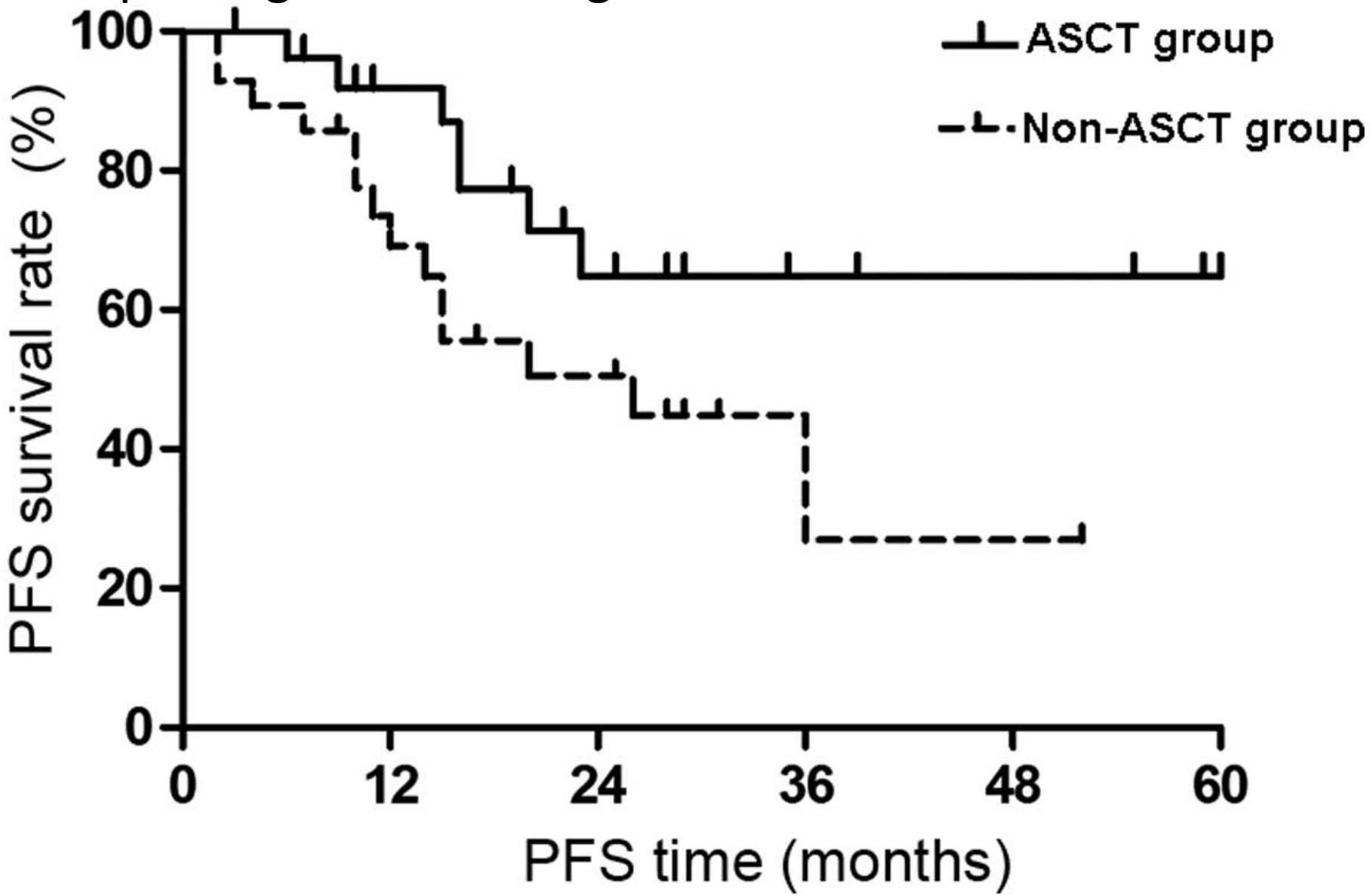
Radich, Jerald P; Olavarria, Eduardo; Apperley, Jane F (2004). Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia. Hematology/Oncology Clinics of North America, 18(3), 685–702. doi:10.1016/j.hoc.2004.03.013

Resultados en patologías hematológicas seleccionadas



Autologous stem-cell transplantation in diffuse large B-cell non-Hodgkin's lymphoma not achieving complete response after induction chemotherapy: the GEL/TAMO experience. https://doi.org/10.1093/annonc/mdh391

Resultados en patologías hematológicas seleccionadas



Fu, C., Wang, J., Xin, X., Liu, H., Xue, S., Ma, X., Jin, Z., Sun, A., Qiu, H., Wu, D."Therapeutic effects of autologous hematopoietic stem cell transplantation in multiple myeloma patients". Experimental and Therapeutic Medicine 6, no. 4 (2013): 977-982. https://doi.org/10.3892/etm.2013.1261

Resultados en patologías hematológicas seleccionadas

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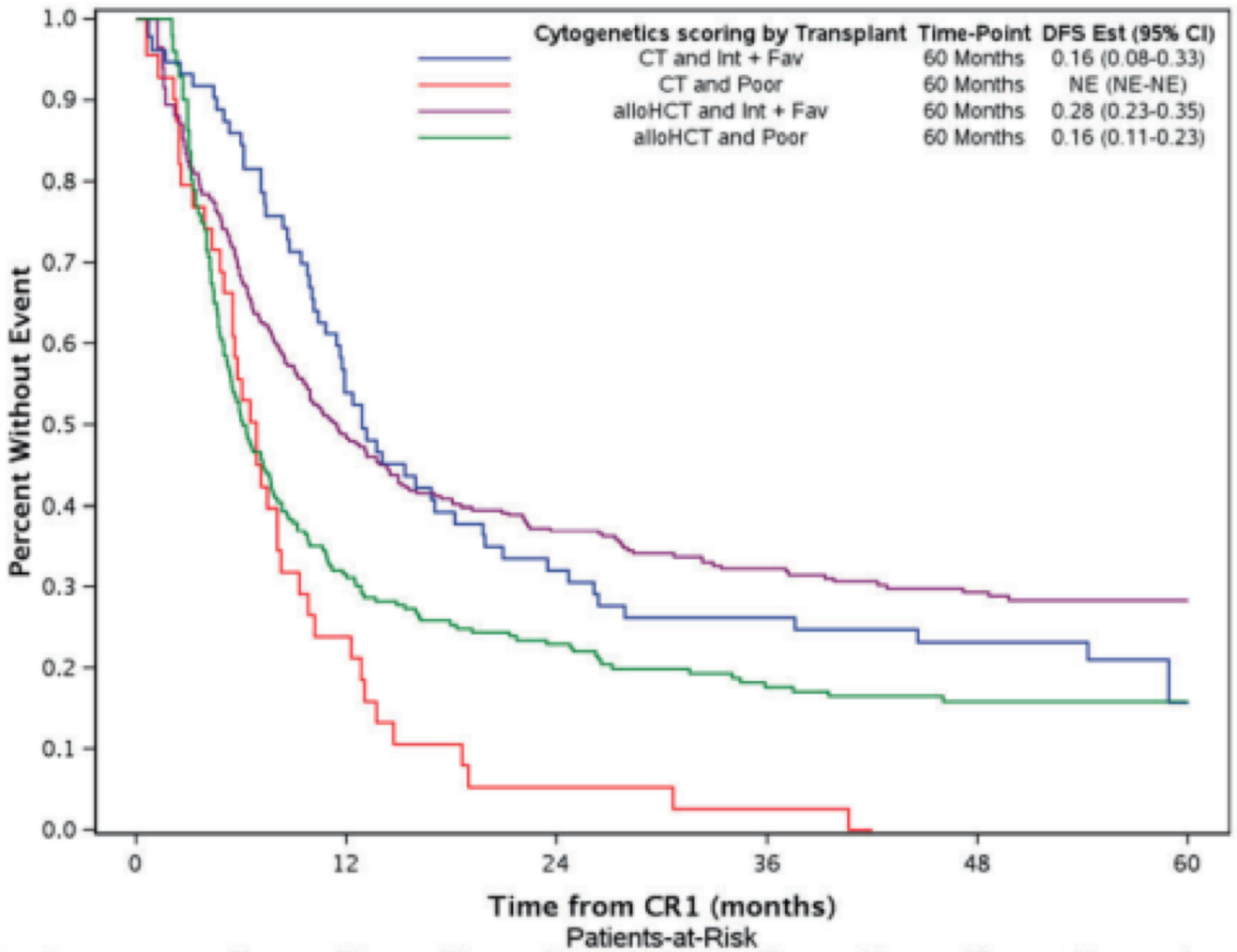
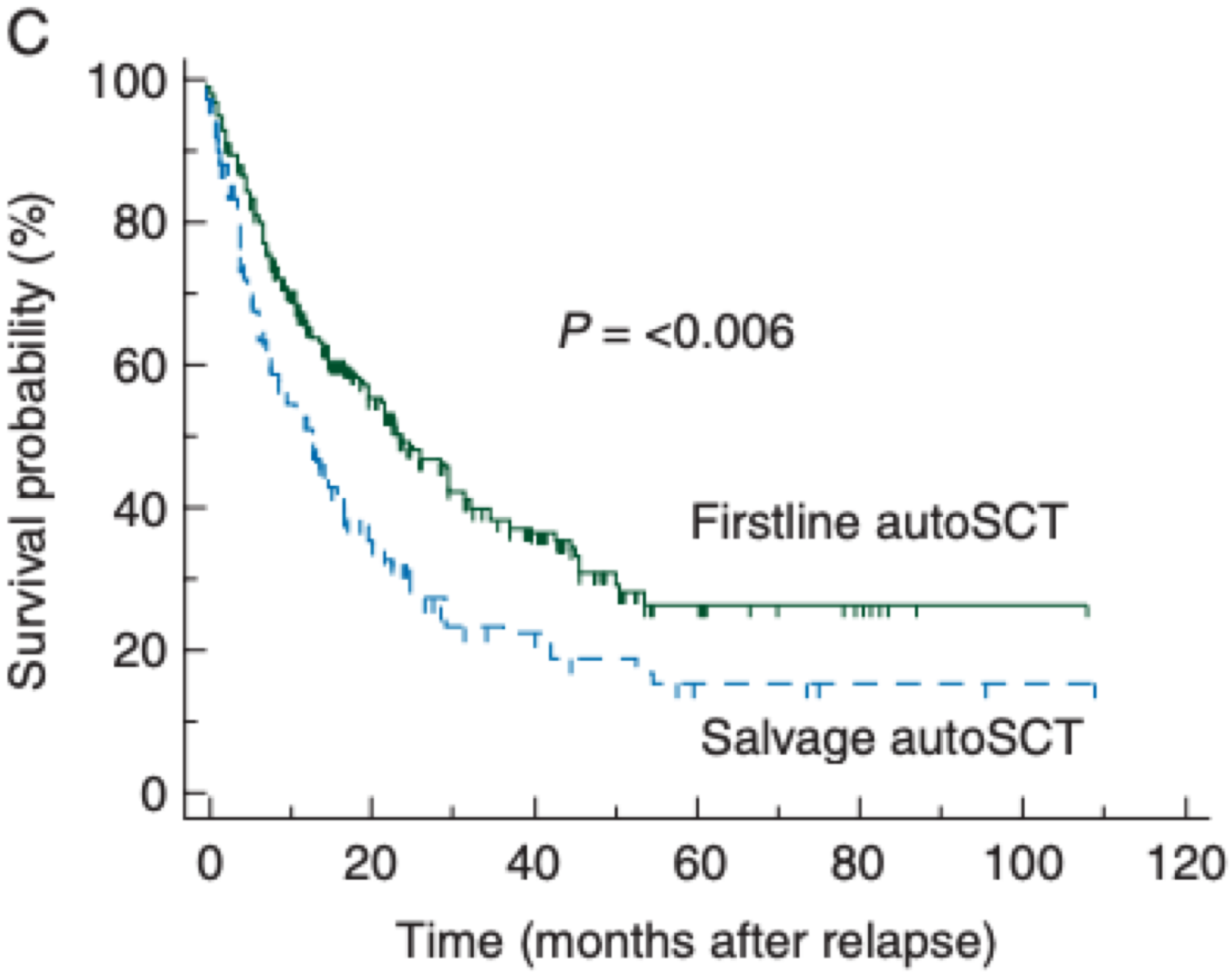


Patients-at-Risk

CT and Int + Fav	58	37	27	22	18	17	16	15	12	2
CT and Poor	21	9	4	2	2	1	0			
alloHCT and Int + Fav	186	151	125	114	92	85	72	62	53	48
alloHCT and Poor	87	64	53	48	36	31	27	25	22	22

Allogeneic hematopoietic cell transplantation compared to chemotherapy consolidation in older acute myeloid leukemia (AML) patients 60–75 years in first complete remission (CR1): an alliance (A151509), SWOG, ECOG-ACRIN, and CIBMTR study. Leukemia, (), –. doi:10.1038/s41375-019-0477-x

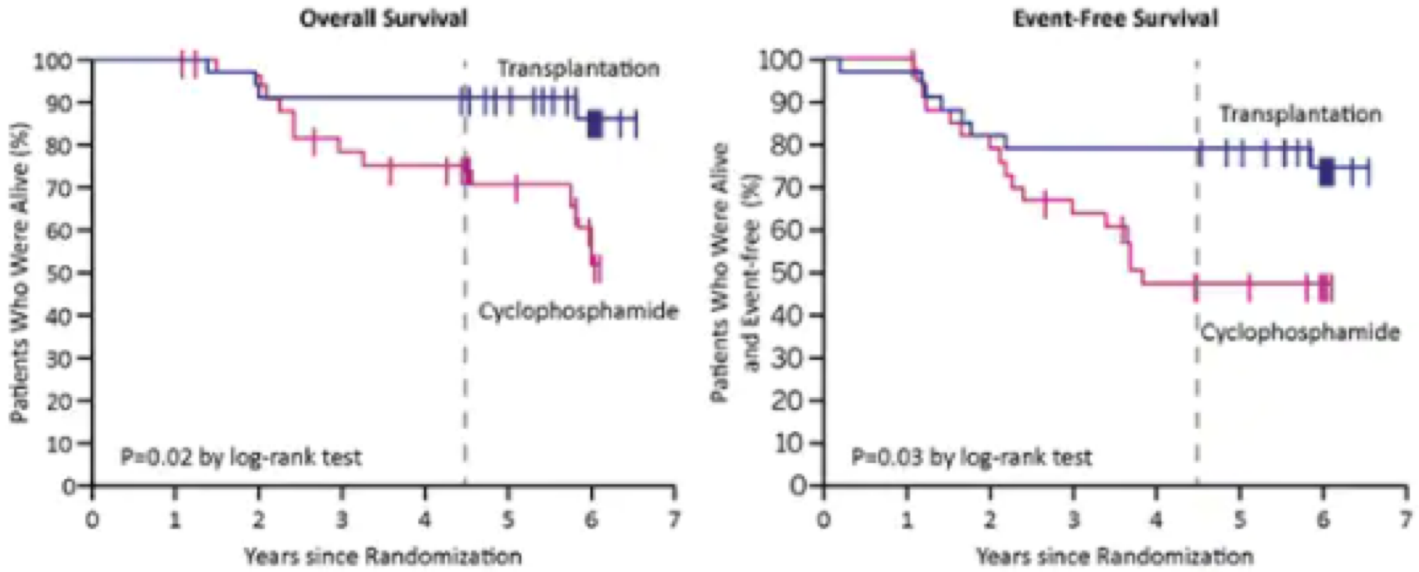
Resultados en patologías hematológicas seleccionadas



Dietrich et al. Outcome and prognostic factors in patients with mantle-cell lymphoma relapsing after autologous stem-cell transplantation: a retrospective study of the European Group for Blood and Marrow Transplantation (EBMT). Annals of Oncology 25: 1053–1058, 2014

Resultados en patologías NO hematológicas seleccionadas

FIGURE 1. Select Results From the SCOT Trial: Overall and Event-Free Survival, Per-Protocol Population



No. at Risk													
Transplantation	33	33	31	30	30	25	9	33	32	27	26	26	24	9
Cyclophosphamide	34	34	31	24	22	15	7	34	34	26	20	14	12	6

Reprinted with permission from Sullivan KM, Keyes-Elstein L, McSweeney PA, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med*. 2018;378(1):35-47.

Resultados en patologías NO hematológicas seleccionadas

Table. Clinical Trials of Autologous Hematopoietic Stem Cell Transplant Reports Since 2015

Source	Identifier	Protocol	Sample size, No.	Conditioning regimen	Primary outcome	Mortality, %
Canadian report[16]	NCT01099930	Phase 2 single-arm clinical trial	26 Enrolled; 24 who received transplant	Busulfan, mean total dose, 10.9 mg/kg; cyclophosphamide, 200 mg/kg; rabbit ATG, 5 mg/kg	Activity-free survival at 5 y: 69.6%	4.2
HALT-MS[17]	NCT00288626	Phase 2, single-arm clinical trial	25 Enrolled; 24 who received transplant	BEAM; rabbit ATG, 5 mg/kg	Event-free survival at 5 y: 69.2%; progression-free survival: 91.3%	0
Australian report[4]	ACTRN12613000339752	Phase 2 single-arm clinical trial	35	BEAM; horse ATG, 40 mg/kg	NEDA at 1 y: 82%; NEDA at 2 y: 65%; NEDA at 3 y: 60%	0
ASTIMS[18]	EudraCT 2007-000064-24	Phase 2 clinical trial AHSCT vs mitoxantrone	21 Total; 9 randomized to AHSCT	BEAM; rabbit ATG, 7.5 mg/kg	Over 4 y, median new T2 lesions 2.5 in AHSCT group vs 8 in mitoxantrone group (rate ratio, 0.21; $P < .001$)	0
MIST[19]	NCT00273364	Phase 3 clinical trial AHSCT vs conventional DMT	110 Total; 55 randomized to AHSCT; 52 in primary analysis	Cyclophosphamide, 200 mg/kg; rabbit ATG, 6 mg/kg	Confirmed disability worsening, 5.8% in AHSCT group vs 66.7% in DMT group	0

Abbreviations: ASTIMS, Autologous Stem Cell Transplantation International–Multiple Sclerosis; ATG, antithymocyte globulin; BEAM, bis-chloroethylnitrosourea, etoposide, cytarabine, and melphalan; DMT, disease-modifying therapy; EudraCT, European Union Drug Regulating Authorities Clinical Trials Database; HALT-MS, High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis; MIST, Multiple Sclerosis International Stem Cell Transplant; NEDA, no evidence of disease activity.

Complicaciones del Auto-TPH

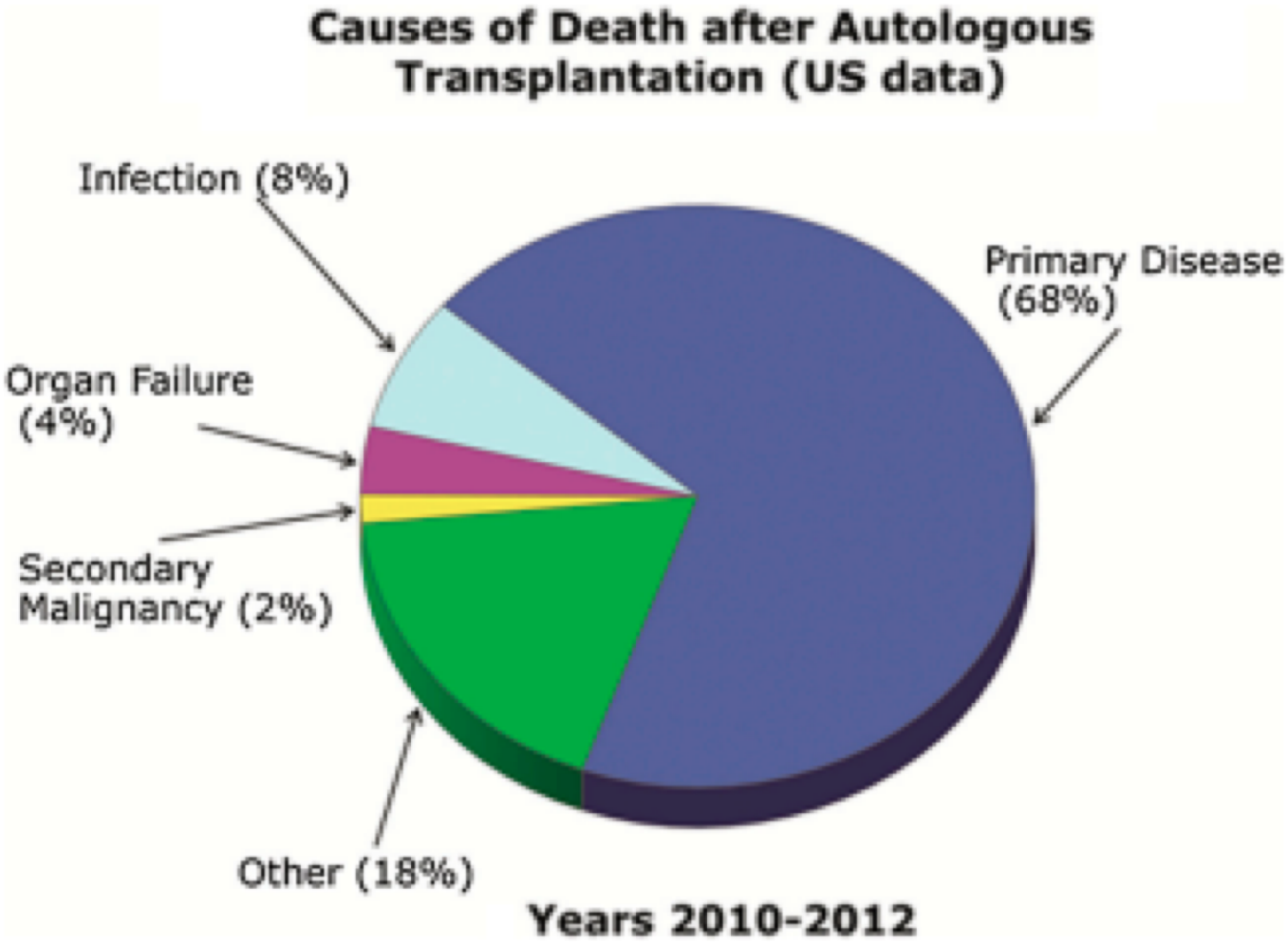
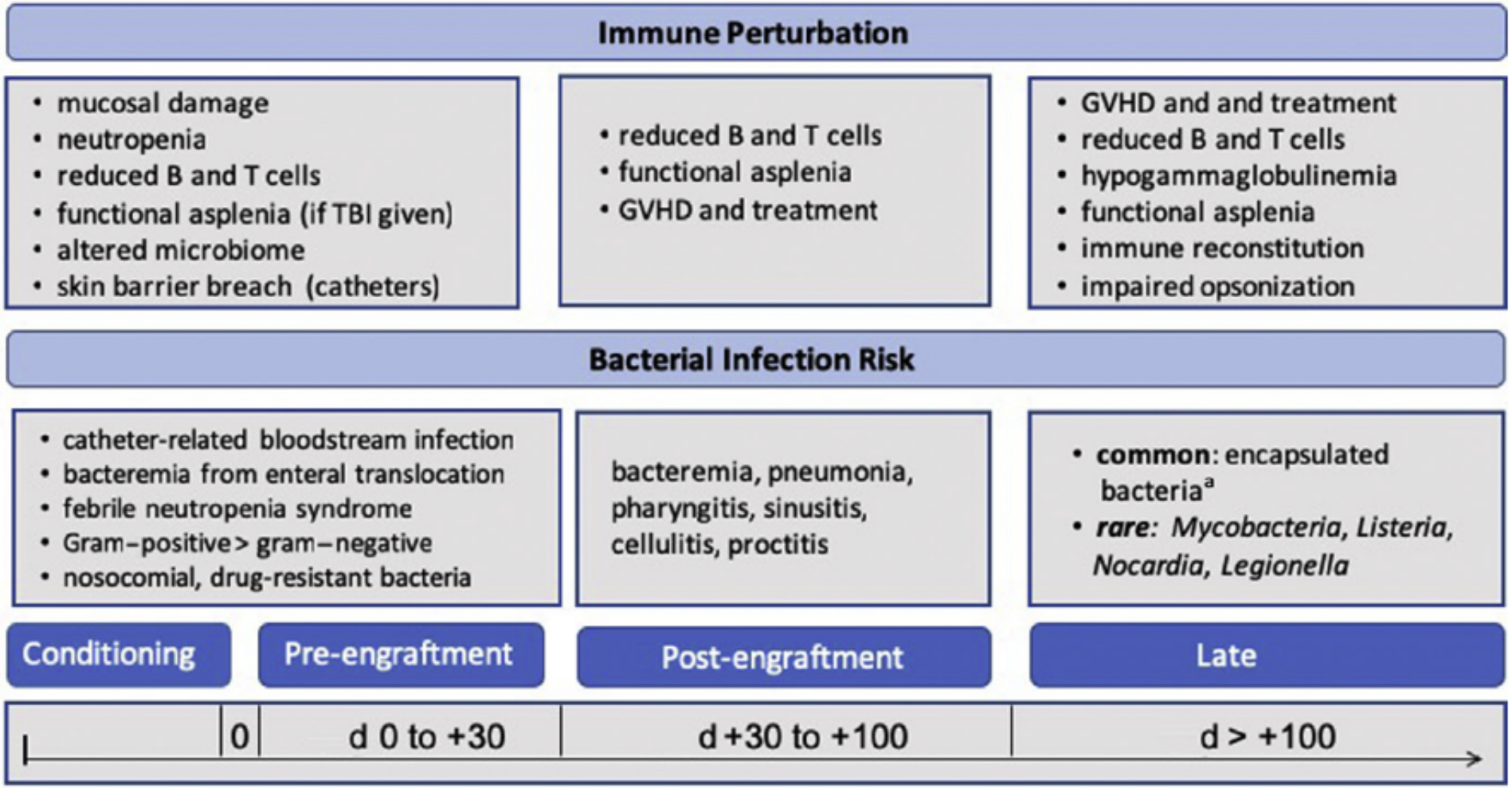


Figure 2. Causes of death after autologous HCT (US data) reported to CIBMTR during 2010–2012.

Table III. Complications following autologous transplantation.

Complications[a]	Prophylaxis/management
Conditioning regimen-related toxicities	
Nausea/vomiting	Antiemetics
Diarrhea	Antidiarrheals and fluids to prevent dehydration
Alopecia	
Loss of appetite	Dexamethasone to stimulate appetite
Altered taste sensation	Zinc tablets or lemon candy
Mucositis	Pelifermin, anesthetic mouth wash, supersaturated calcium phosphate oral rinse, opioid analgesic, parenteral nutrition in severe case
Myelosuppression	G-CSF, blood component transfusions
Fevers	Evaluate for infections, antipyretics
Fatigue	Exercise
Infections (bacterial, viral, fungal, etc.)	Antibiotic prophylaxis/treatment as appropriate
Clostridium difficile diarrhea	Hand washing/metronidazole, oral vancomycin
Pulmonary toxicity (carmustine, busulfan, radiation)	Careful patient selection, smoking cessation/steroids for therapy
Cardiac toxicity	Careful patient selection
Renal toxicity	Patient selection, avoiding nephrotoxic agents
Hemorrhagic cystitis (cyclophosphamide)	Mesna for prophylaxis
Dermatitis (etoposide)	
Cataracts	Topical corticosteroids or emollients
Parotitis (radiation)	Chewing gums, lemon drops
Infertility	Sperm or oocyte cryopreservation
Hypothyroidism	Avoid TBI
Osteoporosis	Avoid TBI
Stem cell infusion	
Flushing	Interrupting and slowing infusion rate
Hypotension	
Breath odor due to DMSO	
Allergic reactions	Acetaminophen, histamine blockers, corticosteroids
Chest tightness/dyspnea	
Miscellaneous	
Transfusion-associated graft-versus-host disease	Irradiated blood products; only curative therapy for tMDS/AML is allogeneic HCT
Second malignancies (especially tMDS/AML)	Short-course corticosteroids; high-dose corticosteroids and platelet transfusions
Engraftment syndrome	
Diffuse alveolar hemorrhage	

Complicaciones del Auto-TPH



JACIE
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ISCT | EBMT

<u>Sept-Nov 2021</u>
Protocolos, infraestructura, equipos, formación int/ext.
<u>Diciembre 2021</u>
Mejora de cartera de servicios→ Dirección Dept
<u>Enero-Marzo 2022</u>
Conselleria, JACIE