BHS Educational Course on Transfusion and Cell Therapy

Hematopoietic stem cell mobilization and collection

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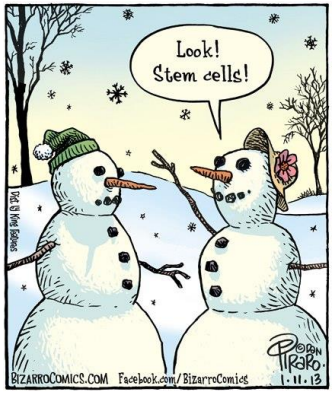

Daan Dierickx – UZ Leuven

BHS Educational Course – Seminar 5

March 2th 2024

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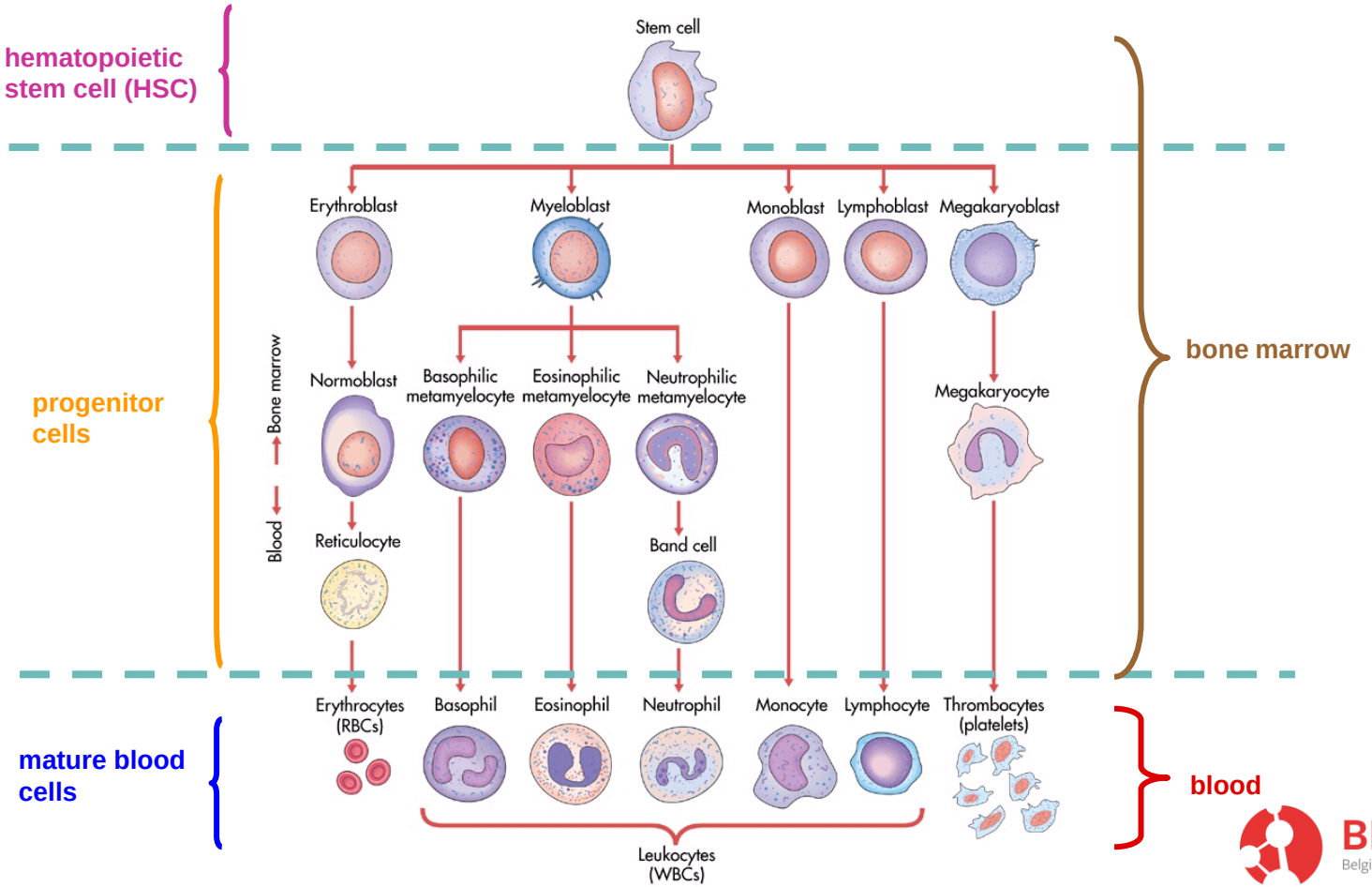
Introduction



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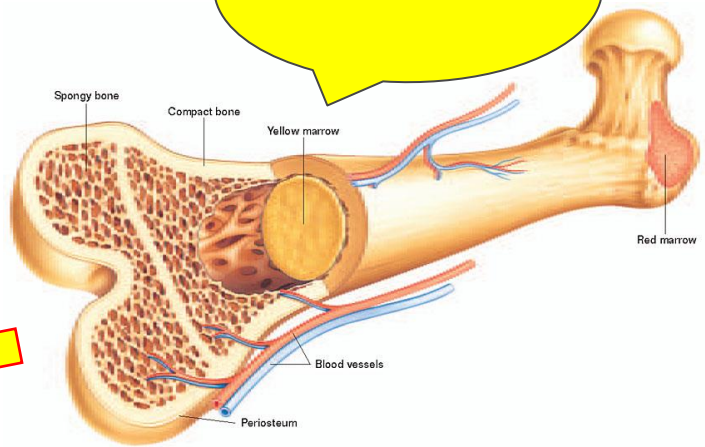
Collection

Collection



Mobilization

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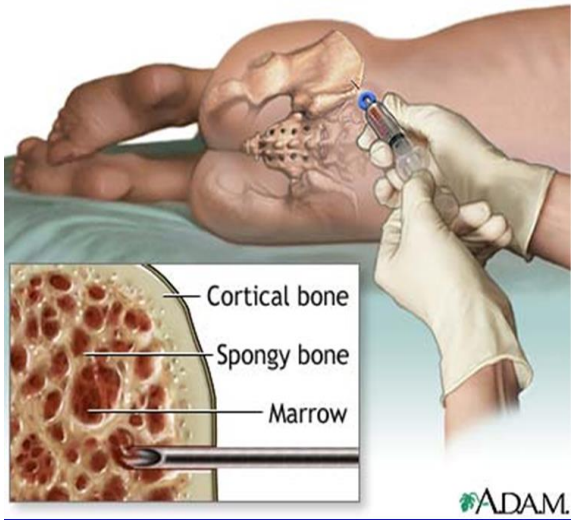
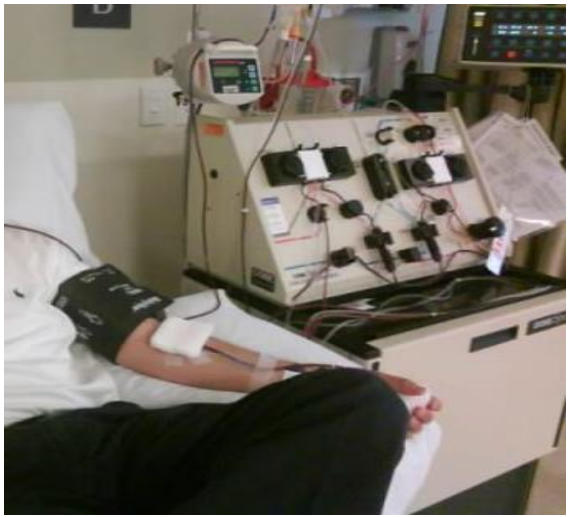
Bone marrow stem cells (HPC-M)



Peripheral blood stem cells (HPC-A)



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- Apheresis

- **Extracorporal system**: whole blood from patient/donor ➔ device: specific component separated ➔ remaining components back to patient/donor

- **Aim**:
  - Removal of harmful component (removal, exchange, depletion)
  - Collection of desired component (collection)

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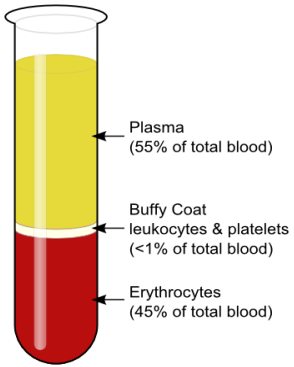
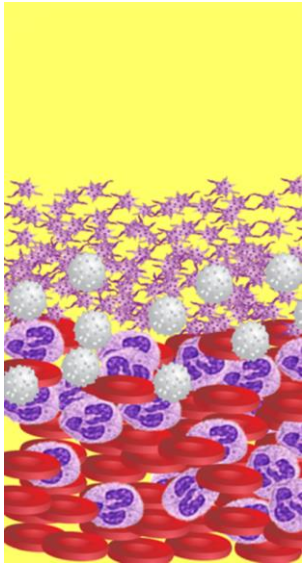
- Separation of blood components based on density

- Whole blood: different layers: (specific gravity)
  - **Plasma** **1.025-1.029**
  - **Platelets** **1.040**
  - **Lymphocytes** **1.050-1.061**
  - **Monocytes** **1.065-1.070**
  - **Granulocytes** **1.087-1.092**
  - **Erythrocytes** **1.093-1.096**





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Substance / Need for substitution	Plasma (plasmapheresis)	Cell (cytapheresis)
Yes	**Plasma exchange**	**Cellular exchange**
No	**Plasma removal**	Peripheral stem cell / T cell collection

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Introduction

Flashback 1997: collection of hematopoietic progenitor cells by peripheral blood apheresis after stimulation with granulocyte–colony-stimulating factor

Willy A. Flegel, Karen M. Byrne, and Harvey G. Klein

Efficacy

Safety

Mobilization necessary	Advantages
Chemotherapy Chemotherapy + G(M)-CSF G(M)-CSF steady state Association of plerixafor	No anesthesia needed Less painful Faster engraftment

HPC-A: replaced HPC-M for most indications (adults)

Transfusion 2017;57:3067-8
Panch SR, et al. Biol Blood Marrow Transplant 2017;23:1241-9

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More CD34+ cells
Faster engraftment

More T-cells
More cGvHD

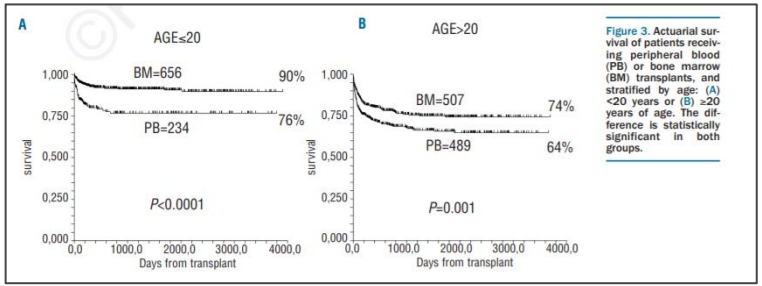
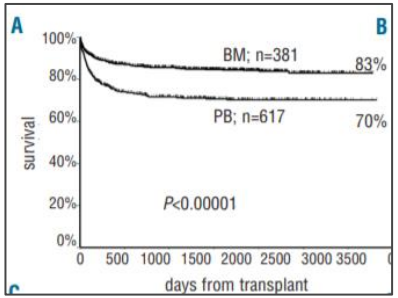


Figure 3. Actuarial survival of patients receiving peripheral blood (PB) or bone marrow (BM) transplants, and stratified by age: (A) <20 years or (B) ≥20 years of age. The difference is statistically significant in both groups.



Aplastic anemia

Bacigalupo A, et al. Haematologica 2012;97:1142-8
Bacigalupo A, et al. Haematologica 2015;100:696-702

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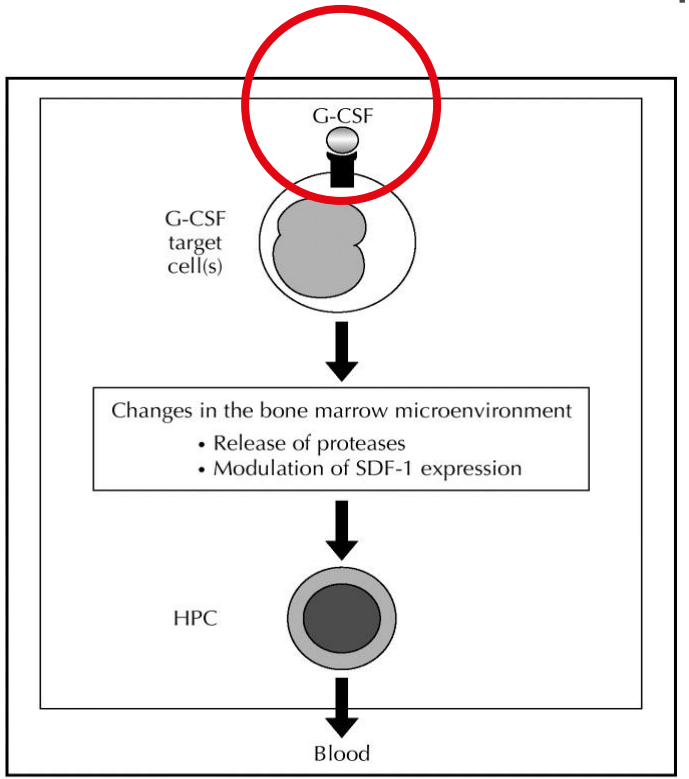
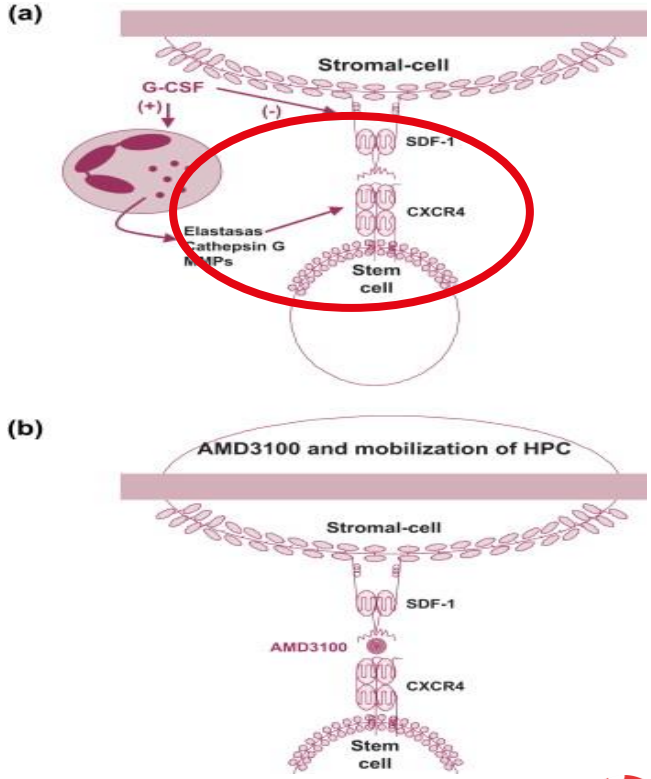
HPC-A





Thomas J, et al. Curr Opin Hematol 2002;9:183-9
Urbano-Ispizua A. Best Pract Res Clin Haematol 2007;20:265-80

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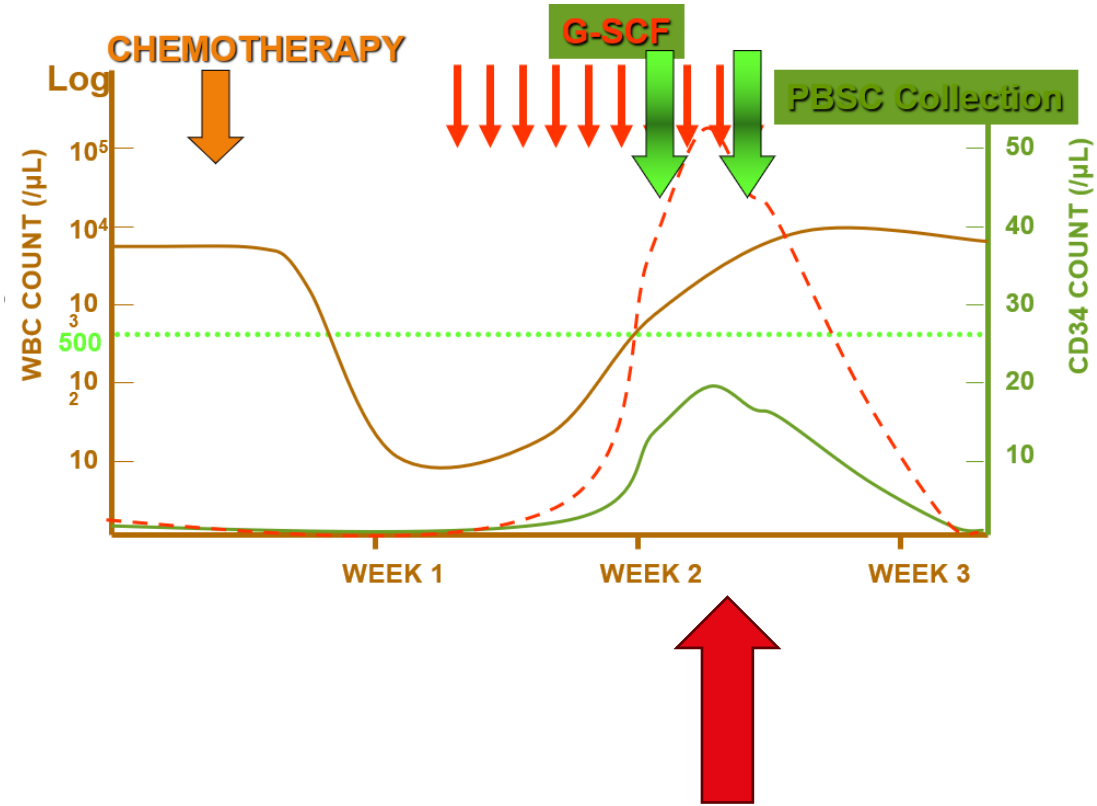
HPC-A: chemotherapy + G-CSF



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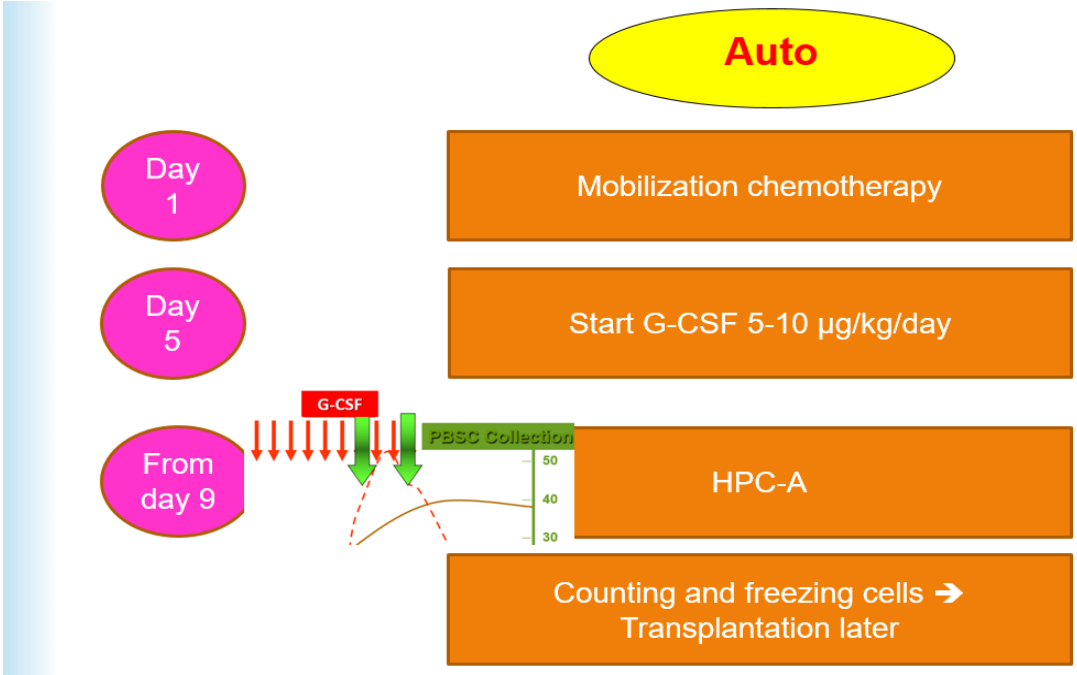
HPC-A: chemotherapy + G-CSF



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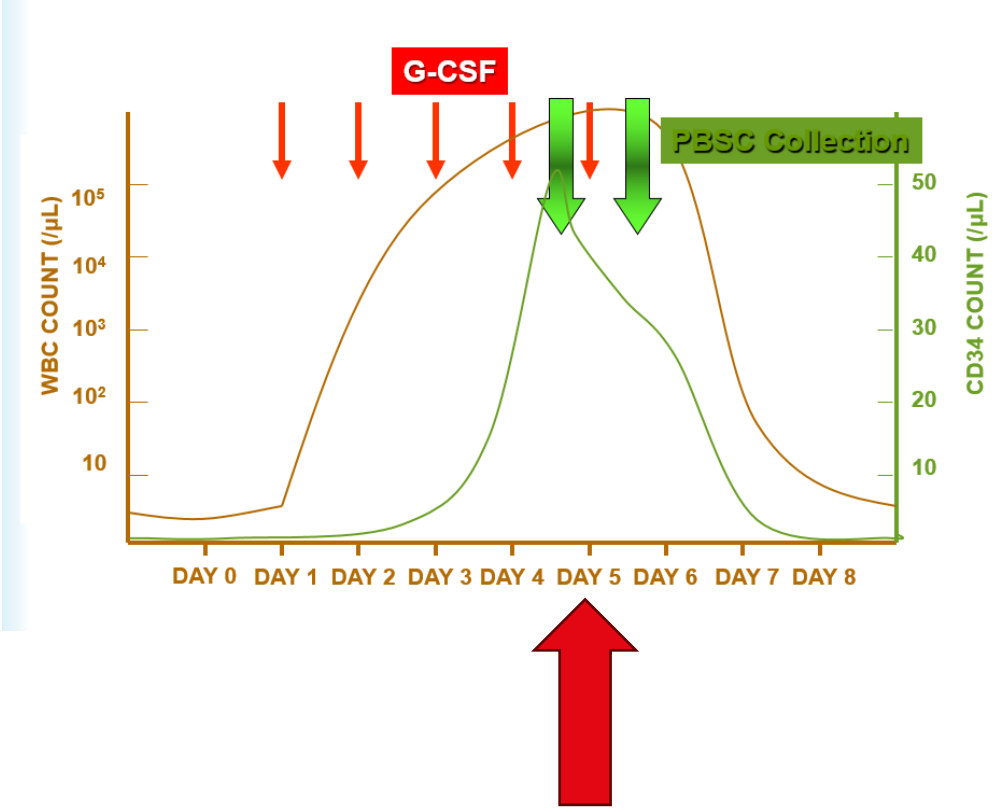
HPC-A: G-CSF only



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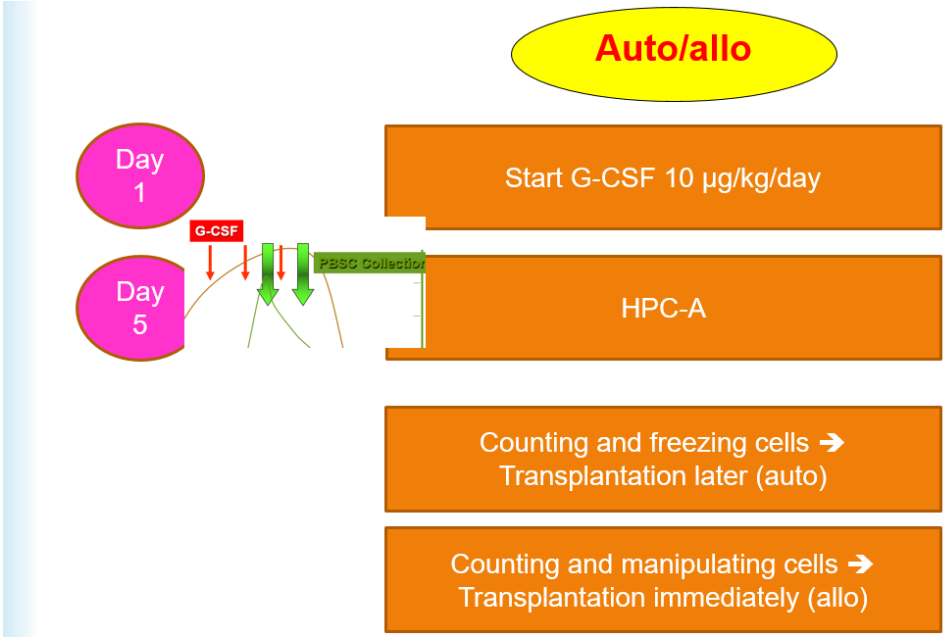
HPC-A: G-CSF only



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HPC-A

- Timing collection + estimation yield: based on
  - WBC count
  - CD34+ cell count
    - ➔ CD34+: more predictive (Yu J, et al. Transfusion 1999;39:442-50; Tohoku J, et al. J Exp Med 2003;199:111-8)

- Start collection if CD34-count > 10/µL (literature: 5-20)

- Prediction:
  - Yield:
    - Yield (x 10 CD34+cells/kg) = (CD34-count pre-apheresis / 10) if 4x TBV
  - Volume needed to process:
    - Amount of blood to be processed =

$$\text{Target CD34+ cells} \times \frac{\text{weight patiënt (kg)}}{\text{(CD34+cells/µL x collection efficiency)}}$$

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HPC-A

- Yield: dependent from
  - Number of progenitor cells in peripheral blood
  - Collection efficiency of device
  - Blood volume needed to be processed
  - Other factors

- Blood volume to be processed:
  - Conventional: 1-2 x TBV or procedure over 4 hours
  - Large volume leucapheresis (LVL): 3-5 x TBV
    ➔ prospective trial: 1x 25L vs 2 x 15L ➔ similar yield

(Bolan CD, et al. Br J Haematol 2003;120:801-7)

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HPC-A

- (First) apheresis:
  - Day 5 following start G-CSF monotherapy
  - Day 9-14 following last dose of chemotherapy if chemotherapy + G-CSF

- Target:
  - > 2-3 x 10^6 CD34+ cells/kg if back up or 1 ASCT planned
  - > 5-6 x 10^6 CD34+ cells/kg if tandem ASCT planned
  - > 5-10 x 10^6 CD34+ cells/kg if alloTx (dependent from graft manipulation)
  - > 10 x 10^6 CD34+ cells/kg if haplo-identical alloTx with T cell depletion

- CAVE loss of red blood cells and platelets (20-30%, LVL up to 50%)

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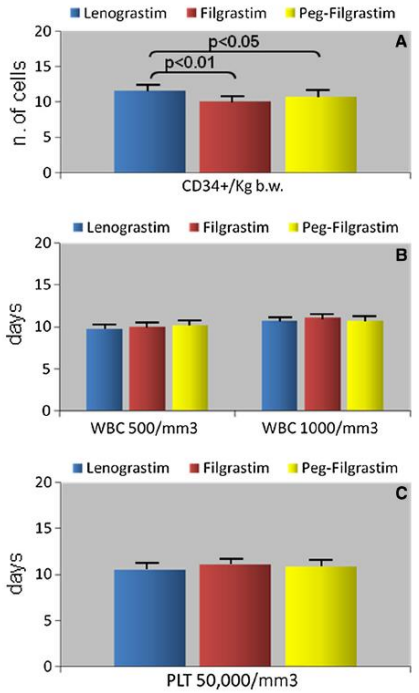
HPC-A

- Differences between subtypes of G-CSF?
  - Glycosylated = lenograstim
  - Non-glycosylated = filgrastim
  - Pegylated = pegfilgrastim

➔ Lenograstim > filgrastim



Höglund M, et al. Eur J Haematol 1997;59:177-83
Watts MJ, et al. Br J Haematol 1997;98:474-9
Fisher JC, et al. Br J Haematol 2005;130:740-6
Ings SJ, et al. Br J Haematol 2006;134:217-25
Ria R, et al. Clin Exp Med 2015;15:145-50

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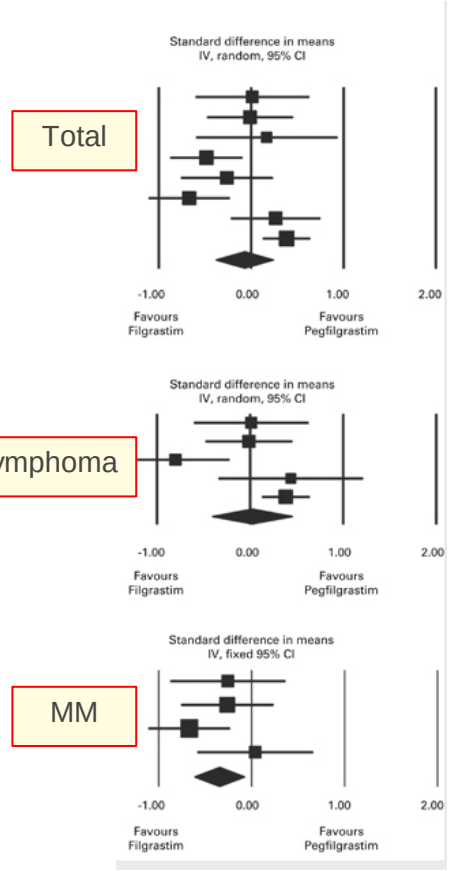
HPC-A

- Pegfilgrastim *versus* filgrastim



- Biosimilars

Brand name Europe	Marketing company	Manufacturing company
Ratiograstim	Ratiopharm GmbH, Germany	SICOR Biotech UAB, Vilnius, Lithuania
Tevagrastim	Teva GmbH, Germany	SICOR Biotech UAB, Vilnius, Lithuania
Zarzio	Sandoz GmbH, Austria	Sandoz GmbH, Kundl, Austria
Filgrastim Hexal	Hexal AG, Germany	Sandoz GmbH, Kundl, Austria
Nivestim	Hospira UK Ltd, United Kingdom	Hospira Zagreb d.o.o., Croatia
Grastofil	Apotex Europe BV, Netherlands	Intas Biopharmaceuticals Ltd, Ahmedabad, India
Accofil	Accord Healthcare Ltd, United Kingdom	Intas Biopharmaceuticals Ltd, Ahmedabad, India

the reference product Neupogen. Mobilisation of CD34 + cells as well as reported adverse events are also found to be comparable, although there is still a lack of long-term follow up for both Neupogen and filgrastim biosimilars. No evidence is found of a higher risk of filgrastim antibody formation using filgrastim biosimilars. Based on this increased experience, the WMDA therefore recommend that Stem Cell Donor Registries can use filgrastim biosimilars for the mobilisation of peripheral blood progenitor cells in healthy donors, provided that they are approved by national and/or regional agencies.

Ria R, et al. Clin Exp Med 2015;15:145-50
Kim MG, at al. Bone Marrow Transplant 2015;50: 523-30
Pahnke S, et al. Bone Marrow Transplant 2019;54:856-66

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HPC-A

- Once-dialy versus twice-daily G-CSF??

Table I. Collection and immunophenotyping data.

Variable	Group A ($n = 40$) 6 × 2/d	Group B ($n = 41$) 12 × 1/d	*P*-value
Donor TBV (l)	4·6 ± 1·3	4·9 ± 0·9	0·32
No. of TBVs processed	2·8 ± 0·2	2·8 ± 0·3	0·66
$CD34^+$ ($\times 10^6$ cells/kg recipient)*	5·6 ± 3·3	5·6 ± 4·3	0·94
$CD34^+$ ($\times 10^6$ cells/l blood processed)*	30 ± 17·2	30·4 ± 19·5	0·92

- Timing of collection

TABLE 4 Expected day of first PBSC collection depending on mobilizing chemotherapy regime. This Table was developed following audit of historical data from 3 large UK centers, and is now in routine use at several centers in the UK

Chemotherapy regime	Recommended weekday to start chemo	Anticipated first apheresis day	Anticipated weekday for first apheresis
CHOP	Friday	10	Monday
Cyclo 1.5 or 2 g/m^2	Monday	8–9	Tuesday or Wednesday
Cyclo 3 or 4 g/m^2	Friday	10–11	Monday or Tuesday
Cytarabine 4–6 g/m^2 (Nordic protocol for mantle cell lymphoma)	Thursday	12–14	Tuesday to Thursday
DHAP	Wednesday	13	Tuesday
ESHAP	Wednesday	13	Tuesday
IVE	Wednesday	13	Tuesday
GDP	Tuesday or Wednesday	13	Monday or Tuesday
MATRIX	Tuesday	13	Monday
Etoposide 2.4 g/m^2	Tuesday or Wednesday	14	Tuesday or Wednesday
IVAC	Tuesday or Wednesday	14	Tuesday or Wednesday
TIP	Friday	11	Tuesday
VIDE	Tuesday	13–14	Monday or Tuesday

Anderlini P, et al. Br J Haematol 2000;109:770-2
Douglas KW, at al. J Clin Apher 2018;33:46-59

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“Poor mobilizers”

Risk Factors Associated with Poor Mobilization

Baseline	At Time of Mobilization
Treatment-related • Numerous cycles of previous chemotherapy • Previous exposure to melphalan, fludarabine, platinum-containing regimens, alkylating agents, or lenalidomide • Previous radiation therapy to the bone marrow	Low steady-state PB $CD34^+$ cell count Steady-state thrombocytopenia Low preapheresis PB $CD34^+$ cell count Low day 1 apheresis yield
Patient-related • Advanced age • Diagnosis of NHL • Diabetes	
Bone marrow–related • Bone marrow involvement • Thrombocytopenia	

Daratumumab
(CASSIOPEIA: VTD *vs* D-VTD: 8% *vs* 22% plerixafor need)

Pros	Cons
Chemotherapy + G-CSF	
Sufficient collection in 1 session in most patients (depending on collection targets)	Need for hospitalization (depending on the regimen used) Potential need for transfusions Potential impact on the quality of life
More $CD34^+$ cells	Less lymphocytes Do not improve the control of MM or outcome
G-CSF alone	
Easy outpatient procedure Cheaper (depending on the need of PLER)	May need more aphereses More need for PLER use
PLER	
Improves $CD34^+$ cell yield Improves lymphocyte yield	Expensive[a]

[a]Unless generic preparation is available.

Giralt S, et al, Biol Blood Marrow Transplant 2014;20:295-308
Moreau P, et al. Lancet 2019;394:29-38
Yoshihara S, et al. Hematology 2021;26:388-92
Chen J, et al. Blood Rev 2021;47:100771
Wei X, Wei Y. Ann Hematol 2023;102:995-1009
Jantunen E, et al. Transfus Med Hemother 2023;50:438-47

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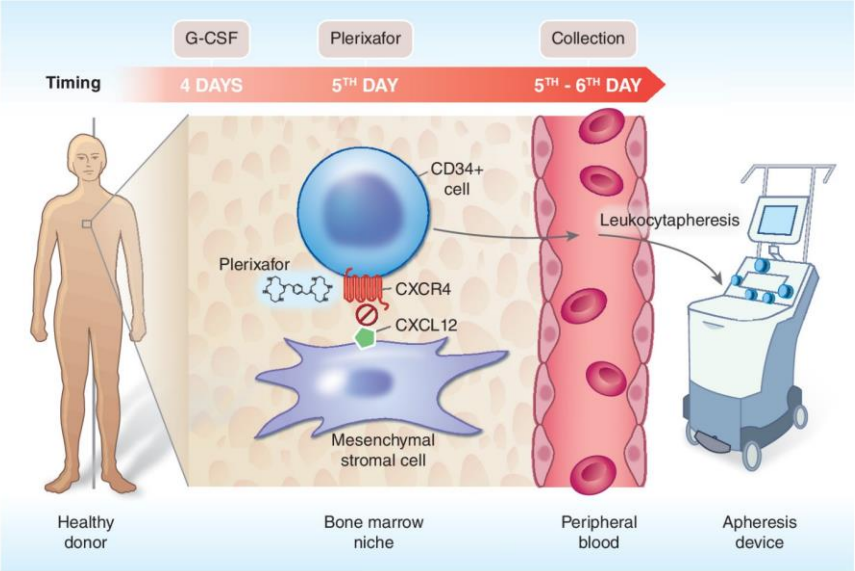

Romon I, et al. Vox Sang 2022;117:6-16

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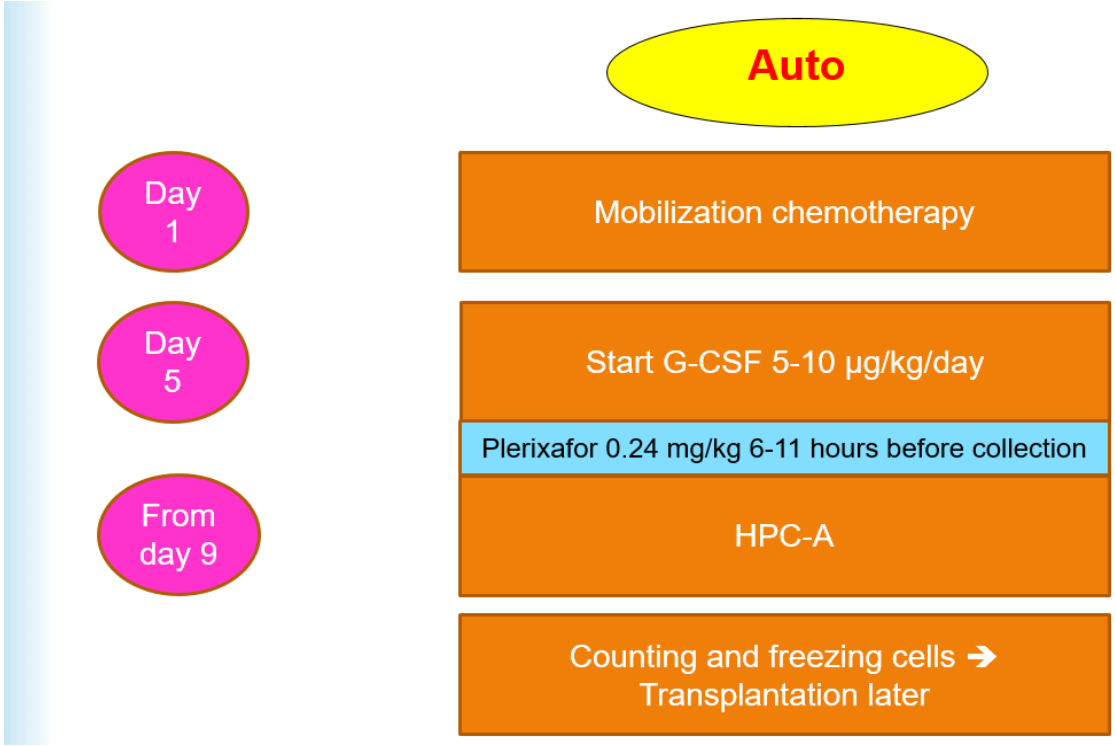
“Poor mobilizers”: chemotherapy + G-CSF



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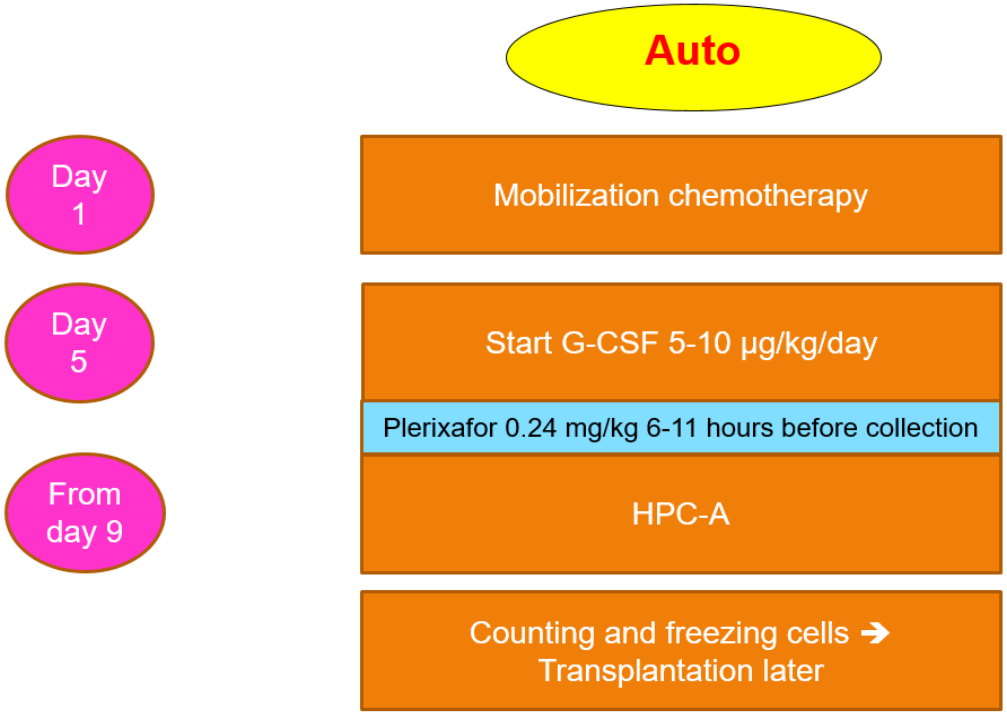

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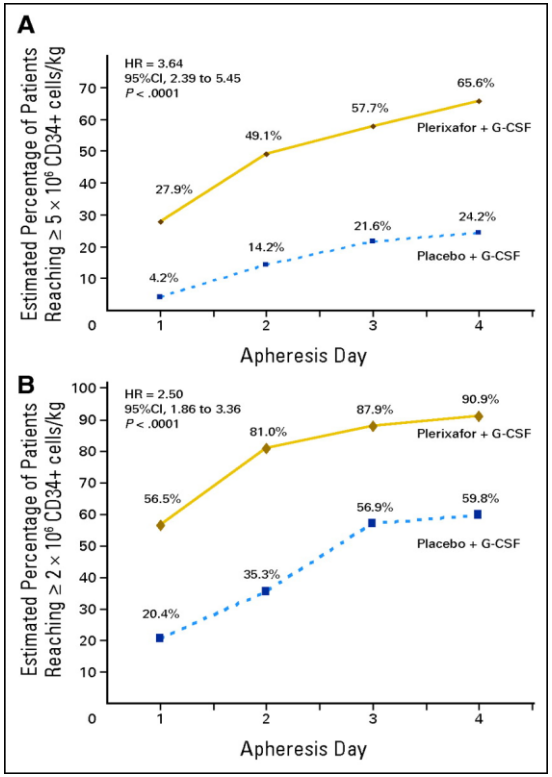

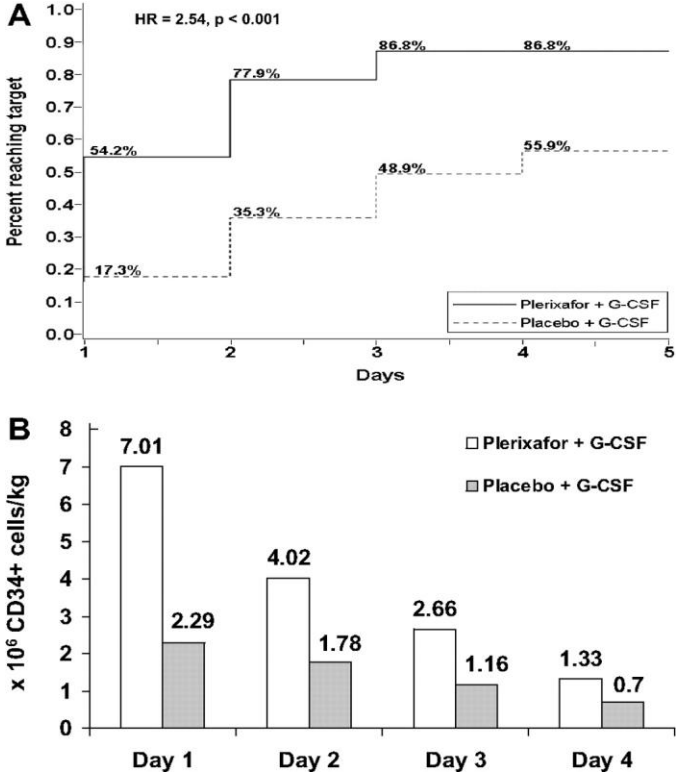

DiPersio J F et al. J Clin Oncol 2009;27:4767-73
DiPersio J F et al. Blood 2009;113:5720-6

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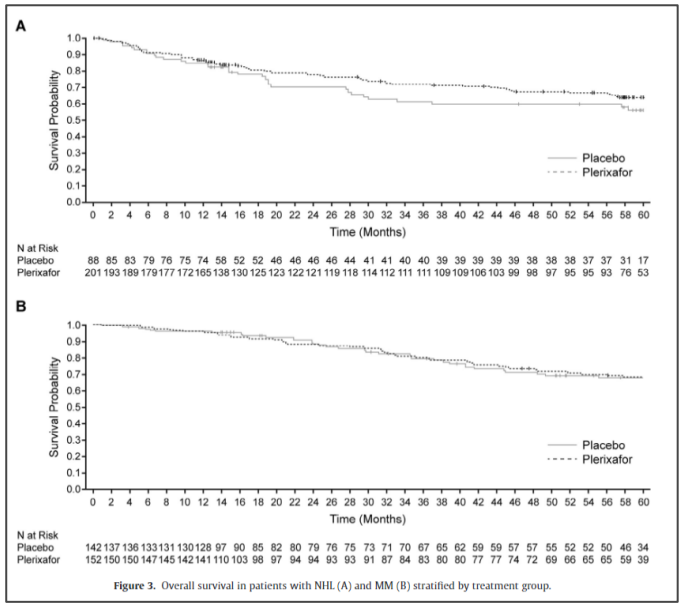

Figure 3. Overall survival in patients with NHL (A) and MM (B) stratified by treatment group.

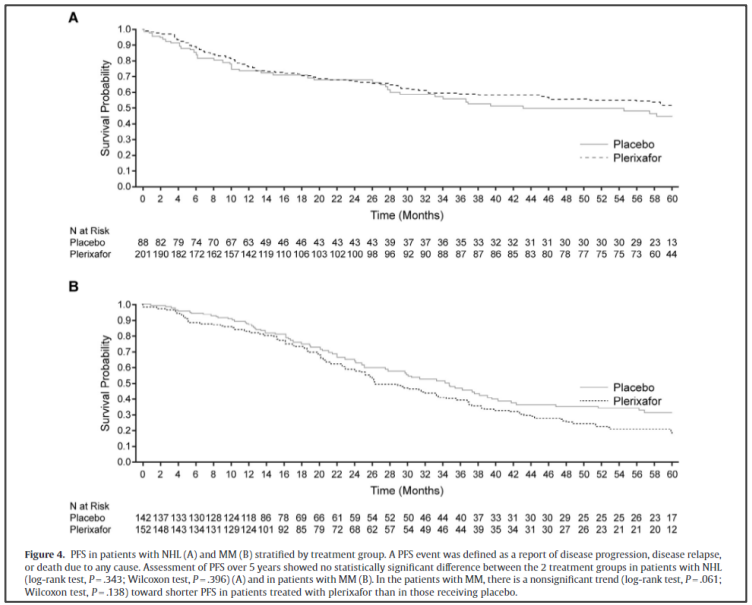

Figure 4. PFS in patients with NHL (A) and MM (B) stratified by treatment group. A PFS event was defined as a report of disease progression, disease relapse, or death due to any cause. Assessment of PFS over 5 years showed no statistically significant difference between the 2 treatment groups in patients with NHL (log-rank test, $P = .343$; Wilcoxon test, $P = .396$) (A) and in patients with MM (B). In the patients with MM, there is a nonsignificant trend (log-rank test, $P = .061$; Wilcoxon test, $P = .138$) toward shorter PFS in patients treated with plerixafor than in those receiving placebo.

Micallef IN, et al. Biol Blood Marrow Transplant 2018;24:1187-95

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“Poor mobilizers”

Table 2. Summary of mobilization strategies and outcomes

Author, year	*Strategy*			*>2 × 10⁶ CD34+ cells/kg, %*	*HSCT, %*
	Upfront, %	*Preemptive, %*	*Salvage, %*		
Arcaini, 2011[5]	0	P+S	P+S	37	17
Attolico, 2012[40]	0	32	68	73	65
Basak, 2011[23]	0	30	66	78	65
Basak, 2011[41]	0	84	16	66	56
Calandra, 2003[31]	0	P+S	P+S	66	76
D’Addio, 2011[26]	0	100	0	100	39
Douglas, 2011[24]	0	19	81	95	71
Duarte, 2011[12]	0	4	96	75	63
Hubel, 2011[28]	0	0	100	75	67
Hubel, 2012[29]	0	0	100	74	NA
Selleslag, 2011[30]	0	0	100	64	59
Shaughnessy, 2013[39]	98	0	0	92	87
Worel, 2011[32]	0	P+S	P+S	63	48

Abbreviations: HSCT = hematopoietic SCT; NA = not available; P+S = preemptive and salvage strategies used although proportions not stated.

Sheppard D, et al, Bone Marrow Transplant 2014;49:751-5

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Plerixafor

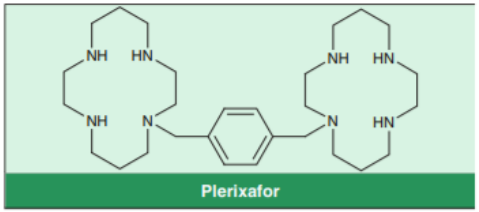
“Poor mobilizers”

- **Dose:** 0.24 mg/kg/day (renal insufficiency: 0.16 mg/kg/day)
  6-11 hours before collection (real life: one vial 20 mg)

- **Reimbursement:** only for MM and lymphoma!
  - < 10-15 CD34+ cells/µL blood after mobilization

    OR
  - < 2 x 10^6 CD34+ cells/kg following collection

- **Side effects:**
  - Local injection reaction
  - Headache
  - Gastrointestinal complaints



Wagstaff AJ. Drugs 2009;69:319-26
Keating GM, et al. Drugs 2011;71:1623-47

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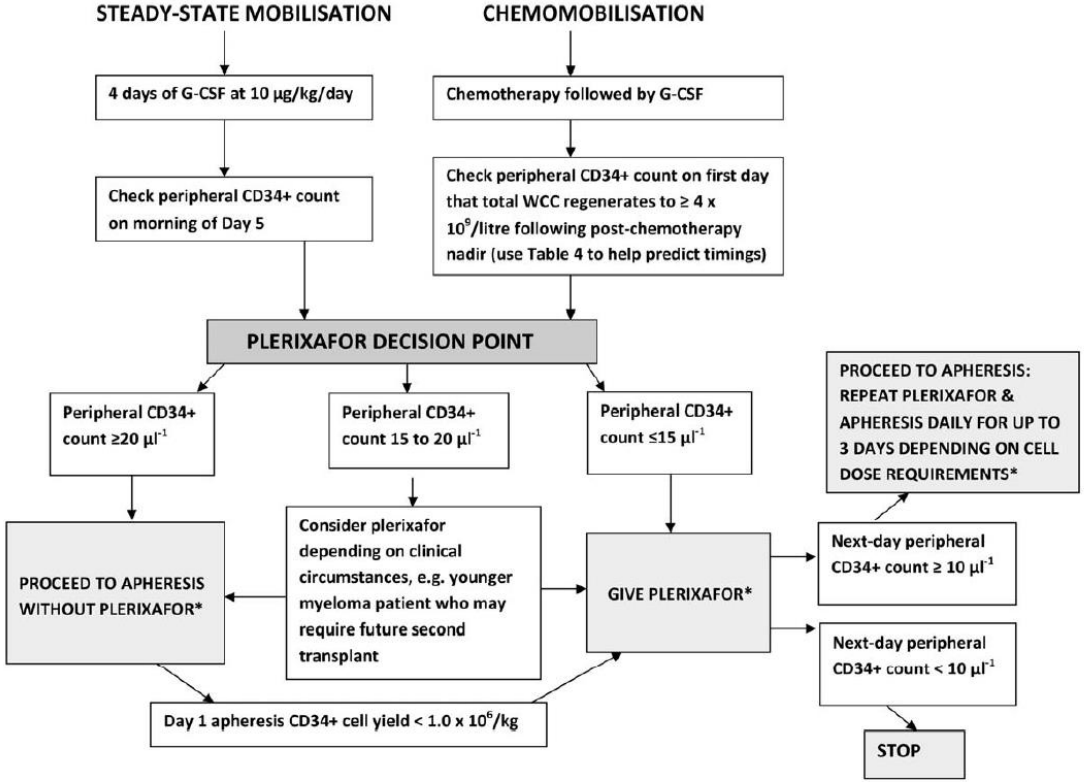

* G-CSF should also be continued daily.

Douglas KW, at al. J Clin Apher 2018;33:46-59

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“Poor mobilizers”

	Healthy related donors			Mobilization strategy		CD34+ cells in peripheral blood				CD34+ cells collected ($\times 10^6$/kg recipient)		
First author [ref]	n	Gender (M/F)	Age (years)	G-CSF (µg/kg/day)	Plerixafor (mg/kg)	After G-CSF (/µl)	After plerixafor (/µl)	Increase	Timing[a] (h)	Without plerixafor	With plerixafor	Total
Devine [22]	25	20 M/25 F	24–60	No	0.24	No	16 (4–54)	No	4	No	2.9 (1.2–6.3)	2.9 (1.2–6.3)
Hauge [23]	6	All F	44 (35–55)	10–16 (3–4 days)	0.24	19 (10–41)	96 (19–157)	3.2 (1.6–12.8)	10	1.4 (0.4–3.4)	7.0 (0.9–13.3)	10.2 (2.3–13.3)
Gattillo [24]	10	5 M/5 F	57 (37–73)	10 (4 days)	0.35 (0.24–0.47)	27 (11–34)	41 (17–147)	2.8 (1.1–4.3)	9–11	1.2 (1.1–3.9)	4.2 (1.3–8.5)	5.9 (1.8–9.5)
Schroeder [25]	50	NR[b]	NR[b] (18–70)	No	0.08–0.48 (SC and IV)	No	23 (4–157)	No	4	No	2.9 (2.0–9.7)	2.9 (2.0–9.7)
Teipel [26]	35	NR[b]	NR[b]	7.5–10 (4 days)	0.24	NR[b]	NR[b]	NR[b]	10	1.0 (0.5–1.9)[c]	2.2 (0.9–3.8)[c]	NR[b]
De Greef [27]	23	16 M/7F	47 (24–60)	No	0.32	No	26 (9–71)	No	10 (8–11)	No	3.3 (1.9–6.5)	3.9 (1.9–6.5)
Chen [28]	64	41 M/23F	56 (range: 18–65)	No	0.24	No	19 (range: 1.7–52)	No	4	No	2.8 (0.3–9.6)	4.7 (0.9–9.6)
Zubicaray [29]	9	NR[b]	3 (range: 1–17)	10 (4 days)	0.24	NR[b]	208	Yes	6–11	NR[b]	11.42 (5–17.85)	NR[b]
Hölig [30]	37	17 M/20F	34 (IQR: 26–48)	15 (4 days)	0.24	15 (IQR: 12–18)	44 (IQR: 38–61)	Yes	12	1.31 (IQR: 0.8–1.65)	2.8 (IQR: 2.26–4.69)	5.16 (IQR: 3.06–6.10)
Kharya[d] [31]	25	10 M/15F	35 (9–51)	10 (5 days)	0.24	NR[b]	NR[b]	NR[b]	10–12	NR[b]	NR[b]	10
Cid [32]	30	9 M/21F	51 (IQR: 34–59)	10–16 (IQR: 4–6 days)	0.24	17 (IQR: 11–27)	56 (IQR: 39–81)	3.3 (IQR: 2.8–4.8)	11 (IQR: 10–12)	1.6 (IQR: 0.9–2.5)	5.0 (IQR: 3.5–5.8)	6.1 (IQR: 4.8–7.3)

No significant differences:

- Time to engraftment
- aGvHD/cGvHD
- Overall survival

Romon I, et al. Vox Sang 2022;117:6-16

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Motixafortide

"Poor mobilizers"

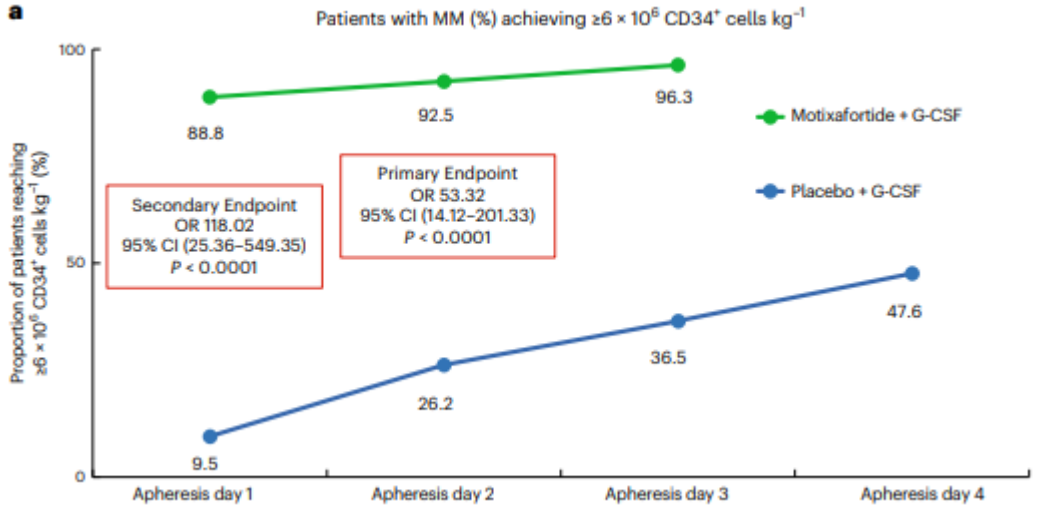

Table 2 | GENESIS trial safety and toxicity

TEAEs (frequency >10%)	Motixafortide + G-CSF		Placebo + G-CSF	
	Any grade	Grade 3	Any grade	Grade 3
Total, % (*n*)	**93.8 (75 of 80)**	**27.5 (22 of 80)**	**83.3 (35 of 42)**	**4.8 (2 of 42)**
Local injection site reactions, % (*n*)				
Pain	50 (40 of 80)	6.3 (5 of 80)	4.8 (2 of 42)	0
Erythema	27.5 (22 of 80)	0	0	0
Pruritis	21.3 (17 of 80)	0	0	0
Systemic injection reactions, % (*n*)				
Flushing	32.5 (26 of 80)	7.5 (6 of 80)	0	0
Pruritis	33.8 (27 of 80)	11.3 (9 of 80)	0	0
Urticaria	12.5 (10 of 80)	1.3 (1 of 80)	0	0
Erythema	12.5 (10 of 80)	0	0	0
Other, % (*n*)				
Bone pain	17.5 (14 of 80)	0	31.0 (13 of 42)	0
Back pain	17.5 (14 of 80)	0	14.3 (6 of 42)	0
Nausea	13.8 (11 of 80)	0	11.9 (5 of 42)	0
Hypokalemia	13.8 (11 of 80)	0	11.9 (5 of 42)	0
Catheter site pain	11.3 (9 of 80)	0	14.3 (6 of 42)	0

September 2023: motixafortide FDA approved for use in combination with filgrastim to mobilize HSCs to the peripheral blood for collection and subsequent autologous transplantation in patients with multiple myeloma

Crees ZD, et al. Nat Med 2023;29:869-79
Hoy SM, et al. Drugs 2023;83:1635-43

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Side effects

Short term risks

Mobilization-related	Procedure-related
Chemotherapy-related **G-CSF-related** *Headache* *Skeletal pain* *Nausea* *Splenomegaly* *Fever* *Injection site reaction* **Plerixafor-related** *Headache* *Nausea & diarrhea* *Arthralgia* *Injection site reaction*	**Vasovagal reaction** **Catheter-related** *Infection* *Bleeding* *Thrombosis* **Citrate-induced hypocalciemia**

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Side effects

Long term risks in healthy donors

Table 4. Publications reporting haematological malignancies in normal donors

Reference	*Study design*	*Type and number of onors*	*Years of donation*	*Median follow -up*	*% Survey compliance*	*Haematologic cancer*	*Comparison between stem cell source and to general population*
Pulsipher *et al.*[35]	Prospective registration study	Unrelated, PBSC 6768 BM 2726	2004–2009	PBSC 36 m (range 1-89 m) 20570 donor years BM 36 m (1–86 m) 8642 donor years	Prospective	AML (1: PBSC) myeloma (1: PBSC) lymphoma (1: BM)	PBSC vs BM: NS
Kodera *et al.*[41]	Prospective national registration study BM donor survey	Related PBSC 3114 BM 5291	2000–2010; 1991–2003		67%	AML (1)	Similar to sibling BM donors
Schmidt *et al.*[37]	Donor centre survey	Unrelated PBSC 8730 BM 3556 Both 273		30777 23037 1414 (Observation years)	81.3%	HD (2: PBSC)* plasmacytoma (1: PBSC) AML (1: BM) NHL (1:BM) CLL (1: both)	PBSC vs BM: NS No difference compared with normal population
Halter *et al.*[17]	EBMT survey	Unrelated/ Related PBSC 23254 BM 27770	1993–2005	99 875 200 786 (Observation years)	65–78%	AML (2:BM, 1:PBSC) ALL (2: BM, 1:PBSC) NHL (4 BM, 3:PBSC) HD (1:PBSC) CLL (1:PBSC) plasmacytoma (1: PBSC) MPN (1:PBSC)	No difference compared with normal population
Holig *et al.*[18]	Single centre retrospective study	Unrelated PBSC 3928	1996-2008	Not given	Not given	AML (1) CLL (1) HD (2)*	AML/CLL NS HD significantly higher than normal population
Holig *et al.*[36]		Unrelated PBSC 8290	1996-2012 (Overlaps with above study population)		67% at 4 weeks, 38% at 5 years	AML (2) CLL (1) HD (3) CML (1) ALL (1) (overlaps with above study population)	AML and HD significantly different from the natural incidence in the German population; others NS
Pulsipher 2008	Prospective registration study	Unrelated PBSC 2408	1999–2004	49 months	Prospective	CLL (1 case)	
De la Rubia *et al.*[39]	National registry retrospective study	Unrelated PBSC 736	1998–2006	320 had been followed for 2 years or more	320 followed for 2 years or more	No cases	
Jeger *et al.*[42]	Single centre retrospective cohort study	Related BM 212 PBSC 119	1974–2001	13.8 years	92%	ALL (1:BM) CLL (1:BM)	No difference compared with normal population
Anderlini 2002	Single centre survey	Related PBSC 281	1994–1998	median time post donation 39 months	82%	No cases	
Cavallaro *et al.*[22]		Related PBSC 95	1993–1995	median time post donation 43.13 months	95%	No cases	
Wiersum-Osselton *et al.*[38]	Single centre survey	Related PBSC 268	1996–2006	Median follow-up 4.5 years	60%	HD (1)	No difference compared with normal population
Mueller *et al.*[40]	Prospective long-term follow-up study	Unrelated PBSC 198	2001–2006	367 donor years	30% at 5 years	No cases	

Shaw BE, et al. Bone Marrow Transplant 2015;50:334-40

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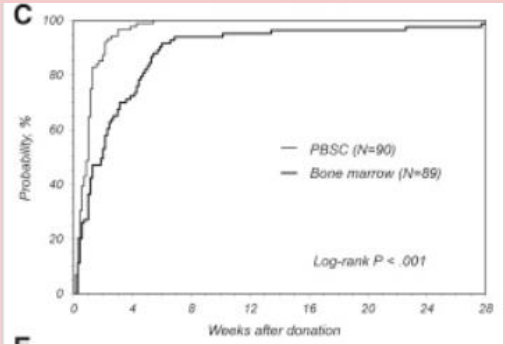
Side effects

Long term risks in healthy donors

Short term	Long term
	In view of this evidence the WMDA released a revised statement for inclusion in all WMDA donor consent forms in 2012. As related donors may receive G-CSF by varying doses and schedules and may have a different underlying cancer risk compared with unrelated donors, it is not certain that the impact of G-CSF is identical in the related donor setting. Thus, the WMDA statement if focused on unrelated donors: 'normal individuals are at risk for developing cancer, including leukemia, lymphoma or other blood diseases throughout their life time. G-CSF stimulates normal blood cell growth. In some patients with cancer or abnormal blood cells, it has been shown to stimulate leukemic blood cells. Studies following large numbers of unrelated donors have shown that the risk of developing cancer within several years after the use of G-CSF is not increased compared with donors not receiving G-CSF.'

Burns LJ, et al. Biol Blood Marrow Transplant 2016;22:1108-16
Shaw BE, et al. Bone Marrow Transplant 2015;50:334-40

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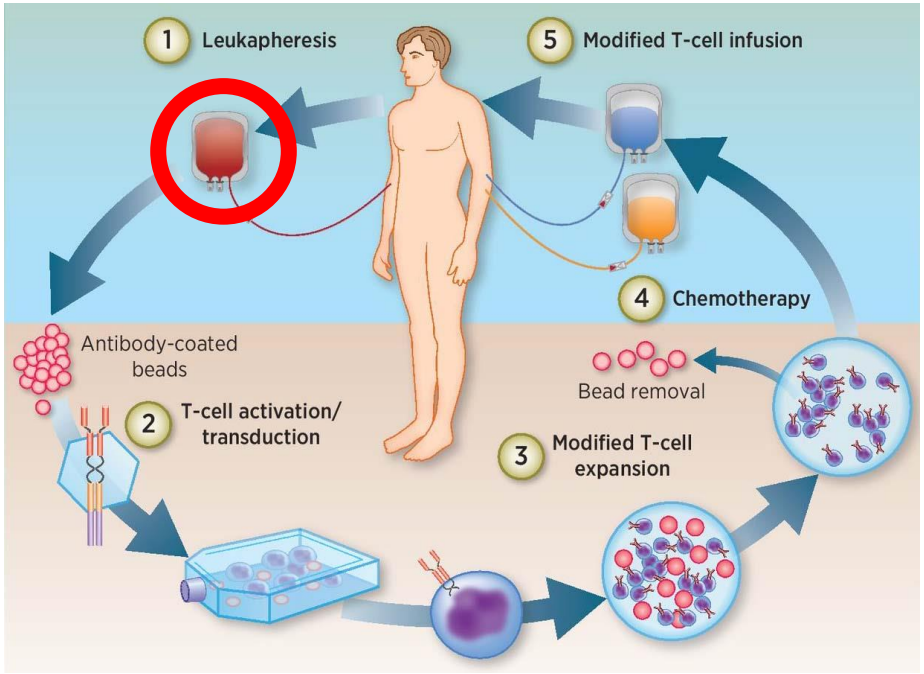
CAR-T cells



Levine BL. Cancer Gene Ther 2015;22:79-84

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CAR-T cells

Washout period	Agent
> 6 months	Alemtuzumab, ATG
> 12 weeks	Fludarabine, bendamustine
12 weeks	Allogeneic HSCT
8 weeks	Clofarabine
4 weeks	DLI, PegAsparaginase
2 weeks	Systemic chemotherapy, GVHD therapy, long acting growth factors, imatinib, dasatinib, ponatinib, blinatumomab
1 week	IT MTX, high dose steroids (dexa), lenalidomide
5 days	short acting growth factors, nilotinib
3 days	Short acting cytotoxic/antiproliferative medication (hydroxyurea, low dose steroids)

CAR-T cells

CAR-T yescarta: #MNC = #WBC * (lymfo+mono%) via LAG → in te geven in tool

Gewenste opbrengst: tussen 5-10 x10^9 MNC (min. 12l en max 15l bloed bewerke

CAR-T kymriah: CD3+/µl vóór (via Tx labo) → in te geven in de tool

Gewenste opbrengst: 2-4 x10^9 CD3+ // ≥ 2 x 10^9 TNC // CD3+: ≥ 3% van TNC

CAR-T Cartitude: #MNC = #WBC * (lymfo+mono%) via LAG → in te geven in tool

Gewenste opbrengst: ≥6x10^9 MNC

CAR-T Karmma 3: #WBC vóór en lymfo % via LAG → in te geven in tool om ALC te berekenen

ALC > 500/µL → 2 x TBV bewerken

ALC < 500/µL → 3 x TBV bewerken

CAR-T Zuma: #MNC = #WBC * (lymfo+mono%) via LAG → in te geven in tool

Gewenste opbrengst: 5-10x10^9 MNC

CAR-T Sbrink: #MNC = #WBC * (lymfo+mono%) via LAG → in te geven in tool

Gewenste opbrengst: ≥4 x10^9 MNC

CAR-T Sangamo Nefro: #MNC = #WBC * (lymfo+mono%) via LAG → in te geven in tool

Gewenste opbrengst: ≥12.75 x10^9 MNC

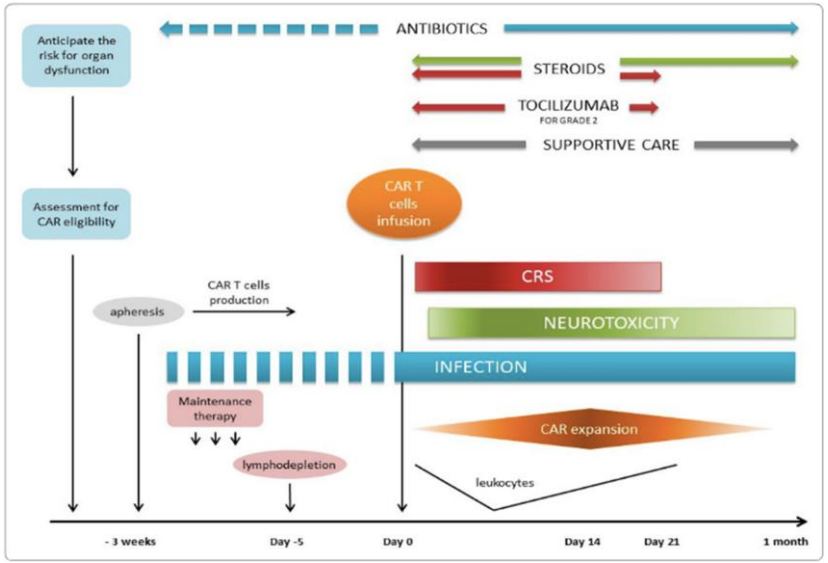
CAR-T Nefro TX200-KT02: #MNC = #WBC * (lymfo+mono%) via LAG → in te geven in tool

Gewenste opbrengst: ≥10-20 x10^9 MNC

CAR-T Belinda/Novartis: CD3+/µl vóór (via Tx labo) → in te geven in de tool

Gewenste opbrengst: 2-4 x10^9 CD3+ // ≥ 2 x 10^9 TNC // CD3+: ≥ 3% van TNC

CAR-T cells



CRS = cytokine release syndrome

ICANS = immune effector cell-associated neurotoxicity syndrome

COMPLICATION	FREQUENCY	TREATMENT OPTIONS
CRS	37% - 93%	Tocilizumab if no response to tocilizumab glucocorticoids
ICANS	23% - 67%	Glucocorticoids
Sepsis	8% - 16%	Empiric antibiotic therapy
B-cell aplasia/hypogammglobulinemia	56% - 88%	Intravenous immunoglobulins

June CH, et al. Science 2018;359:1361-5
Neelapu SS, et al. Nat Rev Clin Oncol 2018;15:47-62
Yanez L, et al. ESMO Open 2020;4(Suppl4):e000746
Shimabukuro-Vornhagen A, et al. CA Cancer J Clin 2022;72:78-93

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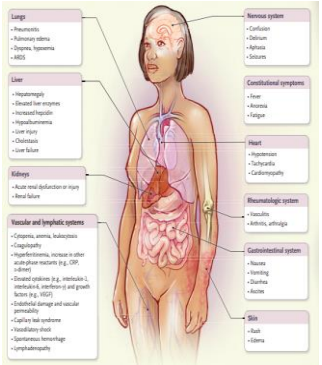
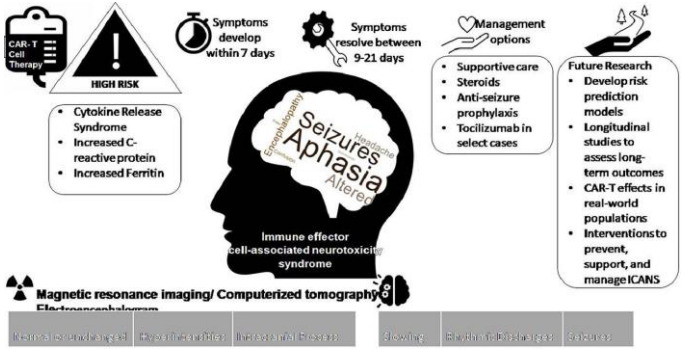
CAR-T cells





CRS

Hypotension	Hypoxia	Fever	Grade	ICE score	Conciousness	Weakness	Seizures	Edema
No	No	Yes	1	7-9	depressed level of consciousness but awakens spontaneously	No motor weakness	No seizures	No raised ICP or cerebral edema
Hypotension not requiring vasopressors	Hypoxia requiring low-flow nasal cannula	Yes	2	3-6	depressed level of consciousness but awakens to voice	No motor weakness	No seizures	No raised ICP or cerebral edema
Hypotension requiring one vasopressor with or without vasopressin	Hypoxia requiring HFNC, faceмask, non- rebre-ather/venturi mask	Yes	3	0-2	depressed level of con-sciousness but awakens to tactile stimulus	No motor weakness	Any focal/generalized/ nonconvulsive seizures that rapidly resolve	Focal/local edema on neuroimaging
Hypotension requiring multiple vasopressors (excluding vasopressin)	Hypoxia requiring positive pressure (CPAP, BiPAP, MV)	Yes	4	0 and unarousable	requires vigorous or repetitive tactile stimuli to arouse or stupor or coma	Deep focal motor weakness (hemiparesis, paraparesis)	Repetitive or life-threa-tening prolonged seizure (>5 min)	Clinical signs or imaging findings consistent with diffuse cerebral edema

ICANS

Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625-38
Fajgenbaum DC, June HC. N Engl J Med 2020;283:2255-73
Grant SJ, et al. Transplant Cell Ther 2022;28:294-302
Shimabukuro-Vornhagen A, et al. CA Cancer J Clin 2022;72:78-93

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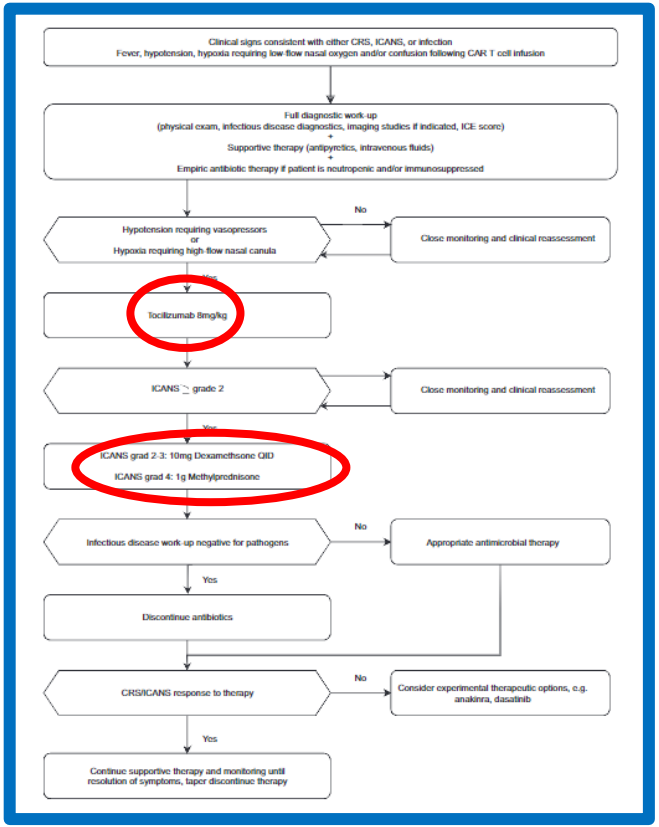

Shimabukuro-Vornhagen A, et al. CA Cancer J Clin 2022;72:78-93

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