Associazione Italiana
Ematologia Oncologia Pediatrica
(AIEOP)

Il trapianto di cellule staminali emopoietiche in pediatria: stato dell'arte

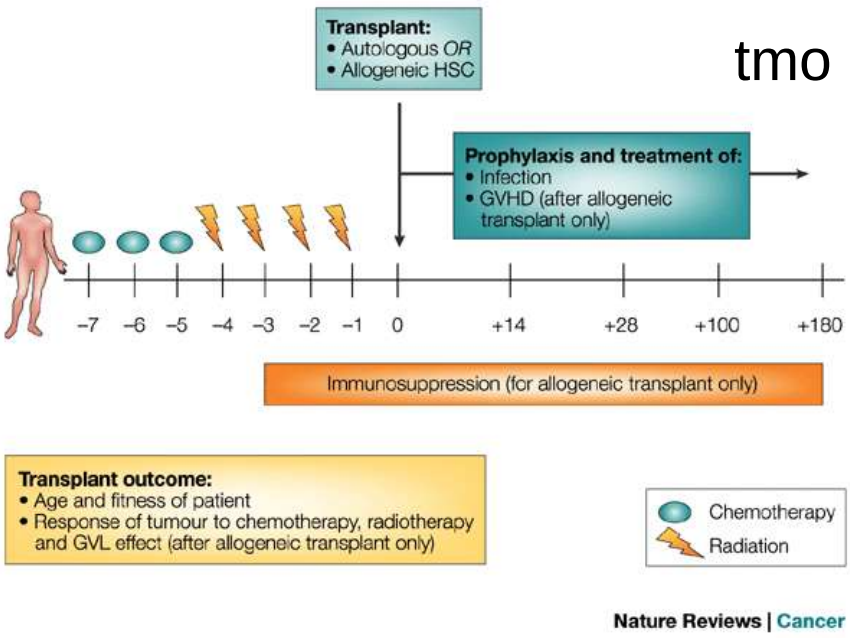
D. Caselli

"Percorsi pediatrici del Val di Noto 2016"
Vittoria, 19.03.2016

Cos'è il "trapianto di midollo osseo"?

E’ una infusione
staminali emopoi
fatto:
•da un individuo a
• nello stesso ind

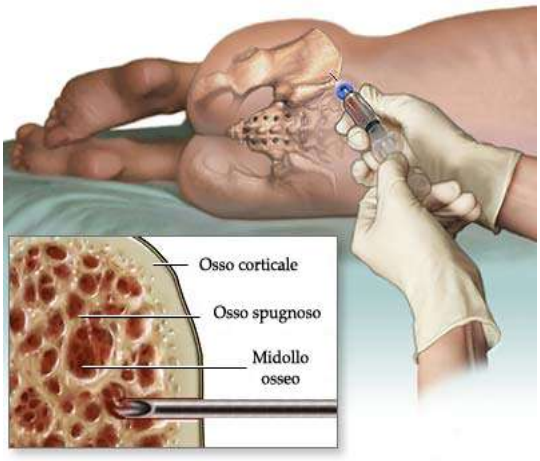
tmo



Homing…tornare a casa

Queste cellule riescono, infatti, a trovare da sole la strada
per colonizzare la sede ossea di loro competenza
e iniziare a produrre i normali elementi cellulari del sangue.

Il midollo osseo come fonte di CSE

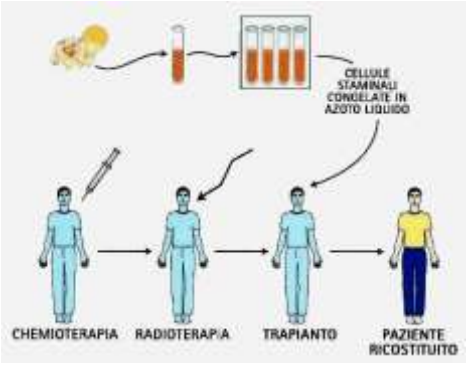


Il sangue periferico come fonte di CSE

si possono prelevare tramite aferesi da una vena periferica, dopo stimolazione specifica con G-CSF

Se non servono subito, midollo o CSE possono essere congelati

“Auto-trapianto”



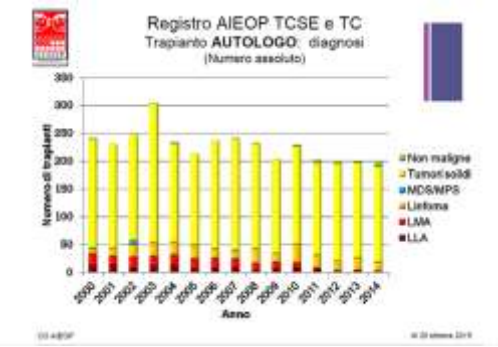
- **Non è un vero trapianto**
- **Solo un accorgimento per tollerare (meglio) la chemioterapia ad alte dosi (c.d. “sopra-vitale”)**

Trapianto autologo in pediatria: ha senso solo se….

- Non servono cellule geneticamente diverse
- La malattia è prevalentemente extra-midollare

Trapianto autologo in pediatria

- Tumori solidi
- Malattie autoimmuni
- Morbo di Hodgkin recidivato
- LLA, recidiva SNC
- LMA HR o recidivata



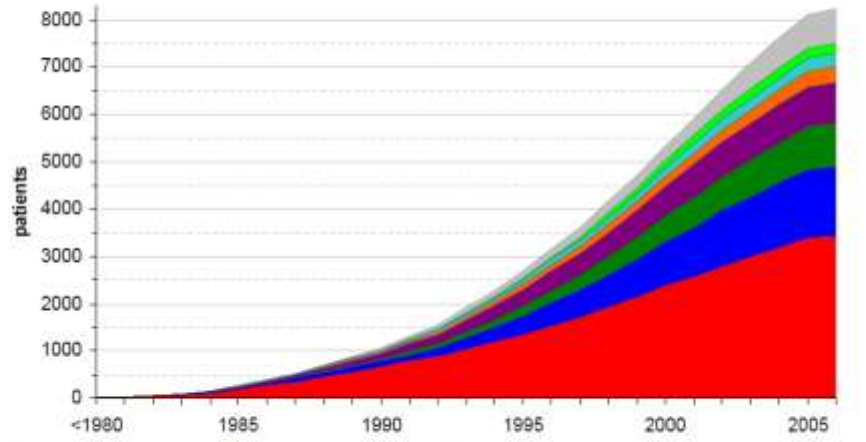
Trapianto autologo in pediatria
Tumori solidi

- **Neuroectodermici (neuroblastoma)**
- **Cerebrali**
- **Sarcomi dei tessuti molli (rabdomiosarcoma)**
- **Ossei (Ewing, osteosarcoma)**
- **Renali (T.di Wilms)**
- **Epatici (epatoblastoma)**
- **Istotipi rari a prognosi sfavorevole**

EBMT PWP-Solid Tumors

>8000 Patients with Autologous SCT

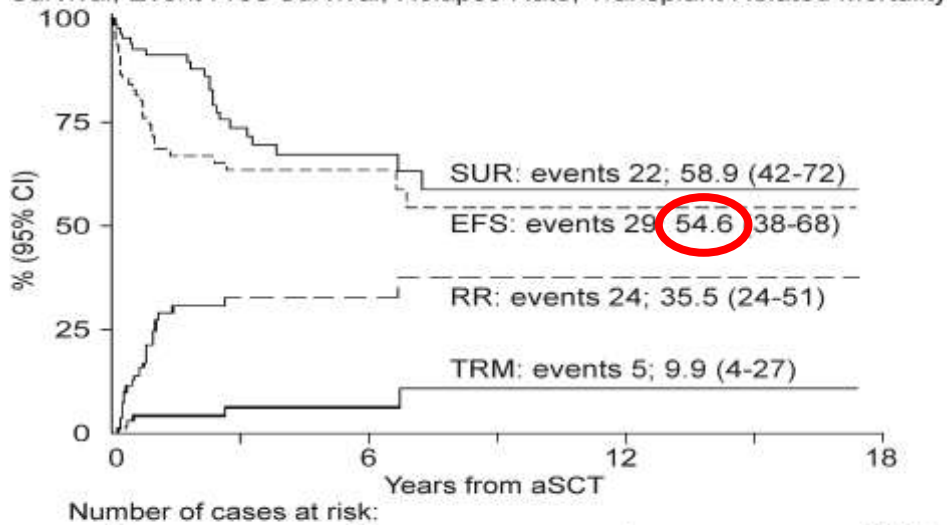
Selected Data



AIEOP BMT Registry

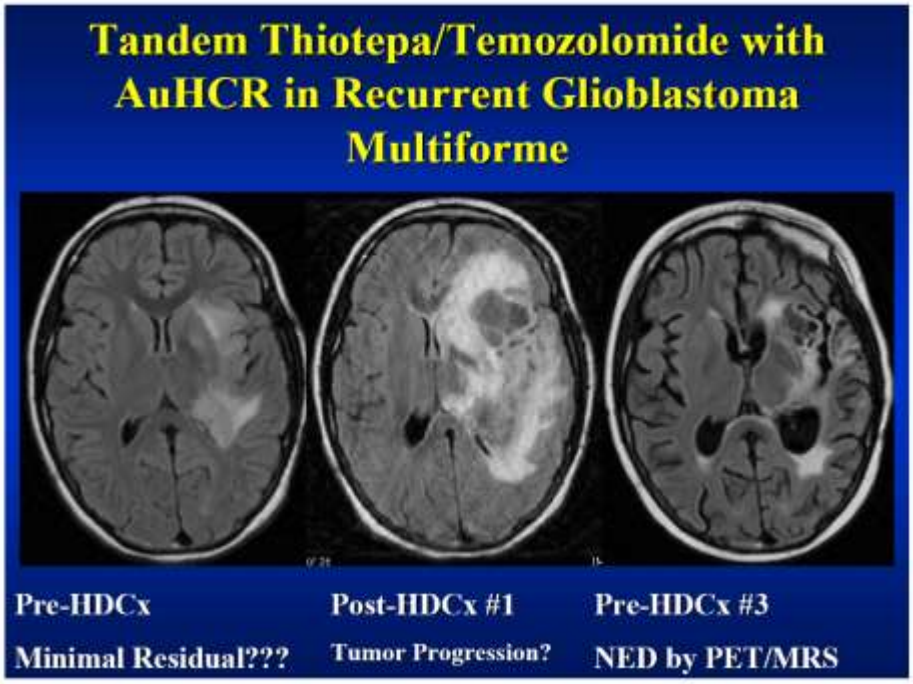
Hodgkin's Disease - aSCT

Survival, Event Free Survival, Relapse Rate, Transplant Related Mortality

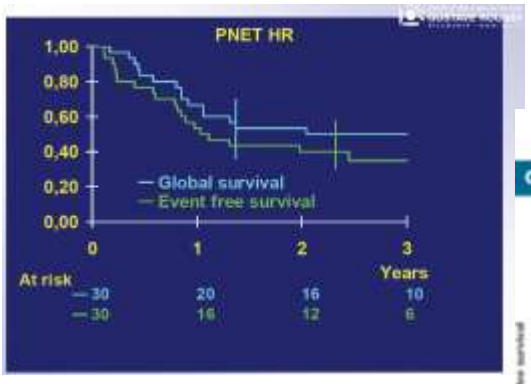


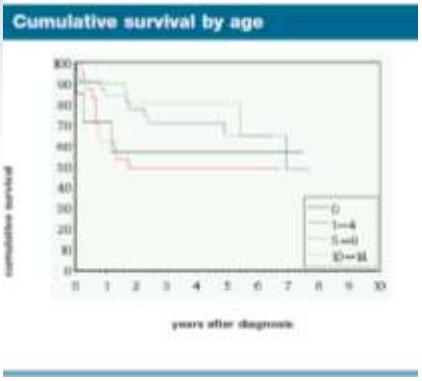
Number of cases at risk:

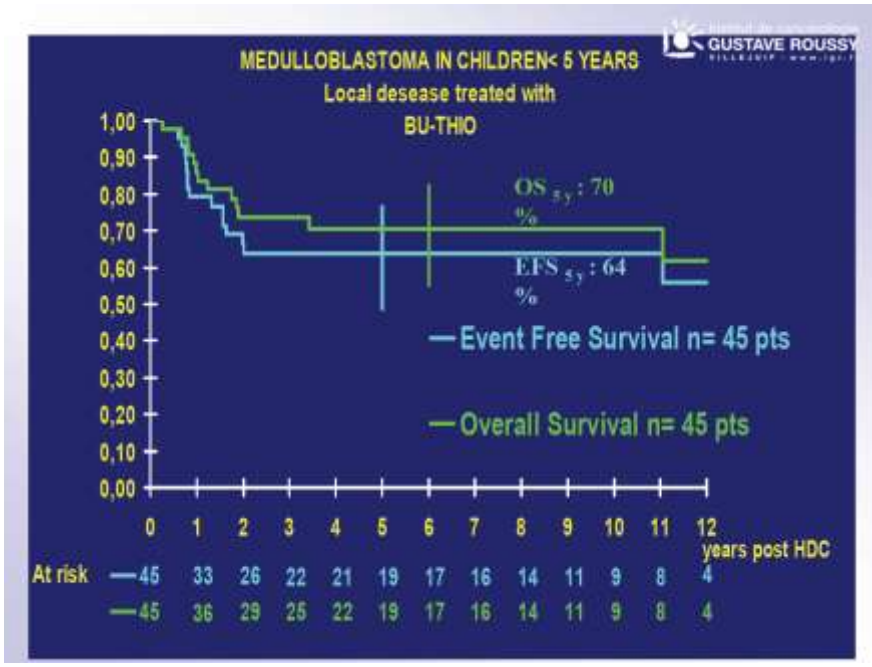
91	22	5	SUR
91	19	4	EFS
91	19	4	RR
91	19	4	TRM



Tumori neuroectodermici primitivi (PNET)







Retinoblastoma

ORIGINAL ARTICLE

Tandem high-dose chemotherapy and autologous stem cell rescue in children with bilateral advanced retinoblastoma

SH Lee[1], KH Yoo[2], KW Sung[2,4], JY Kim[3], EJ Cho[2], HH Koo[2], SE Chang[2], SW Kang[2], SY Oh[1], D-I Han[3,4] and Y-D Kim[3]

[1]Pediatric Oncology Clinic, National Cancer Center, Goyang, Korea; [2]Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea and [3]Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

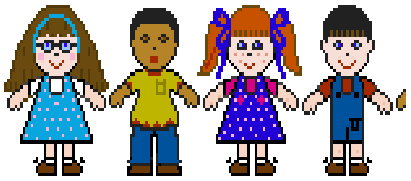
Pediatric Transplantation

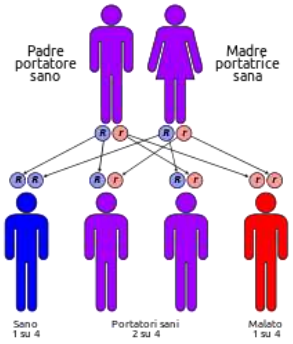
High-dose chemotherapy with autologous stem cell rescue for treatment of retinoblastoma: Report of five cases

Caselli D, Tamburini A, La Torre A, Pollazzi L, Tintori V, Bambi F, Caputo R, Aricò M. (2014) High-dose chemotherapy with autologous stem cell rescue for treatment of retinoblastoma: Report of five cases. *Pediatr Transplant*, 00: 1–6. DOI: 10.1111/petr.12321

Daniele Caselli[1], Angela Tamburini[2], Agostino La Torre[2], Liliana Pollazzi[2], Veronica Tintori[2], Franca Bambi[4], Roberto Caputo[5] and Maurizio Aricò[2,6]

Allogenico: chi può donare?





Un fratello HLA identico
(25%)

Allogenico: chi può donare?

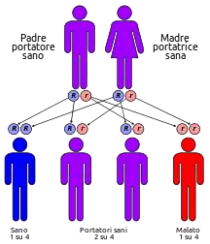
Un donatore “casualmente” identico
Matched unrelated donor, MUD
(1:50.000)

Il sangue placentare (“cordone”)

donato* da una mamma al parto
può entrare in una “banca”

NB: ricordiamoci che la donazione dedicata autologa è ingiustificabile!

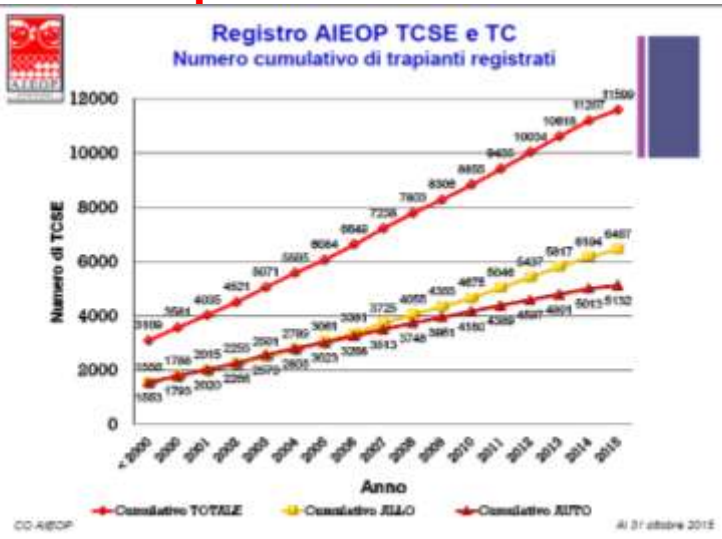
Donatore “parzialmente compatibile”



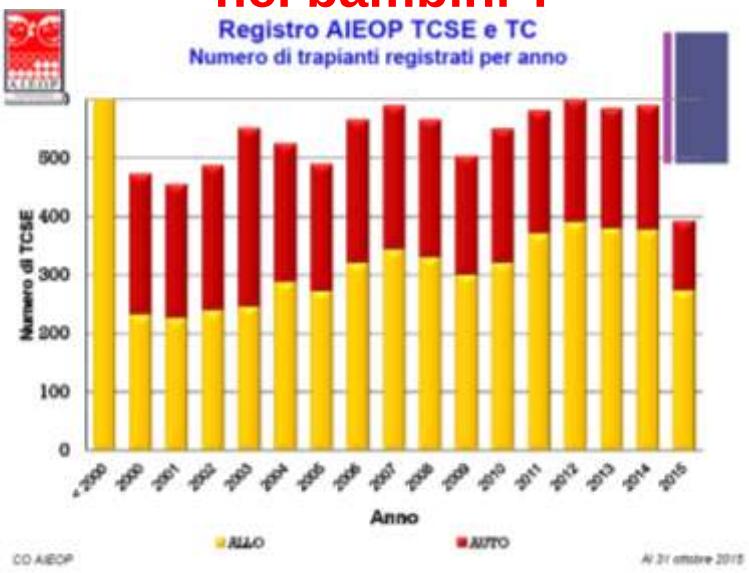
- Tutti abbiamo un donatore compatibile almeno al 50% (genitore, fratello, figlio)

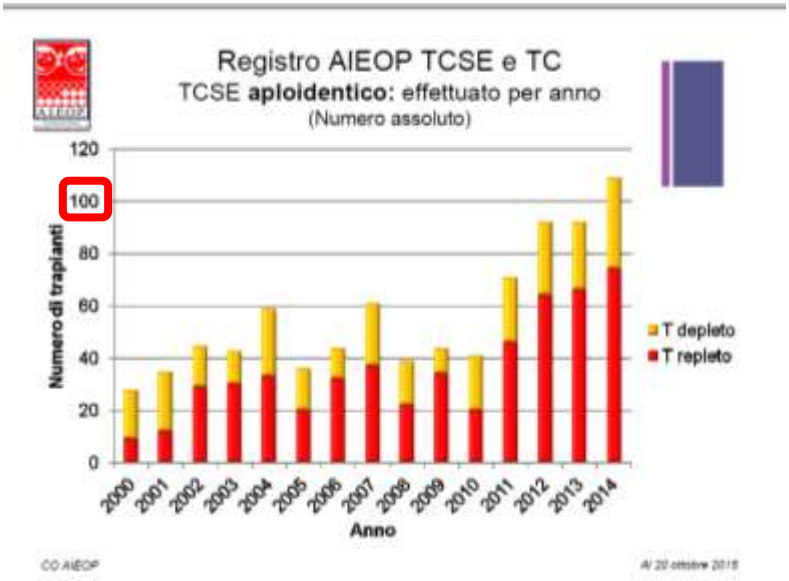
- I progressi nelle tecniche di induzione della tolleranza rendono fattibile il trapianto aploidentico

Che dimensione numerica ha il fenomeno trapianti nei bambini in Italia ?



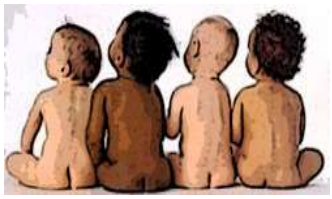
Quanti trapianti all'anno in Italia nei bambini ?





Per quali malattie si utilizza il trapianto di midollo da donatore allogenico ?

Quando bisogna **cambiare** la emopoiesi congenitamente difettosa



- Sindromi da immunodeficienza congenita
- Deficit enzimatici congeniti
- Difetti congeniti della emopoiesi

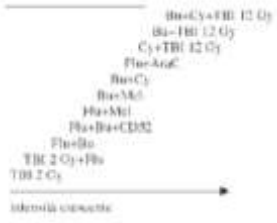
Per quali malattie si utilizza il trapianto di midollo da donatore allogenico ?

Quando bisogna sterminare le cellule malate

•Leucemie / malattie emo-proliferative refrattarie

Diversa la esigenza, diversa anche la chemioterapia di preparazione..

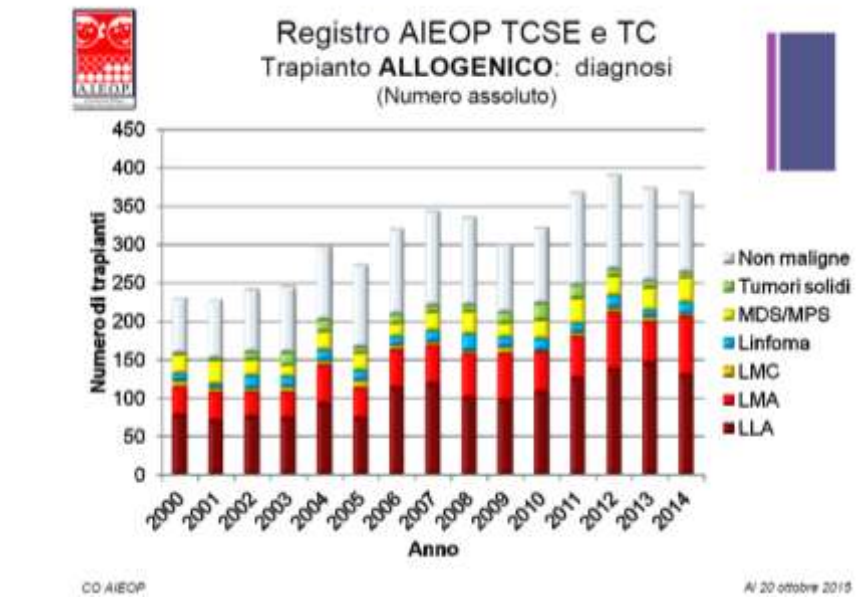
- Mielo-ablativa (MAC)
  - Se dobbiamo eliminare tutto il midollo del ricevente



- Non mielo-ablativa / intensità ridotta (RIC)
  - Se dobbiamo solo “fare spazio”

Diversa la esigenza, diversa anche la preparazione..

- In funzione della compatibilità tra donatore e ricevente, possiamo “tollerare” dosi diverse di linfociti del donatore, che “riconoscerebbero” il ricevente come “diverso (“non-self”)
  - deplezione delle cellule T
  - selezione CD34+



Principali indicazioni al trapianto allogenico in pediatria

Malattie onco-ematologiche · Leucemia LA ad altissimo rischio CR1 · Leucemia MA ad alto rischio in CR1 · Leucemia LA o MA in CR2 · Leucemia MC · Sindromi mielodisplastiche · Anemia aplastica grave · Linfoma (Hodgkin e non-Hodgkin) CR2 · Tumori solidi ad alto rischio ·*Disordini congeniti emopoiesi* · Anemia di Fanconi · Discheratosi congenita · Neutropenia congenita grave (S.Kostmann) · Piastrinopatie · Anemia di Blackfan-Diamond · Thalassemia major · Sickle cell disease	·*Immunodeficienze* · SCID · Deficit di linfocitotossicità T-NK · WAS · CGD, difetti dei neutrofili (S.Schwachmann) · *Errori congeniti del metabolismo* · Mucopolisaccaridosi · Osteopetrosi · Altre *Indicazione in evoluzione* ·Alcuni tipi di malattia autoimmune resistente alla terapia convenzionale

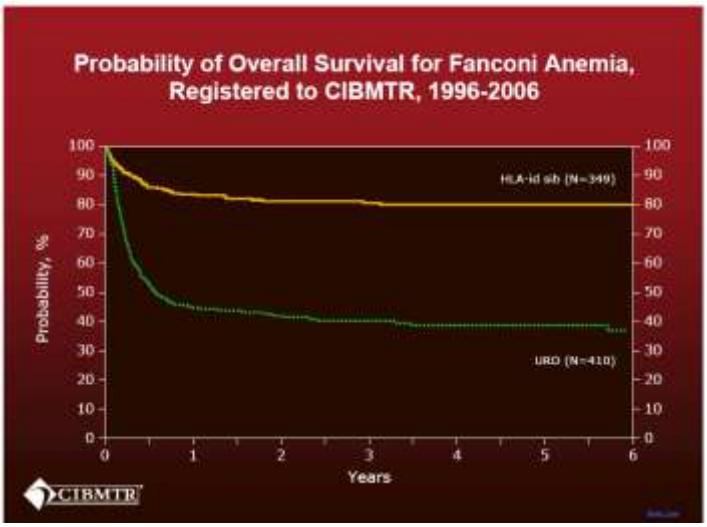
Anemia di Fanconi

- Disordine eterogeneo
- Insufficienza midollare progressiva
- Anomalie congenite ma…25% senza anomalie
- Predisposizione a tumori

Anemia di Fanconi

- Caratteristica instabilità cromosomica
- DEB test
- Alterazioni della riparazione del DNA

TCSE: unico trattamento curativo



Thalassemie

Table 1 Risk factors for BMT in hemoglobinopathies

Risk factors for BMT in thalassemia		
Chelation		Regular vs irregular
Hepatomegaly		Absent vs present
Liver fibrosis		Absent vs present
	Chelation	*Hepatomegaly* *Fibrosis*
Risk classes for BMT in thalassemia		
Class 1	Regular	No No
Class 2	Regular/irregular	No/Yes No/Yes
Class 3	Irregular	Yes Yes

Abbreviations: BMT = bone marrow transplantation.
Reprinted from: Lucarelli G, Andreani M, Angelucci E. The cure of thalassemia by bone marrow transplantation. *Blood Rev* 2002; 16: 81–85. Copyright (2002), with permission from Elsevier.

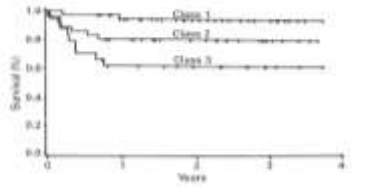


Figure 1 Probabilities of survival after transplantation in 99 patients with thalassemia. The patients in Class 1 (n = 40) had neither hepatomegaly nor portal fibrosis, those in Class 2 (n = 36) had only one of the risk factors, and those in Class 3 (n = 24) had both. Lucarelli G, et al. Bone marrow transplantation in patients with thalassemia. *N Eng J Med* 1990; 322: 417–421. © Copyright (1990) Massachusetts Medical Society. All rights reserved.

Table 2 Outcome of hematopoietic cell transplantation in β-thalassemia (pediatric to young adults)

Author	*N*	*Age median/range (yrs)*	*Stem cell source*	*TRM (%)*	*Survival (%)*	*aGVHD ≥ 2 (%)*	*cGVHD (%)*
Lucarelli *et al.*[7]	116	NA (1–35)	MSD/MRD	NA	TFS: 75	NA	NA
La Nasa *et al.*[8]	68	12 (2–37)	MUD	20	OS: 79.3	40	10
Lucarelli *et al.*[7]	13 Thalassemia 11 SCD	7 (1–20)[a]	Matched: 27 (64%)[a] Mismatched: 17 (39%)[a]	NA	2 years EFS: 70 OS: 100[a]	14[a]	6[a]
Hongeng *et al.*[9]	49	Related: 7.2 (0.5–16.7) Unrelated: 6 (0.7–12)	Related: 28 Unrelated: 21	10	OS (all patients): 89	Related: 32 Unrelated: 42	Related: 14 Unrelated: 14
Guerin *et al.*[6]	29	6 (1.1–13)	HLA-phenotypically identical relatives: 6 Mismatched relatives: 2 mMSD: 13 Mismatched parents: 8	34	OS: 65 EFS: 21	47.3	37.3

Abbreviations: aGVHD = acute graft-versus-host disease; cGVHD = chronic graft-versus-host disease; EFS = event-free survival; mMSD = mismatched sibling donor; MRD = matched related donor; MSD = matched sibling donor; MUD = matched unrelated donor; NA = not available; OS = overall survival; SCD = sickle cell disease; TFS = thalassemia-free survival; TRM = transplant-related mortality.
[a]Includes total cohort (thalassemia/SCD).

Table 3 Criteria for eligibility for transplantation in children with sickle cell disease

Criteria for inclusion
- Sickle cell disease (sickle cell anemia, sickle cell–hemoglobin C disease or sickle cell–β-thalassemia)
- Age less than 16 years
- HLA-identical related donor
- One or more of the following
  - Stroke or central nervous system event lasting longer than 24 h
  - Acute chest syndrome with recurrent hospitalizations or previous exchange transfusions
  - Recurrent vaso-occlusive pain (≥ 2 episodes per year for several years) or recurrent priapism
  - Impaired neuropsychological function and abnormal cerebral MRI scan
  - Stage I or II sickle lung disease
  - Sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30–50% of the predicted normal value)
  - Bilateral proliferative retinopathy and major visual impairment in at least one eye
  - Osteonecrosis of multiple joints
  - Red-cell allo-immunization (≥ 2 antibodies) during long-term transfusion therapy

Criteria for exclusion
- Age greater than 15 years
- Lack of availability of HLA-identical donor*
- One or more of the following
  - Karnofsky or Lansky functional performance score < 70*
  - Acute hepatitis or evidence of moderate or severe portal fibrosis or cirrhosis on biopsy
  - Severe renal impairment (glomerular filtration rate, < 30% of the predicted normal value)
  - Severe residual functional neurologic impairment (other than hemiplegia alone)
  - Stage III or IV sickle lung disease
  - Demonstrated lack of compliance with medical care
  - Seropositivity for the human immunodeficiency virus

Walters MC, Patience M, Leisenring W, *et al.* Bone marrow transplantation for sickle cell disease. *N Engl J Med* 1996; 335: 369–376. Copyright © 1996 *Massachusetts Medical Society. All rights reserved.*[37]
*Patients with HLA-matched related donors with the sickle-cell trait were not excluded.

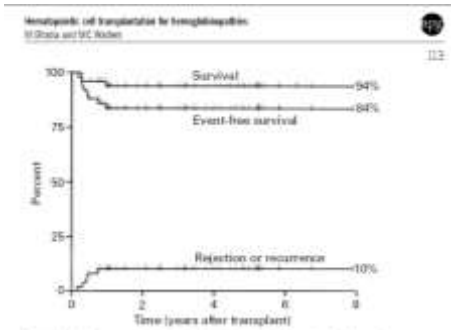


Figure 3 Outcome after transplantation for 91 children with advanced, symptomatic sickle cell disease. Kaplan–Meier estimates for survival and event-free survival following marrow transplantation are shown. An event is defined as death, graft rejection or recurrence of sickle cell disease. A cumulative incidence curve for graft rejection and return of sickle cell disease is also depicted. This research was originally published in *Blood*. Walters *et al.* Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. *Blood* 2000; 95: 1918–1924. © The American Society of Hematology.[37]

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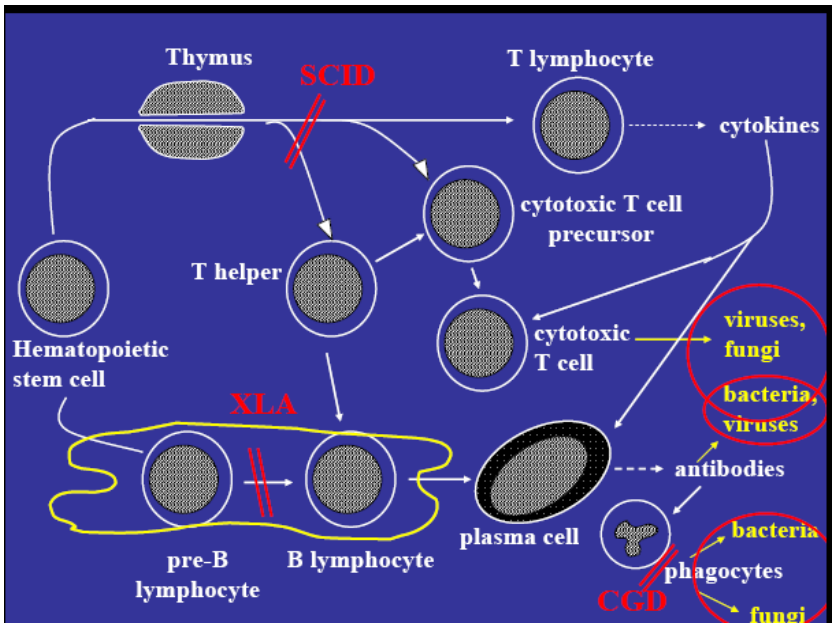

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Primary Immune Deficiency Treatment Consortium (PIDTC) Report

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Principali indicazioni al trapianto allogenico in pediatria

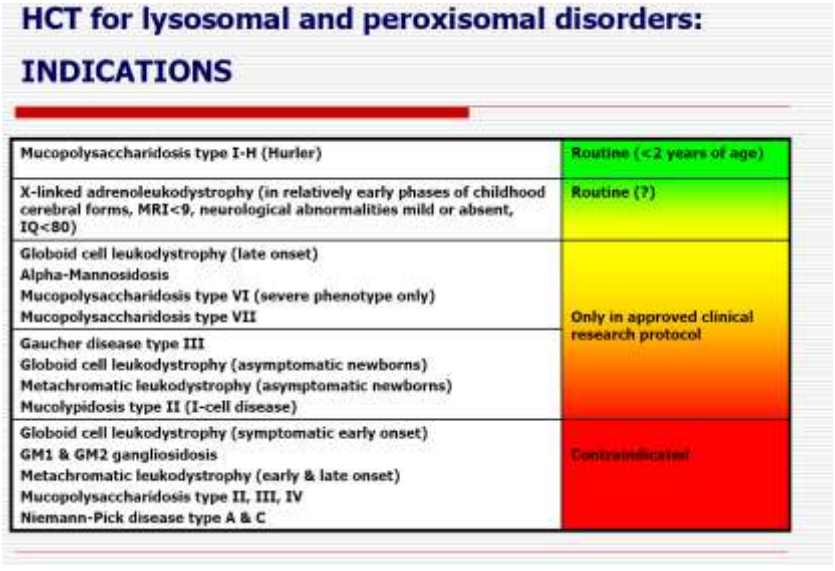
Malattie onco-ematologiche	·***Immunodeficienze***
· Leucemia LA ad altissimo rischio CR1	· SCID
· Leucemia MA ad alto rischio in CR1	· Deficit di linfocitotossicità T-NK
· Leucemia LA o MA in CR2	· WAS
· Leucemia MC	· CGD, difetti dei neutrofili (S.Schwachmann)
· Sindromi mielodisplastiche	
· Anemia aplastica grave	· ***Errori congeniti del metabolismo***
· Linfoma (Hodgkin e non-Hodgkin) CR2	· Mucopolisaccaridosi
· Tumori solidi ad alto rischio	· Osteopetrosi
·***Disordini congeniti emopoiesi***	· Altre
· Anemia di Fanconi	
· Discheratosi congenita	***Indicazione in evoluzione***
· Neutropenia congenita grave (S.Kostmann)	·Alcuni tipi di malattia autoimmune resistente alla terapia convenzionale
· Piastrinopatie	
· Anemia di Blackfan-Diamond	
· Thalassemia major	
· Sickle cell disease	

Lancet. 1981 Oct 3;2(8249):709-12.

Hobbs JR, Hugh-Jones K, Barrett AJ, Byrom N, Chambers D, Henry K, James DC, Lucas CF, Rogers TR, Benson PF, Tansley LR, Patrick AD, Mossman J, Young EP.

Reversal of clinical features of Hurler's disease and biochemical improvement after treatment by bone-marrow transplantation.

A one-year-old boy with type I H mucopolysaccharidosis (Hurler's disease) was given a bone-marrow transplant (BMT) from his mother in an attempt to replace the deficient enzyme, alpha-L-iduronidase (iduronidase). These is definite evidence of engraftment, the enzyme activity of the recipient's leucocytes reaching heterozygote levels within 37 days of the BMT. Graft-versus-host disease (GVHD) developed but was partially controlled by steroids. From 3-4 months after graft until the present (13 months after the graft) iduronidase activity has been present in the serum and the urine and there has been evidence of considerable degradation of glycosaminoglycans excreted in the urine. The hepatosplenomegaly has disappeared, corneal clouding has cleared, and deterioration in the child's development seems to have been arrested.



Il beneficio del TCSE varia in funzione degli organi interessati

Fegato e milza

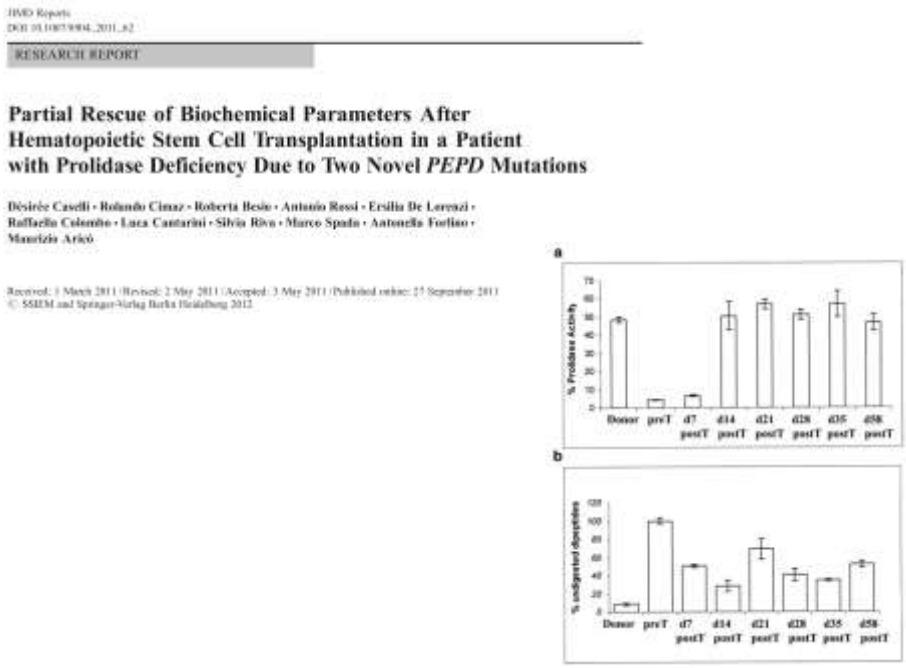
- Il sistema reticoloendoteliale si può ridurre rapidamente quando i macrofagi ingolfati assumono l'enzima

Sistema nervoso centrale

- Il miglioramento è lento come il turnover della microglia che viene rimpiazzata da cellule del donatore

Osso

- Purtroppo il TCSE ha impatto scarso sulle ossa
  - Scarsa penetrazione nei condrociti ?
  - Scarsa capacità di correggere o rimpiazzare gli osteociti?



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RESEARCH REPORT

Partial Rescue of Biochemical Parameters After Hematopoietic Stem Cell Transplantation in a Patient with Prolidase Deficiency Due to Two Novel *PEPD* Mutations

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Principali indicazioni al trapianto allogenico in pediatria

Malattie onco-ematologiche	·*Immunodeficienze*
· Leucemia LA ad altissimo rischio CR1	· SCID
· Leucemia MA ad alto rischio in CR1	· Deficit di linfocitotossicità T-NK
· Leucemia LA o MA in CR2	· WAS
· Leucemia MC	· CGD, difetti dei neutrofili (S.Schwachmann)
· Sindromi mielodisplastiche	
· Anemia aplastica grave	
· Linfoma (Hodgkin e non-Hodgkin) CR2	· *Errori congeniti del metabolismo*
· Tumori solidi ad alto rischio	· Mucopolisaccaridosi
·*Disordini congeniti emopoiesi*	· Osteopetrosi
· Anemia di Fanconi	· Altre
· Discheratosi congenita	
· Neutropenia congenita grave (S.Kostmann)	*Indicazione in evoluzione*
· Piastrinopatie	·Alcuni tipi di malattia autoimmune resistente alla terapia convenzionale
· Anemia di Blackfan-Diamond	
· Thalassemia major	
· Sickle cell disease	

Neurology. 2015 Mar 10;84(10):981-8. doi: 10.1212/WNL.0000000000001329. Epub 2015 Feb 11.

Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial.

Mancardi GL[1], Sormani MP[2], Gualandi F[3], Saiz A[4], Carreras E[5], Merelli E[6], Donelli A[7], Lugaresi A[8], Di Bartolomeo P[9], Bobbio MR[10], Rambaldi A[11], Amato MP[12], Massacesi L[13], Di Gioia M[14], Vuolo L[15], Currò D[16], Roccatagliata L[17], Filippi M[18], Aguglia U[19], Iacobini P[20], Farge D[21], Saccardi R[22]; ASTIMS Haemato-Neurological Collaborative Group. On behalf of the **Autoimmune** Disease Working Party (ADWP) of the European Group for Blood and **Marrow Transplantation** (EBMT); ASTIMS Haemato-Neurological Collaborative Group On behalf of the **Autoimmune** Disease Working Party ADWP of the European Group for Blood and **Marrow Transplantation** EBMT.

Collaborators (15)

Author information

Abstract

OBJECTIVE: To assess in multiple sclerosis (MS) the effect of intense immunosuppression followed by autologous hematopoietic stem cells **transplantation** (AHSCT) vs mitoxantrone (MTX) on disease activity measured by MRI.

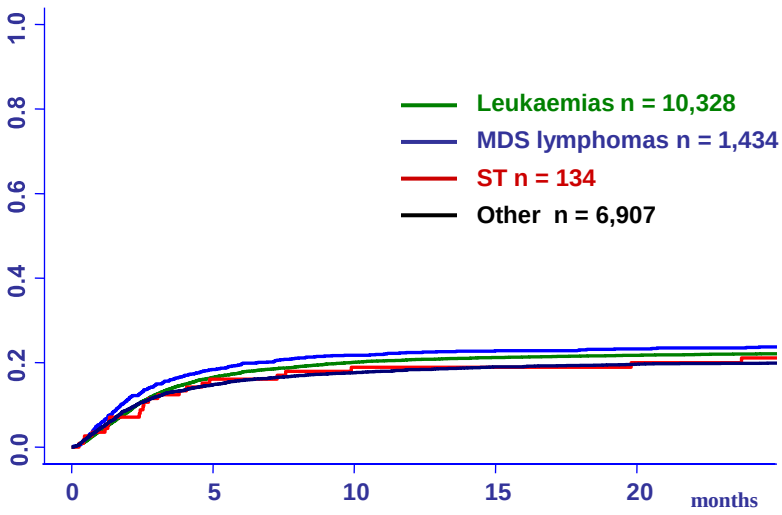
METHODS: We conducted a multicenter, phase II, randomized trial including patients with secondary progressive or relapsing-remitting MS, with a documented increase in the last year on the Expanded Disability Status Scale, in spite of conventional therapy, and presence of one or more gadolinium-enhancing (Gd+) areas. Patients were randomized to receive intense immunosuppression (mobilization with cyclophosphamide and filgrastim, conditioning with carmustine, cytosine-arabinoside, etoposide, melphalan, and anti-thymocyte globulin) followed by AHSCT or MTX 20 mg every month for 6 months. The primary endpoint was the cumulative number of new T2 lesions in the 4 years following randomization. Secondary endpoints were the cumulative number of Gd+ lesions, relapse rate, and disability progression. Safety and tolerability were also assessed. Twenty-one patients were randomized and 17 had postbaseline evaluable MRI scans.

RESULTS: AHSCT reduced by 79% the number of new T2 lesions as compared to MTX (rate ratio 0.21, p = 0.00016). It also reduced Gd+ lesions as well as the annualized relapse rate. No difference was found in the progression of disability.

CONCLUSION: Intense immunosuppression followed by AHSCT is significantly superior to MTX in reducing MRI activity in severe cases of MS. These results strongly support further phase III studies with primary clinical endpoints. The study was registered as EUDRACT No. 2007-000064-24.

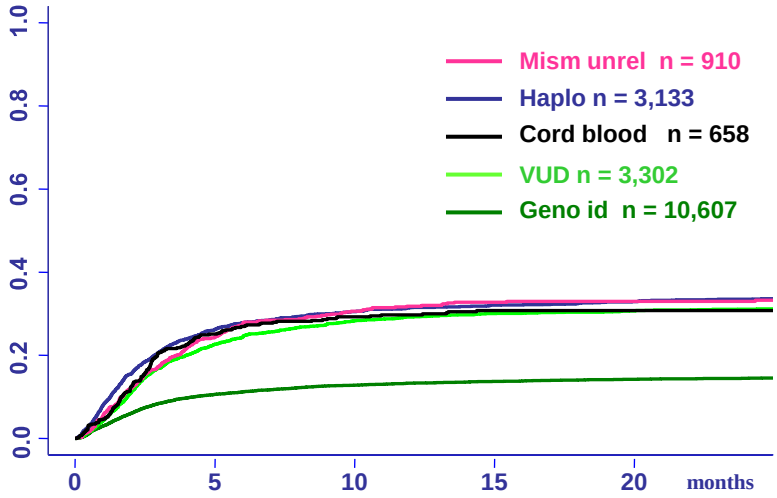
Perché non trapiantare sempre tutti alla minima indicazione?

SCT Allogenico
La TRM è simile nelle diverse malattie



EBMT - G.Dini 2008

SCT Allogenico
La TRM è oggi simile per donatori diversi da MSD

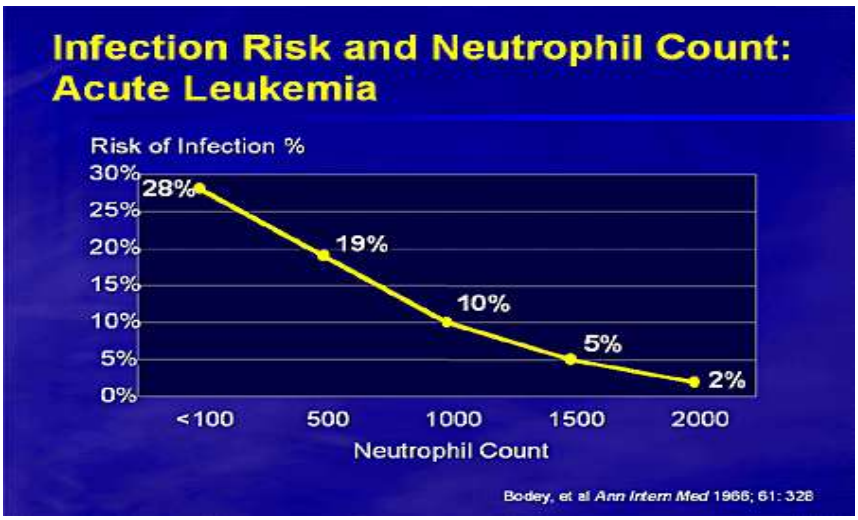


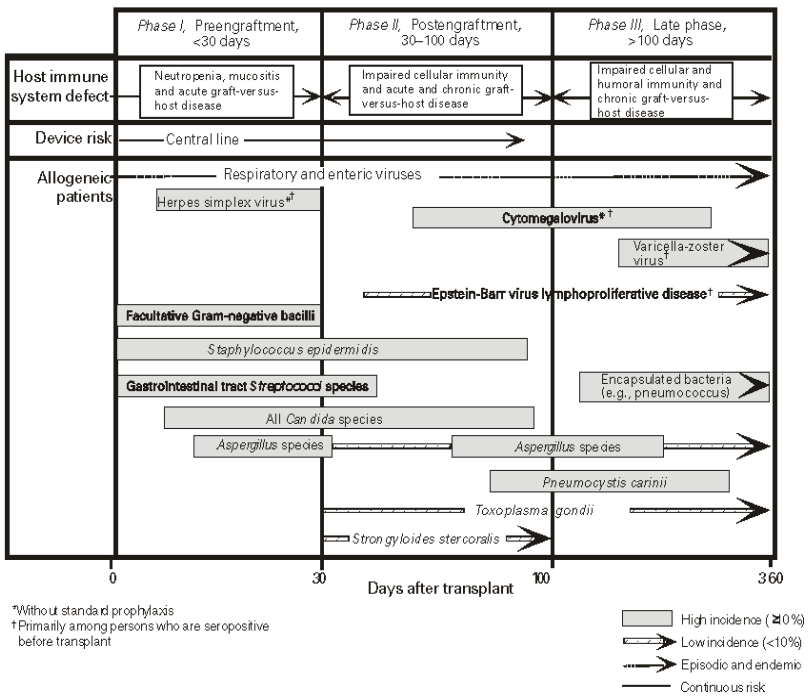
EBMT - G.Dini 2008

Prima causa di morte nel trapiantato:

INFEZIONE

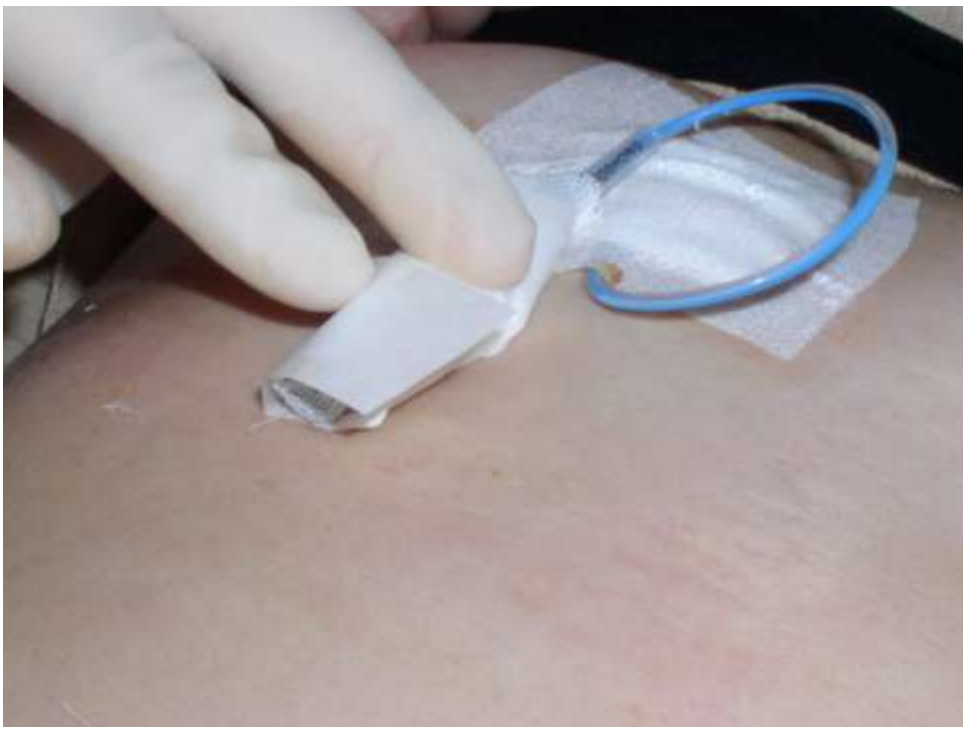
Neutropenia sono 40 anni che sappiamo che è un rischio !!



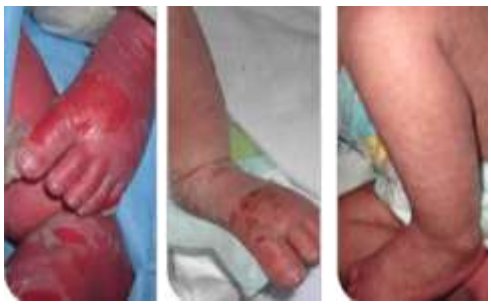


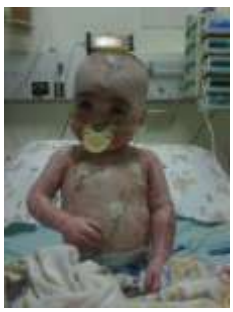
Fattori di rischio specifici nei bambini sottoposti a TMO

- Neutropenia prolungata
- Deficit immunità cellulo-mediata (T-depleti o GVHD acuta grave)
- Colonizzazione micotica del tratto gastroenterico

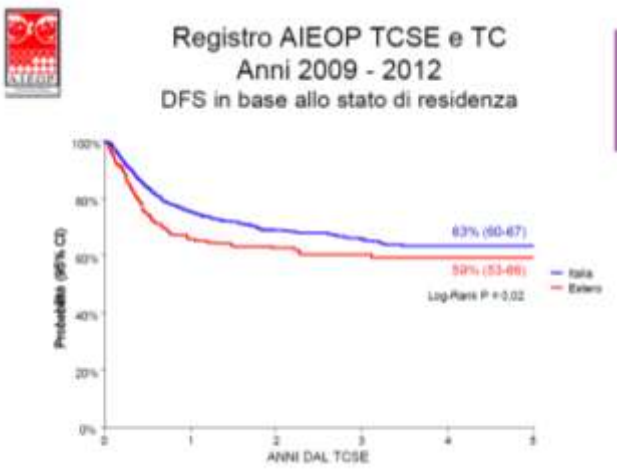


GVHD





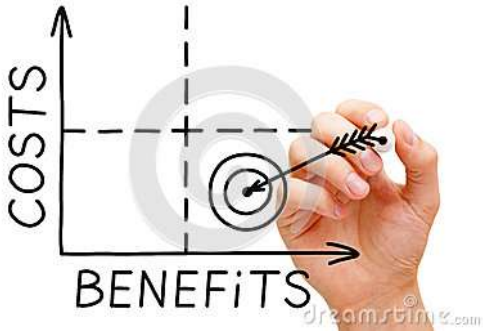
Quanti bambini sono guariti a 5 anni dal trapianto?



I bambini poi sono GUARITI ?

- Infezioni
- Mancato attecchimento
- Rigetto
- GVHD= malattia del trapianto contro l'ospite
- Secondi tumori
- Patologie di vari organi (endocrine,oculari, polmonari, cardiache , ossee,neurologiche , renali, cavo orale)
- Ritardo di crescita
- Pubertà ritardata
- Sterilità
- Effetti dell'irradiazione su SNC
- secondi tumori

Quindi…
il trapianto va fatto solo se



Grazie per l'attenzione !!