LA STORIA DELLA APLASIA MIDOLLARE : dalla diagnosi alla cura

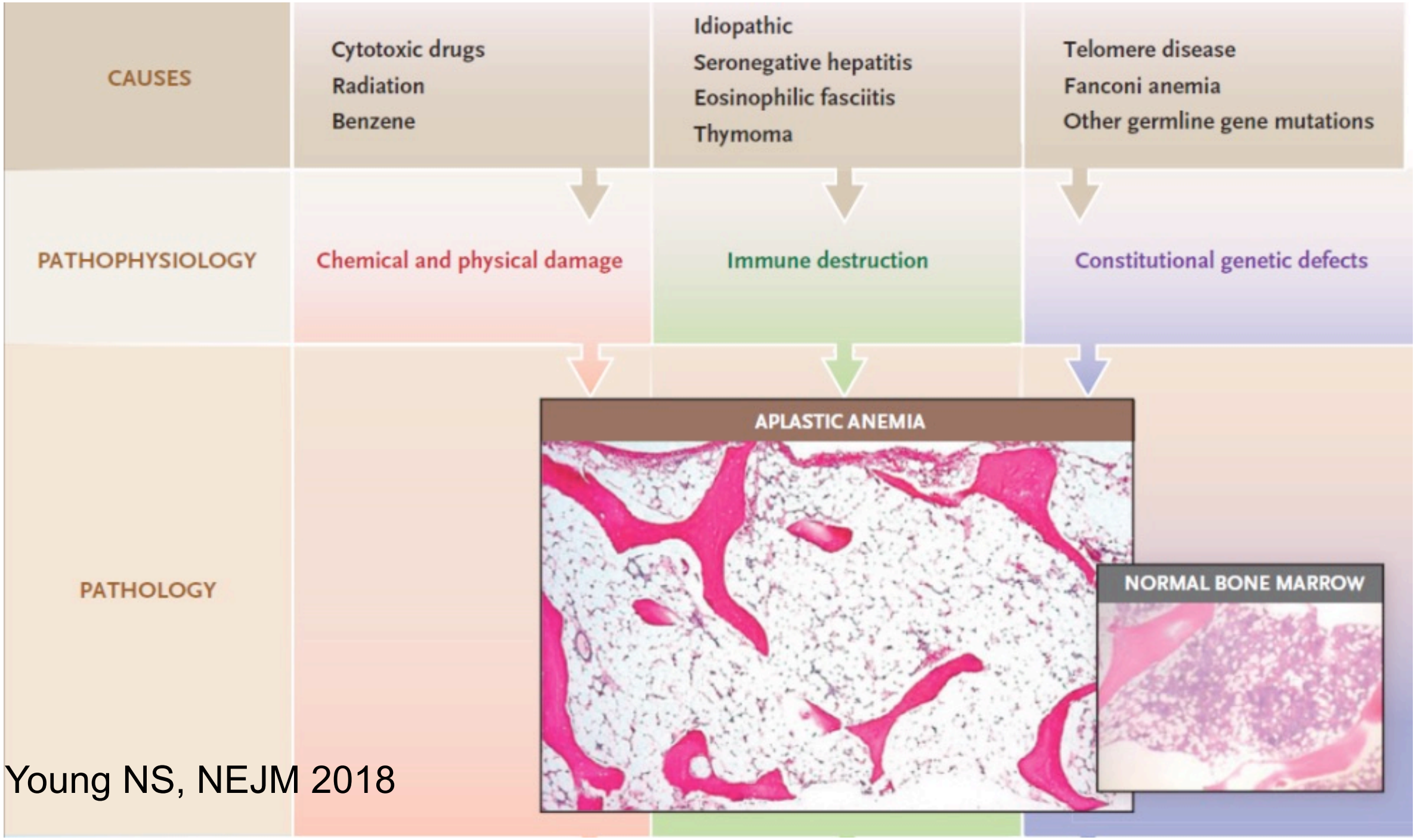
50 anni dal primo trapianto di midollo osseo :

26 aprile 1976- 26-aprile 2026

Andrea Bacigalupo

1974- 2014
Divisione Ematologia
Ospedale San Martino
Genova

2015-2026
Istituto di Ematologia, Policlinico A. Gemelli
Universita' Cattolica del Sacro Cuore
Roma



Young NS, NEJM 2018

Cosa abbiamo imparato in 50 anni: SAA

1978-1990: patogenesi autoimmune (linfociti T CD8+ IFNγ) (Neal Young)

1989 :the «escape model» di Luzzatto e Rotoli (GPI neg Stem Cells)

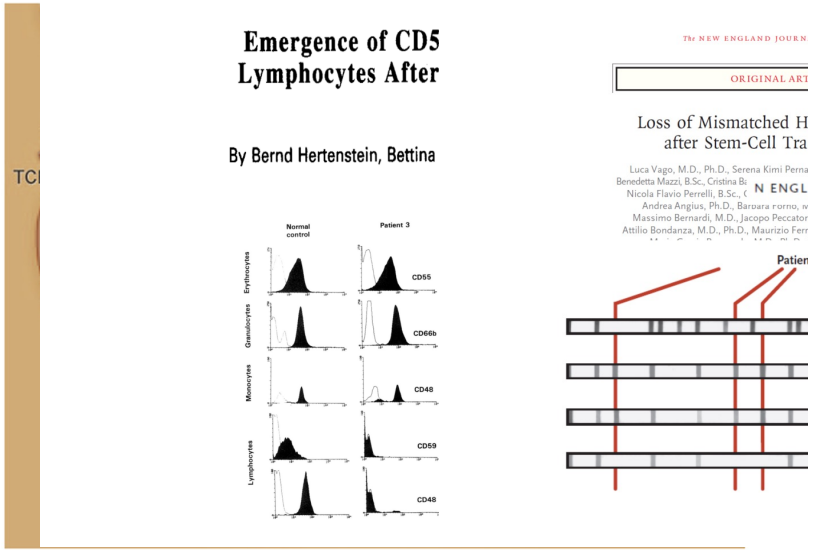
1995 CD52- T cells after Campath in CLL (H Schrezenmeier)

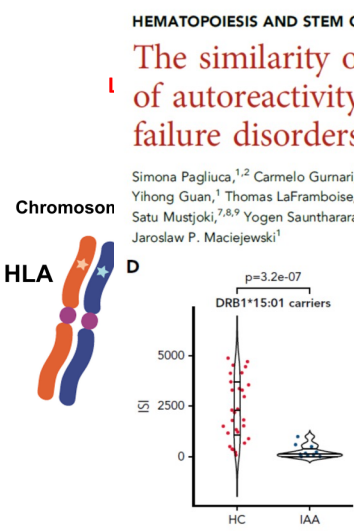
2009 HLA loss di Luca Vago nelle recidive dopo Trapianto Aplo

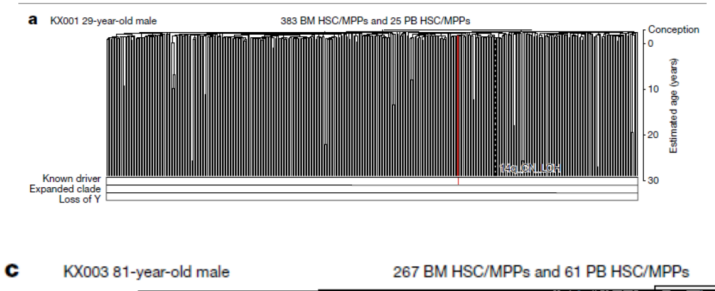
2011 HLA loss nelle SAA (Shinji Nakao)

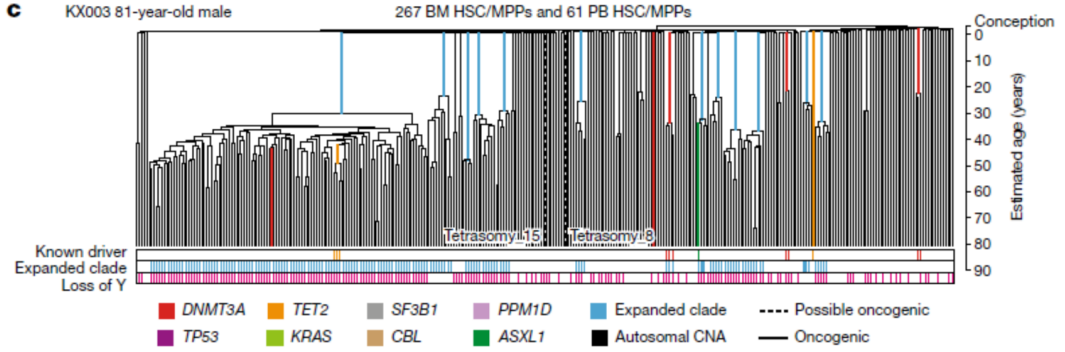
2021 :bassa divergenza HLA → bassa diversita' TCR: favorisce cross-reattivita' → autoimmunita' *(S Pagliuca e J Maciejewski)*

2022: aging ,ridotta diversita' clonale e mutazioni somatiche (P Campbell)









Katagiri *et al*, Bloc

Diagnosi e Patogenesi

ruolo dei linfociti T
escape mechanism
espansione popolazione SC GPI-
modifica HLA delle SC
autoimmunita' (ridotta divergenza HLA)
ridotta diversita' TCR →crossreatt
effetto di una riduzione delle CSE e riduzione della diversita' clonale (invecchiamento come modello)

Cosa abbiamo imparato in 50 anni: SAA

Terapia immunosoppressiva

ATG → 1970

*TREATMENT OF APLASTIC ANÆMIA BY ANTILYMPHOCYTE GLOBULIN **(horse)** WITH AND WITHOUT ALLOGENEIC BONE-MARROW INFUSIONS*

B.Speck[a] E.Gluckman[b] H.L.Hark[ce] J.J.Van Rood[de]

The Lancet Volume 310, Issue 8049, 3 December 1977, Pages 1145-1148

29 patients with severe aplastic anæmia were treated with either antilymphocyte globulin (A.L.G.) alone (15 patients) or A.L.G. followed by infusion of allogeneic bone-marrow (14 patients). The overall response to both forms of treatment in terms of 1-year survival was 55%

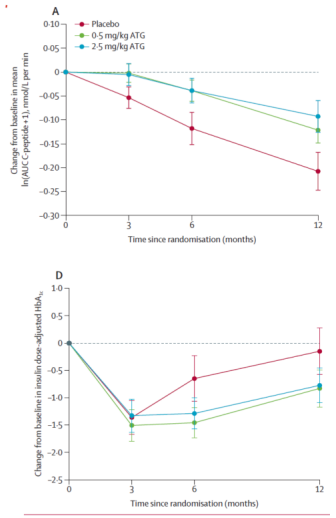
Lancet 2025; 406: 1375–88

Published Online September 18, 2025

Minimum effective low dose of antithymocyte globulin in people aged 5–25 years with recent-onset stage 3 type 1 diabetes (MELD-ATG): a phase 2, multicentre, double-blind, randomised, placebo-controlled, adaptive dose-ranging trial

Chantal Mathieu, Julie Wych, A Emile J Hendriks, Lisa Van Ryckeghem, Timothy Tree, Piotr Chmura, Christopher Möller, Kristina Casteels, Thomas Danne, Felix Reschke, Darja Šmigoc Schweiger, Tadej Battelino, Jesper Johannesen, Birgit Rami-Merhar, Thomas Pieber, Christophe De Block, Mark Evans, Robert Hilbrands, Emanuele Bosi, Ruben H Willemsen, Supriyo Basu, Mari-Anne Pulkkinen, Mikael Knip, Miriam Cnop, Almut Nitsche, Anke M Schulte, Elisabeth Niemöller, Mark Peakman, Charlotte Wilhelm-Benartzi, David Gillespie, Lut Overbergh, Adrian P Mander, M Loredana Marcovecchio, on behalf of INNODIA

Interpretation In young people with recent-onset, clinical type 1 diabetes, 2·5 mg/kg and 0·5 mg/kg ATG reduced loss of β-cell function, showing the potential of an affordable, repurposed agent, ATG, in a low and safe dose, as a disease-modifying agent in this population



ATG 1983

Antithymocyte Globulin Treatment in Patients with Aplastic Anemia — A Prospective Randomized Trial

•List of authors.Richard Champlin, M.D.,
•Winston Ho, M.D.,
•and Robert Peter Gale, M.D., Ph.D

•January 20, 1983; N Engl J Med 1983; 308:113-118

•11/21 randomized to ATG (8 days) responded
•0/21 randomized to supportive care responded (p=0.0005)
•Six of 12 control patients who subsequently received antithymocyte globulin improved.

•These data indicate that antithymocyte globulin is effective in improving hematopoiesis in some patients with aplastic anemia.

Cosa abbiamo imparato in 50 anni: SAA

Terapia immunosoppressiva

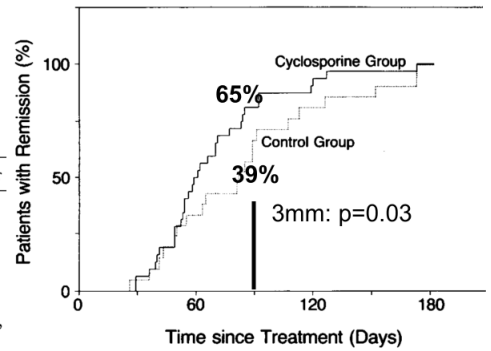
ATG → ATG CSA →
1970 1980-90

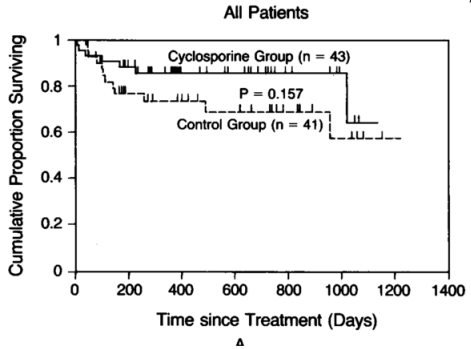
The New England
Journal of Medicine

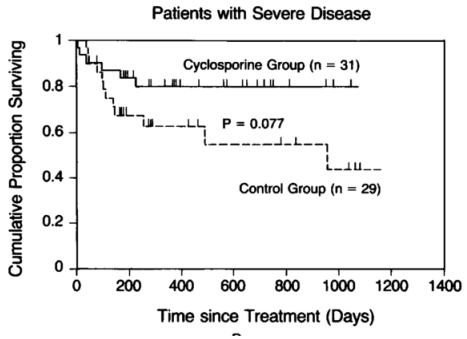
Volume 324 MAY 9, 1991 Number

TREATMENT OF APLASTIC ANEMIA WITH ANTILYMPHOCYTE GLOBULIN AND METHYLPREDNISOLONE WITH OR WITHOUT CYCLOSPORINE

Norbert Frickhofen, M.D., Joachim P. Kaltwasser, M.D., Hubert Schrezenmeier, M.D., Aruna Raghavachar, M.D., Hans G. Vogt, M.D., Friedhelm Herrmann, M.D., Ph.D., Mathias Freund, M.D., Peter Meusers, M.D., Abdul Salama, M.D., and Hermann Heimpel, M.D., ia Study Group*



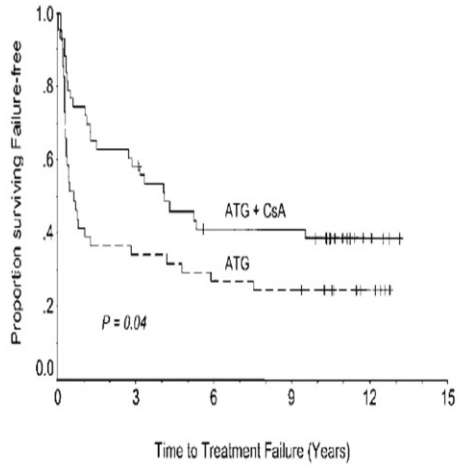


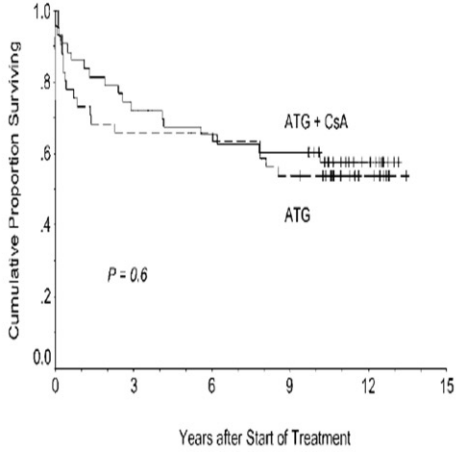


Antithymocyte globulin with or without cyclosporin A: 11-year follow-up of a randomized trial comparing treatments of aplastic anemia

Norbert Frickhofen, Hermann Heimpel, Joachim P. Kaltwasser, and Hubert Schrezenmeier, for the German Aplastic Anemia Study Group

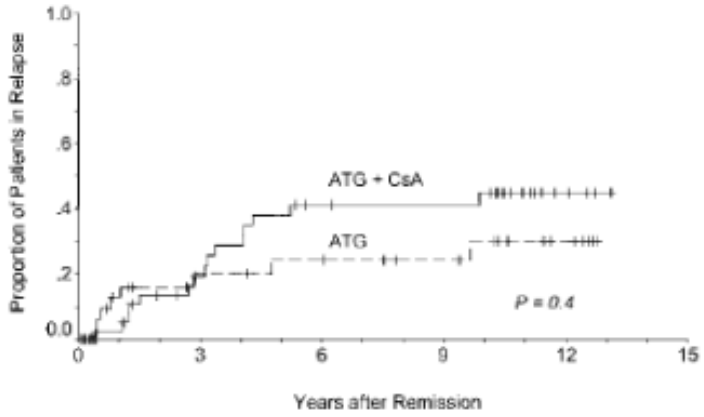
Blood 2003; 101: 1236





ıre 2. Overall survival. Patients treated with (ATG + CsA) or without CsA (ATG) similar overall survival times.

Failure: death, relapse, second treatm, clonal



4. Relapse of AA after immunosuppressive treatment. Patients treated ATG + CsA) or without CsA (ATG) had similar relapse rates.

Cosa abbiamo imparato in 50 anni: SAA

Terapia immunosoppressiva

ATG → ATG CSA → ATG CSA GCSF →

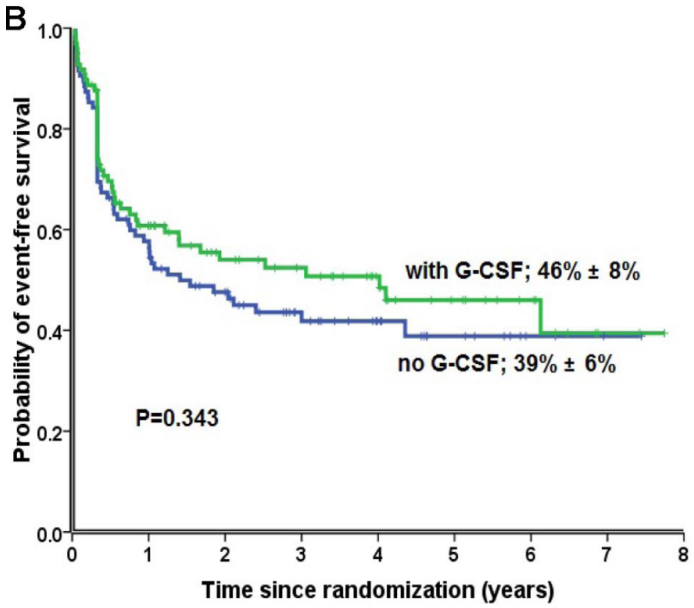
1970 1980-90 1990

blood

2011 117: 4434-4441
Prepublished online January 13, 2011;
doi:10.1182/blood-2010-08-304071

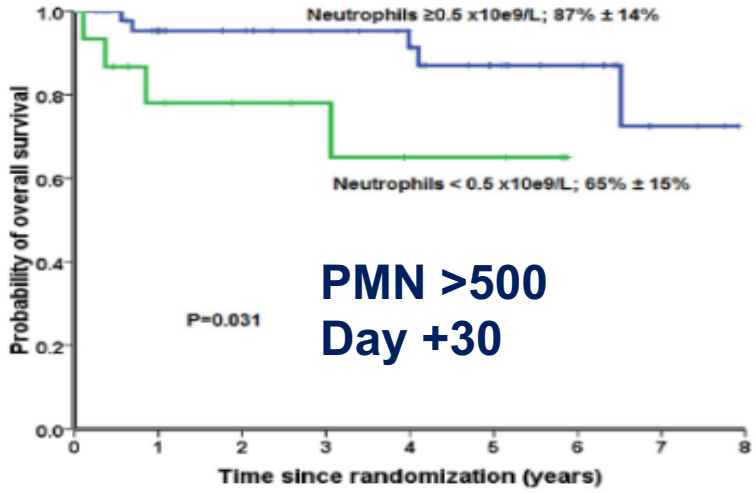
A randomized controlled study in patients with newly diagnosed severe aplastic anemia receiving antithymocyte globulin (ATG), cyclosporine, with or without G-CSF: a study of the SAA Working Party of the European Group for Blood and Marrow Transplantation

André Tichelli, Hubert Schrezenmeier, Gérard Socié, Judith Marsh, Andrea Bacigalupo, Ulrich Dührsen, Anke Franzke, Michael Hallek, Eckhard Thiel, Martin Wilhelm, Britta Höchsmann, Alain



Response
ATG CSA 66%
ATG CSA G 73%

ATG+CSA
ATG +CSA+ GCSF 1v/dayx120- 240dd
Primary end point = EFS ast 5 yy



PMN >500
Day +30

This is true ONLY for patients randomized to receive GCSF

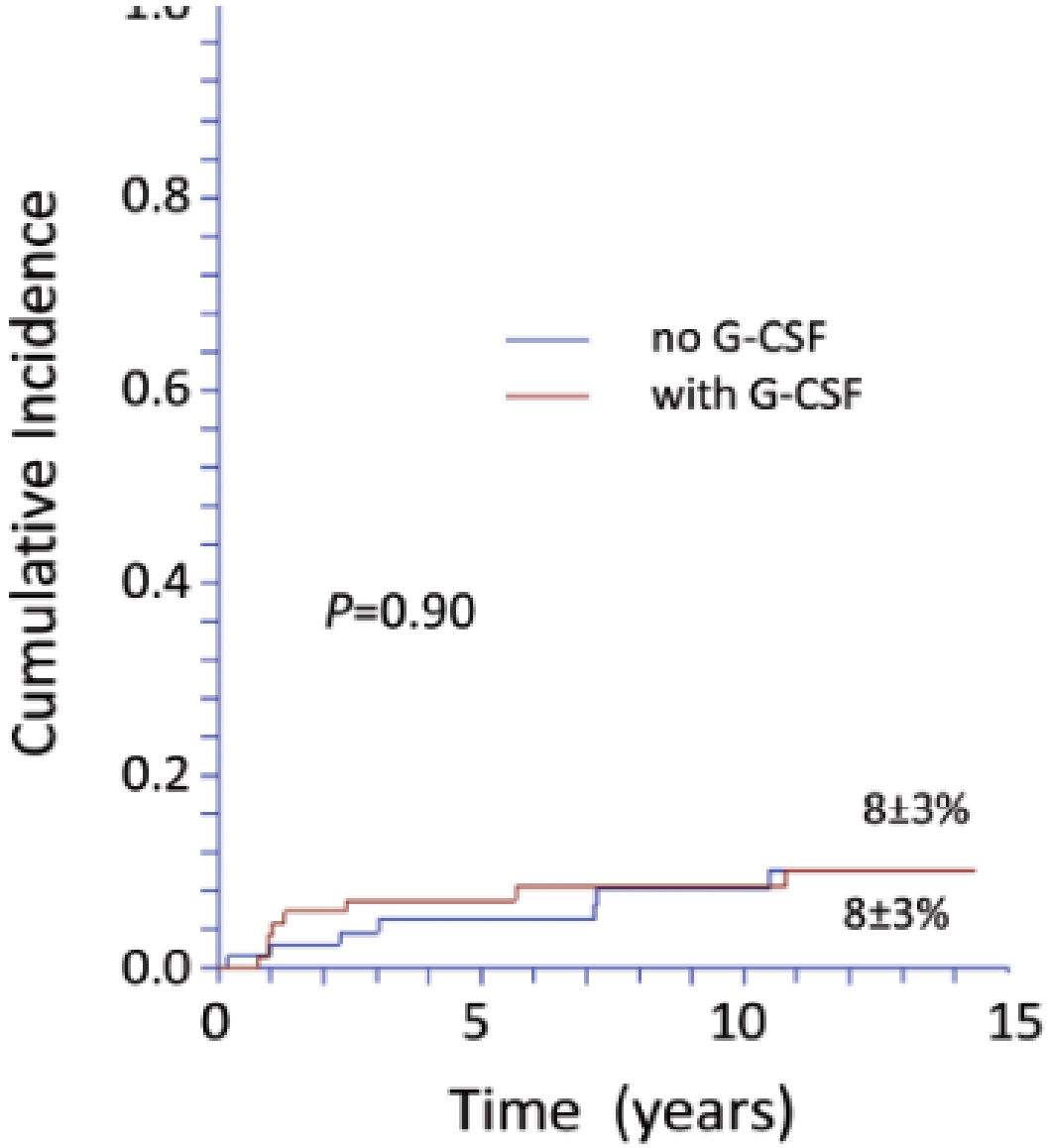
Long-term outcome of a randomized controlled study in patients with newly diagnosed severe aplastic anemia treated with antithymocyte globulin and cyclosporine, with or without granulocyte colony-stimulating factor: a Severe Aplastic Anemia Working Party Trial from the European Group of Blood and Marrow Transplantation

Haematologica 2020
Volume 105(5):1223-1231

With a median FU of 11 year

No difference in the incidence of late clonal events, including MDS, AML , in patients receiving **GCSF 150 µg/m^2/day from day 8 to day 240**

(except for patients achieving CR before)



Cosa abbiamo imparato in 50 anni: SAA

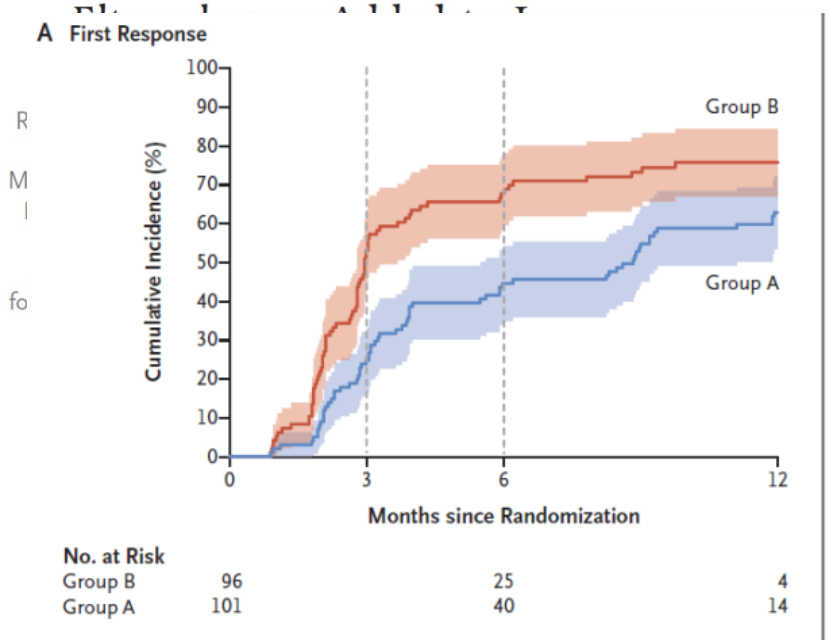
Terapia immunosoppressiva

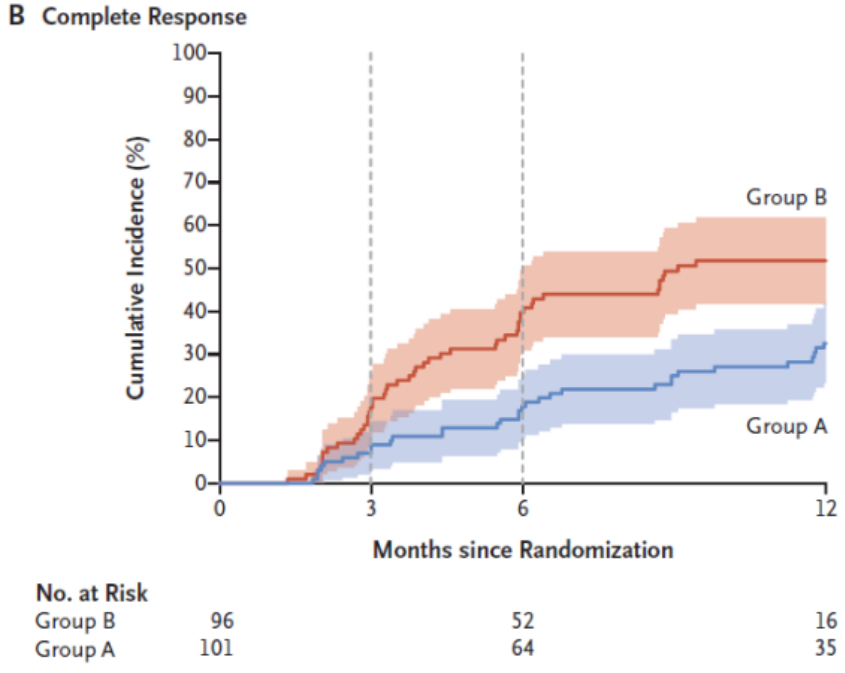
ATG → ATG CSA → ATG CSA GCSF → ATG CSA EPAG (ACE)

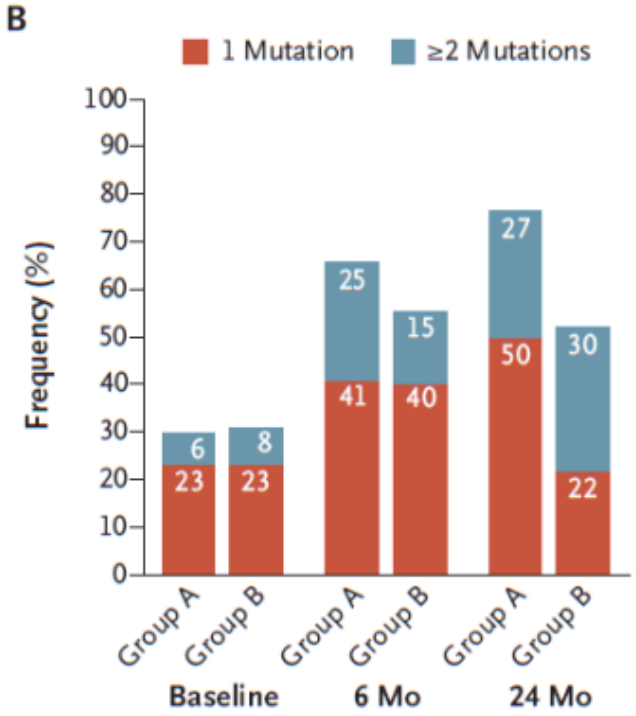
1970 1980-90 1990 2020

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 6, 2022 VOL. 386 NO. 1







Terapia Immunosoppressiva

ATG attore principale
ATG+CSA :migliore FFS rispetto a ATG
ma uguale OS
GCSF+ ATG+CSA non migliora la OS vs ATG+CSA
consente di selezionare a 30 gg i NON responder
ACE: standard attuale
problem NON risposte
recidive alla sospensione CSA o EPAG
evoluzione clonale (RACE2)

Terapia Immunosoppressiva

no cortisone basse dosi o fattori crescita come prima linea (GCSF, EPO)
ricerca cellule GPI- su sangue periferico
utile per conferma natura immunomediata
mutazioni in NGS non sono indicative di evoluzione clonale (PIGA , TET, DNMT3, ASXL1,)
Con eccezione per TP53, o monosomia 7 in FISH
la seconda linea per non responder= trapianto
ACE standard per l'adulto (Coniglio ATG in assenza di cavallo)

Cosa abbiamo imparato in 50 anni: SAA

TRAPIANTO

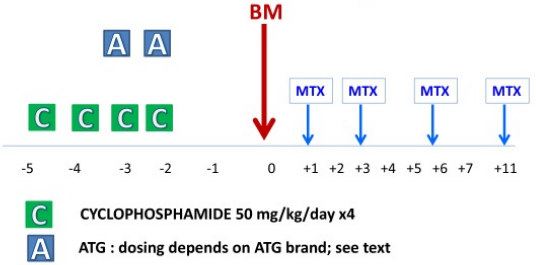
Rainer Storb SEATTLE

Anni '70 , Storb sviluppa condizionamento con CICLOFOSFAMIDE 200 mg/kg

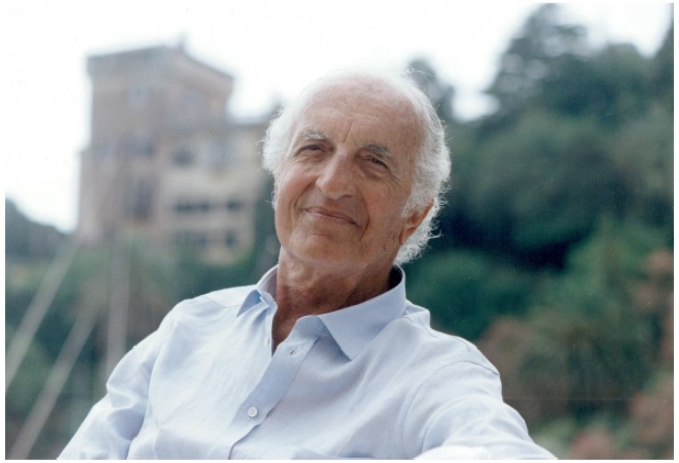
Storb R, Epstein RB, Rudolph RH, Thomas ED.
Allogeneic canine bone marrow transplantation following cyclophosphamide.
Transplantation. 1969 May;7(5):378-86.

Thomas ED, Storb R, Fefer A, Slichter SJ, Bryant JI, Buckner CD, Neiman PE, Clift RA, Funk DD, Lerner KE.
Aplastic anaemia treated by marrow transplantation.
Lancet. 1972 Feb 5;1(7745):284-9.

4 pts; 1 died GvHD, 1 died of rejection; 2 survive



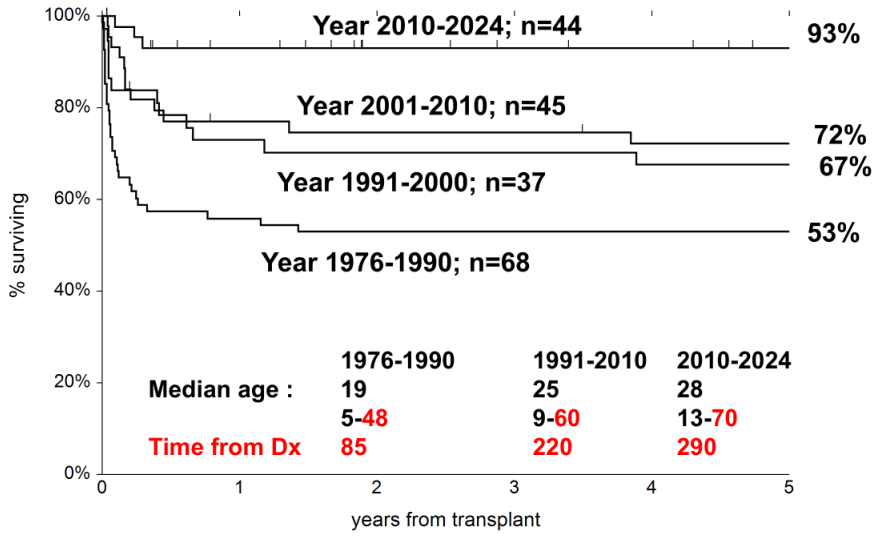
1976 AM Marmont ; *primo trapianto con Ciclofosfamide 200/kg a Genova*



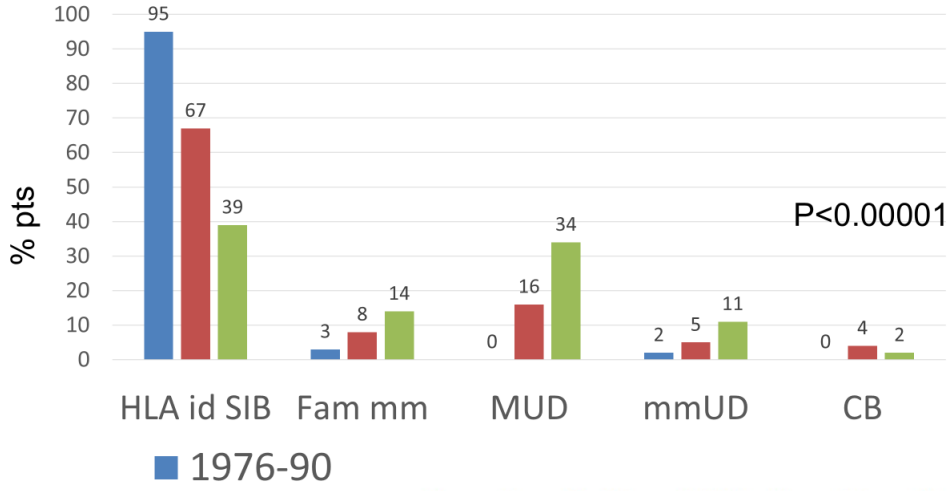
1972-1973 Bruno Speck a Leiden da J van Rood
*Trapianti nel coniglio usando **ATG** come condizionamento*
1974 Bruno Speck torna a Basilea -*primo trapianto con Ciclofosfamide 200/kg*

Cosa abbiamo imparato in 50 anni: SAA
TRAPIANTO

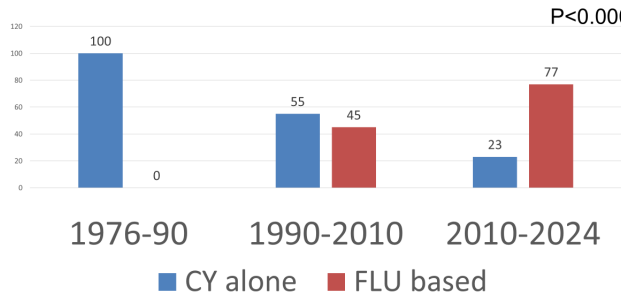
BMT for SAA Genova- Rome ; n=196



Changes in donor type for SAA Genova- Gemelli n=196



Changes in conditioning regimens for SAA Genova- Rome; n=196



Transplantation and Cellular Therapy 000 (2024) 1–16

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT American Society for Transplantation and Cellular Therapy

ELSEVIER

Guideline

Allogeneic Hematopoietic Cell Transplantation for the Treatment of Severe Aplastic Anemia: Evidence-Based Guidelines From the American Society for Transplantation and Cellular Therapy

Raheel Iftikhar[1,*], Zachariah DeFilipp[2], Amy E. DeZern[3], Michael A. Pulsipher[4], Nelli Bejanyan[5], Lauri M. Burroughs[6], Mohamed A. Kharfan-Dabaja[7], Sally Arai[8], Adetola Kassim[9], Ryotaro Nakamura[10], Blachy J. Dávila Saldaña[11], Mahmoud Aljurf[12], Mehdi Hamadani[13], Paul A. Carpenter[6], Joseph H. Antin[14]

Question 9: Should Fludarabine Containing HCT Conditioning be Prioritized Over Other Regimens for Aplastic Anemia?

Recommendation

The panel recommends cyclophosphamide-ATG conditioning for children and young adults receiving MRD-HCT. Fludarabine containing conditioning is recommended for adults or those with a high-risk of graft failure (Strength of recommendation, Strong; Certainty of evidence, low ⊕⊕◯◯).

All patients receiving MUD-HCT, CBT or haplo-HCT should receive fludarabine-containing conditioning (Strength of recommendation, Strong; Certainty of evidence: low ⊕⊕◯◯)

Cosa abbiamo imparato in 50 anni: SAA

TRAPIANTO

condizionamento

CY 300 mg^m2 x4	**tot 2000 mg**
CY 30 mg/kg x4	**tot 7200 mg**

Donor Type	Conditioning Regimen
Matched related donor	Age < 30 yr: CY200 mg/kg + r-ATG [20,88,89] or CY200 mg/kg + Alemtuzumab [75] Age >30 yr: FLU 30 mg/m2 × 4-5 d, CY 300 mg/m2 × 4 d and r-ATG (FCA regimen) [20] High risk of Graft failure: Flu 120-150 mg/m^2 + CY 120 mg/kg + r-ATG [15]
Matched unrelated donor	Adults: 1. FCA-TBI: fludarabine 30 mg/m^2 x 4, cyclophosphamide 300 mg/m^2 x 4 and ATG 3.75 mg/kg x 2, TBI 2 Gy [1] 2. FCC: fludarabine 30 mg/m^2 x 4, cyclophosphamide 300 mg/m^2 x 4, alemtuzumab 0.2 mg/kg x 5 d (total dose 40-100mg) [76] 3. For 9/10 MMUD: FCC plus 2G TBI [1] 4. Alternative for 8/8 or 7/8–BMT CTN 0301: fludarabine 30 mg/m^2 x 4, cyclophosphamide 50mg/kg x 1 (older patients) or x 2 (pediatric/young adult patients), rATG 3 mg/kg x 3, TBI 2 Gy [90] Pediatric 5. Flu 30mg/m^2 x 5 d, CY 60 mg/kg x 2 d with r-ATG (5-20 mg/kg) or alemtuzumab 0.3 mg/kg for 3 d and CSA± MTX for GVHD prophylaxis [91] 6. 8/8 or 7/8–BMT CTN 0301: fludarabine 30 mg/m^2 x 4, cyclophosphamide 50mg/kg x 2, rATG 3 mg/kg x 3, TBI 2 Gy [90]

Cosa abbiamo imparato in 50 anni: SAA

TRAPIANTO

GvHD profilassi

Question 11: What Should be the Preferred Regimen for GVHD Prophylaxis?

Recommendation

The panel suggests either calcineurin inhibitor (CNI) plus methotrexate (MTX) or PTCy based prophylaxis for patients undergoing MRD or MUD HCT (Strength of recommendation, weak; Certainty of evidence: low ⊕⊕◯◯).

For patients undergoing Haploidentical HCT, our panel recommends PTCy-based prophylaxis (Strength of recommendation; Strong, Certainty of evidence: Moderate ⊕⊕ ⊕◯).

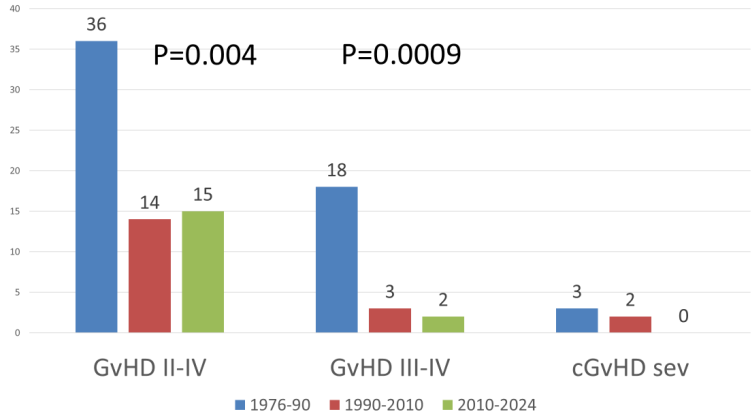
GvHD prophylaxis 2026

CSA +MTX young patients (<40) ; MRD

Campath UK based programs

ATG+ CSA+MMF+PTCY haplo donors
MUD mmUD
older patients (>40)

Reduction of GvHD with time ; Genova- Gemelli n=196



www.nature.com/bmt

EBMT

Bone Marrow Transplantation (2026) 61:232–234;

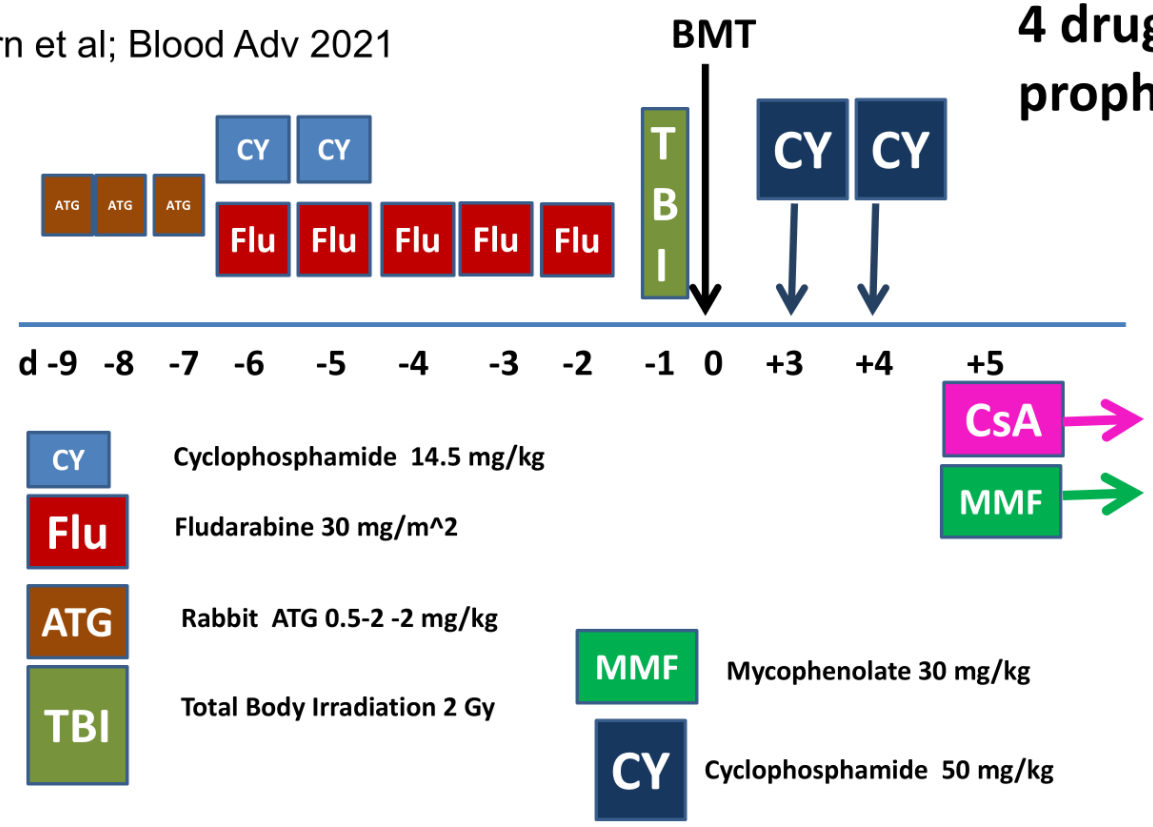
CORRESPONDENCE

Check for updates

Unrelated donor transplantation for relapsed refractory aplastic anemia, with quadruple GvHD prophylaxis

De Zern et al; Blood Adv 2021

4 drug GvHD prophylaxis



Centri GITMO

Roma Gemelli, S Giammarco
Cuneo, N Mordini
Monza, E Terruzzi
Torino Molinette, A Busca
Roma Umberto 1, AP Iori
Perugia, A Carotti
Alessandria, F Zallio
Milano Policlinico, G Saporiti
Bolzano, I Cavattoni
Udine, F Patriarca
Palermo, L Castagna
Bari, P CArluccio
Pisa, L Bernasconi
San Giovanni Rotondo, AM Carella
Firenze, C Nozzoli
Treviso, M Stanzani

MUD 8/8 =20 UD 7/8 = 8 SIB =2
Failed ATG CSA= 20;: rela after ATG=10
Age = 40 (18-70); Int DxTx 487 (90-5177)

BM= 18 PB =12
Engr PMN 500 = day 19; Engr Plt 20 = day 22

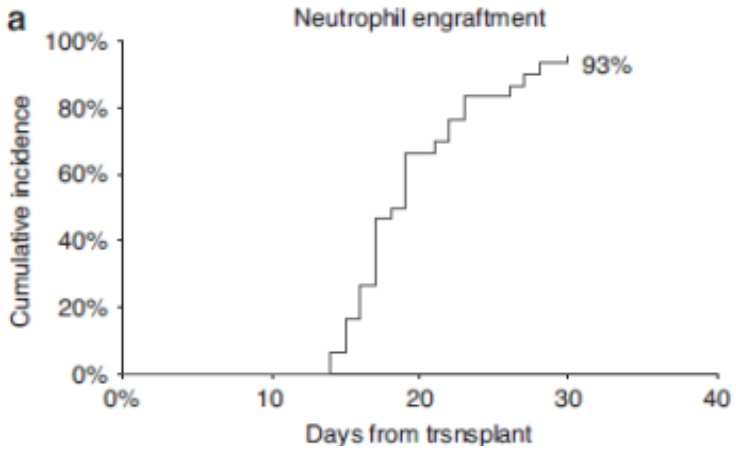
www.nature.com/bmt

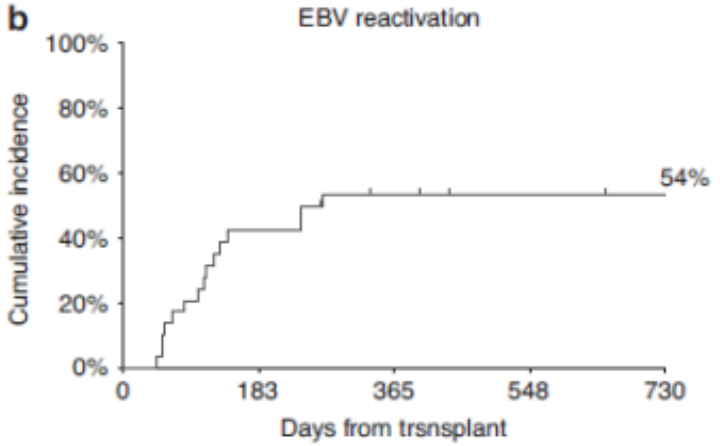
EBMT

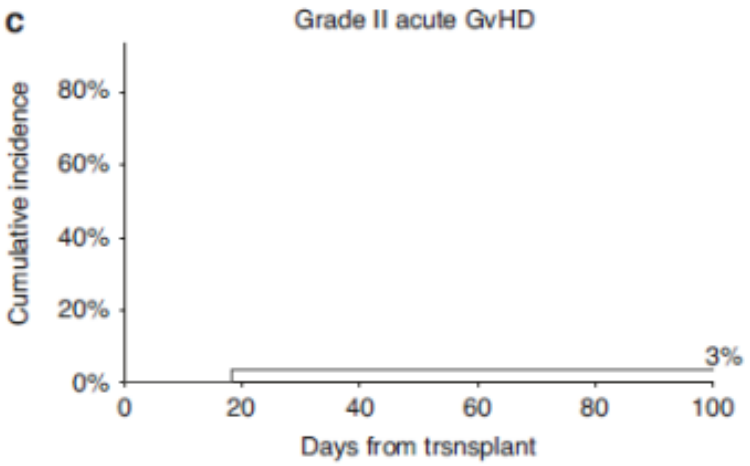
Bone Marrow Transplantation (2026) 61:232–234;

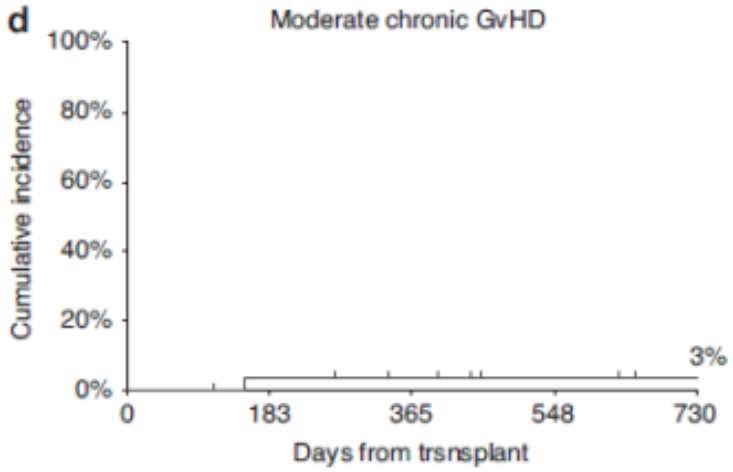
CORRESPONDENCE

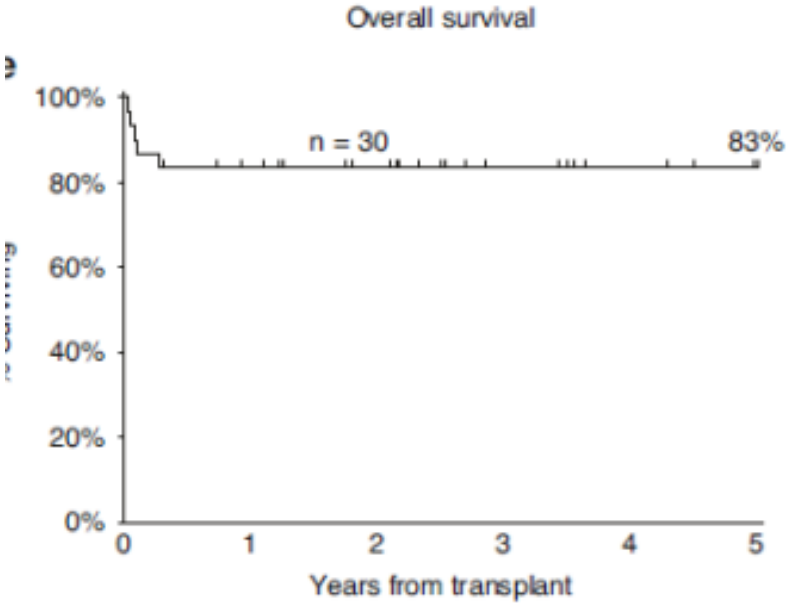
Unrelated donor transplantation for relapsed refractory aplastic anemia, with quadruple GvHD prophylaxis

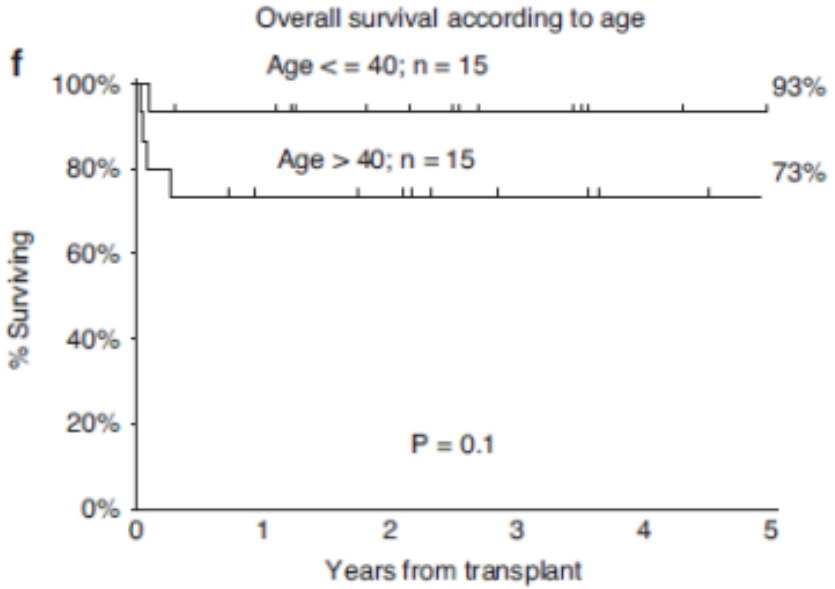












Zhang et al. Experimental Hematology & Oncology (2026) 15:31
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Experimental Hematology & Oncology

2026; 15-31

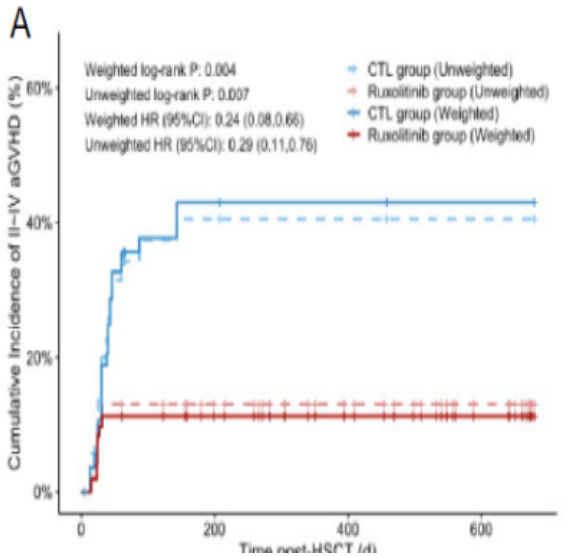
RESEARCH Open Access

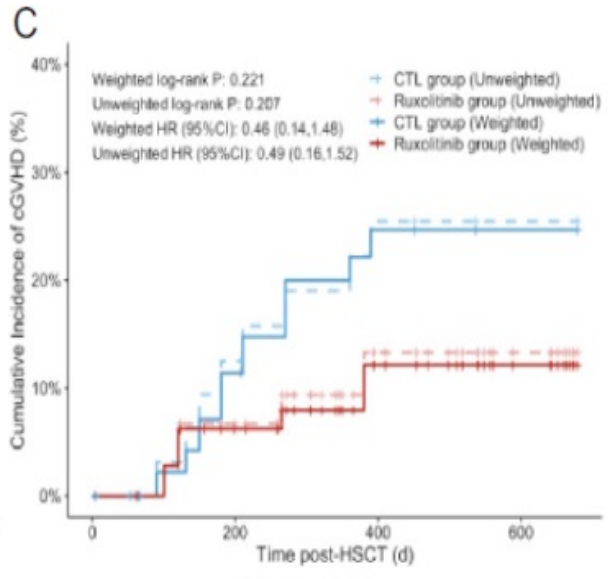
Efficacy and safety of ruxolitinib for graft-versus-host disease prophylaxis in patients with aplastic anemia undergoing PBSC-only allogeneic stem cell transplantation: a prospective phase II study

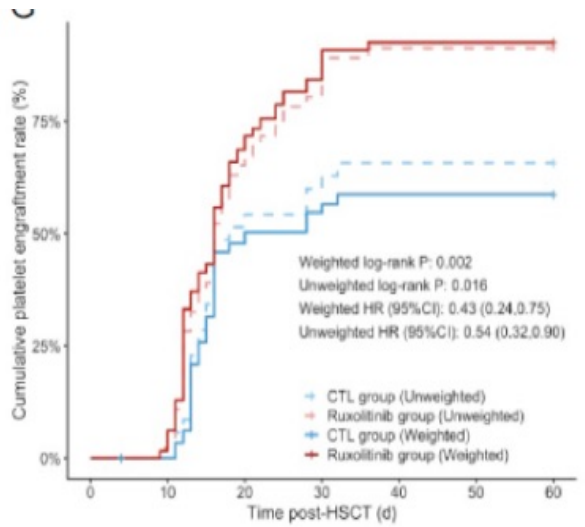
Xiaoyu Zhang[1,2], Lulu Pan[3], Yanhong Zhao[1,2], Runzhi Ma[1,2], Lining Zhang[1,2], Ying Zhang[1,2], Gang Li[1,2], Weihua Zhai[1,2], Qiaoling Ma[1,2], Aiming Pang[1,2], Donglin Yang[1,2], Sizhou Feng[1,2], Ping Zhang[4,5], Yi He[1,2,6*†], Guoyou Qin[3*†], Erlie Jiang[1,2*†] and Mingzhe Han[1,2]

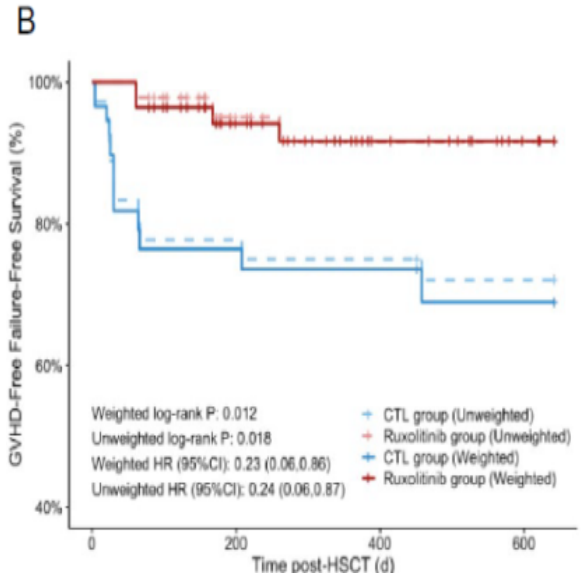
GvHD proph=
CNI + MTX + RUXO 5mg day -7 →day+30

	RUXO	Contr
N=	36	46
MSD	11	11
Haplo	25	35









Cosa abbiamo imparato in 50 anni: SAA

TRAPIANTO

Priorita' dei donatori alternativi

TRANSPLANTATION

blood 18 JULY 2024 | VOLUME 144, NUMBER 3 323

CME Article

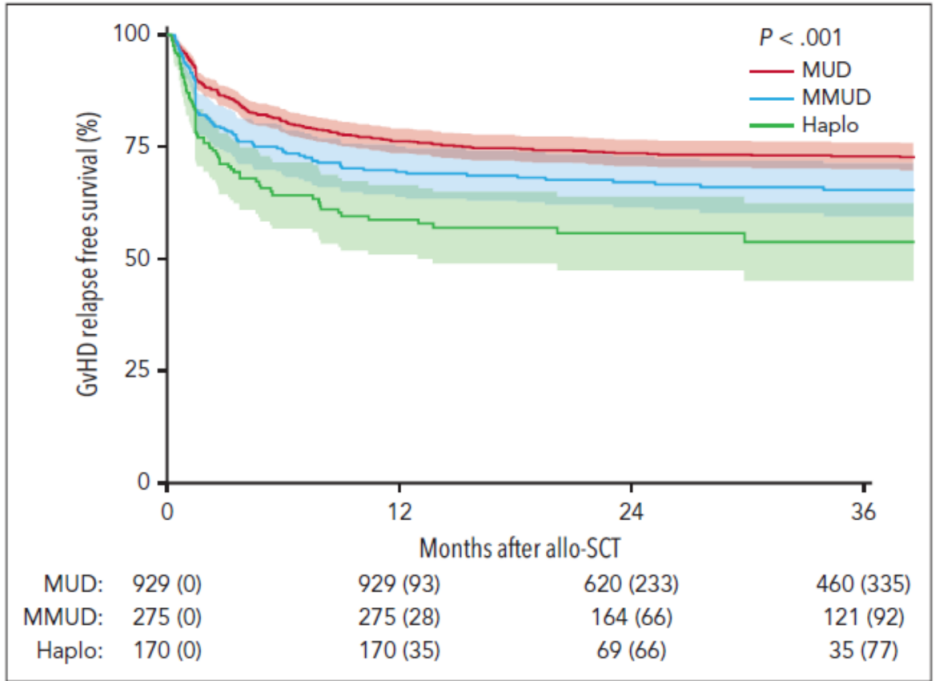
Alternative donor transplantation for severe aplastic anemia: a comparative study of the SAAWP EBMT

Juan Montoro,[1,2] Dirk-Jan Eikema,[3] Joe Tuffnell,[3] Victoria Potter,[4] Krzysztof Kalwak,[5] Constantijn J. M. Halkes,[6] Alexander Kulagin,[7] Matthew Collin,[8] Robert F. Wynn,[9] Stephen Robinson,[10] Emma Nicholson,[11] Henrik Sengeloev,[12] Jennifer Clay,[13] Khalid Halahleh,[14] Elena Skorobogatova,[15] Jaime Sanz,[1] Jakob Passweg,[16] Stephan Mielke,[17] Samppa Ryhänen,[18] Ben Carpenter,[19] Tobias Gedde-Dahl,[20] Eleni Tholouli,[21] Renato Fanin,[22] Philippe Lewalle,[23] Austin Kulasekararaj,[4] Antonio Risitano,[24] and Régis Peffault de Latour[25]

KEY POINTS

- **SCT from MUD offers superior survival outcomes for severe aplastic anemia compared with both MMUD and Haplo SCT.**
- **The decision between an MMUD and Haplo donor in the absence of an available MUD remains uncertain.**

	MUD	mMUD	HAPLO	
n=	1106	340	170	
Age	21 (11-42)	17 (10-34)	20 (10-37)	
Engr	85%	84%	75%	0.03
Plt Engr	88%	82%	72%	<0.001
PGF	3%	2%	13%	<0.001
NRM	14%	19%	27%	<0.001



Cosa abbiamo imparato in 50 anni: SAA

TRAPIANTO

fertilita'

Sabrina Giammarco con WPSAA EBMT

889 females
BMT 1980-2020

SAAWP:BUSINESS MEETING

EBMT 52nd Annual Meeting
22-25 March 2026 | Madrid

Most popular regimens for acquired SAA

CY 200

FLU 120 mg/m^2 + CY 120 mg/kg

FLU 120 mg/m^2 + CY 120 mg/kg+ TBI 2 Gray

Cond	n	% pregnan
CY 200	**473**	**38%**
FLU-CY	**277**	**22%**
FLU-CY-TBI2	**139**	**11%**

Question

Does the addition of TBI 200 impair fertility in females??

18-40 years old /EBMT WPSAA

Cond	AGE	MSD%
CY 200	**27yy**	**88%**
FLU-CY	**27 yy**	**52%**
FLU-CY-TBI2	**27yy**	**11%**

SAA Trapianto Fratello HLA identico

CY 200+ATG – CSA MTX : paz <30 anni
CY 120+ FLU 120 + ATG – CSA MTX : paz 31-40
Baltimore De Zern : paz 41 -75

SAA Trapianto donatore ALTERNATIVO

MUD 8/8 poi mmUD 7/8 poi APLO
Baltimore De Zern : tutte le eta’- certo >18
FCC per Centri con esperienza
Altri protocolli (AIEOP ?)

Cosa abbiamo imparato in 50 anni: SAA

pazienti over 40 e over 60

IST

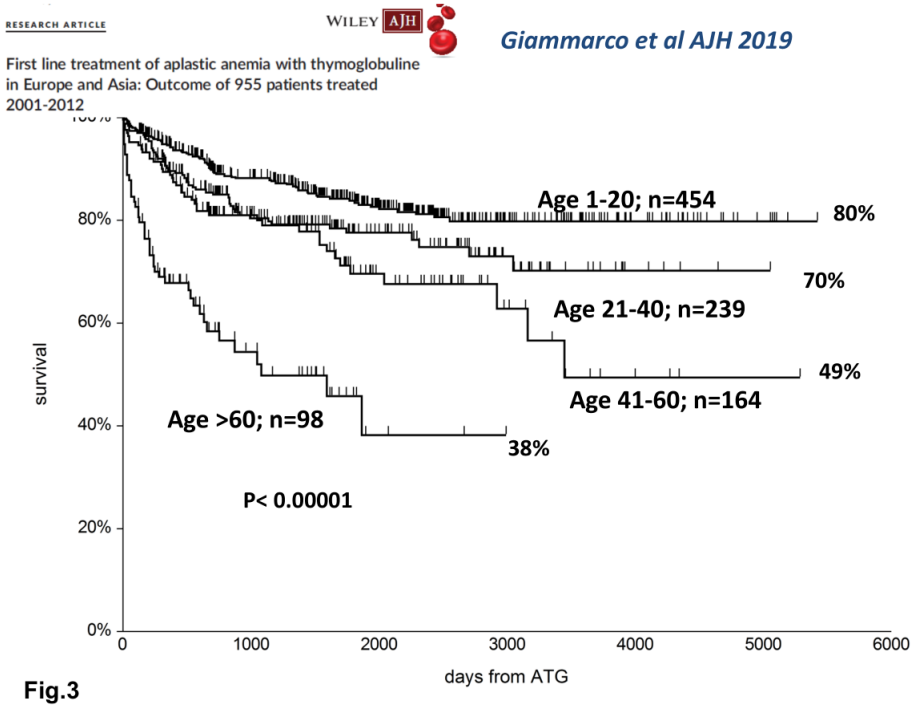


Fig.3

TRAPIANTO

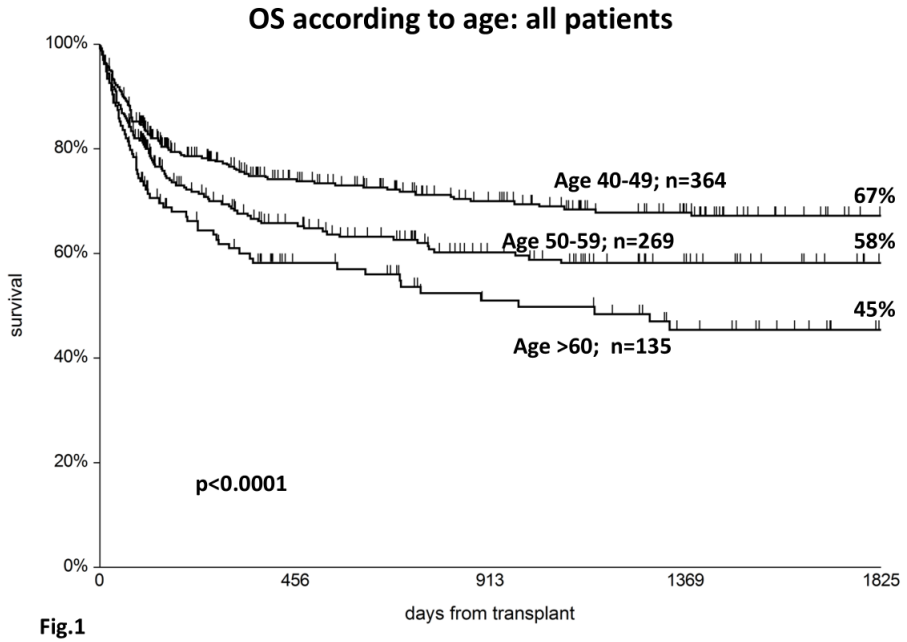


Fig.1

DOVE POSSIAMO MIGLIORARE?

programmi condivisi:
 # se non eleggibile al trapianto →ACE subito anche >60
ATG di cavallo e' la prima scelta
ATG di coniglio meglio che CSA EPAG senza ATG

 # se eleggibile trapianto → condividere

≤40 anni : tutto abbastanza chiaro (SIB / ALT)
> 40 anni : piattaforma DZ (studio retrospettivo-> i 16 centri proporli per studio prospettico)

 # terapia supporto (rituximab : Regis Peffault ha messo 200 mg al giorno +5, nel protocollo prospettico DeZern per MUD in Francia)

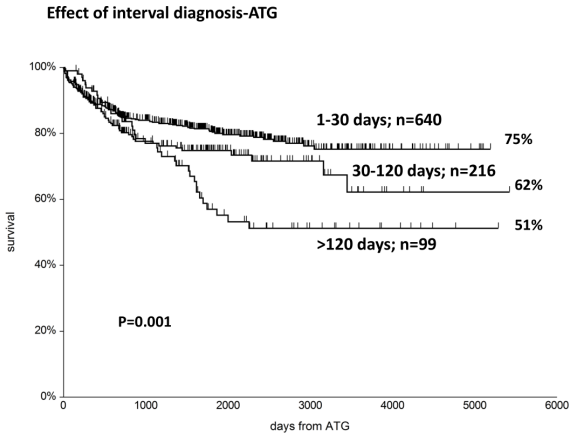


Fig.4

DOVE ANDIAMO ? Treg

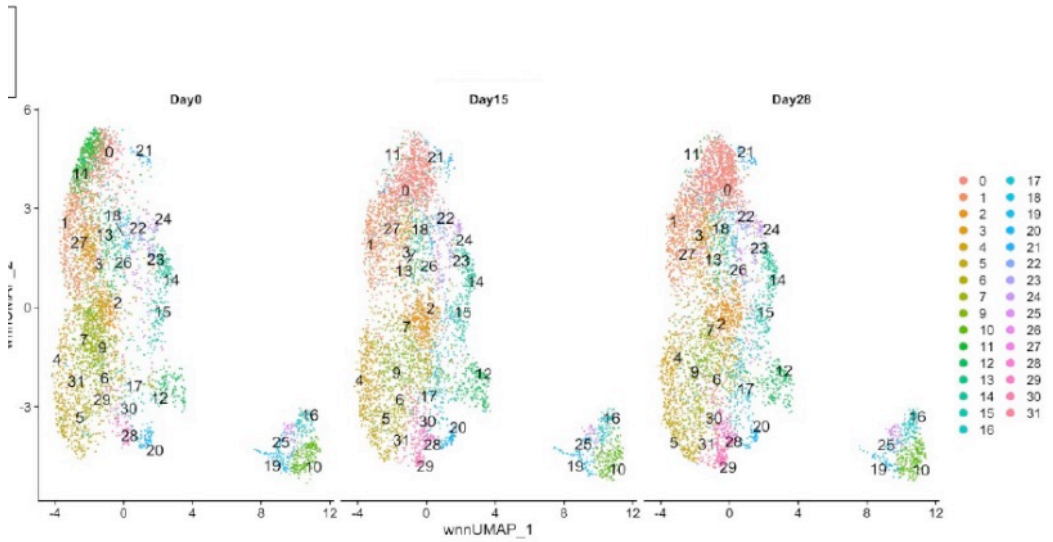
haematologica

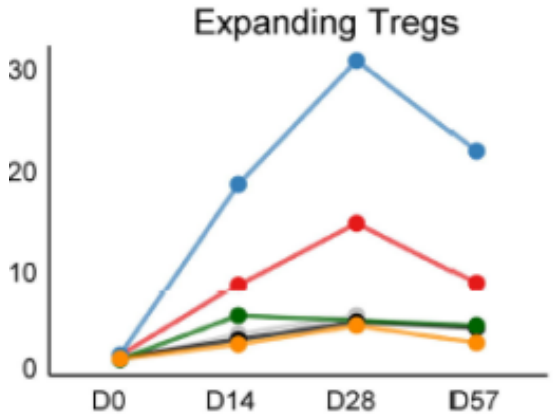
Journal of the Ferrata Storti Foundation

Febbraio 2026

Phase I trial of autologous regulatory T cells for immune aplastic anemia

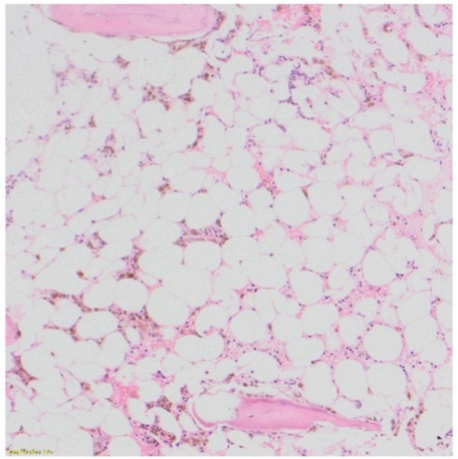
by Nazia Matto, Shreyans Gandhi, Marta Rzepkowska, Sila Gerlevik, Mohammad M. Karimi, Austin Kulasekararaj, Abdel Douiri, Anjie Miller, Lynne Duran, Haili Cui, Jen Lewis, Shahram Kordasti, Giovanna Lombardi, Giorgio Napolitani and Ghulam J. Mufti

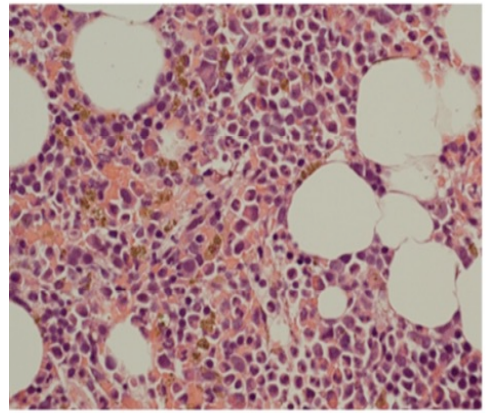




6 patients Refractory to ACE
Age 67-79

Collection, expansion, infusion
T regs 5x10^6/kg day 1 day 15





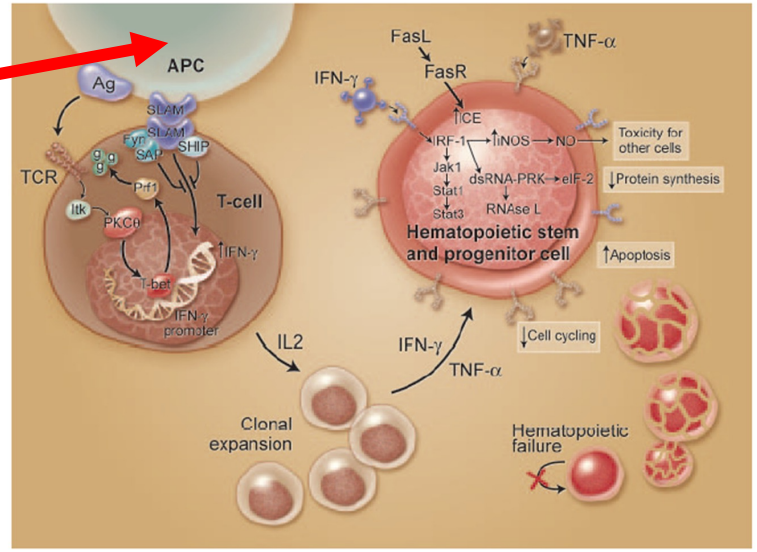
3 patients PR transf independent

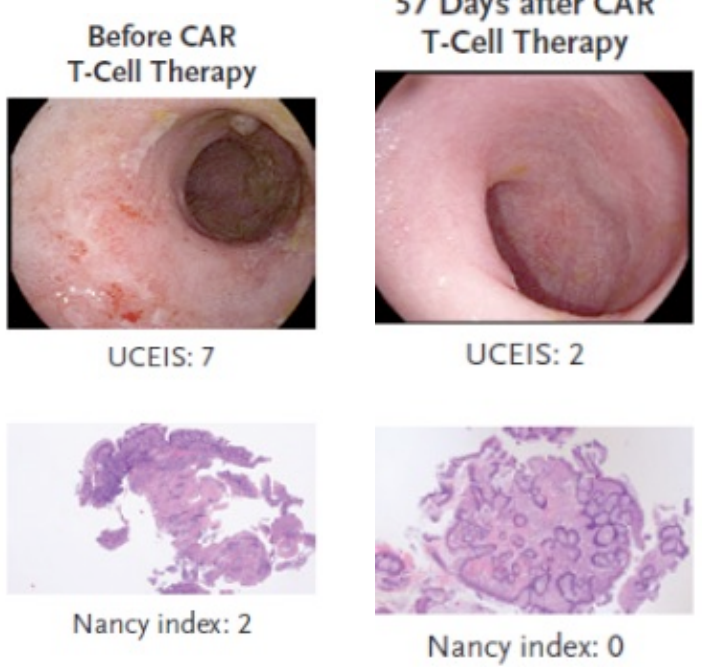
DOVE ANDIAMO ?

NEJM.ORG SEPTEMBER 25, 2025

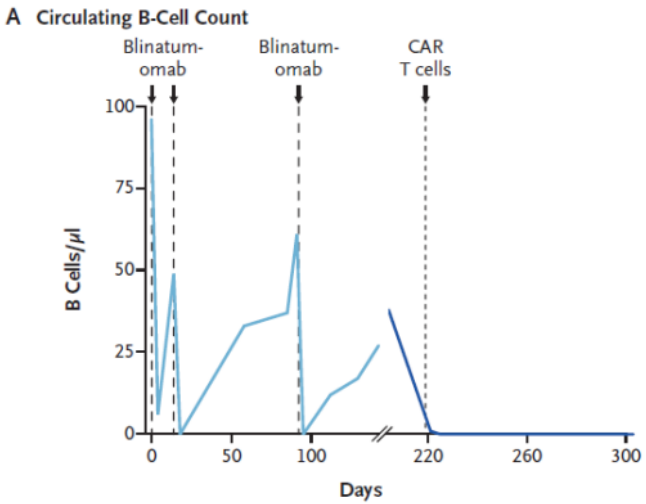
CORRESPONDENCE

CD19 CAR T-Cell Therapy in Multidrug-Resistant Ulcerative Colitis





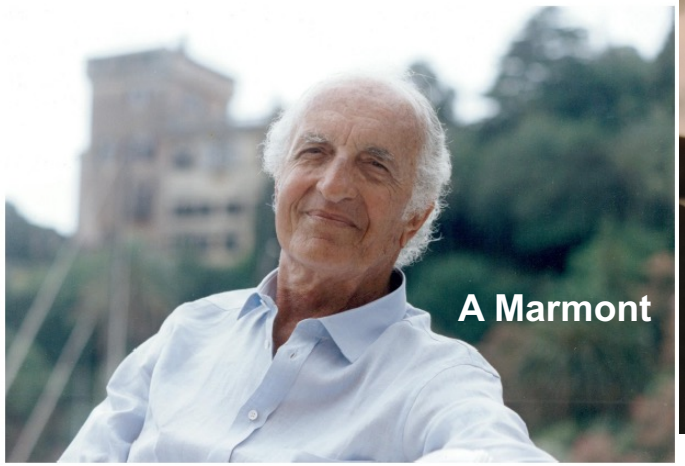
Paz 21 anni
Ulcerative colitis ; multi drug resistant
Declined colectomy



C

D Biochemical Remission

These data suggest the possibility that CD19 CAR T-cell therapy can induce rapid drug-free remission in refractory ulcerative colitis, a disease that was previously thought to be largely B-cell–independent, given that rituximab treatment showed no efficacy.[5] Because these find-



SAA WP

Antonio Risitano, Regis Peffault
Locasciulli, Franco Locatelli, Chri
Lint,
er, C

BMT S Martino

E Angelucci, AM Raiola, S Bregante, R Varaldo, T Lamparelli, F Gualandi, A Ibatici, C Di Grazia, A Ghiso, R Oneto, E Tedone, G Piaggio, S Luchetti, M Daneri, G Conti

BMT Gemelli

S Sica, P Chiusolo, F Sorà, S Giammarco, E Metafunui, I innocenti, E Galli, MA Limongiello, L Teofili, M Bianchi, N Piccirillo, L Pagano, S Hohaus, L Laurenti, C Frau

Koj
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ong

dini, C Tarella, R Fanin, B Bruno, F
ne', G Milone, F Onida, A Risitano, A
, R Raimondi , L Castagna, F
zo, A Locasciulli, S Cesaro, A Zecca,
, R Saccardi