Aplastic anemia in older patients (40, 50…)

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Disclosures

- **Expert consultant / orateur** pour des symposia pour les laboratoires Alexion, Amgen, Gilead, Jazz, Keocyte, MSD, Novartis, Pfizer, Roche, Samsung & Therakos

- **Bourse de recherche** des laboratoires Alexion, Amgen, Jazz pharmaceutical, Novartis, Pfizer

Introduction: IST versus BMT

- **Response to immunosuppressive treatment** has always been associated with better long-term prognosis in patients with aplastic anaemic compared to those without response[1,2]
- In a prospective randomised EBMT study, the 6-year survival of **immunosuppressive treatment was strongly age-dependent**:[2]
  - 100% for patients <20 years of age
  - 92% for patients 20–40 years of age
  - 71% for patients 40–60 years of age
  - 56% for patients >60 years of age
- **Age has a strong impact on survival after transplantation** in patients with severe aplastic anaemia. Transplantation is rarely considered for those over 60 years of age due to high mortality rates[2]

EBMT, European Society for Blood and Marrow Transplantation. 1. Peffault de Latour R, personal opinion; 2. Bacigalupo A. *Haematologica*. 2019;104(2):215–16.

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Introduction: incidence of AA (/Age and Sex)

Incidence in Europe and Israel[1]

	Male		Female	
Age (yr)	n	Incidence (per 10^6/yr)[a]	n	Incidence (per 10^6/yr)[a]
<15	12	1.7	5	0.7
15–24	22[b]	3.5	4	0.9
25–44	12	1.1	18	1.8
45–59	11	1.8	15	2.0
≥60	16	3.2	51	6.3
Total	73	2.1	93	2.4

SAA Working Party study:

- 1980–1984, n=168
- Prospective

Incidence in Sweden[2]

	Male		Female		Total	
Age (yr)	n	Incidence (per 10^6/yr)	n	Incidence (per 10^6/yr)	n	Incidence (per 10^6/yr)
0–4	0	0	2	0.7	2	0.3
5–9	5	1.6	6	2.0	11	1.8
10–14	8	2.3	7	2.1	15	2.2
15–19	13	3.6	8	2.4	21	3.0
20–24	9	2.7	4	1.2	13	2.0
25–29	4	1.2	4	1.2	8	1.2
30–34	2	0.5	8	2.3	10	1.4
35–39	2	0.5	3	0.8	5	0.7
40–44	2	0.5	4	1.1	6	0.8
45–49	5	1.4	7	2.0	12	1.7
50–54	5	1.4	5	1.4	10	1.4
55–59	6	1.6	7	1.9	13	1.8
60–64	11	3.3	11	3.3	22	3.3
65–69	13	5.0	10	3.7	23	4.4
70<	39	6.9	47	6.0	86	6.4

- 2000–2011, n=257
- Retrospective

- [a]Standardised to the regional distribution of the study population. [b]Includes nine cases from Barcelona.1. Used with permission of Elsevier, from Incidence of aplastic anemia: the relevance of diagnostic criteria. Heimpel H. *Blood.* 1987;70(6):1718–21; permission conveyed through Copyright Clearance Center, Inc.; 2. Used with permission of Ferrata Storti Foundation, from Incidence and outcome of acquired aplastic anemia: real-world data from patients diagnosed in Sweden from 2000–2011. Vaht K, *et al. Haematologica.* 2017;102(10):1683–90; permission conveyed through Copyright Clearance Center, Inc.

Introduction: Specificity

Characteristics of aplastic anaemia in 810 patients from the EBMT Registry (1974 and 1997)[1]

Characteristic	All Patients (n = 810)	Patients ≥60 Years of Age (n = 127)	Patients 50 to 59 Years of Age (n = 115)	Patients 20 to 49 Years of Age (n = 568)*	P Value
Median age (range), *y*	36 (20–89)	67 (60–89)	54 (50–59)	30 (20–49)	
Men, *n (%)*†	438 (54)	52 (41)	54 (47)	332 (59)	<0.001
Neutrophil count at diagnosis, *n (%)*†					
$<0.2 \times 10^9$ cells/L	206 (26)	22 (17)	25 (22)	159 (28)	
$0.2–0.5 \times 10^9$ cells/L	292 (36)	56 (44)	44 (38)	192 (34)	
$>0.5 \times 10^9$ cells/L	269 (33)	39 (31)	38 (33)	192 (34)	
Unknown	43 (5)	10 (8)	8 (7)	25 (4)	>0.056
Cause of aplastic anemia, *n (%)*†					
Idiopathic	551 (68)	93 (74)	84 (73)	374 (65)	
Viral	37 (5)	0 (0)	3 (3)	34 (6)	
Drugs	116 (14)	17 (13)	21 (18)	78 (13)	
Other	106 (13)	17 (13)	7 (6)	82 (14)	0.0032

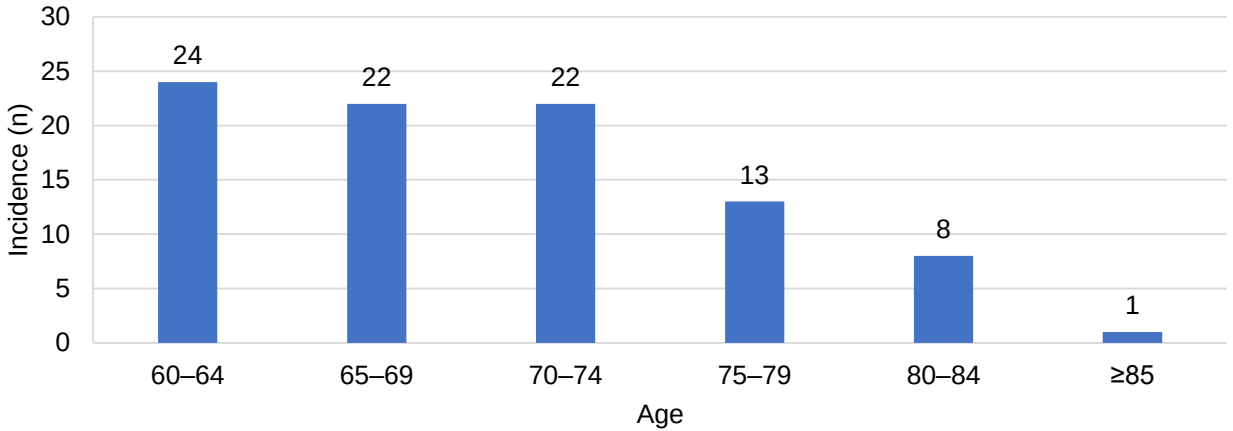
- Almost no patients have inherited bone marrow failure[2]
- Differential diagnosis is not always easy between AA and hypoplastic MDS[3,4]
- Increase of somatic mutations with age[5]

AA, aplastic anaemia; EBMT, European Society for Blood and Marrow Transplantation; MDS, myelodysplastic syndromes.

1. Used with permission of American College of Physicians, from Effectiveness of immunosuppressive therapy in older patients with aplastic anemia. Tichelli A, *et al. Ann Intern Med.* 1999;130(3):193–201; permission conveyed through Copyright Clearance Center, Inc.; 2. Peffault de Latour R, personal knowledge of the data; 3. Bennett JM and Orazi A. *Haematologica.* 2009;94(2):264–8; 4. Bono E, *et al. Leukemia.* 2019;33(10):2495–505; 5. Yoshizato T, *et al. N Engl J Med.* 2015;373:35–47.

IST: The French experience (specificity)

Incidence of aplastic anaemia according to age (88 patients, >60 years)[1]



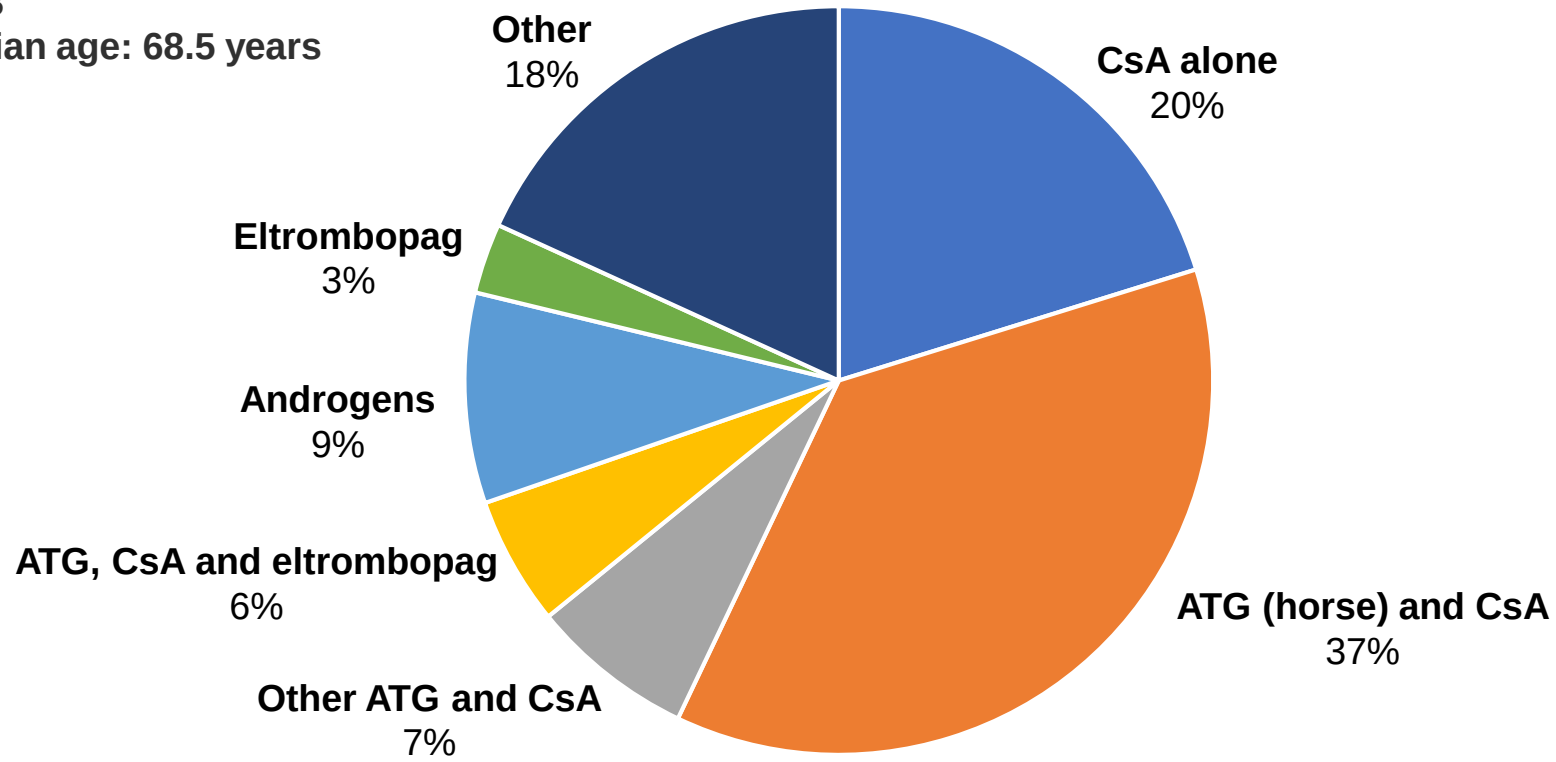
Cytogenetic analysis was performed in 80 aplastic anaemia patients over 60 years old in a retrospective study:[2]

- Normal results: 80%
- Failure: 11%
- Cytogenetic abnormalities: 8% (n=6, two delY, one del13p, one del4q, one split of IgH locus and one tri8)
- Unknown: 1%

IgH, immunoglobulin heavy.
1. Peffault de Latour, unpublished data; 2. Contejean A, *et al. Haematologica*. 2019;104(2):256–62.

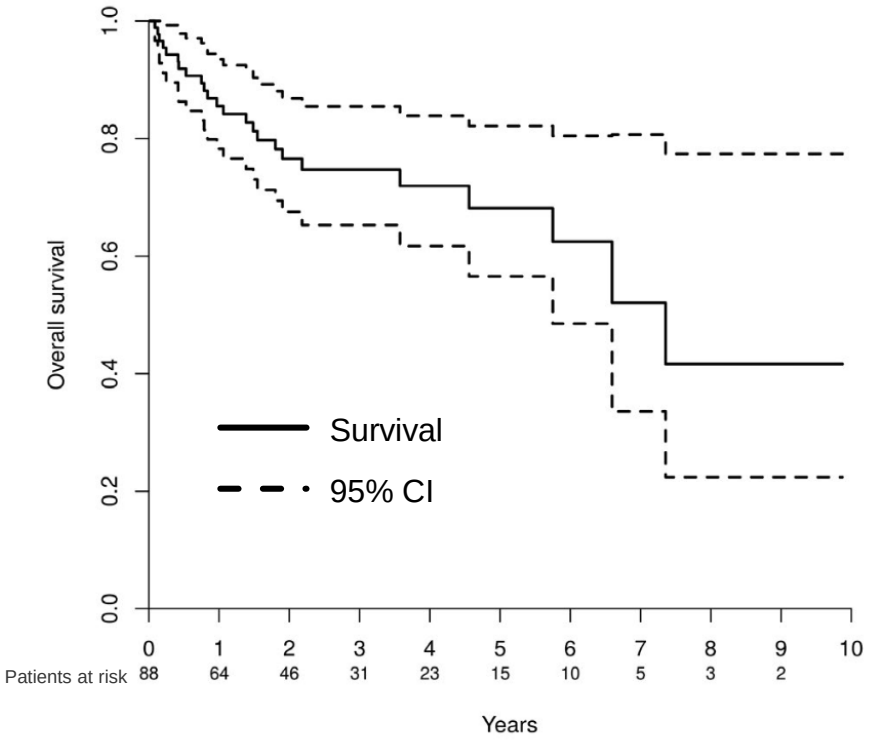
The French experience: 1st line treatment

n=88
Median age: 68.5 years



Please refer to the SmPC for full prescribing information.
ATG, anti-thymocyte globulin; CsA, ciclosporin A.
Contejean A, *et al. Haematologica.* 2019;104(2):256–62.

The French experience: mortality



- Survival at 1 year: 84.7%[2]
- Survival at 3 years: 74.7%[1]
- Median OS: 7.4 years[1]

- 88 patients, 24 deaths:[1]
  - Infection: 9 (38%)
  - Haemorrhage: 4 (17%)
  - Palliative care: 5 (21%)
  - Unknown: 6 (25%)

The survival curve (solid line) was obtained using the Kaplan-Meier estimator. Dashed lines represent confidence intervals (CI 95%).
CI, confidence interval; OS, overall survival.
1. Used with permission of Ferrata Storti Foundation, from Aplastic anemia in the elderly: a nationwide survey on behalf of the French Reference Center for Aplastic Anemia. Contejean A, *et al. Haematologica.* 2019;104(2):256–62; permission conveyed through Copyright Clearance Center, Inc.; 2. Peffault de Latour R, personal knowledge of the data.

IST: The French experience (factors associated with mortality)

	Univariable analysis		Multivariable analysis	
	HR (CI95%)	*P*	HR (CI95%)	*P*
Male	1.74 (0.76;3.99)	0.19	–	–
Age (per year)	1.05 (0.99;1.11)	0.079	1.07 (1.01;1.14)	0.03
Charlson comorbidity index (for each one-point increase)	1.38 (1.11;1.72)	0.0043	1.34 (1.07;1.67)	0.01
Performance status (for each one-point increase)	1.77 (1.11;2.83)	0.017	–	–
Weight (for each one-kg increase)	1.03 (1;1.07)	0.059	–	–
SAA	1.24 (0.45;3.45)	0.68	–	–
vSAA	3.02 (1.12;8.12)	0.029	3.67 (1.51;8.91)	0.004
PNH clone ≥ 5%	0.66 (0.09;5)	0.69	–	–

ATG, anti-thymocyte globulin; CI, confidence interval; CsA, ciclosporin A; HR, hazard ratio; PNH, paroxysmal nocturnal hemoglobinuria; SAA, severe aplastic anaemia; vSAA, very severe aplastic anaemia.

IST: The French experience (response to treatment in older patients)

ATG + CsA (all patients)
- 62%
- 70% 1st line

CsA alone
- 35%
- 39% 1st line

Eltrombopag
- 22%

Androgens
- 21%

ATG + CsA (>70 years of age)
- 81%

Impact of treatment on overall response, after adjustment for treatment line, disease severity and performance status (multivariable analysis, with ATG-CsA as a baseline)

	OR (CI95%)	*P*
ATG-CsA	1	1
CsA alone	0.35 (0.13;0.96)	0.042
Eltrombopag alone	0.12 (0.03;0.54)	0.0057
Androgens alone	0.17 (0.05;0.58)	0.0047
Other	0.24 (0.09;0.63)	0.0038

Age is not a limiting factor to aplastic anaemia treatment with ATG and CsA

Please refer to the SmPC for full prescribing information.
ATG, anti-thymocyte globulin; CI, confidence interval; CsA, ciclosporin A; OR, odds ratio.
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The Spanish experience: treatment in older patients

Treatment employed based on the patient's age

Treatments	Total ($N=95$)	<60 ($N=46$)	≥ 60 ($N=49$)
First-line treatment, n (%)			
ATG/CsA	42 (44.2)	23 (50.0)	19 (38.8)
ATG/CsA/EPAG	7 (7.3)	5 (10.9)	2 (4.1)
CsA alone	28 (29.5)	13 (28.3)	15 (30.6)
CsA/EPAG	5 (5.3)	1 (2.2)	4 (8.2)
CsA/Androgens	3 (3.1)	1 (2.2)	2 (4.1)
CsA/Rituximab	1 (1.1)	0 (0.0)	1 (2.0)
Androgens	1 (1.1)	0 (0.0)	1 (2.0)
EPAG/Androgens	1 (1.1)	0 (0.0)	1 (2.0)
Prednisone	1 (1.1)	0 (0.0)	1 (2.0)
IVIG	1 (1.1)	1 (2.2)	0 (0.0)
HSCT	1 (1.1)	1 (2.2)	0 (0.0)
No treatment initiated	4 (4.2)	1 (2.2)	3 (6.1)
Second-line treatment, n			
ATG ± CsA	12	7	5
EPAG	7*	4*	3
HSCT	2	2	0

National observational and descriptive study that included 95 patients diagnosed with AA with a median age of 61

First-line treatment regimens that included ATG were considered optimal

These data indicate an improvement in prognosis in the past decade, particularly in middle-aged and elderly patients

*+ CsA (n = 1),+ tacrolimus (n = 1).
Please refer to the SmPC for full prescribing information.
ATG, anti-thymocyte globulin; CsA, ciclosporin A; EPAG, eltrombopag; HSCT, haematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin.

What about BMT?

TO THE EDITOR:

Transplant outcome for patients with acquired aplastic anemia over the age of 40: has the outcome improved?

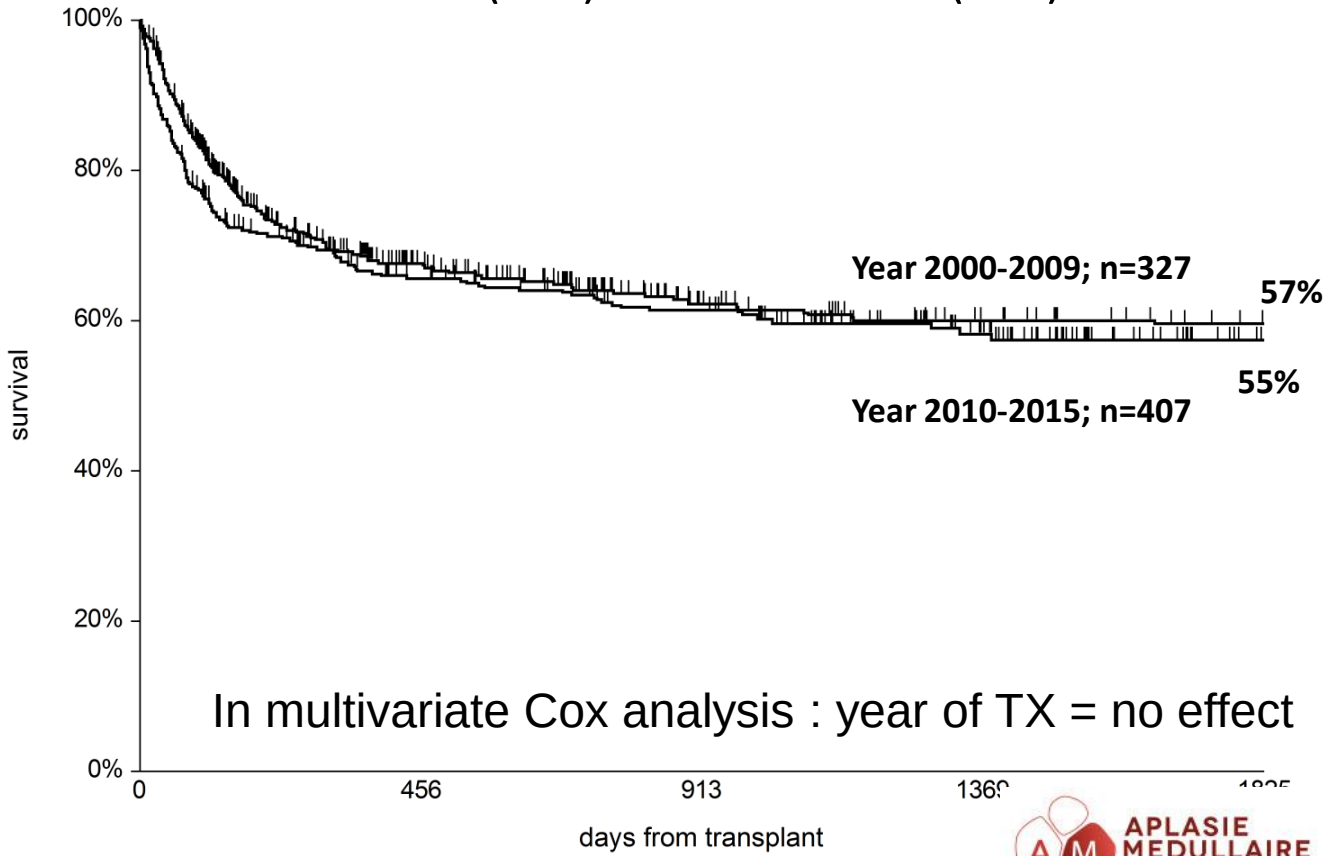
Sabrina Giammarco,[1] Regis Peffault de Latour,[2] Simona Sica,[1] Carlo Dufour,[3] Gerard Socie,[2] Jakob Passweg,[4] Nicolaus Kro¨ ger,[5] Eefke Petersen,[6] Maria Teresa Van Lint,[7] Rosi Oneto,[1] Alessio Signori,[8] and Andrea Bacigalupo,[1] for the European Group for Blood and Marrow Transplantation Severe Aplastic Anemia Working Party

Blood 2018; 17:1989

Year of transplant	2001-2009	2010-2015	
N patients	**329**	**439**	
Median age (rang)	50 (40-69)	52 (40-77)	0.001
>60 years	12%	21%	0.001
Alternative donor	29%	52%	0.001
Interval Dx-BMT days	246 (10-10340)	313 (11-13512)	-

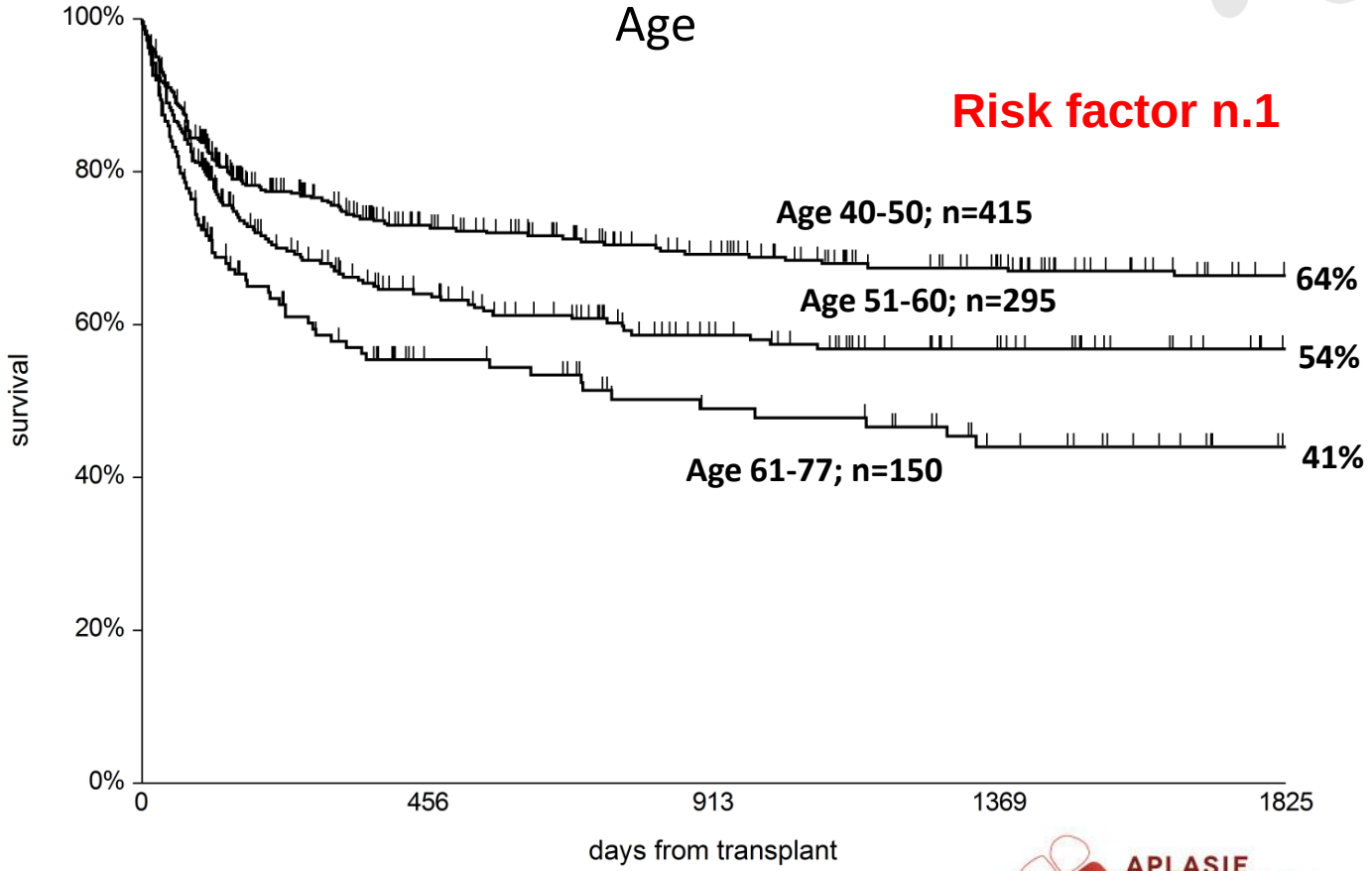
Outcome of acquired SAA >= 40 years

2000-2009 (327) and 2010-2015 (407)



In multivariate Cox analysis : year of TX = no effect

Outcome of acquired SAA >= 40 years



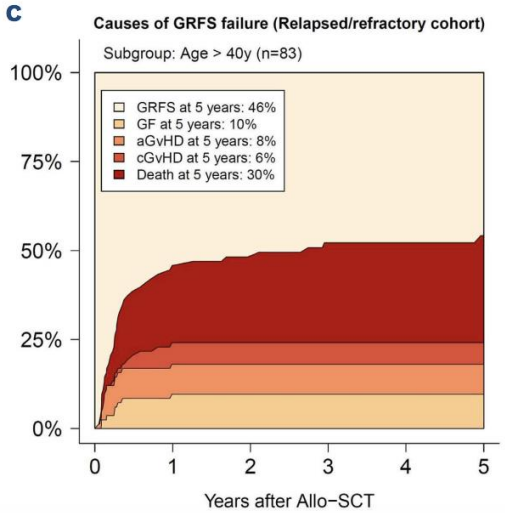
Graft versus host disease and relapse/rejection-free survival

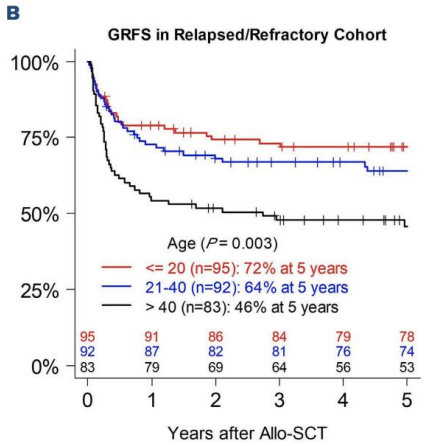
ARTICLE - Aplastic Anemia

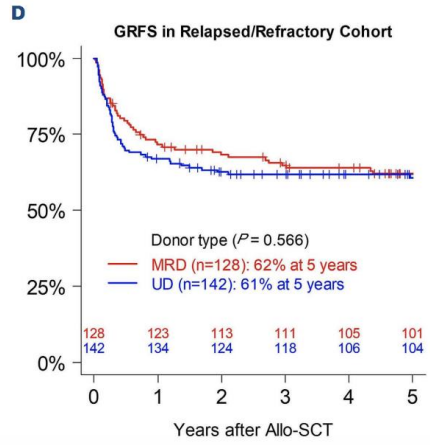
Graft-*versus*-host disease and relapse/rejection-free survival after allogeneic transplantation for idiopathic severe aplastic anemia: a comprehensive analysis from the SAAWP of the EBMT

Raynier Devillier,[1] Dirk-Jan Eikema,[2] Carlo Dufour,[3] Mahmoud Aljurf,[4] Depei Wu,[5] Alexei Maschan,[6] Alexander Kulagin,[7] Constantijn J. M. Halkes,[8] Matthew Collin,[9] John Snowden,[10] Cécile Renard,[11] Arnold Ganser,[12] Karl-Walter Sykora,[12] Brenda E. Gibson,[13] Johan Maertens,[14] Maija Itäla-Remes,[15] Paola Corti,[16] Jan Cornelissen,[17] Martin Bornhäuser,[18] Mercedes Colorado Araujo,[19] Hakan Ozdogu,[20] Antonio Risitano,[21] Gerard Socie[22] and Regis Peffault de Latour[22]

Sept 2023

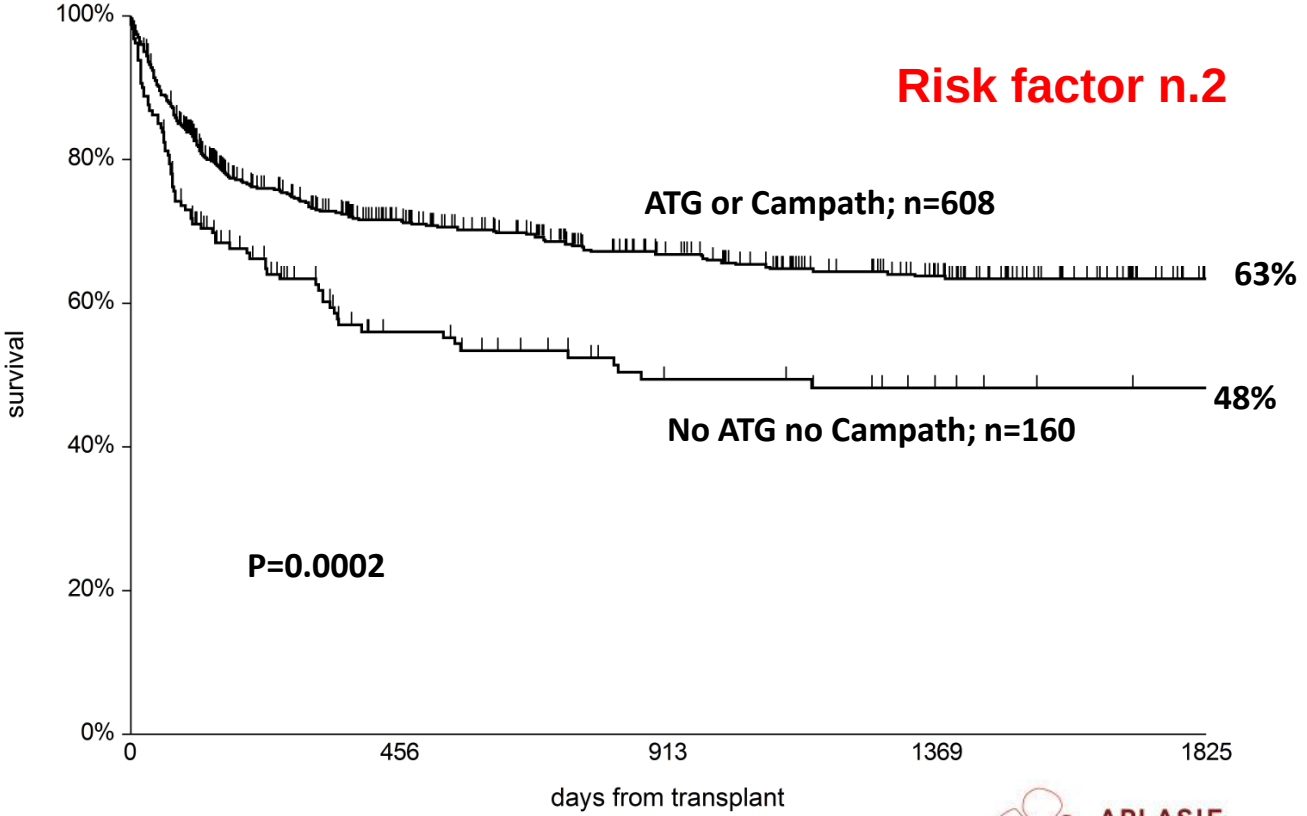






Outcome of acquired SAA >= 40 years

ATG or Campath versus no ATG /Campath



Campath

UK experience

REGULAR ARTICLE

blood advances

Similar outcomes of alemtuzumab-based hematopoietic cell transplantation for SAA patients older or younger than 50 years

Vipul Sharad Sheth,[1] Victoria Potter,[1] Shreyans A. Gandhi,[1,2] Austin Gladston Kulasekararaj,[1] Hugues de Lavallade,[1,2] Petra Muus,[1] Antonio Pagliuca,[1,2] Carmel F. M. Rice,[1] Varun Mehra,[1] Francesco Grimaldi,[2,3] Shafqat Inam,[1] Linda D. Barber,[2] Ghulam J. Mufti,[1,2] and Judith C. Marsh[1,2]

[1]Department of Haematological Medicine, King's College Hospital, London, United Kingdom; [2]Department of Haematological Medicine, King's College London, London, United Kingdom; and [3]Department of Hematology, Federico III University of Naples, Naples, Italy

- 65 consecutive patients (38 patients < 50 years / 27 aged 50 or more)
- Older cohort: 21 MUD (3 MMUD) and 6 siblings
- FCC conditioning regimen: 30 mg/m2 (4 days), CY 300 mg/m2 (4 days) and alemtuzumab (0.2 mg/kg each day, days -7 to -3).

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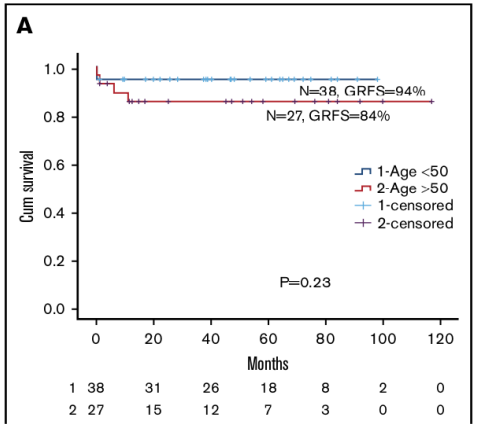
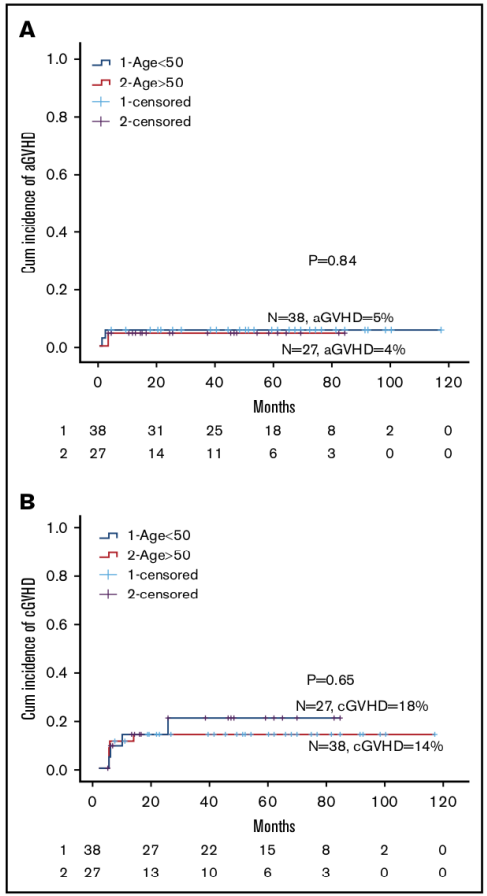
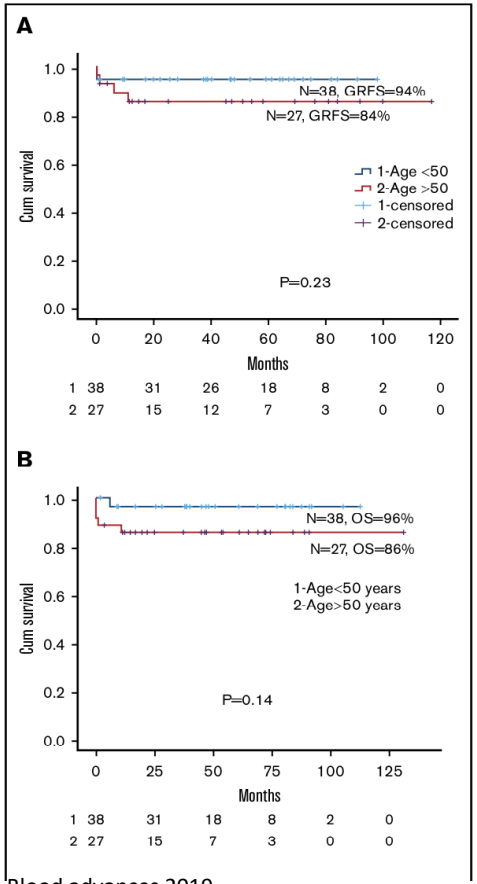
Campath (UK experience)

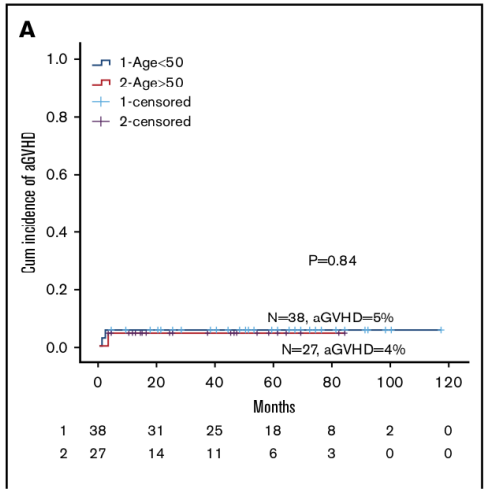




Shed *et al*, Blood advances 2019

Campath (UK experience)





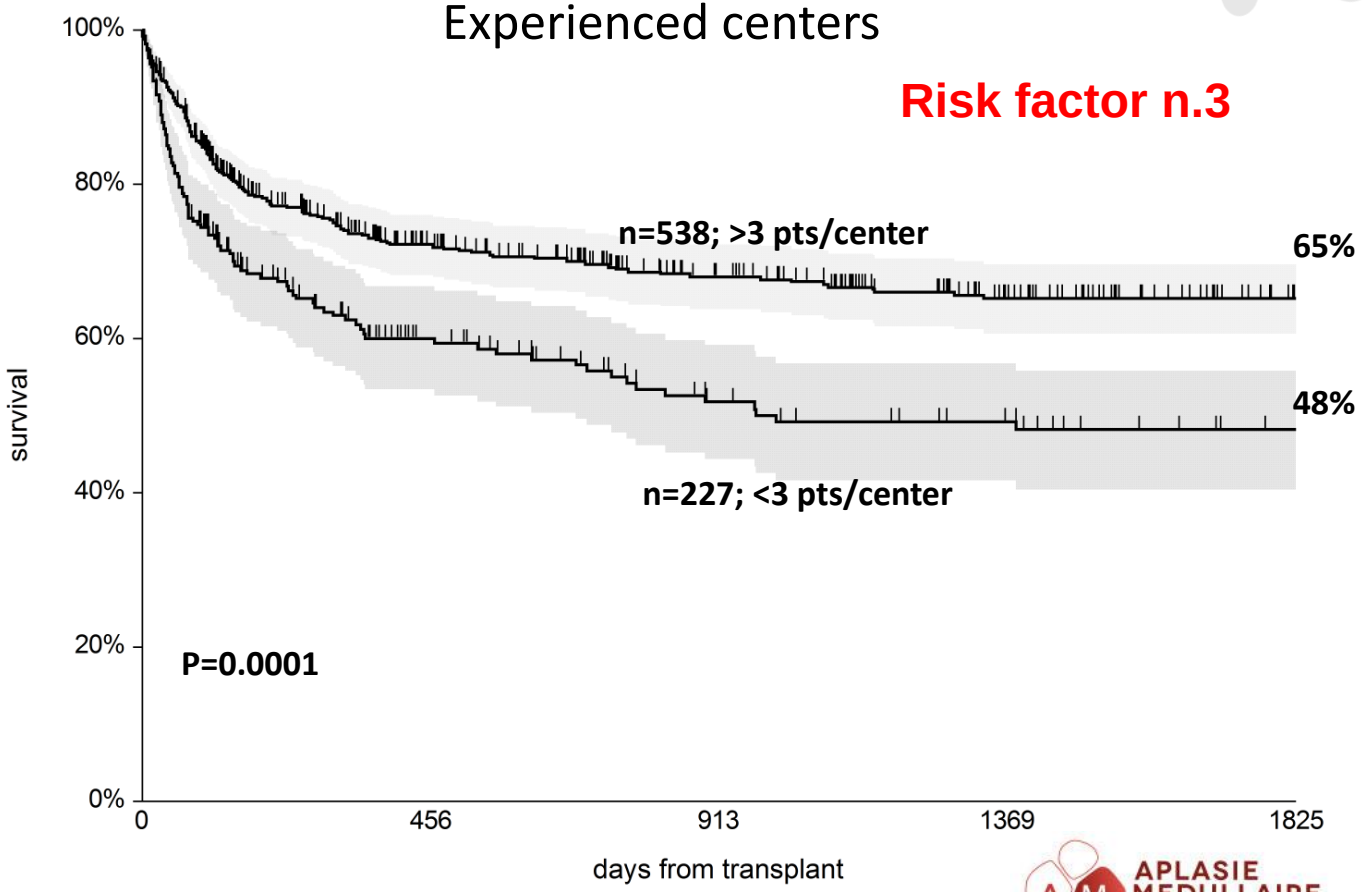
- <50: fungal disease (2); MOF (1)
- 50 or more: fungal disease (3); MOF and CMV (1)

Shed *et al*, Blood advances 2019

Outcome of acquired SAA >= 40 years

Experienced centers

Risk factor n.3



Outcome of acquired SAA >= 40 years

2000-2009 (327) and 2010-2015 (407)

Cox analysis

		HR	P
Center >3 pts		0.59	0.0001
Age	50-59	1.3	0.05
	>60	2.0	0.0001
ATG/C	yes	0.3	0.0001
Year	≥2010	0.9	0.5
DxTx >180		1.17	0.2
Donor	UD	1.24	0.1

Outcome of acquired SAA >= 40 years

Age > 40 (50) remains a significant risk factor for BMT

results have not improved over the past years

additional risk factors are

. No ATG/CAMP

. Unexperienced centers

different transplant platform needed

Different transplant platform needed

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/issn/0268960X

Review

Combining PTCy and ATG for GvHD prophylaxis in non-malignant diseases

Amy E. DeZern [a,*], Robert A. Brodsky [b]

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[b] *Division of Hematology, The Johns Hopkins University School of Medicine, 720 Rutland Avenue | Ross 1025, Baltimore, MD 21205, United States of America*

Different transplant platform needed

Bone marrow transplantation for acquired aplastic anemia: What's new

Andrea Bacigalupo [a,b,*], Giulia Benintende [b]

[a] Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy
[b] Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy

Furthermore, PTCy can be of use even in SIB BMT. Small case series from the Baltimore group, including old patients at high risk of graft failure and GvHD due to massive transfusions and alloimmunization, demonstrated its feasibility [41]. Research also investigated the possibility to use PTCy as the sole GvHD prophylaxis compared to CsA and MTX in patients receiving PBSC, owing lower rates of grade II-IV acute GvHD (22.2% vs 37.1%, p = 0.56) and chronic GvHD (22.7% vs 63.6%, p = 0.013) but higher rate of viral infections (60% vs 23.3%, p = 0.008) [42]. The combination of PTCy with standard immunosuppression (CsA + MTX) has proven superiority to CsA + MTX alone in patients receiving PBSC – who are known to have higher rates of graft failure and GvHD – with lower grade II-IV acute GvHD (22-6% vs 52.2%, p = 0.0015) but similar chronic GvHD (16.7% vs 26%, p = 0.306) [43].

Further studies are needed to explore the use of PTCy for SIB BMT with bone marrow stem cells source and to validate its role in MUD BMT.

- The combination of Flu and CY has changed the paradigm of conditioning regimen.
- PTCy may be the turning point of GvHD prophylaxis, but new trials are needed to validate its use with donors other than HLA mismatched related HAPLO donors.

Different transplant platform needed

Bone marrow transplantation for acquired aplastic anemia: What's new

Andrea Bacigalupo [a,b,*], Giulia Benintende [b]

[a] Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy
[b] Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy

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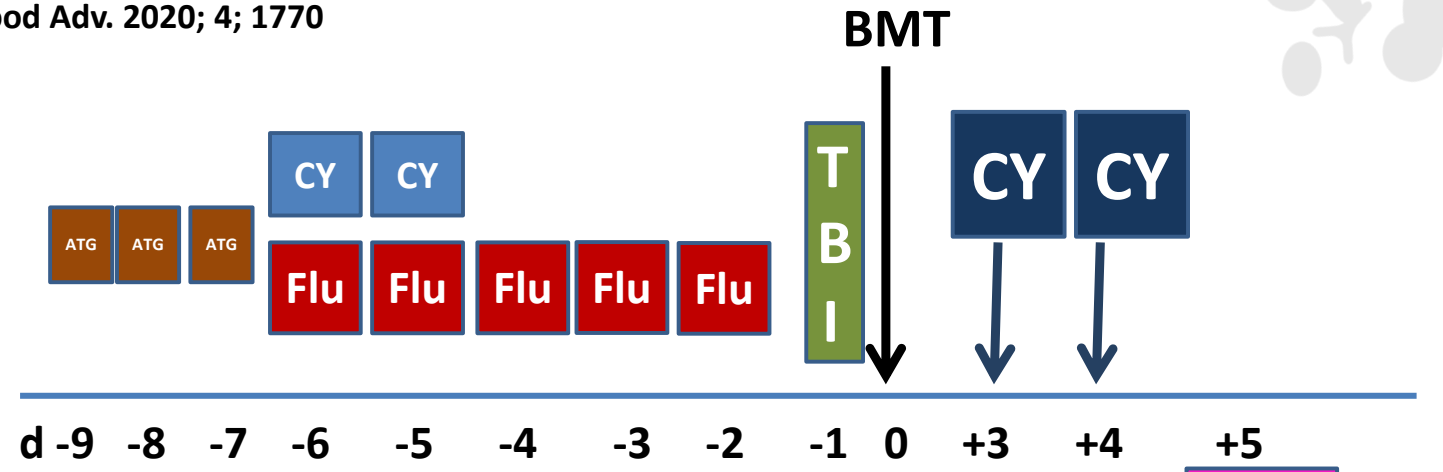
De Zern Blood Adv. 2020; 4; 1770



CY Cyclophosphamide 14.5 mg/kg

Flu Fludarabine 30 mg/m^2

ATG Rabbit ATG 0.5-2 -2 mg/kg

TBI Total Body Irradiation 2 Gy

CsA Cyclosporin 3 mg/kg

MMF Mycophenolate 30 mg/kg

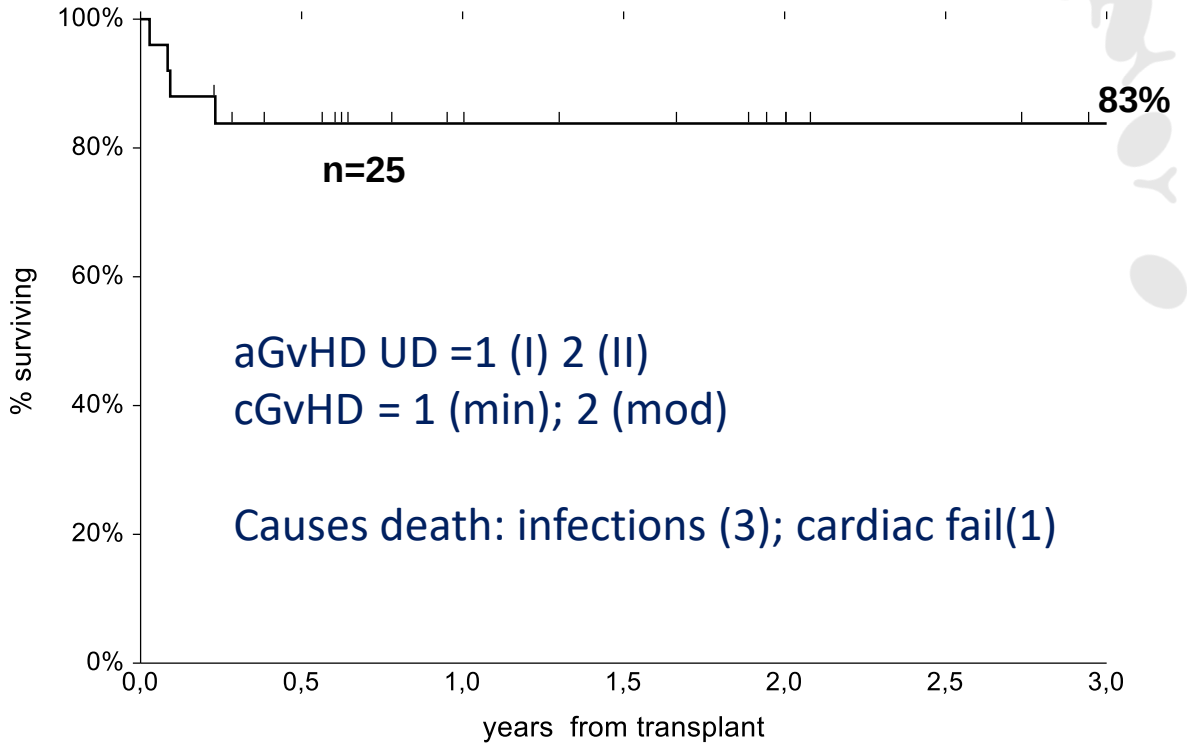
CY Cyclophosphamide 50 mg/kg

HSCT for older AA patients – FCA-TBI 2gray / PTCy CsA+MMF

Roma, Perugia, Cuneo, Alessandria, Milano, Bolzano, Verona, Udine, Palermo, Torino

MUD =16
UD 7/8 = 6
HAPLO = 2
SIB =1

Age = 42 (26-70)
Int DxTx 536 (90-3000)
Engr PMN 500 = day 19
Engr Plt 20 = day 22



aGvHD UD =1 (I) 2 (II)
cGvHD = 1 (min); 2 (mod)

Causes death: infections (3); cardiac fail(1)

Andrea Bacigalupo, unpublished data

Conclusion – APARR ☺

Allogeneic hematopoietic stem cell transplantation in Patients Aged 40 to 60 years old with acquired aplastic anemia Refractory or in Relapse after immunosuppression

- **Main endpoint:** to demonstrate a benefit in term of the 2-year GRFS (Graft Versus Host Disease {GvHD} and Relapse/rejection-Free Survival) from 50% (historical rates in patients with refractory/relapse AA undergoing HSCT) up to 70% using marrow as source of stem cells and a PTCy strategy.
- **Design:** A phase II multicenter, national, prospective cohort study in patients aged from 40 to 60 years with refractory/relapse AA after IST eligible to HSCT.
- **Regimen:** FCA-TBI / Bone marrow / PTCy+CSA+MMF
- **Number of participants:** 52 patients in 28 centres
- **Duration of the study:** Inclusion period: 36 months / Participation period (treatment + follow-up): 24 months. Total duration: 60 months

Summary: conclusion

- The incidence of aplastic anemia is higher in older patients
- Older patients are rarely offered the reference treatment ATG, although treatment type is not associated with worse overall survival (age, comorbidities and disease severity impact overall survival)
- Transplantation is an option between 40 and 60 and rarely after 60 years of age)

> Clinical trials

Please refer to the SmPC for full prescribing information.
ATG, anti-thymocyte globulin; CsA, ciclosporin A.
Peffault de Latour R, personal opinion.

Thank you!

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APLASIE MEDULLAIRE centre de référence

MaRIH Filière de santé Maladies Rares ImmunoHématologiques

SFGM TC Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

2016 EBMT European Society for Blood and Marrow Transplantation