La fotoaferesi extracorporea va utilizzata precocemente nel trattamento della GvHD acuta e cronica?

Le ragioni del NO

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UNIVERSITÀ DEGLI STUDI DI UDINE
hic sunt futura

CONVEGNO EDUCAZIONALE GITMO

HOT QUESTIONS IN TRASPLANTATION AND CELLULAR THERAPIES

Udine
13-14 novembre 2023
Aula Polifunzionale - Ospedale di Udine

Conflitto di interessi

Sono uno specialista ematologo e lavoro in un Servizio di Aferesi

L´unico trattamento per la GvHD che somministro é la fotoaferesi extracorporea (ECP)

ECP nel trattamento della GvHD acuta

Prophylaxis and management of graft versus host disease after stem-cell tra malignancies: upd European Society f

Lancet Haematol 2020; e157–67

There is no standard second-line treatment for acute GVHD. Current practice is to prescribe one of the following drugs: alemtuzumab, α1-antitripsin, basiliximab, cellular therapies (eg, mesenchymal cells and regulatory T-cells) daclizumab, extracorporeal photopheresis, faecal microbiota transplantation, JAK inhibitors (eg, ruxulotinib which is FDA approved), mycophenolate mofetil, methotrexate, pentostatin, rATG, sirolimus, or vedolizumab; for second-line treatment of acute GVHD, centres should follow their institutional guidelines, and patients should be treated in clinical trials when possible

First-line treatment of acute GVHD is m initial dose of 2 mg/kg per day; predniso 2·0–2·5 mg/kg per day is regarded as eq methylprednisolone to the 2 mg/kg per

ls reported a 14% decrease in the nal immunomodulating agents fliximab, and anti-IL2 antibody) ethylprednisolone (10 mg/kg per day) mpared with standard 2 mg/kg

Penack O et al., Lancet Haematol 2020

ECP nel trattamento della GvHD cronica

Prophylaxis and management of graft versus host disease after stem-cell tr malignancies: up European Societ

Lancet Haematol 2020;

67

There is no standard second-line treatment for chronic GVHD: centres should follow their institutional guidelines and enrol patients in trials whenever possible; the most common components of second-line treatment for chronic GVHD, used in addition to corticosteroids, are calcineurin inhibitors, extracorporeal photopheresis, ibrutinib (which is FDA approved), JAK inhibitors, mycophenolate mofetil, rituximab, mTOR inhibitors, pentostatin, proteasome inhibitors, and TKI

The first-line treatment of newly d

ther agents (azathioprine, ychloroquine, and cally meaningful benefit for patients with standard risk (according to NIH classification) chronic GVHD was reported[50–52]

Penack O et al., Lancet Haematol 2020

ECP

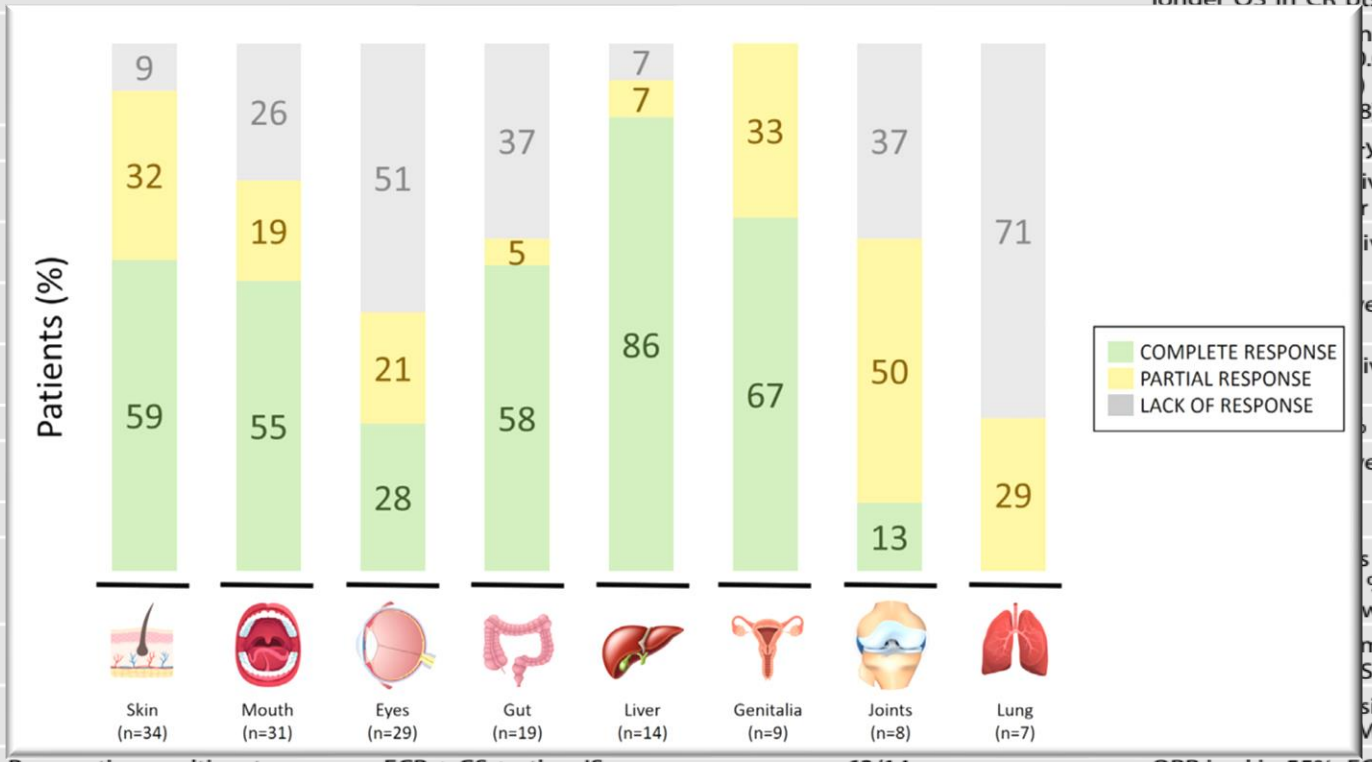
Trattamento della GvHD acuta e cronica steroido-refrattaria

Dalla seconda linea in poi

Treatment	% Overall response*	Survival
ECP	65-70	70%-78% at 1 y
Rituximab	66-86	72% at 1 y
Imatinib	22-79	75%-84% at 1.5 y
Pentostatin	53-56	34%-60% at 1-3 y
Mesenchymal stem cells	50-74	78% at 2 y
Mycophenolate mofetil	26-64	67%-96% at 1 y
mTOR inhibitor	76	72% at 3 y
Interleukin-2	52	Not reported
Other therapies summarized in other reviews**		
Calcineurin inhibitor		
High-dose methylprednisolone		
Methotrexate		
Thalidomide		
Hydroxychloroquine		
Clofazimine		
Thoracoabdominal irradiation		
Alefacept		
Infliximab		
Etanercept[70]		

Flowers ME et al., Blood 2015

Study	Trial design	Treatment	ORR %/CR%	Other results
Acute GvHD				
Greinix et al . [34] ($n = 59$)	Prospective, single-arm, phase II	ECP + CS in second-line	70/60	CR in skin 82%, liver 61% and gut 61%; 4-yr OS 47% (59% and 11% in ECP responders and non-responders); 4-yr TRM 36% (14% and 73% in ECP responders and non-responders)
Amat et al. [35] ($n = 37$)	Prospective, multicenter	ECP + CS in second-line	73/40.5	ORR in skin 71%, liver 54.5% and gut 67%; significant longer OS in CR pts (median > 47 mo vs 12 mo)
Jagasia et al. [36] ($n = 108$)				nt predictor of ORR (HR, 3.42, $p = 0.007$), .018); ECP associated with superior OS in SR aGvHD grade II and lower NRM 8)
DasGupta et al. [37] ($n = 128$)				-yr OS 56%; 2-yr TRM 34%
Worel et al. [38] ($n = 99$)				iver 61% and GI 75%; 1-yr and 5-yr TRM r and 5-yr OS 69% and 50%
Calore et al. [39] ($n = 72$, children)				iver in 84%, and gut in 71%; 5-yr OS 71%
Niittyvuopio et al. [40] ($n = 52$)				er 33%, and gut 34%; 1-yr OS 51%
Perotti et al. [41] ($n = 50$, children)				iver 67%, and gut 73%; 1-yr OS 64%
Malagola et al. [42] ($n = 45$)				and grades III/IV 67%
Messina et al. [43] ($n = 33$, children)				er 60% and gut 75%; 5-yr OS 69%
Chronic GvHD				
Flowers et al. [44] ($n = 95$; 48 vs 47)				s 7% ($p = 0.04$) and mouth 53% vs 27% % improvement of TSS at week 12 week 24 31.4% in the ECP arm.
Greinix et al. [45] ($n = 29$)				mouth 70%, and joints 36%; median % SS at week 24 25.8%
Sakellari et al. [46] ($n = 88$)				sis 83%, visceral involvement 53% and M 24%; 5-yr OS 64.5%
Gandelman et al. [47] ($n = 77$)	Prospective, multicentre	ECP + CS ± other IS	62/14	ORR in skin 55%; ECP responses independent of risk factors of poor outcome
Dignan et al. [48] ($n = 82$)	Retrospective, single center	ECP + CS ± other IS	79/na	ORR in skin 92% and mouth 91% at 6 mo; 3-yr OS 69%
Couriel et al. [49] ($n = 71$)	Retrospective, single center	ECP + CS ± other IS	61/20	ORR in skin 57%, liver 71% and mouth 78%; 1-yr OS 53%; response to ECP and platelet count at ECP start significantly predict NRM
Greinix et al. [50] ($n = 47$)	Retrospective, single center	ECP + CS ± other IS	83/na	CR in skin 68%, mouth 81%, and liver 68%



Greinix H et al., Leukemia 2022, Asenso Cantò et al., TCT 2023

Sicurezza dell´ECP: infezioni

Analysis of extracorporeal photopheresis within the frame of the WAA register

M. Blaha [a], Z. Gasova [e], G. Berlin [b], J. Audzijoniene [c], A. Griskevicius [c], J. Dykes [d], Z. Bhuiyanova [e], M. Lanska [a], T. Eich [f], H. Vrielink [h], V. Witt [i], G.C. Seval [j], O. Ilhan [j], B. Stegmayr [g,*]

560 pazienti, 13.871 procedure su 17 anni

- AEs nel 5.4% (1˚ ECP), 1.2% (successive)
- SAEs nello 0.04%
- Nessun decesso correlato all´ECP

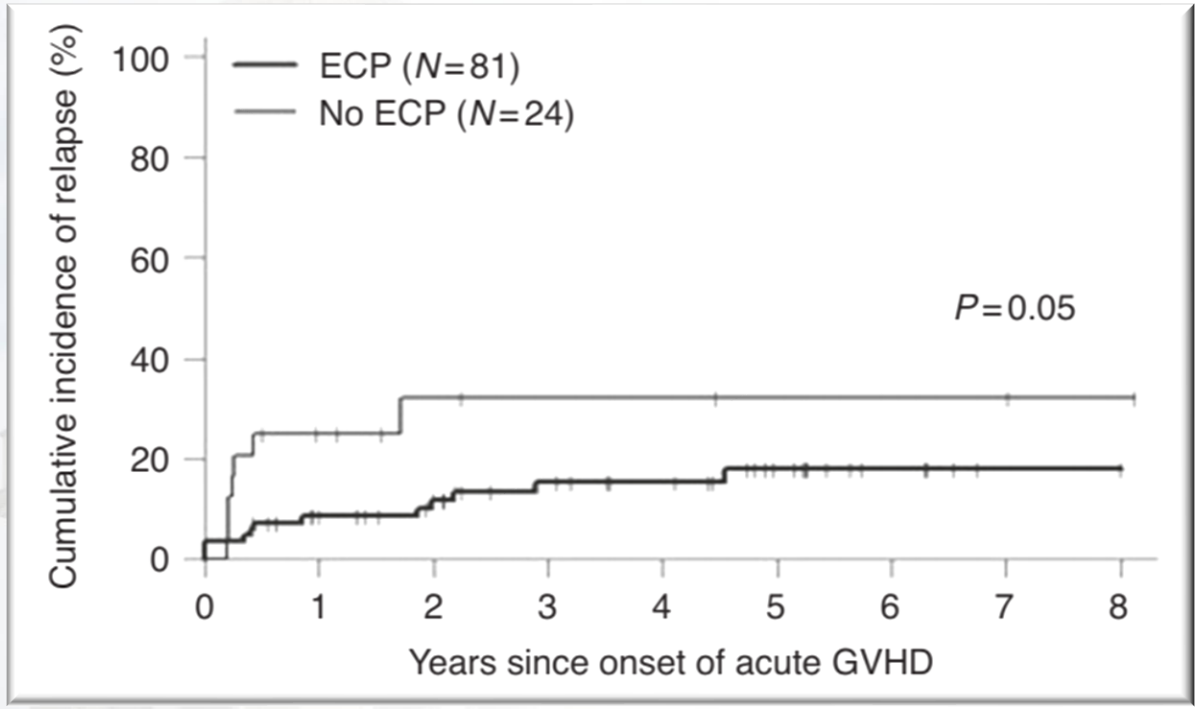
Table 4
Percentage of various adverse events within each grade (excluding access and technical problems, n = 40).

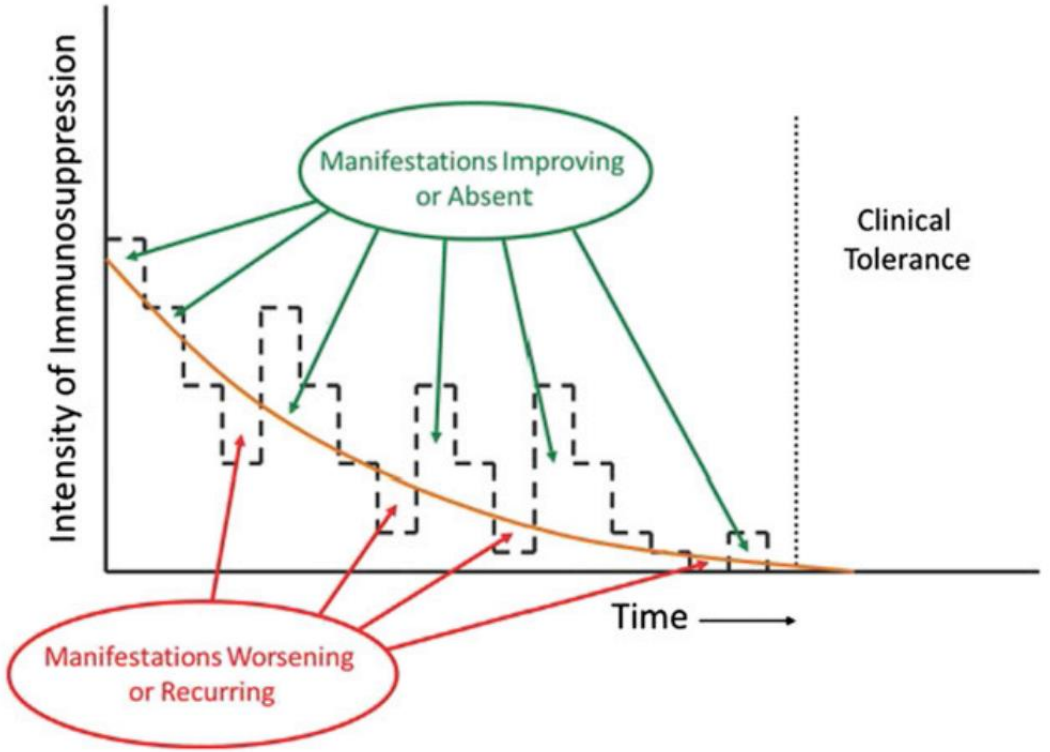
	Severe (n = 3) %	Moderate (n = 180) %	MILD (n = 27) %
Bronchospasm	33.3		3.7
Gastrointestinal bleeding	33.3		
Chills and fever	33.3		3.7
Tingling and stitching*		86.7	29.6
Hypotension		5.5	18.5
Nausea and/or vomiting		1.1	7.4
Sepsis, late complication		0.55	
Abdominal pain		0.55	0.0
Muscle cramps in foot		0.55	
Arrhythmia			11.1
Thrombophlebitis due to puncture			3.7
Itching, late complication			3.7
Local bleeding after prior surgery			7.4

* Stitching – prickly sensation.

Blaha M et al., Transf Apher Sci 2021

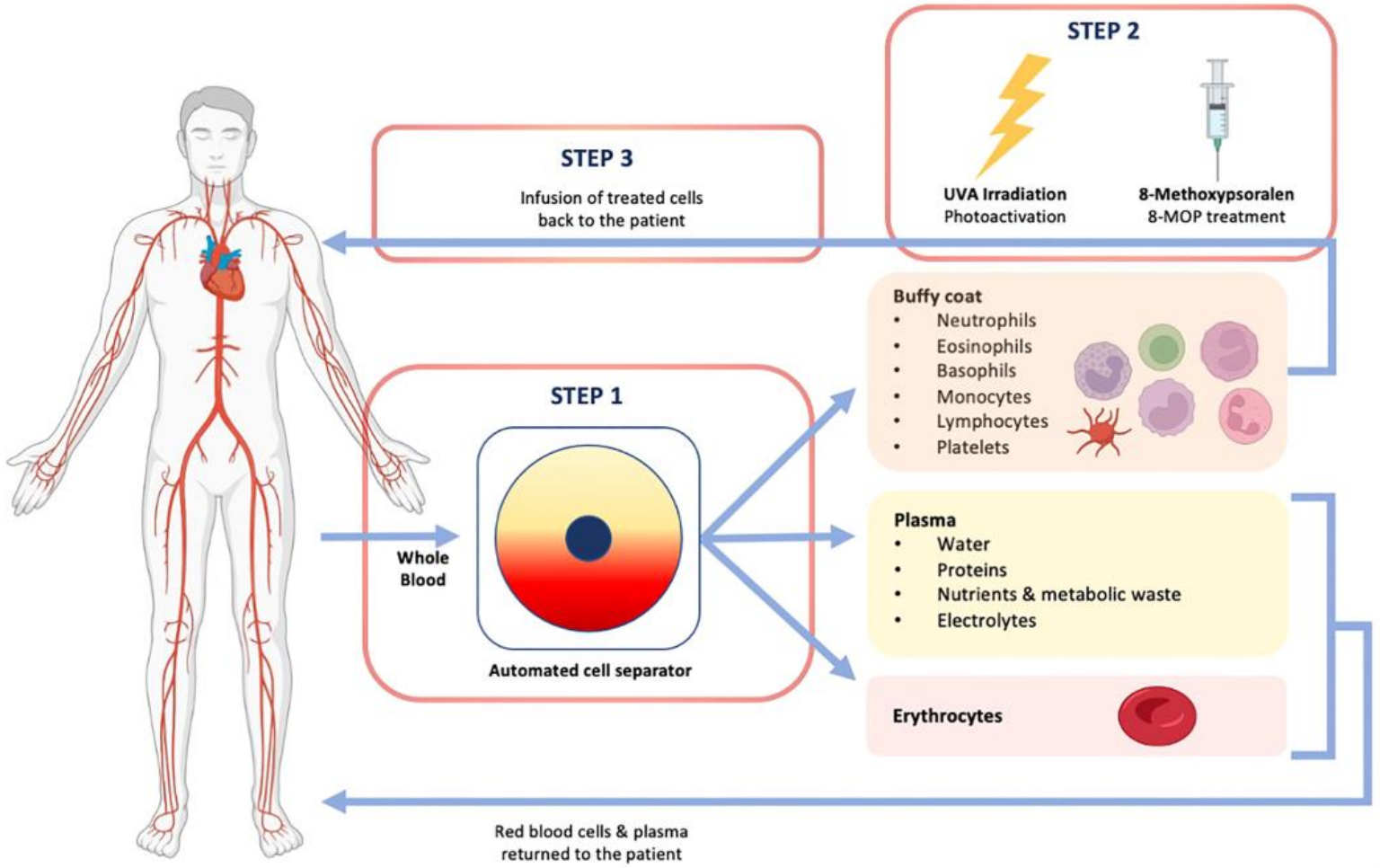
Sicurezza dell´ECP: recidiva di malattia





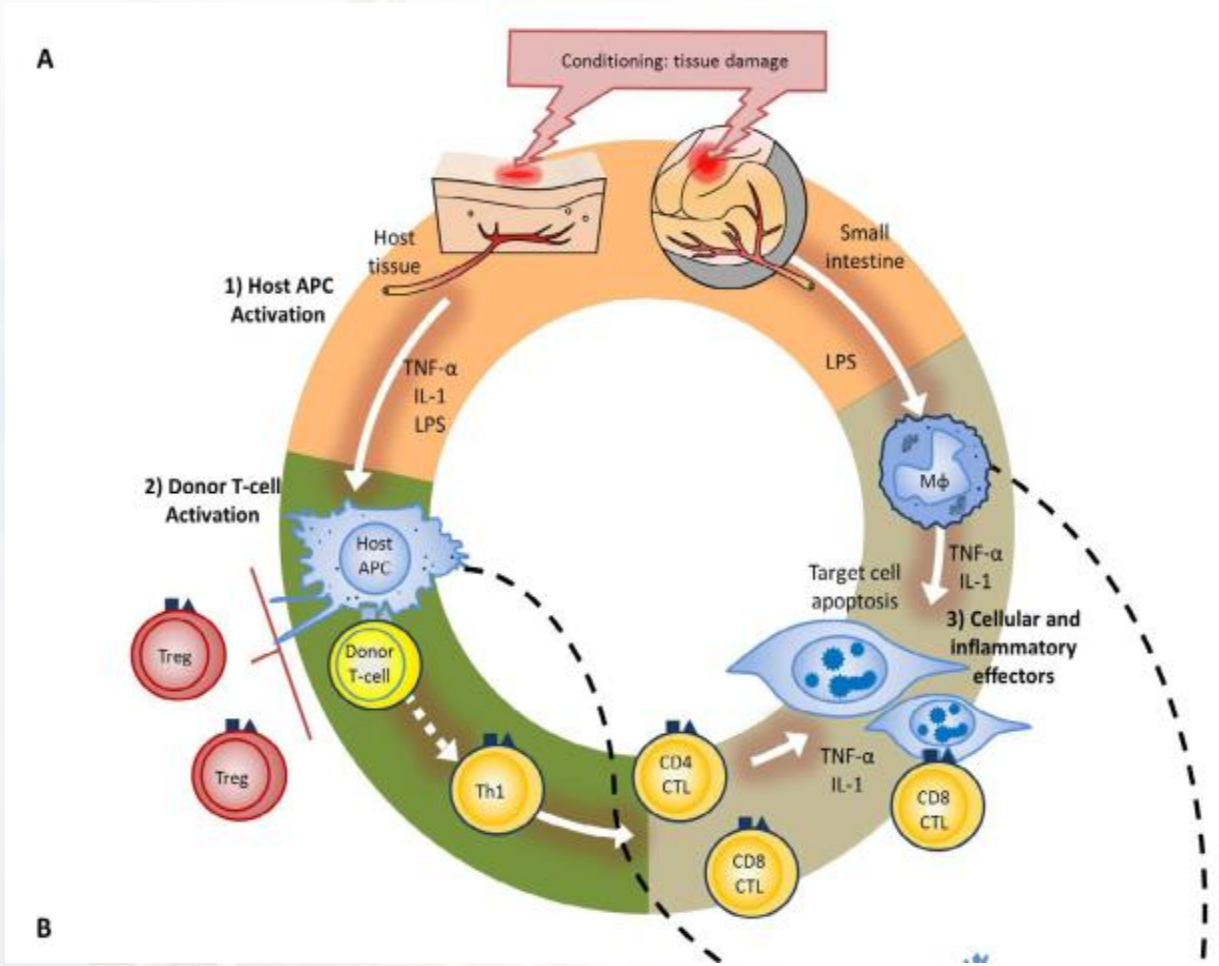
Solh M et al., BMT 2023, Flowers ME et al., Blood 2015

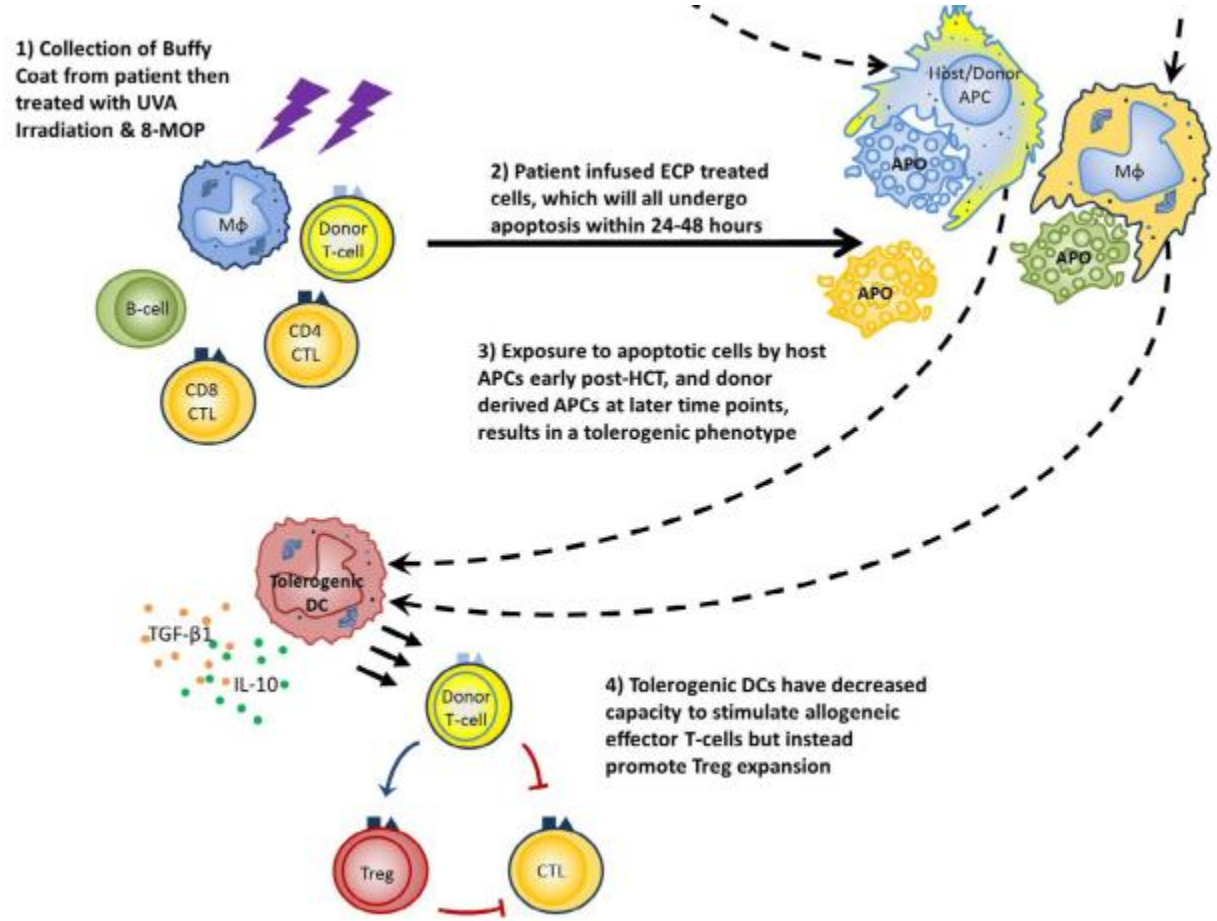
Meccanismi di azione



Bojanic I et al., Front Immunol 2023

Meccanismi di azione





Kitko C et al., Transf Apher Sci 2015

Biomarcatori

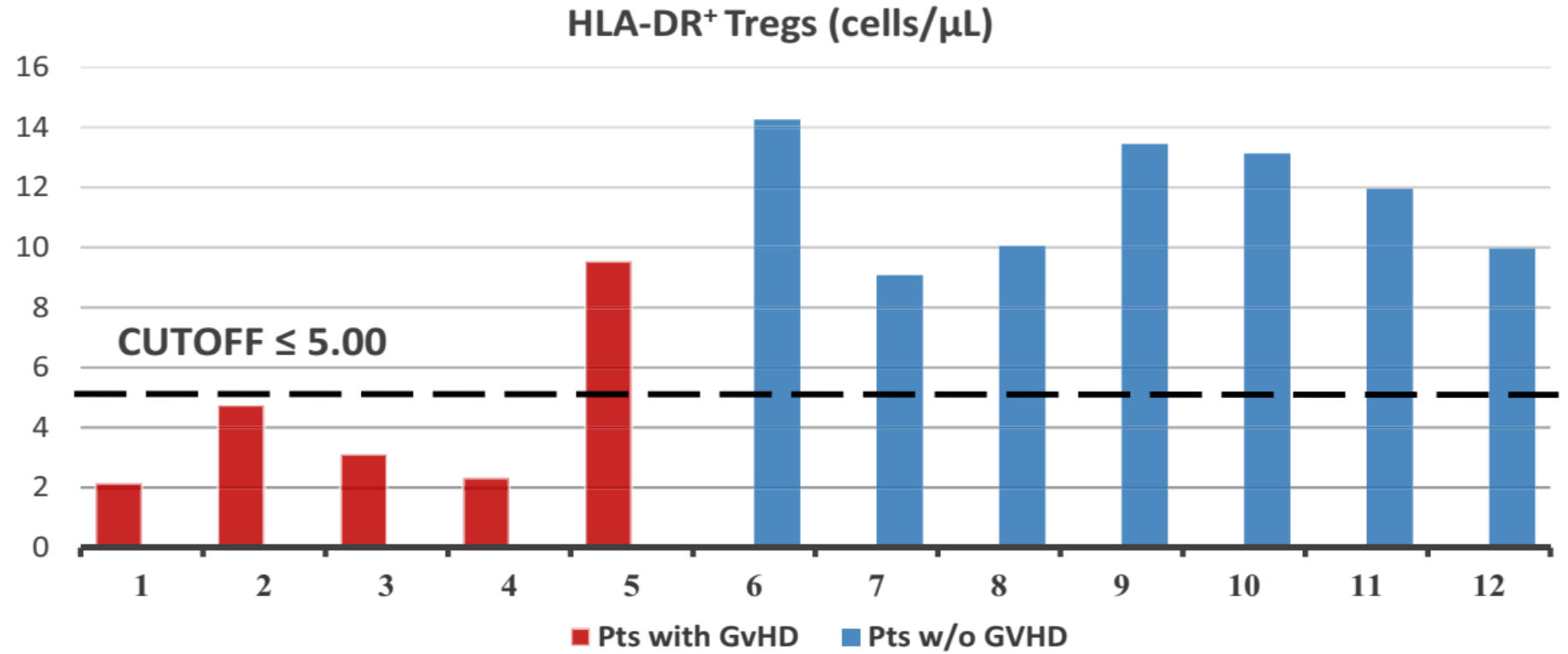
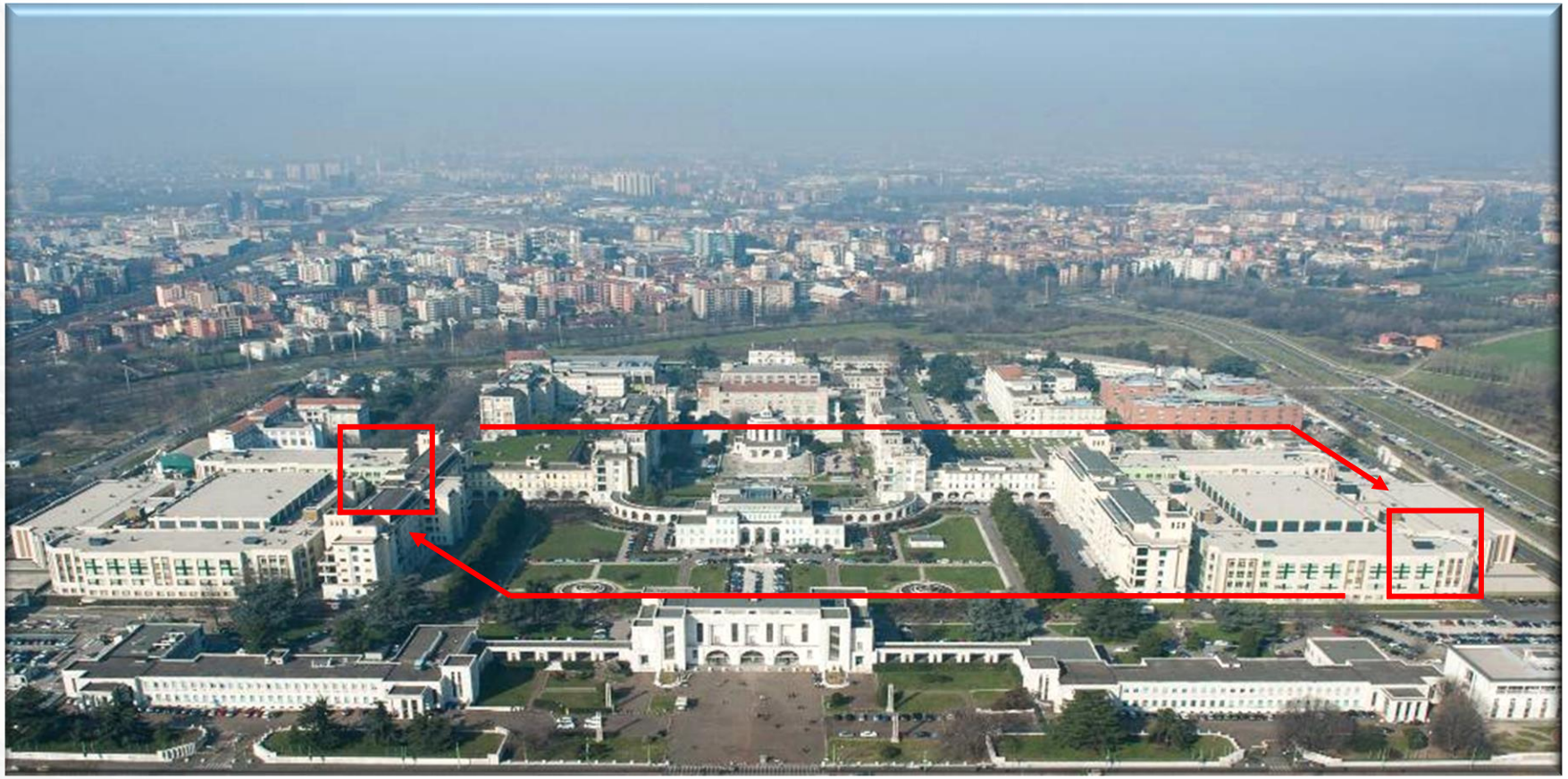


Fig. 1 Analysis of the median absolute counts of peripheral HLA-DR + Tregs in patients with and without GvHD. Data show that 20% (1 out of 5) vs. 100% (7 out of 7) of patients with HLA-DR + Tregs had values of > 5 cells/µL in the GvHD vs. non-GvHD groups, respectively ($p = 0.01$, Fisher exact test)

Crocchiolo R et al., Exp Hematol Oncol 2021

Disponibilità logistica

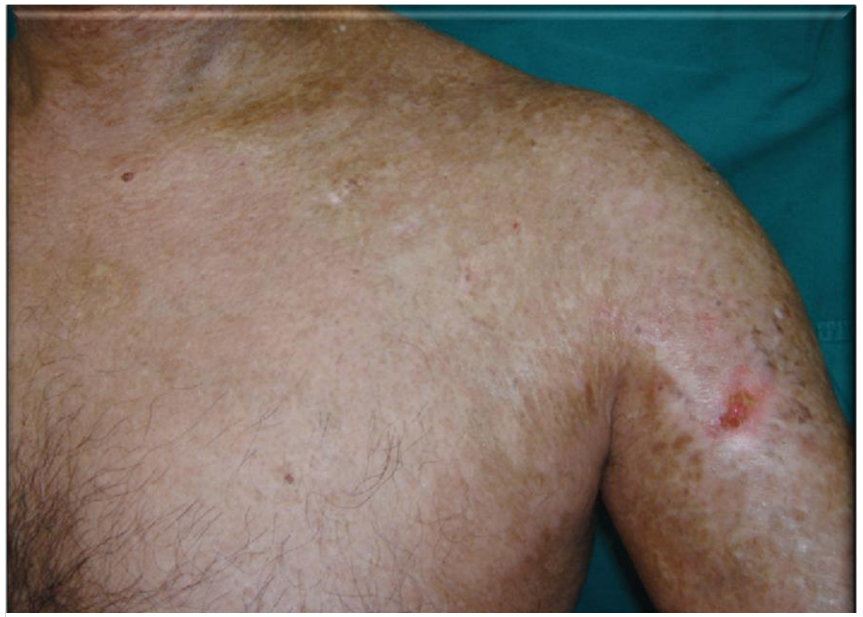


Caratteristiche del paziente candidato ad ECP

CVC

Durata del trattamento

CBC (lymphocytes, Hct, PLT)



Utilizzo «precoce» dell´ECP nel trattamento della GvHD

→ Prima linea

→ Profilassi

ECP nel trattamento di prima linea

ECP nel trattamento di prima linea

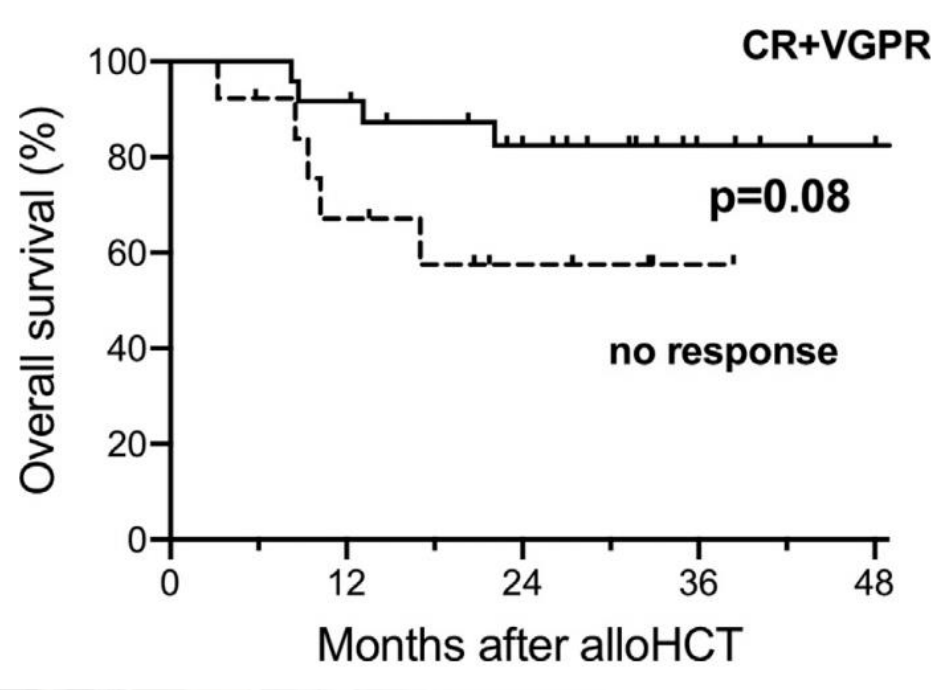


Table 2
Acute GVHD characteristics at baseline.

Revised Glucksberg criteria	Stage I	Stage II	Stage III	Stage IV
Skin, n (%)	3 (8%)	22 (59%)	12 (32%)	0
Gastrointestinal tract, n (%)	6 (16%)	0	0	0
Liver, n (%)	2 (5%)	2 (5%)	0	0
Overall grade	17 (46%)	18 (49%)	2 (5%)	0

Sestili S et al., Cytotherapy 2020

ECP nel trattamento di prima linea

Table 2. Main clinical characteristics of patients treated by ECP

	Pt 1[a]	*Pt 2*	*Pt 3*	*Pt 4*	*Pt 5*	*Pt 6*	*Pt 7*
Diagnosis	HL	HL	HL	Ewing	HL	NHL	NHL
Day diagnosis aGVHD	+48	+66	+39	+42	+32	+30	+71
Grade aGVHD	4	2	2	2	2	2	2
Delay GVHD-ECP start (day)	2	6	3	1	2	30	4
Steroids	Yes	Yes	/	/	/	Yes	Yes
Full-dose steroids (day)	12	7	/	/	/	7	3
Total number of ECP	44	28	40	10	15	9	12
Response	CR	CR	CR	CR	CR	PR	CR
Clinical response after ECP (day)	56	2	14	11	8	57	32
CMV reactivation	+	+	/	/	/	/	+
EBV reactivation	/	+	+	/	/	/	/
cGVHD	No	No	Yes	No	No	No	No

Castagna L et al., BMT 2014

ECP nel trattamento di prima linea

ARTICLE

Randomized phase II trial of extracorporeal phototherapy and steroids vs. steroids alone for newly diagnosed acute GVHD

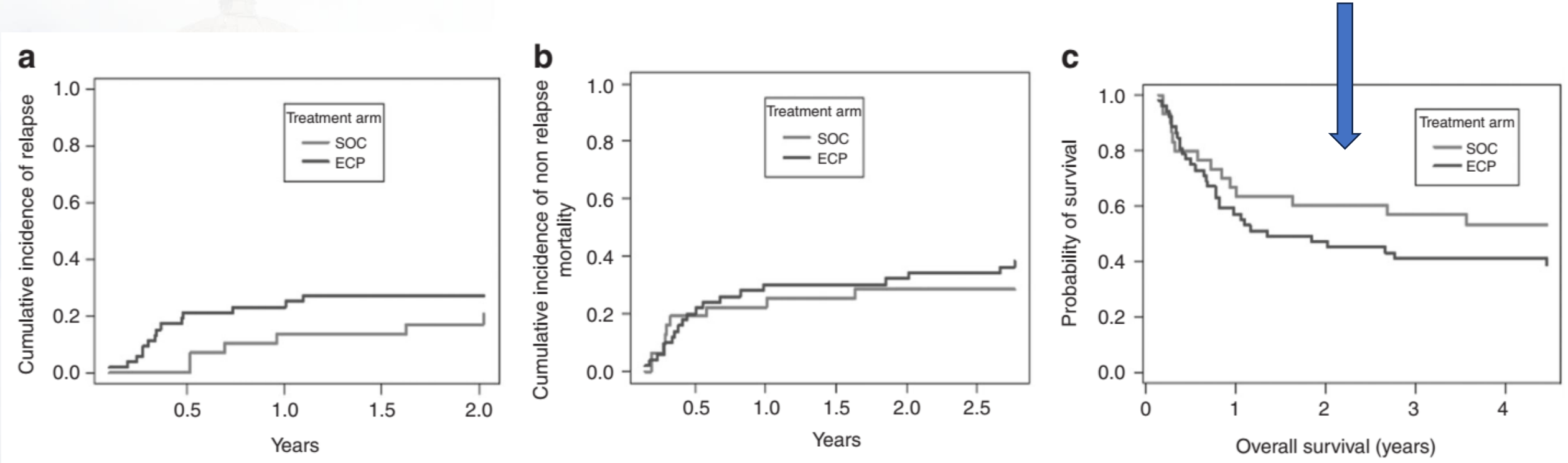
EBMT

Table 2 Primary outcome: day 56 treatment success[a].

Treatment Arm	Risk group	Success	Failure	Total
Steroids alone	All patients	16 (53%)	14 (47%)	30
	Visceral	3 (43%)	4 (57%)	7
	Skin only	13 (57%)	10 (43%)	23
ECP + steroids	All patients	33 (65%)	18 (35%)	51
	Visceral	7 (47%)	8 (53%)	15
	Skin only	26 (72%)	10 (28%)	36

Mehta R et al., BMT 2021

ECP nel trattamento di prima linea



Mehta R et al., BMT 2021

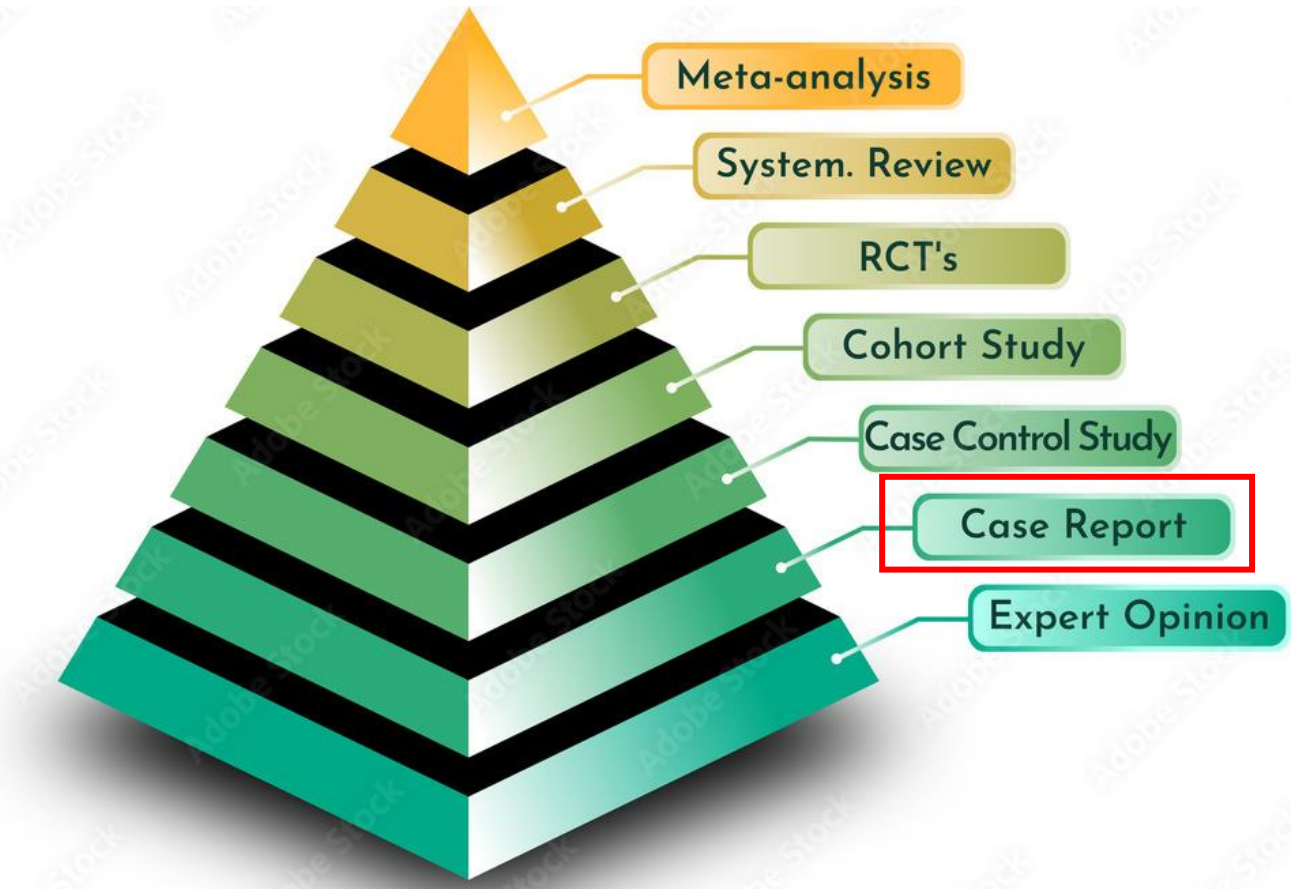
ECP nel trattamento di prima linea

Studi retrospettivi, monocentrici con piccoli numeri

Un solo studio di fase 2, randomizzato

ECP nel trattamento di prima linea

Le ragioni del **NO**



ECP nel trattamento di prima linea

Le ragioni del **NO**

Quanti pazienti sarebbero idonei all´ECP ?

→ condizioni cliniche (paz < +100 da allotx)
→ logistica

«69% of pts received ≥90% of planned sessions»

GB >1500, Hct ≥ 27%, PLT 20000
«Pts excluded if they were felt to be unable to tolerate… (ECP)»

Mehta R et al., BMT 2021

ECP nella profilassi della GvHD acuta e cronica

ECP nella profilassi della GvHD acuta e cronica

therapy. All patients entered on study were not eligible for or at high risk for TRM associated with conventional, ablative, and allogeneic HSCT. Patients were determined to

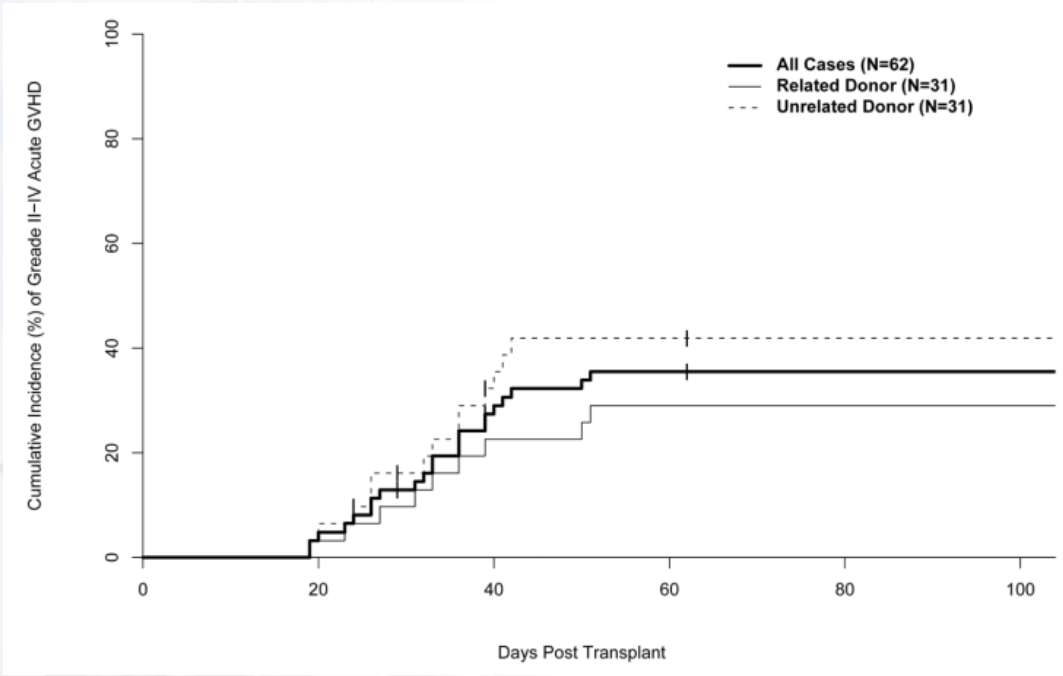
	Preparative Regimen
Day –7, –6	Extracorporeal photopheresis
Day –5, –4	Pentostatin 4mg/m^2/day × 2 days by continuous infusion
Day –3, –2	TBI 200 cGy ×3 (600 cGy total)
Day –1	Rest
Day 0	Hematopoietic Stem Cell Infusion

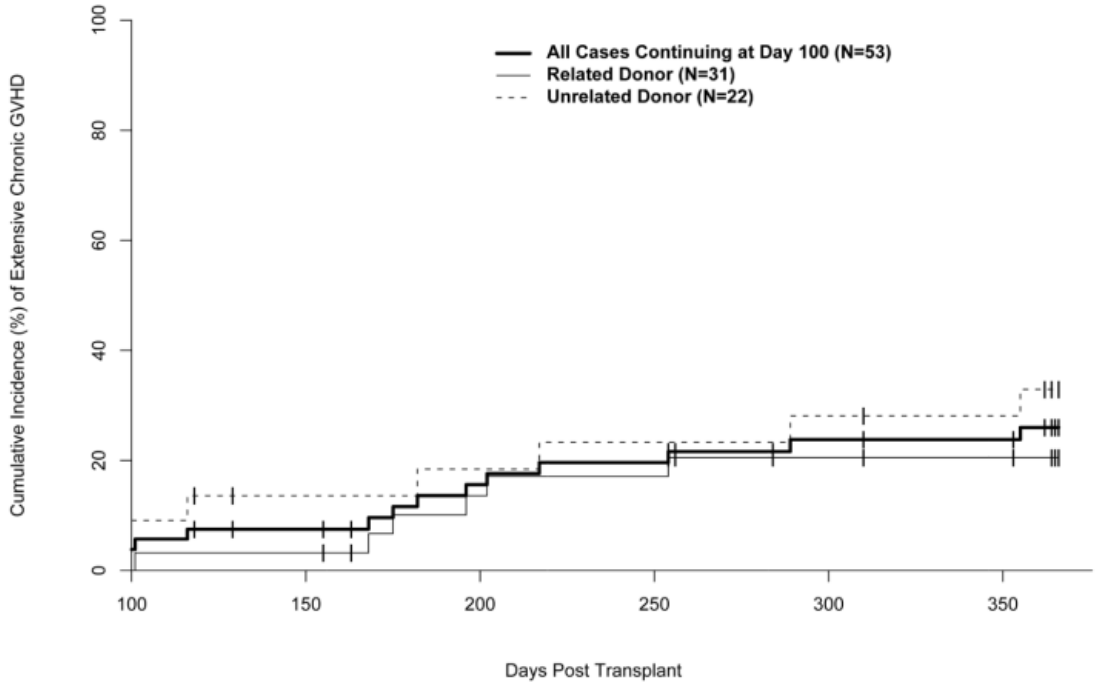
aGvHD grade II-IV = 9% (n=5)
aGvHD grade III-IV = 4% (n=2, all died)

cGvHD extensive = 12%
cGvHD limited = 31%

Miller KB et al., BMT 2004

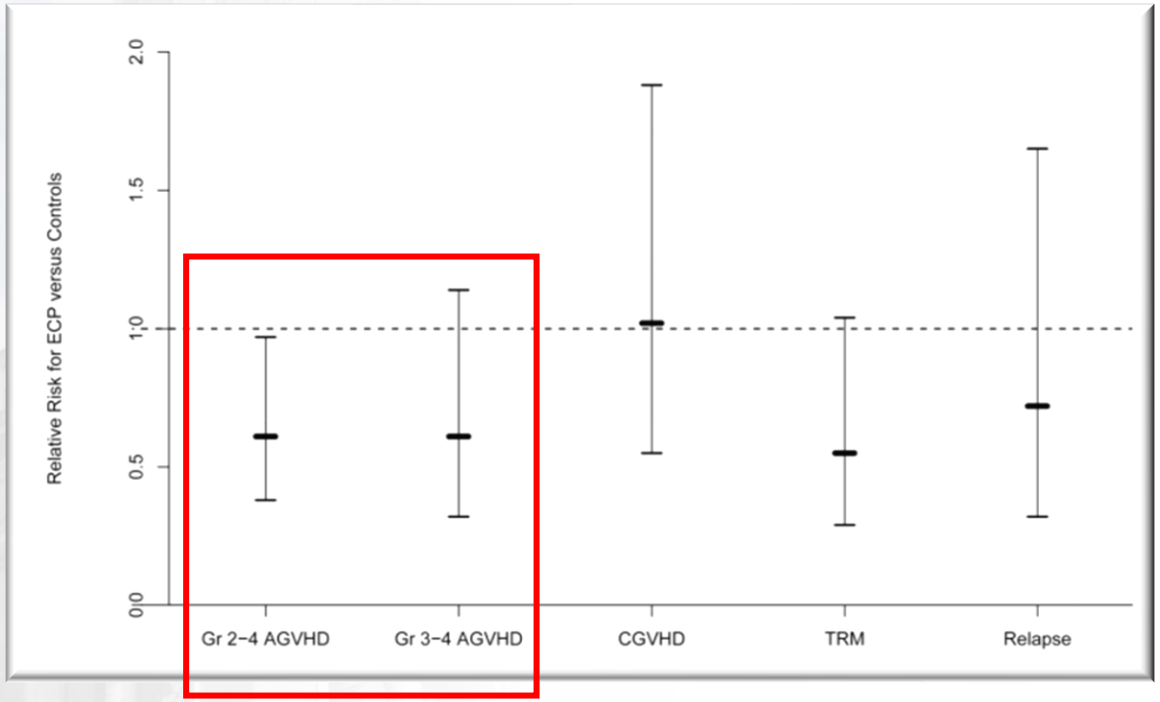
ECP nella profilassi della GvHD acuta e cronica





Shaughnessy PJ et al., BMT 2010

ECP nella profilassi della GvHD acuta e cronica



- First allogeneic transplant in 1997-2003
- Age 18-60 years old
- Disease: ALL, AML, CML, CLL, MDS, NHL and HD
- HLA-id sib, 1-antigen mm related or matched unrelated donor
- Bone marrow or peripheral blood graft
- Conditioning:
  - TBI – 10.0-14.4 Gy
  - CY - 110-140 mg/kg
- GVHD prophylaxis: MTX + CsA alone

Shaughnessy PJ et al., BMT 2010

ECP nella profilassi della GvHD acuta e cronica

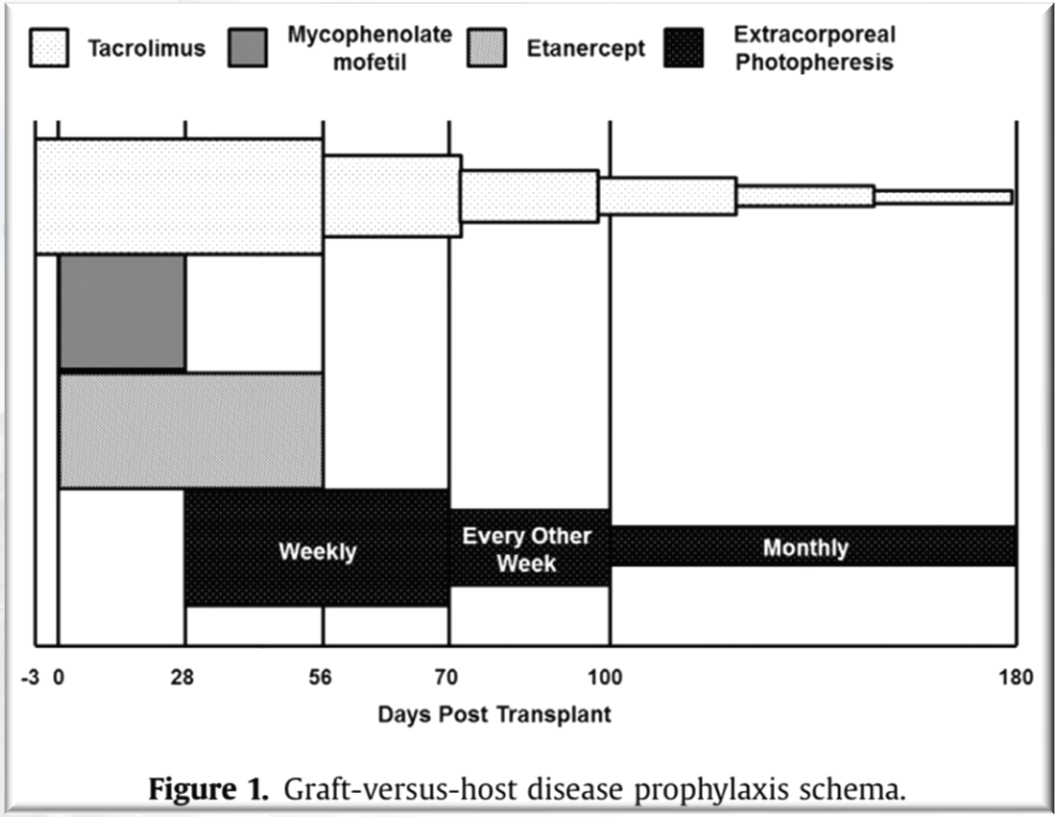
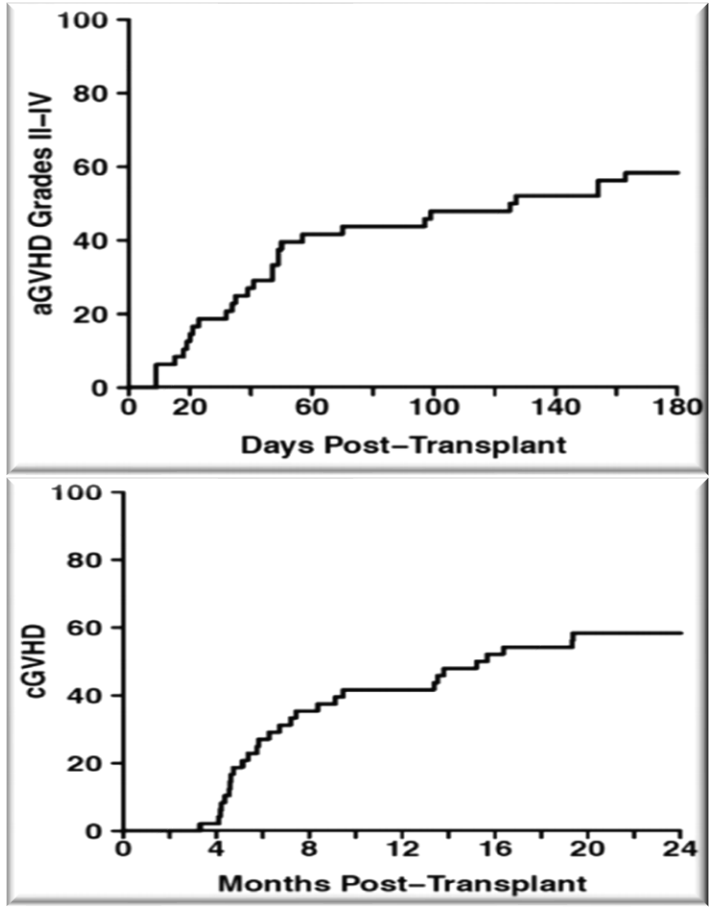


Figure 1. Graft-versus-host disease prophylaxis schema.



Kitko CL et al., BBMT 2016

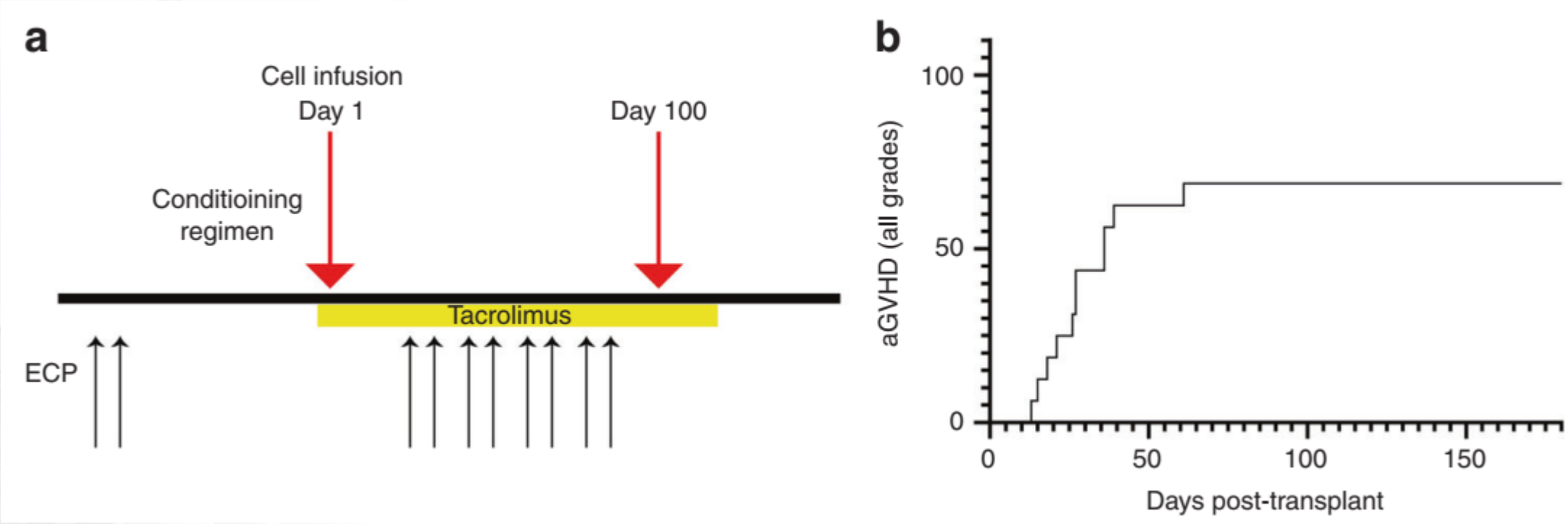
ECP nella profilassi della GvHD acuta e cronica

15% of aGvHD grade ≥ 2
22% of cGvHD at 2 y

«N=20 pts from June 2009 to May 2014 enrolled in five different transplantation centers…»

Michallet M et al., Leuk&Lymph 2018

ECP nella profilassi della GvHD acuta e cronica



Cum Inc cGvHD = 46% (n=6) at a median of 246 days (153 – 330)
Five pts (38%) had extensive cGvHD

Abdelhakim H et al., BMT 2021

ECP nella profilassi della GvHD acuta e cronica

ECP nella profilassi della GvHD acuta e cronica

ELSEVIER

Transplantation and Cellular Therapy

journal homepage: www.astctjournal.org

ASTCT
American Society for Transplantation and Cellular Therapy

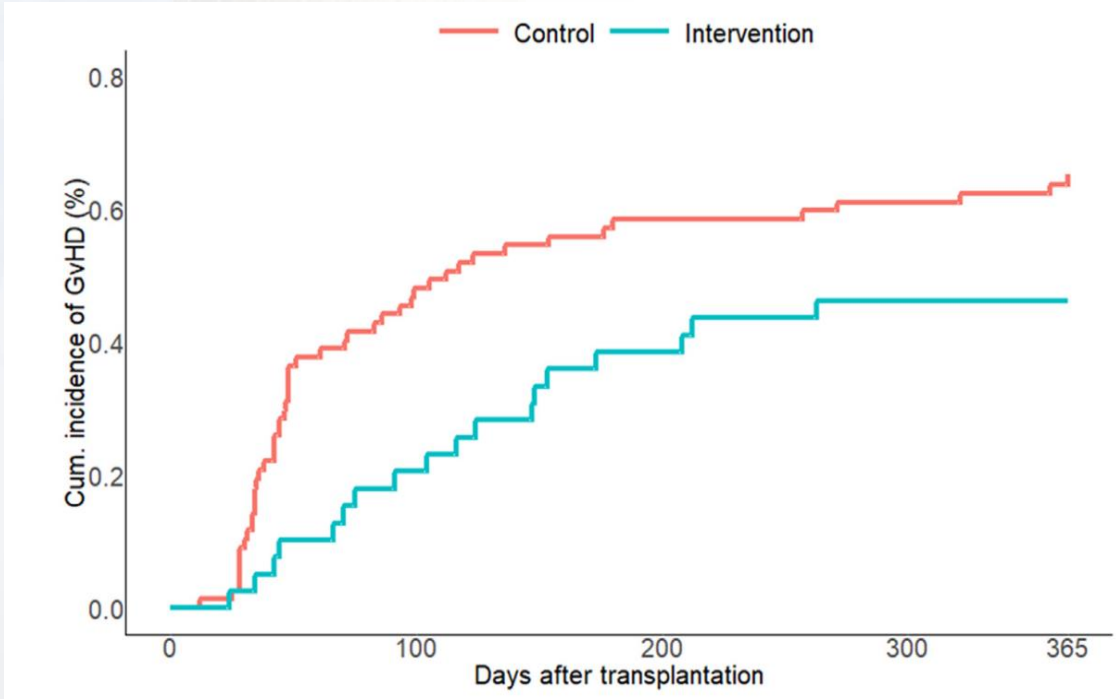
Full Length Article
Allogeneic — Adult

Extracorporeal Photopheresis as Graft-versus-Host Disease Prophylaxis: A Randomized Controlled Trial

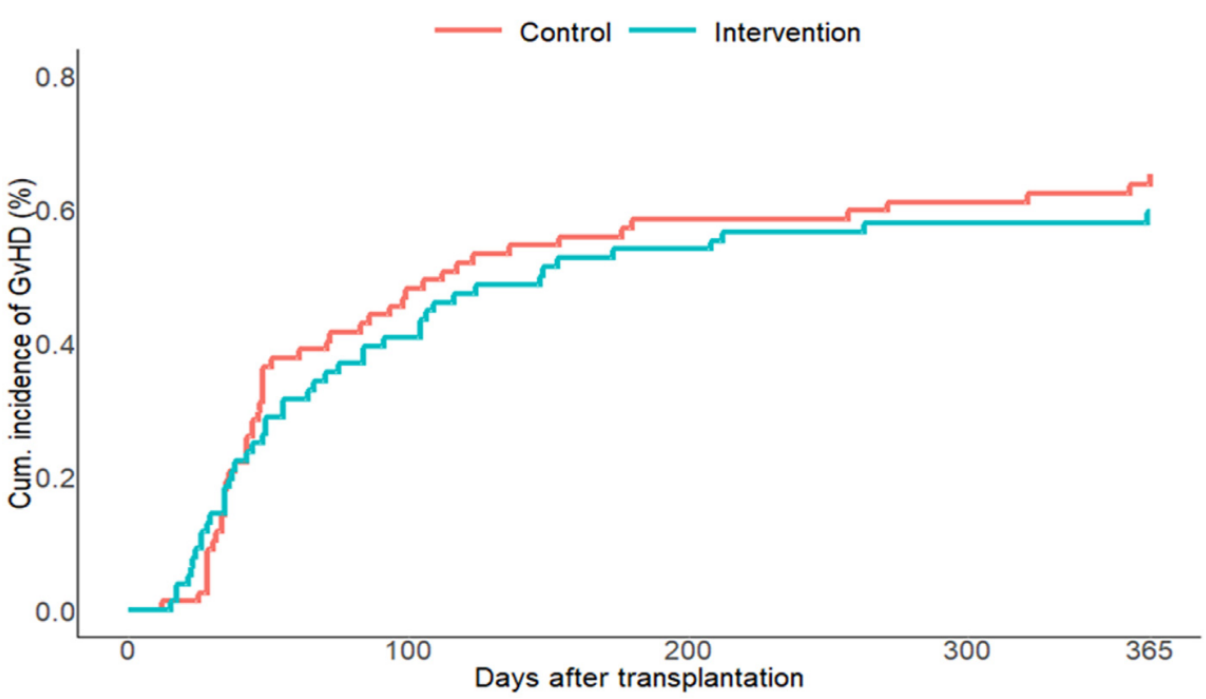
Ali MM et al., TCT 2023

ECP nella profilassi della GvHD acuta e cronica

Per protocol

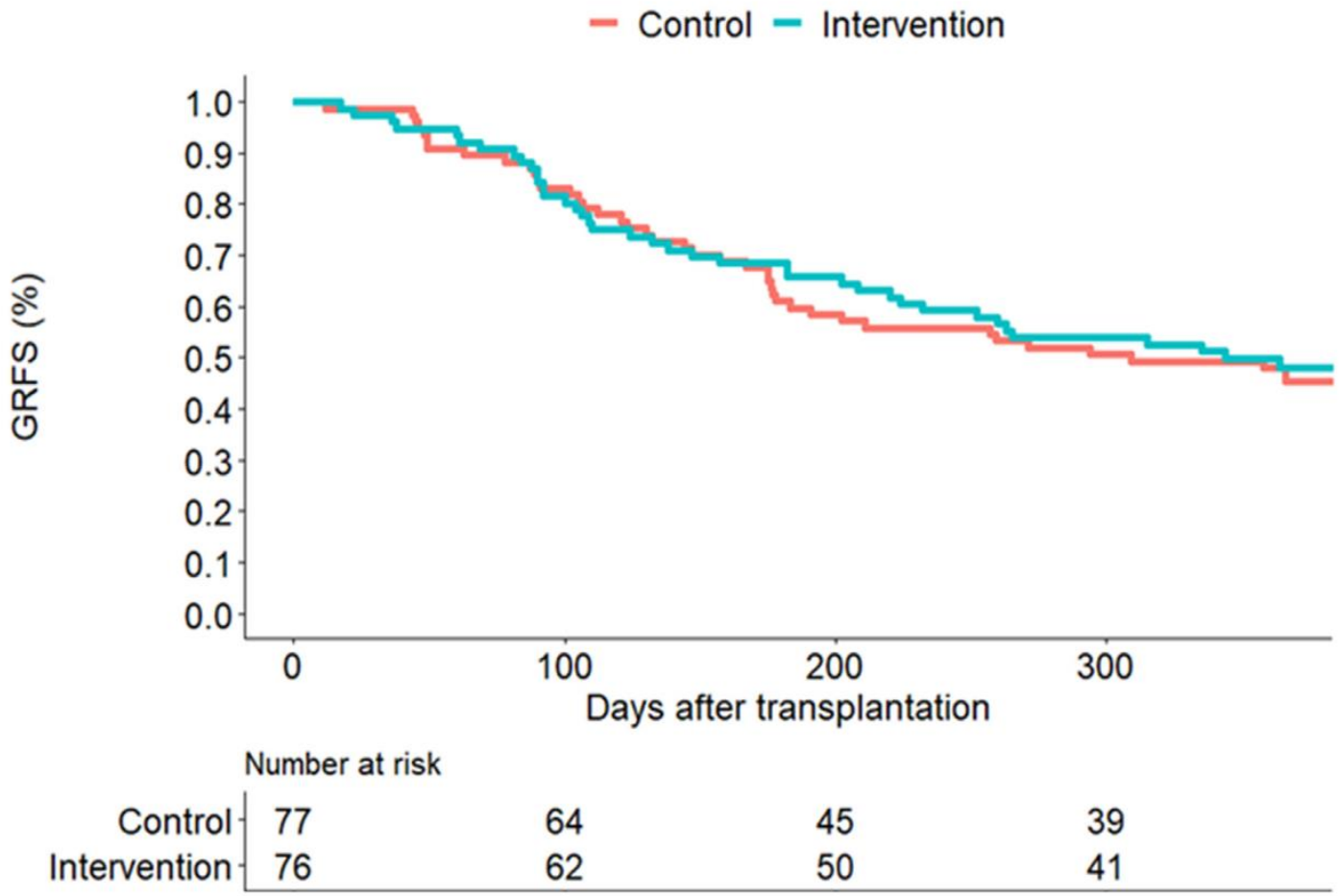


Intention-to-treat



Ali MM et al., TCT 2023

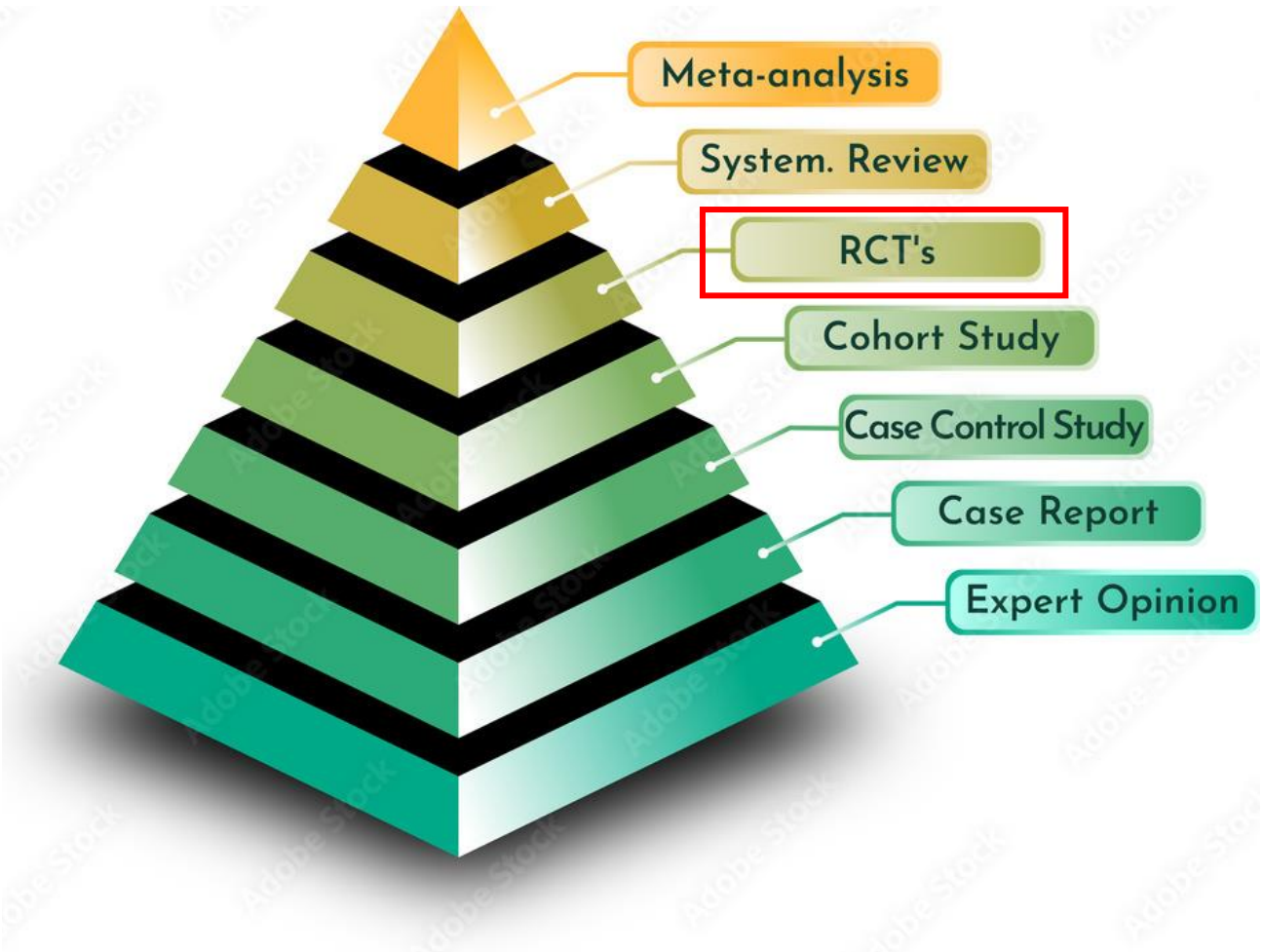
ECP nella profilassi della GvHD acuta e cronica



Ali MM et al., TCT 2023

ECP nella profilassi della GvHD acuta e cronica

Le ragioni del **NO**



EBMT

www.nature.com/bmt

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ARTICLE

First-line steroid-free systemic treatment of acute and chronic graft-versus-host disease after novel prophylaxis regimens

Table 1. Patient, disease and transplantation characteristics.

First line treatment of aGVHD	Cyclosporine A	13 (38.2%)
	Tacrolimus	16 (47.0%)
	Other[b]	5 (14.7%)
First line treatment of cGVHD	Cyclosporine A	10 (25.0%)
	Tacrolimus	20 (50.0%)
	Sirolimus	6 (15.0%)
	Other[c]	4 (10.0%)

[b]Ruxolitinib or MMF.
[c]Ruxolitinib, extracorporeal photopheresis or MMF.

Moiseev I et al., BMT 2023

EBMT

www.nature.com/bmt

CORRESPONDENCE

Check for updates

Steroid-free first line treatment of moderate and severe chronic GVHD: a survey from the Transplant Complications Working Party of the EBMT

accreditation status ($p = 0.48$). Among centers using steroid-free treatments, 75% use them in rare clinical situations, 19% in specific clinical situations and 6% for majority of patients. Most commonly

used treatments included calcineurin inhibitors (CNIs) (71.4%), ruxolitinib (61.2%) and extracorporeal photopheresis (57.1%). A

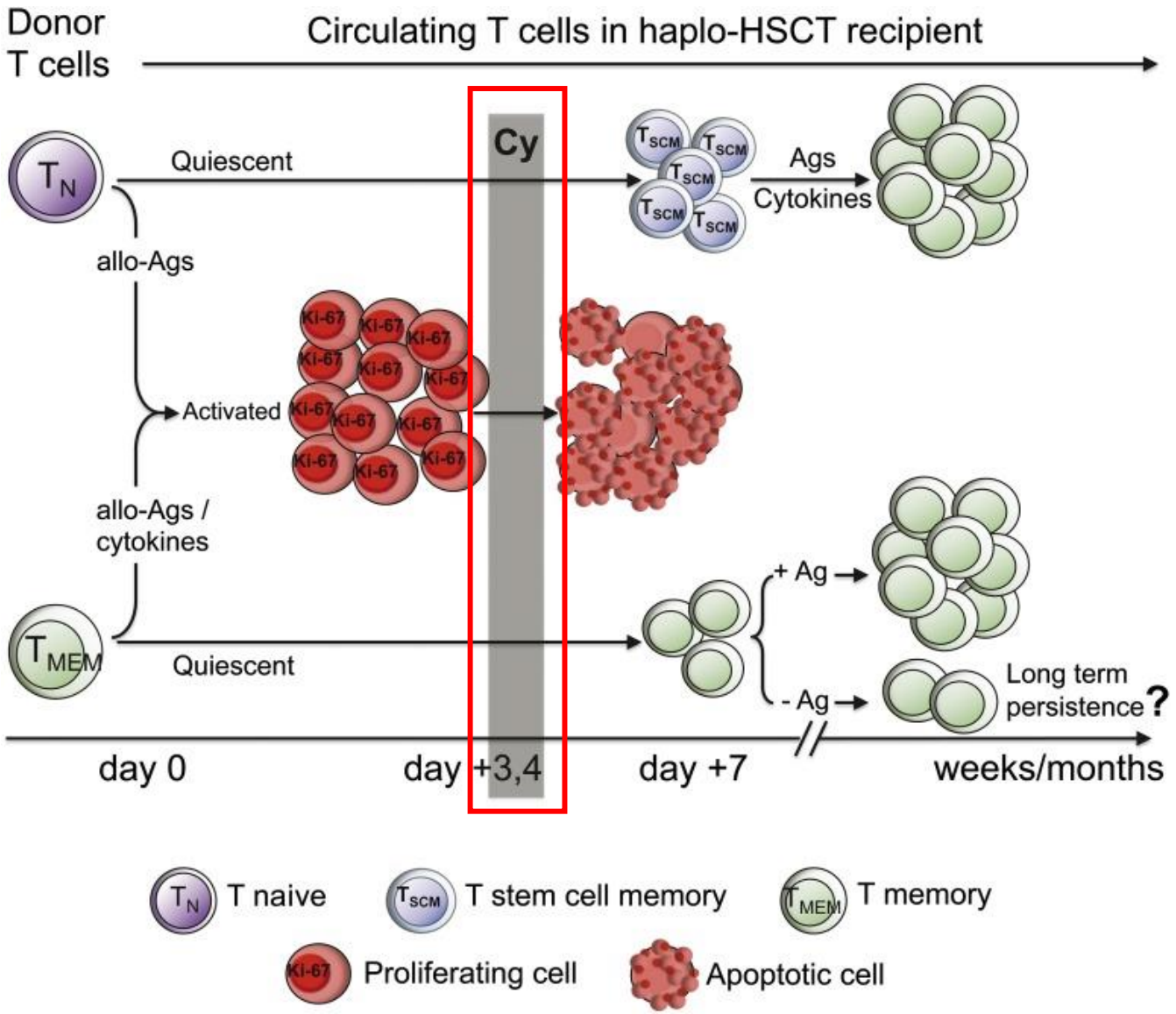
The majority of centers (59.2%) reported that steroid-free treatment was used only in a minority of cGVHD patients (defined by questionnaire as <10%), while 12 centers use this strategy in

Moiseev I et al., BMT 2023

Conclusioni

- Dati di efficacia su ECP consolidati nella GvHD acuta e cronica steroido-refrattaria
- Pochi studi sull´impiego in prima linea nella GvHD acuta, nella maggior parte monocentrici e con piccoli numeri, nessun RCT. Una survey EBMT mostra uso molto limitato di trattamento steroid-free nella GvHD cronica
- Mancanza di evidenza di efficacia in profilassi

Tim(ing) matters…



Roberto A et al., Blood 2015

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Irene Cuppari

Debora Girgenti

Chiara Lupo

Anna Maria Mazza

Lucio Morabito

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Mariateresa Pugliano

Lilian Romero

Elisabetta Volpato

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