ECP in Stem Cell transplantation

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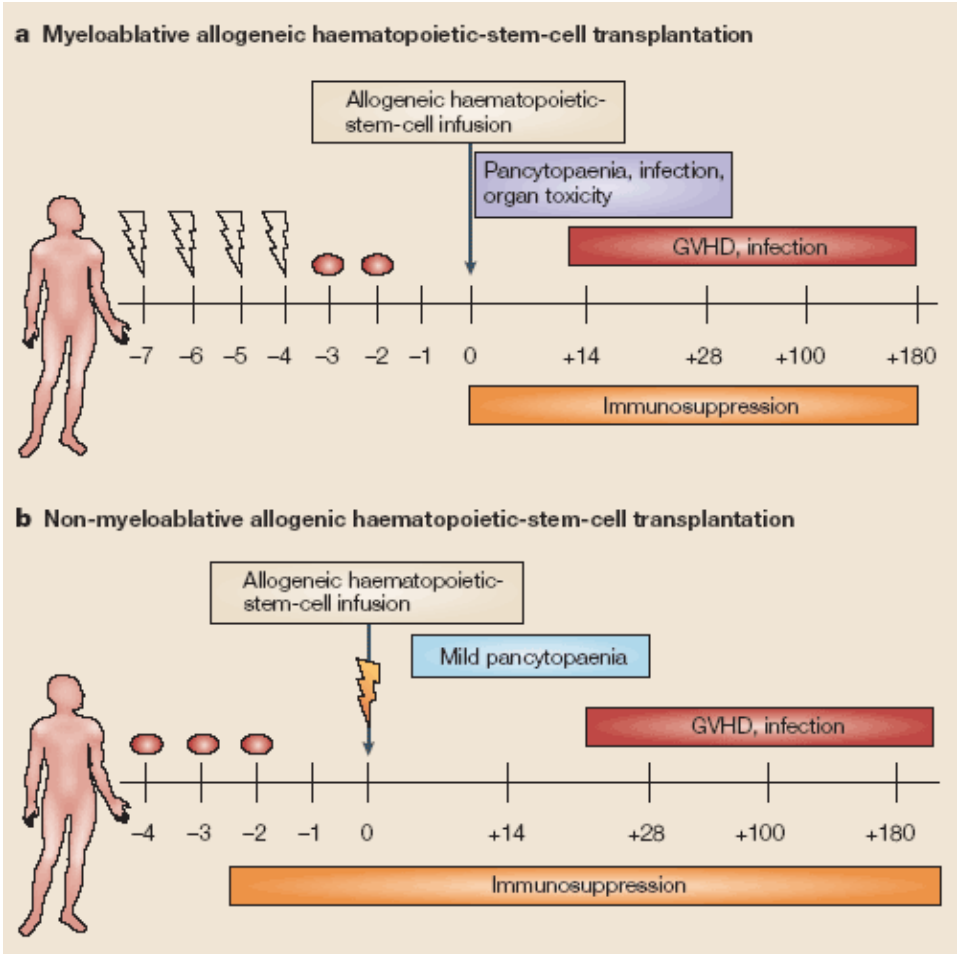
KHP

HSCT Schema


a Myeloablative allogeneic haematopoietic-stem-cell transplantation
Allogeneic haematopoietic-stem-cell infusion
Pancytopaenia, infection, organ toxicity
GVHD, infection
−7 −6 −5 −4 −3 −2 −1 0 +14 +28 +100 +180
Immunosuppression
b Non-myeloablative allogenic haematopoietic-stem-cell transplantation
Allogeneic haematopoietic-stem-cell infusion
Mild pancytopaenia
GVHD, infection
−4 −3 −2 −1 0 +14 +28 +100 +180
Immunosuppression

Introduction

- 1950s
- Billingham and Brent
  - injection of spleen cells from adult mice into newborn mice
  - Thickening and loss elasticity of skin, red soles, exfoliation, diarrhoea
  - Chronic in some
- Runt disease = GVHD

Billinghams Tenets

- Graft must contain *immunologically competent cells*
- Host must possess important transplantation alloantigens that are lacking in the donor graft, *so host seems foreign to graft*
- Host must be incapable of mounting an effective immunological reaction against the graft

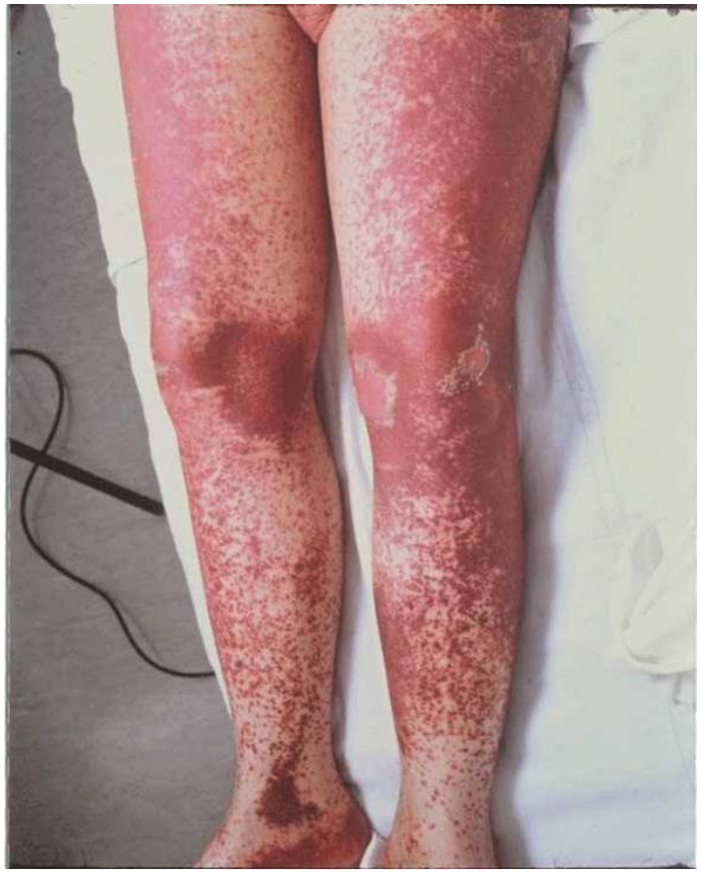
Why is GVHD Important?

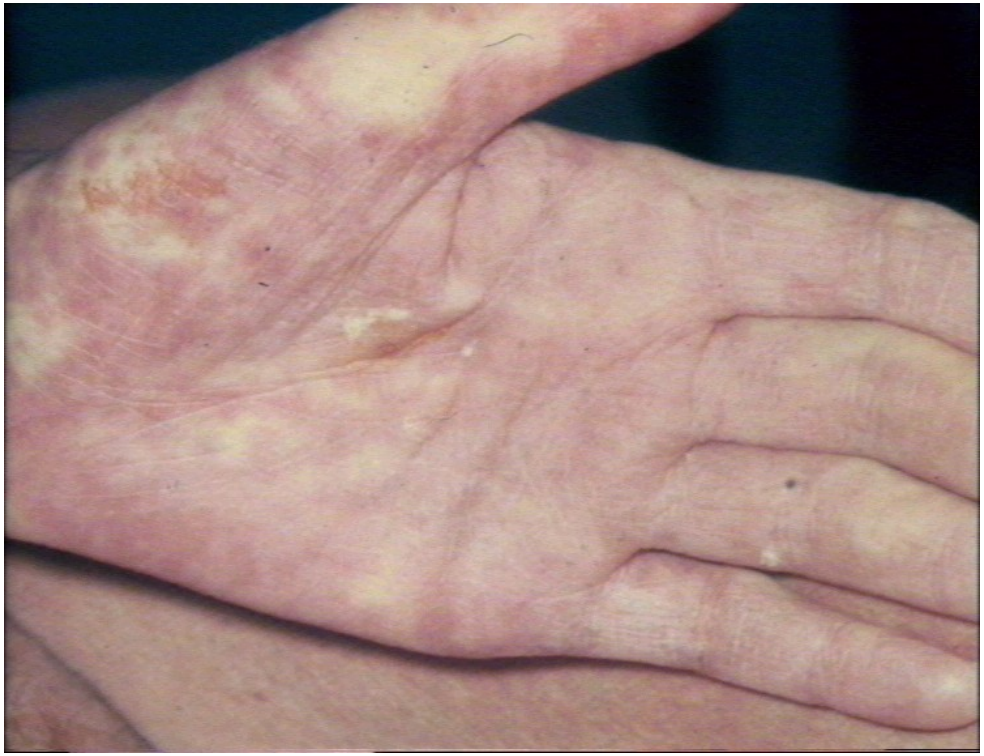
- Major limitation to successful allogeneic transplant
  - Leading cause of non-relapse mortality
  - Acute GVHD risk factor for chronic GVHD
  - Chronic GVHD – resemble autoimmune disease, infections, second malignancies
  - High morbidity and mortality

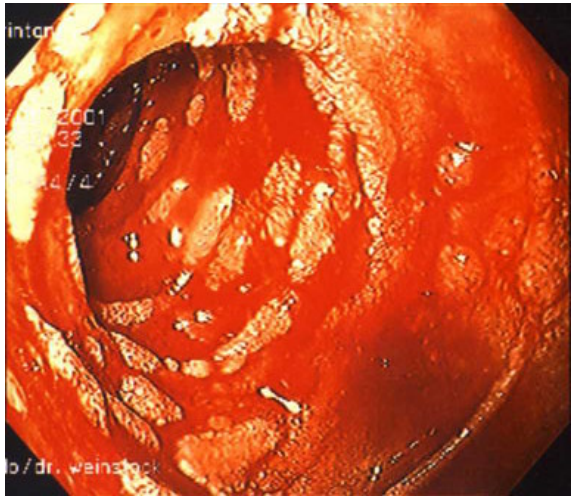
Clinical Features of aGVHD

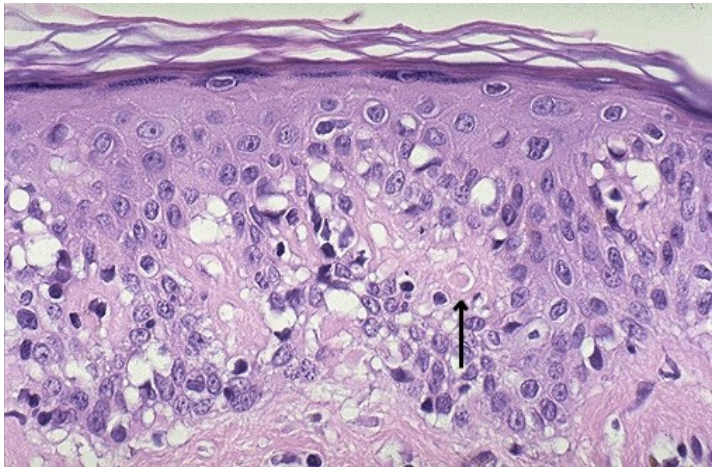
- Typically develops at time of engraftment
- Skin- red palms and soles, → entire body
- Maculopapular rash, desquamation, blistering
- GI – watery diarrhoea, profuse, malabsorption
- Abnormal LFT's

Manifestations of GVHD









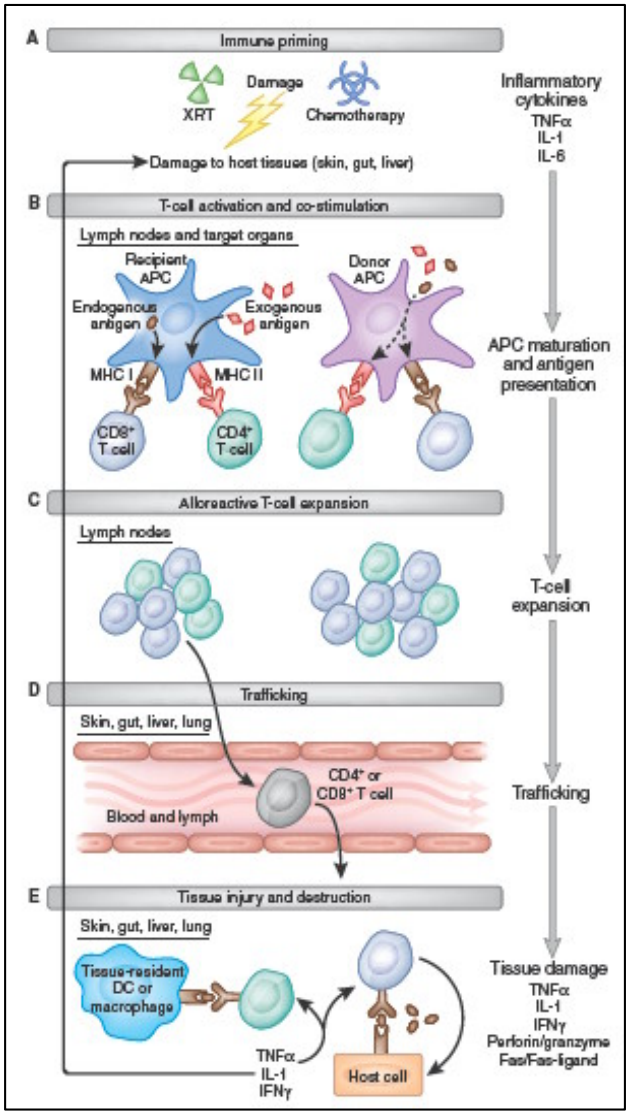
Glucksberg criteria for aGVHD

	Skin	Liver	Gut
1	< 25%	20 - 35	> 500ml/d nausea
2	25 - 50%	35 - 80	> 1000ml/d
3	> 50%	80 - 150	>1500ml/d
4	Erythroderma with bullae	>150	Severe abdo pain with ileus
GRADE			
I	1 - 2	none	none
II	3 or	1 or	1
III		2 - 3 or	2 - 4
IV	4 or	4	

Pathogenesis of GVHD

- 3 phases:
  - Injury to host environment as result of conditioning, exposure of host antigens on APC (allorecognition), cytokine release
  - Donor T cell activation, proliferation, differentiation
  - Cellular and inflammatory attack on target (recipient) tissues

Pathogenesis of aGVHD in a mouse



Treatment options

- steroids
- CNI
- antibodies anti TNF, anti TNF receptor, Rituximab, Campath
- Mesenchymal stem cells

- Morbidity and Mortality

GVHD

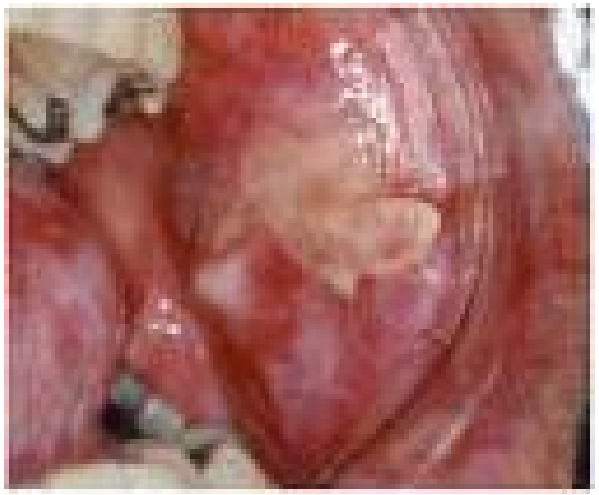
- Steroid Refractory GVHD
- Steroid Dependent GVHD

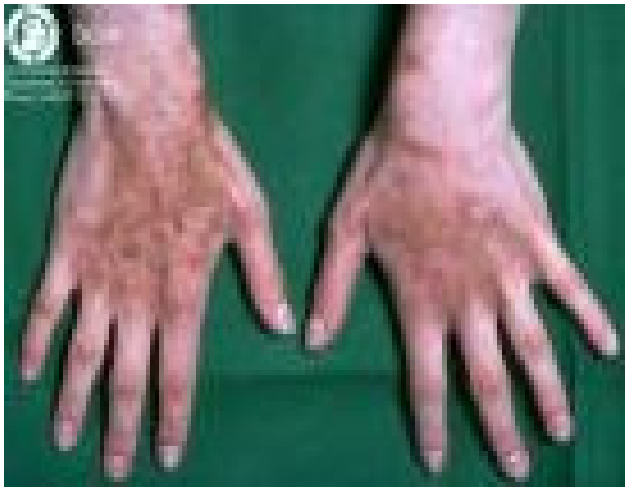
- Problem is of treating the GVHD
- Downward spiral with infection, flare of GVHD
- Can be a terminal condition

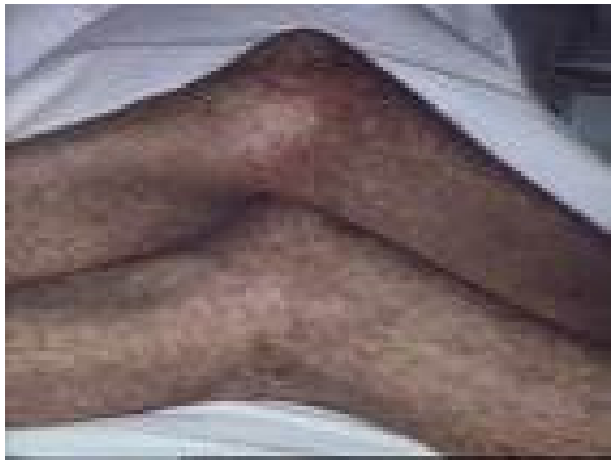
CGVHD

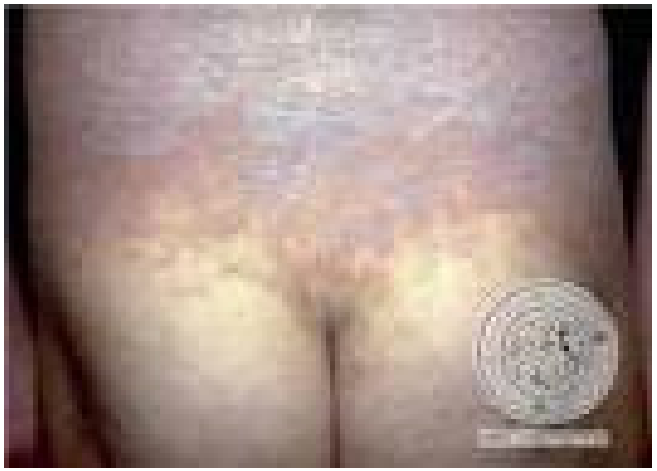
- 60-70% 'survivors' >100d develop cGVHD
- Leading cause NRM after 2 years
- Decreased QoL, need ongoing immunosuppression
- Incidence increasing (more surviving!, older, PBSC, DLI)
- Pathophysiology poorly understood – T cell imbalance, impaired thymic deletion autoreactive T cells

Clinical manifestations of cGVHD

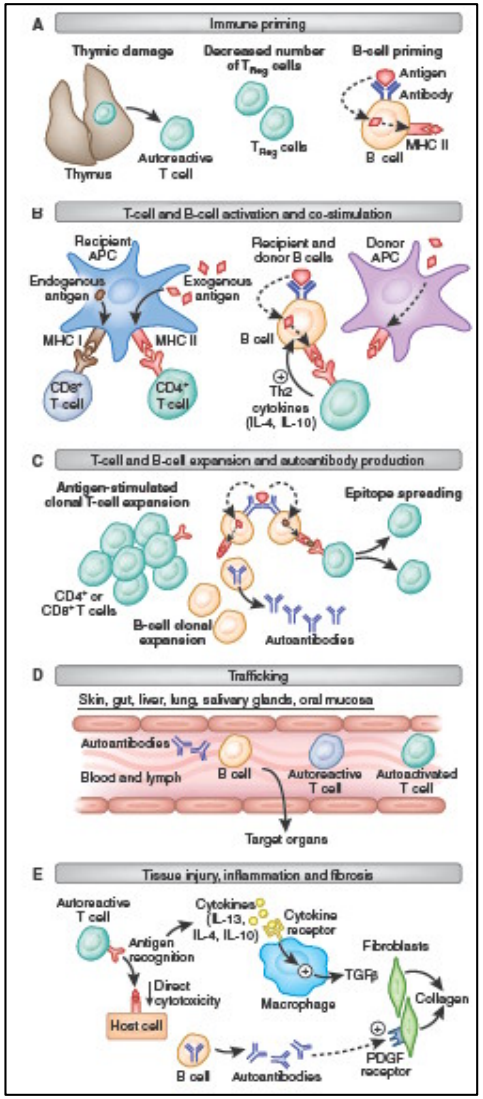








Pathogenesis of cGVHD in a mouse



Effect of GVHD on Relapse

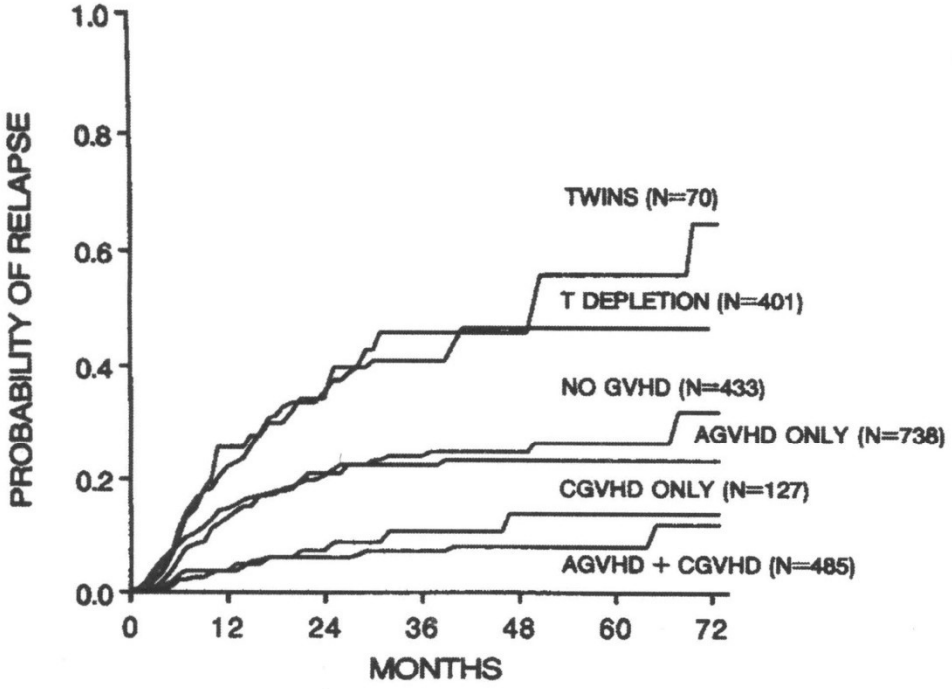


Fig 1. Actuarial probability of relapse after bone marrow transplantation for early leukemia according to type of graft and development of GVHD.

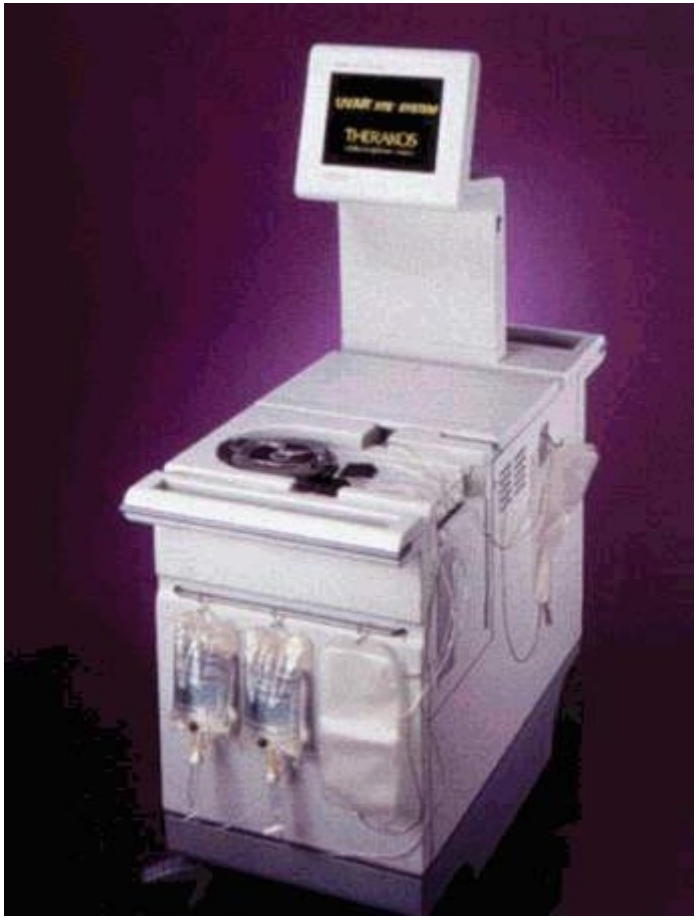
History of ECP

- Extracorporeal photopheresis
- Ancient Egypt recognition that plant derived psoralens sensitised skin to Sunlight
- Used therapeutically for Vitiligo
- Psoralens used in PUVA
- Systemic toxicity

ECP systems

- 1982 Dr Edelson at Yale
- Developed a closed system for treating apheresed lymphocytes with psoralen, exposure to UVA and return of these cells to the individual
- Used for Erythrodermic CTCL

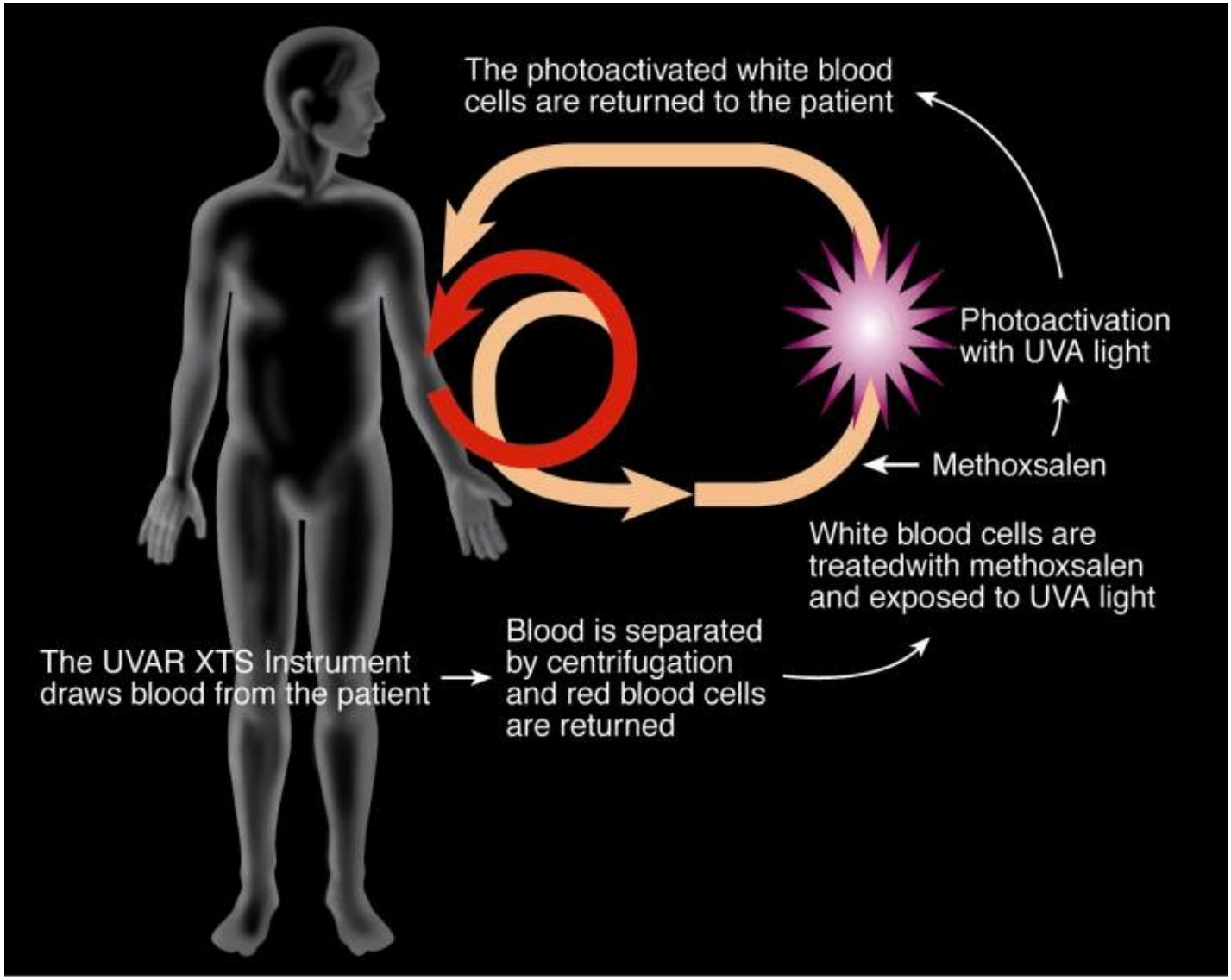
Therakos UVAR XTS and CEllex



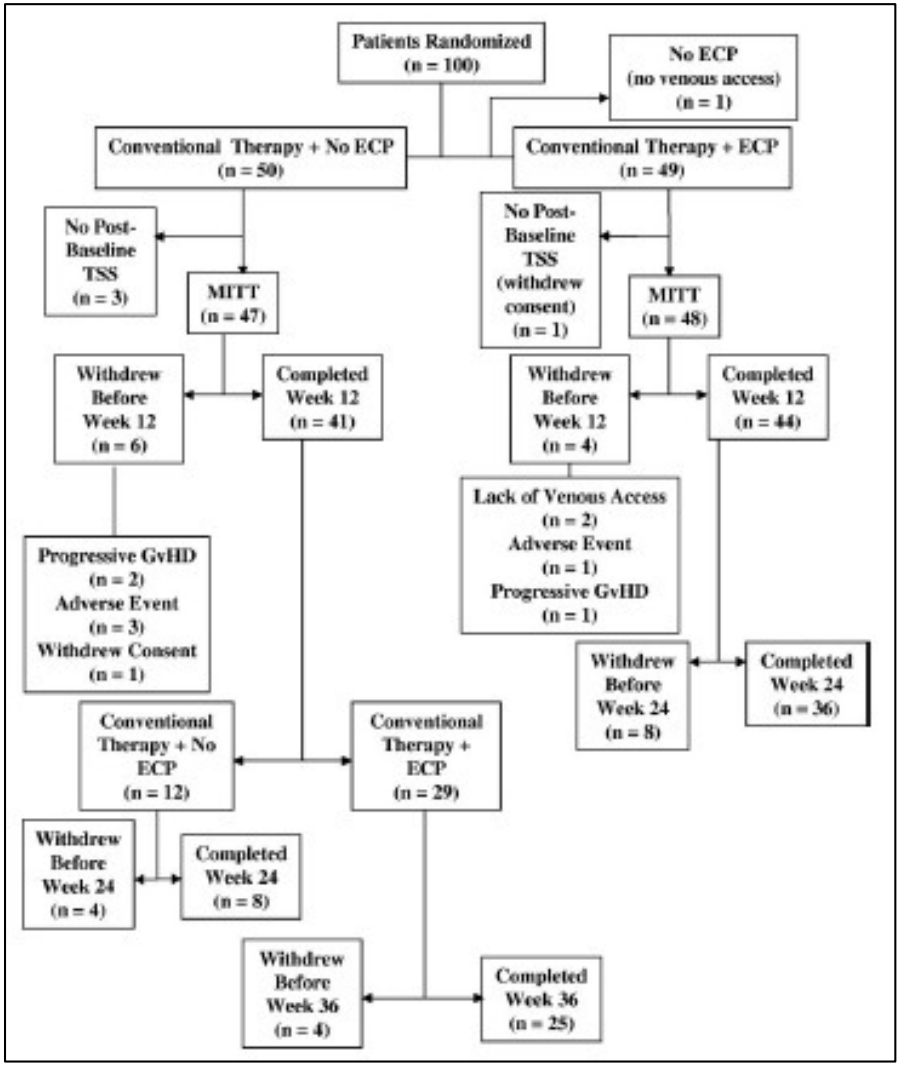
UVAR XTS™

CELLEX™

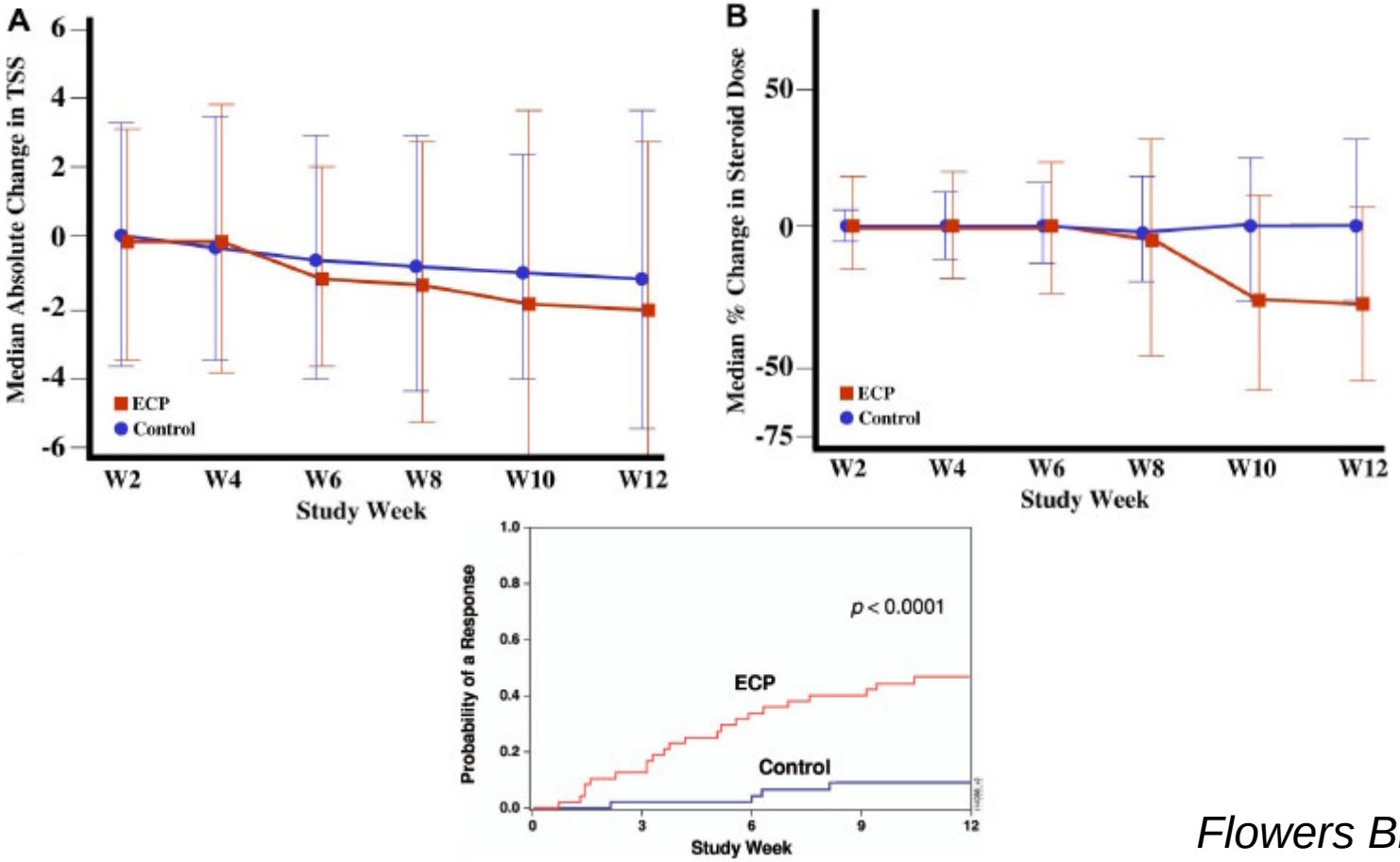
ECP Mechanics



ECP as a treatment for cGVHD

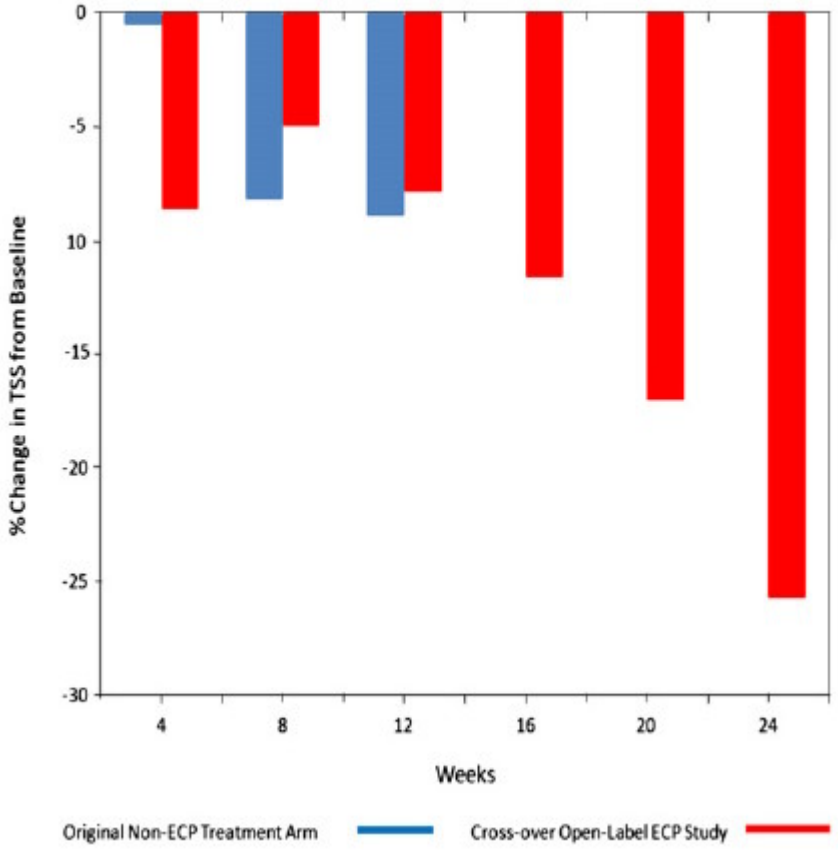


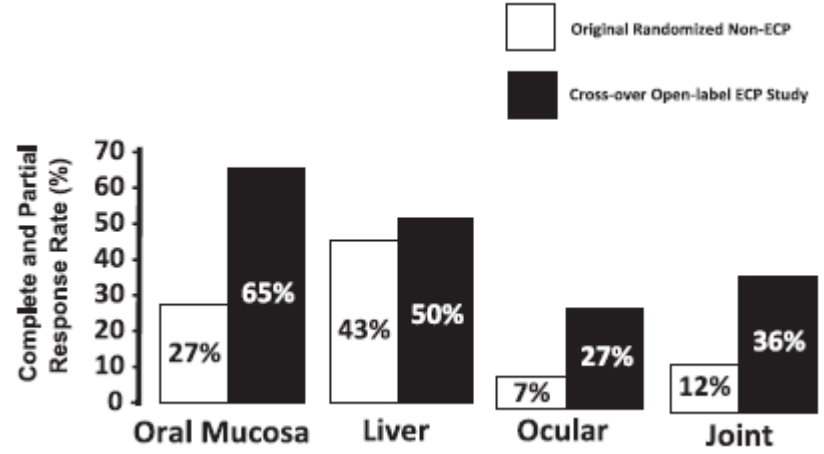
ECP for CGVHD

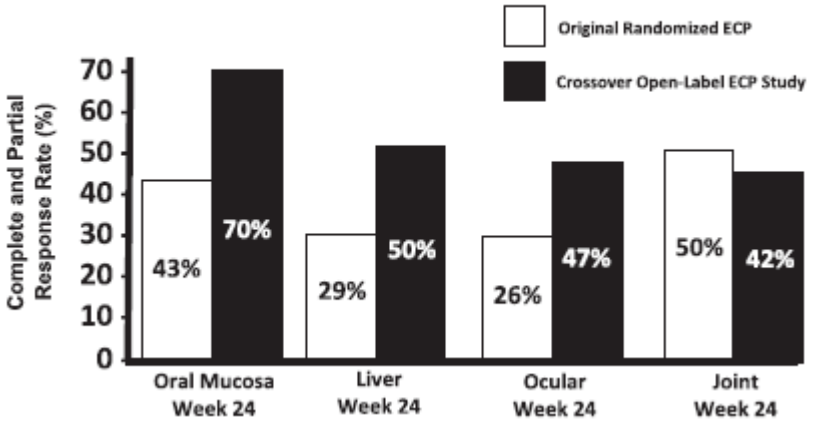


Flowers Blood 2008

Crossover arm





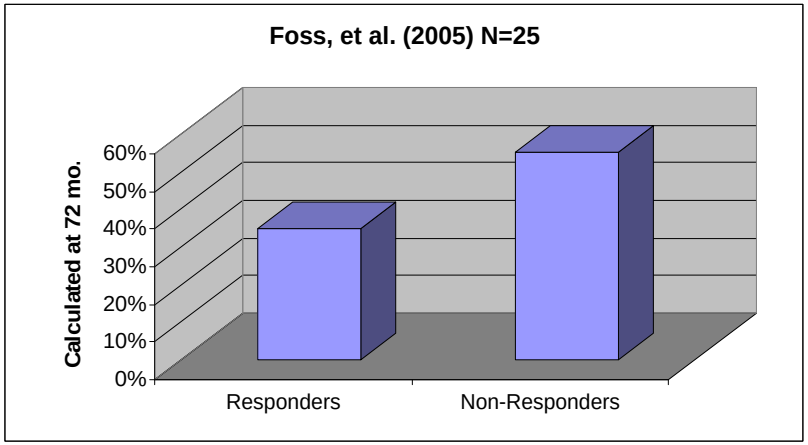


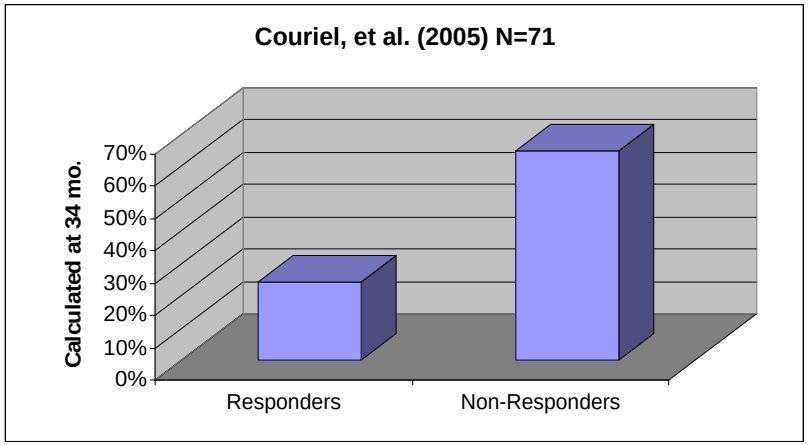
UK ECP in CGVHD

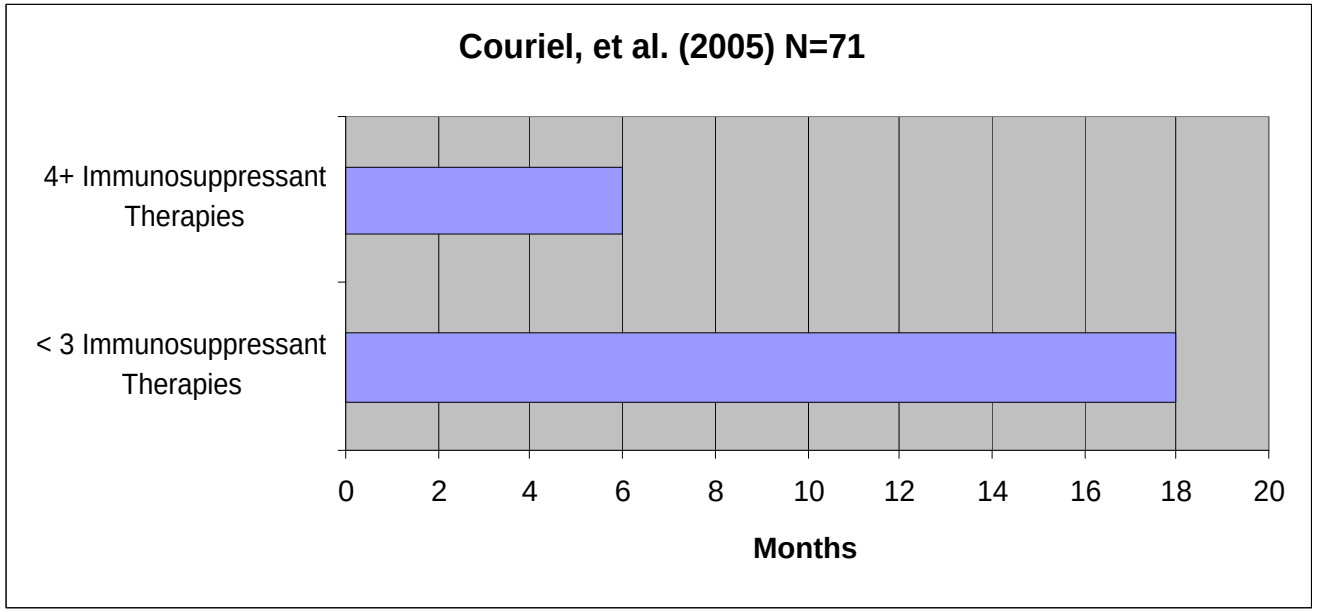
- 82 consecutive patients 2005-2010
- Mucocutaneous and Steroid Refractory/dependent/intolerant
- Median 15 cycles of ECP
- 79% CR/PR rates
- Skin 11% CR, 81% PR, 8% stable disease
- 80% reduced steroid dose

Dignan BJH 2011

Effect on survival in cGVHD







Consensus on 2nd line treatment of cGVHD

Table 4. Second-line Treatment Options in cGVHD

Agent	Recommendation	Evidence	Side Effects	Comments
Steroids	B	III-1	osteoporosis, avascular necrosis, diabetes	important but need to spare steroids because of side effect profile
Photopheresis	C-1	II	venous access required	spares steroids, excellent safety profile
mTOR inhibitors	C-1	III-1	TAM, hyperlipidemia, hematotoxicity	increased risk for TAM in combination with CNI, lower efficacy in thrombocytopenia, requires frequent monitoring
CNI	C-1	III-1	renal toxicity, hypertension	spares steroids, should be avoided in renal impairment
MMF	C-1	III-1	GI complaints, infectious and relapse risk	increased risk for viral reactivation, spares steroids, GI toxicity may mimic GVHD clinically and histologically
Pentostatin	C-2	II	Hematotoxicity, infectious risk	best results in children, caution in presence of impaired marrow function, long-term immunosuppression
MTX	C-2	III-1	Hematotoxicity	best response in mucocutaeous cGVHD, spares steroids
Imatinib	C-2	III-1	Fluid retention	best results in sclerotic skin lesions, potentially effective in mild and moderate BO
Rituximab	C-2	II	Infectious risk	effective in auto-antibody mediated manifestations as well as cutaneous and musculosceletal cGVHD
Hydroxychloroquine	C-2	III-2	GI complaints	best results in mucocutaneous and liver involvement
Clofazimine	C-2	III-2	GI complaints, skin hyperpigmentation	best results in mucocutaneous cGVHD
Thoracoabdominal irradiation	C-2	III-2	Hematotoxicity	best results in fasciitis or steroid dependent mucocutaneous cGVHD, caution in presence of impaired marrow function
Pulse of steroids	C-2	III-2	Infectious risk	rapid control of symptoms, identification of steroid resistance
Thalidomide	C-3	II	Neurotoxicity, sedation, constipation	may be used in concomitant relapse of MM
Azathioprine	C-3	III-1	Hematotoxicity, infectious risk	increased risk for oral malignancies
Retinoids	C-3	III-2	Skin toxicity, Hyperlipidemia	effective in sclerotic skin lesions
Alemtuzumab	C-4	III-3	Infectious risk	last resort
Alefacept	C-4	III-3	Infectious risk	last resort
Etanercept	C-4	III-3	Infectious risk	may be used in overlap syndrome with GI manifestations

Wolff et al BBMT 2011

ECP for BOOP

Study	No of patients	Response
Child et al 1999	5	PR 2 (40%)
Dall Amico 2002	11	CR 4 PR 2 (54%)
Messina 2003	14	CR 4 PR 2 (43%)
Couriel 2006	11	CR 1 PR 5 (54%)
Flowers 2008	9	2 (22%)
Lucid 2011	9	8 (89%)
Greinix 2011	4	3 (75%)

A total of 100 cases in the literature >50% response

ECP for steroid refractory/dependent aGVHD

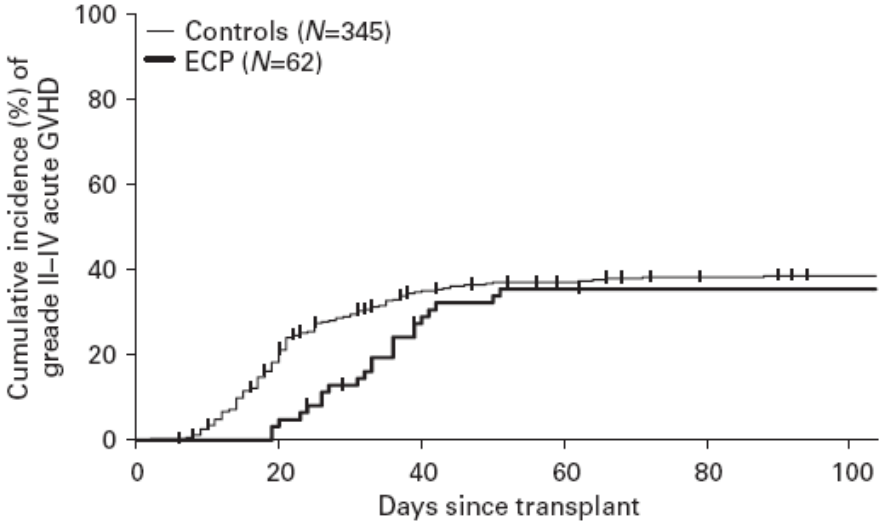
Author	Number	Skin	Liver	Gut	Schedule
Greinix 1998	6	6 (4 CR, 2PR)	2 (2 CR)	0	46 days to start, NI
Greinix 2006	59	57 (82%)	21 (61%)	15 (25%)	17 days , Int 4 cycles to best response
Garban 2005	12	12(8CR, 1 PR, prog 3)	2 no resp	5 (2 CR)	Intensified
Calore	15	13 (92% CR)	1 (CR 100%)	14 (CR 71%)	Intensified
Greinix 2010				11 (71% CR)	
Das Gupta 2012	52	28 (24 CR)	9 (no response 1 developed)	15 (5 CR)	Intensified

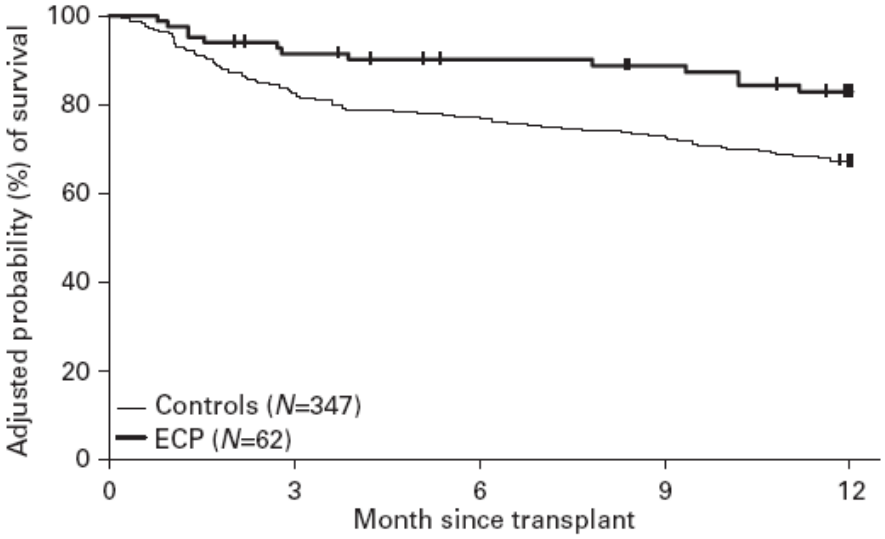
Phase II study Greinix et al earlier onset of ECP and lower grade of aGVHD
Predicted CR
Lower TRM 14% vs 73%

ECP at GSTT

- 9 patients April –September 2011
- Steroid Refractory or Steroid dependent
- 8/9 patients responded CR 2 PR 6
- 2/9 off steroids completely
- Organs responsive; Skin, Liver, gut
- 1 patient cGVHD of the liver
- 1 pt died with PIV-3

ECP prophylaxis for GVHD





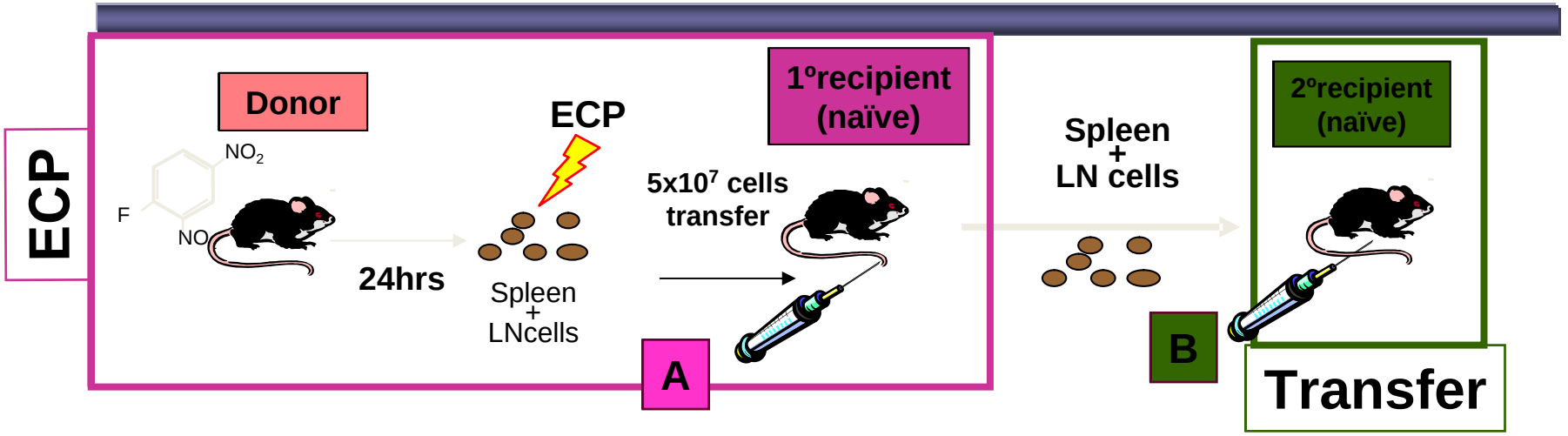
Abhyankar et al BMT 2010

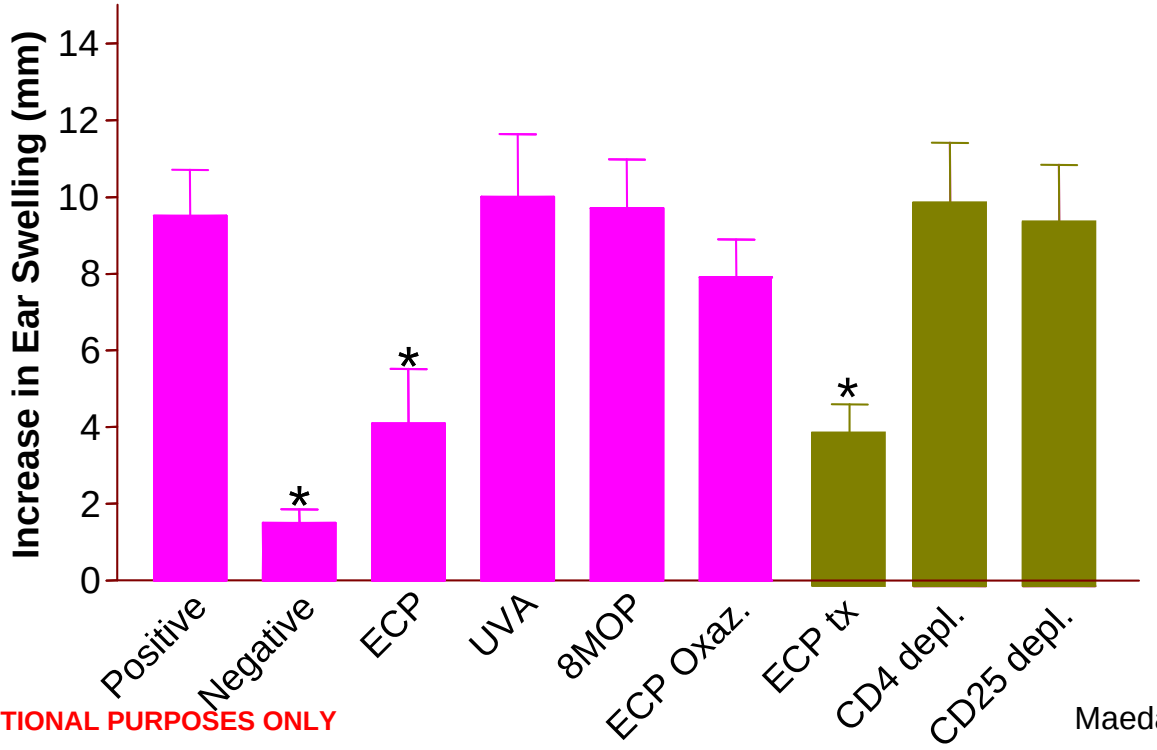
ECP Effect on cytokine and lymphocyte profiles

- Mice ECP treated lympocytes: enhance IL-10 secretion and antigen specific Tregs in the recipient: reducing Contact hypersensitivity and the effector phase of the immune response
- Humans: Depleted host antigen presenting cells, Increased Tregs, reduced inflammatory cytokines, increased anti-inflammatory cytokines

Maeda JI 2008

Generation of Regulatory T Cells *in vivo*





Regulatory T Cells

- **Antigen specific**
- **Cell transferable**

Maeda A et al. *J Immunol.* 2005;174:5968-5976

ECP for solid organ transplantation rejection

- Used post renal transplant
- Once a week for 4 weeks, then fortnightly, then monthly
- Monitor the Treg (CD4+, CD25+, FOXP3 high) maintain levels above 20%, if decline a further ECP will increase this by 5%

The current status of ECP in the UK

- Commissioned for cGHVD
- BCSH guidelines
- Acute GVHD commissioned in Nottingham

Summary

- ECP is recommended 2nd line for cGVHD
- Encouraging data in acute GVHD if started early
- Non-Immunosuppressive
- Low rates of infection
- Low relapse rates
- Safe and effective

Acknowledgements

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