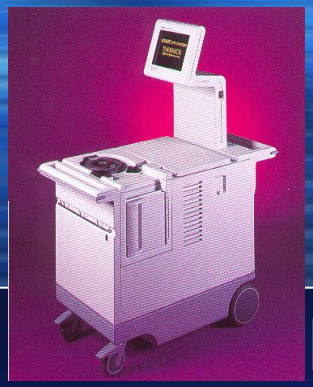

Extracorporeal Photopheresis

Chronic and Acute GVHD
Experience in Brazil

Luis Fernando Bouzas

II WBMT / WHO october 2013

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Chronic and Acute GVHD

1. GVHD: General aspects
2. ECP Mechanisms of Action
3. ECP and Prophilaxis
4. Treatment
   Clinical evidence based indications
5. Results post Treatment

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Chronic and Acute GVHD Incidence

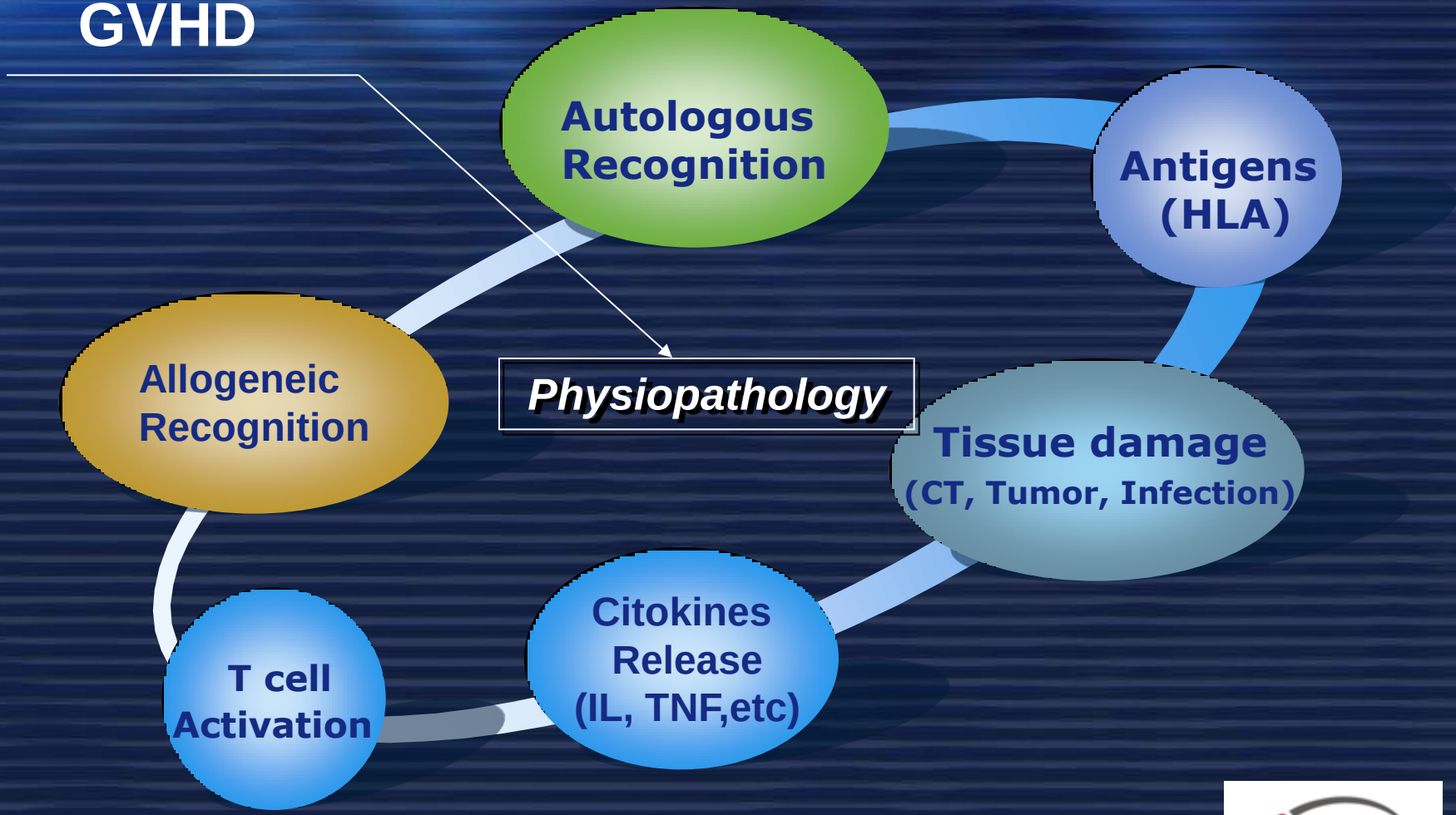
- After allo related BMT: 40 a 70%
- After allo unrelated BMT: 60 a 90%
- After auto or singenic BMT: ~ 10%
- After blood transfusions in immunesuppressed: estimated in 0,1 a 1,0%
- After solid organ transplants: unknown

Chronic and Acute GVHD
Etiology and pathogenesis

- **Effector cells (agression): Linfócitos T**

- **Antigens – target: Ags HLA (major and minor)**

When and how prophilaxis should be for efficacy?



GVHD - *Prevention*

Histocompatibility - Donor and Receptor

Prophilaxys *in vivo*

- ***metotrexate (MTX)***
- ***cyclophosfamida***
- ***ATG***
- ***ciclosporina (CSA) ou Tracolimus (FK 506)***
- ***MTX + prednisona***
- ***MTX + ATG + prednisona***
- ***MTX + CSA ± prednisona***
- ***Other drugs alone or combined***

Total Lymphoid Irradiation

Isolation (Laminar air flow)

In vitro BM treatment

- ***T cell depletion***

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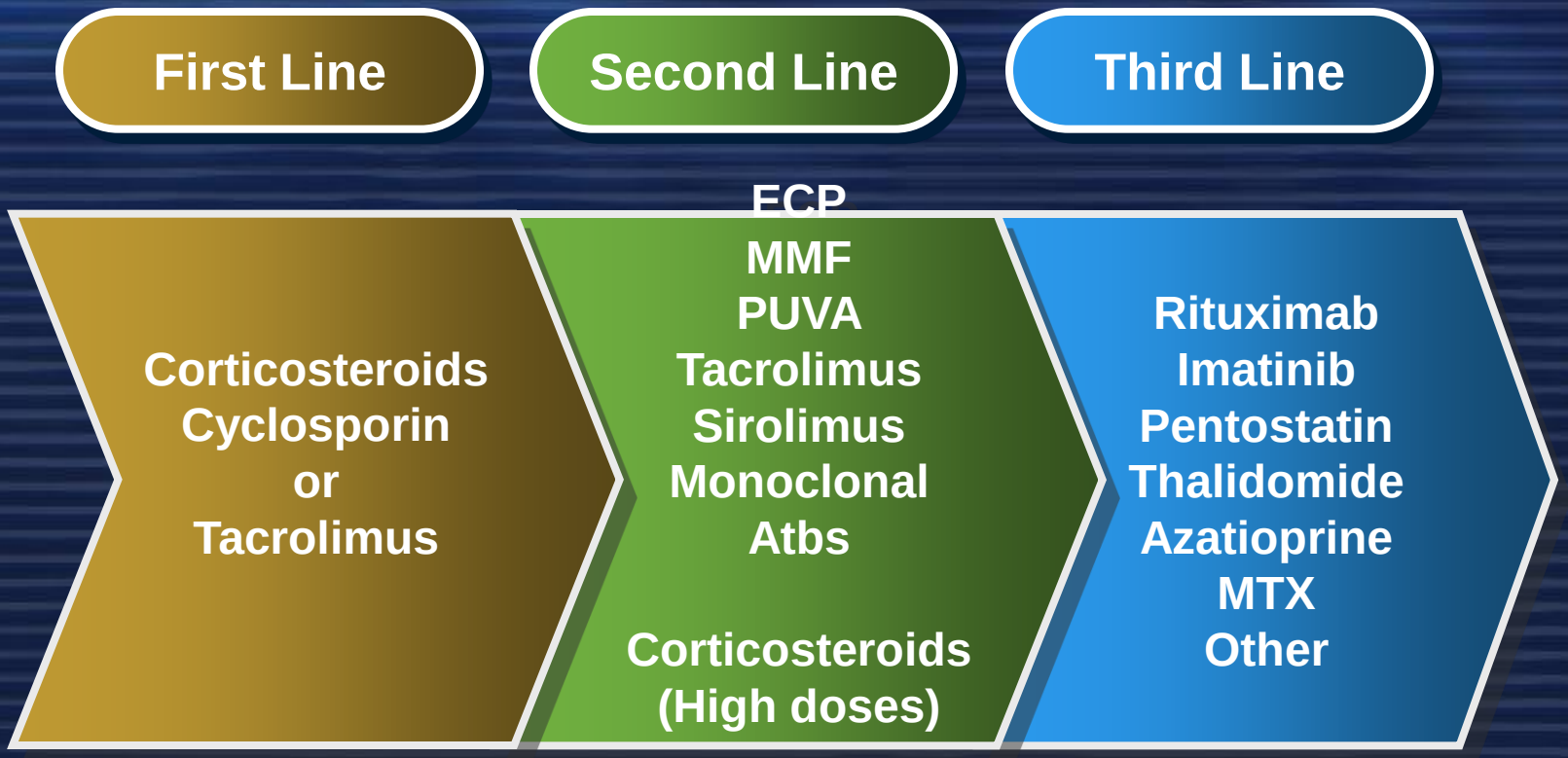
GVHD

Treatment Alternatives



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Indication for Systemic Treatment

Global Severity	High risk for mortality*	Treatment systemic
mild	No	No
mild	yes	yes≠
Moderated	No / Yes	yes
Severe	No / YES	yes

* Plaquetas < 100.000/μL ou recebendo corticóide no momento do diagnóstico da DECH

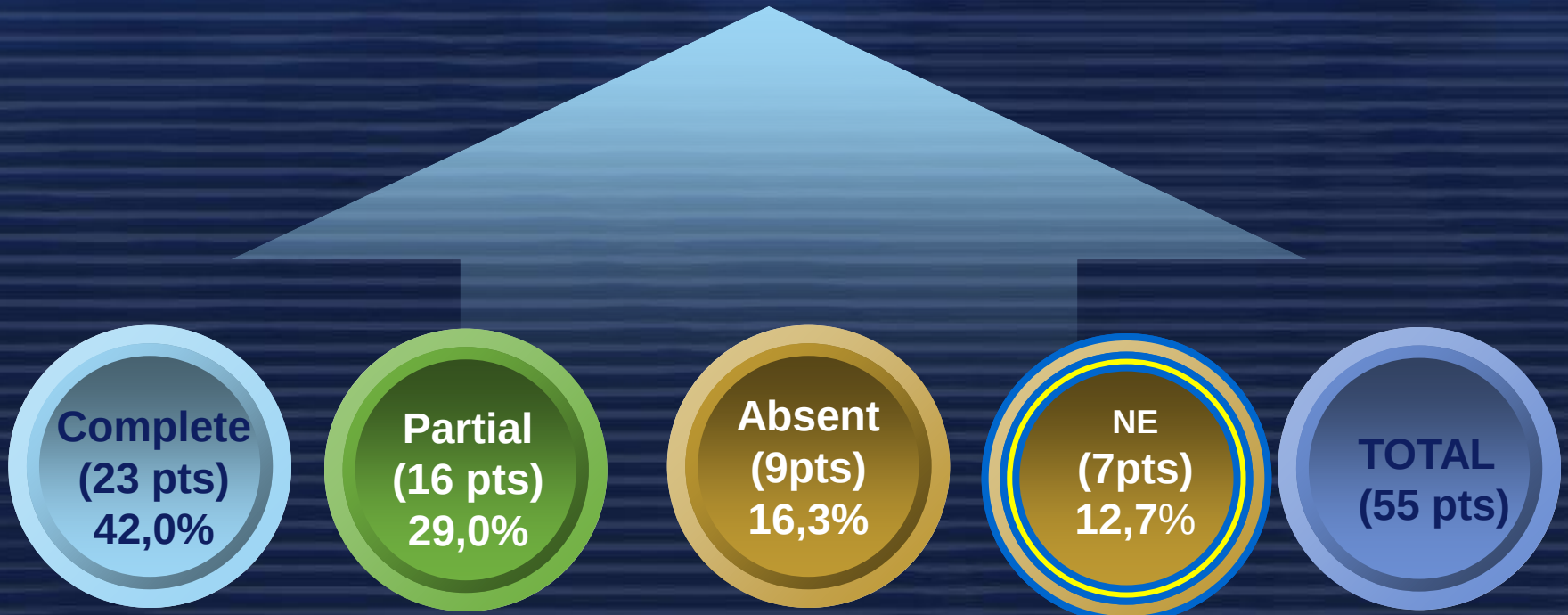
≠ Deve ser pesado o benefício do efeito enxerto-*versus*-tumor e o risco da DECH

Phototherapy in GVHD

- PUVA
- UVB narrow-band (311nm)

CEMO / INCA
1991 - 2012

PUVA for Chronic GVHD



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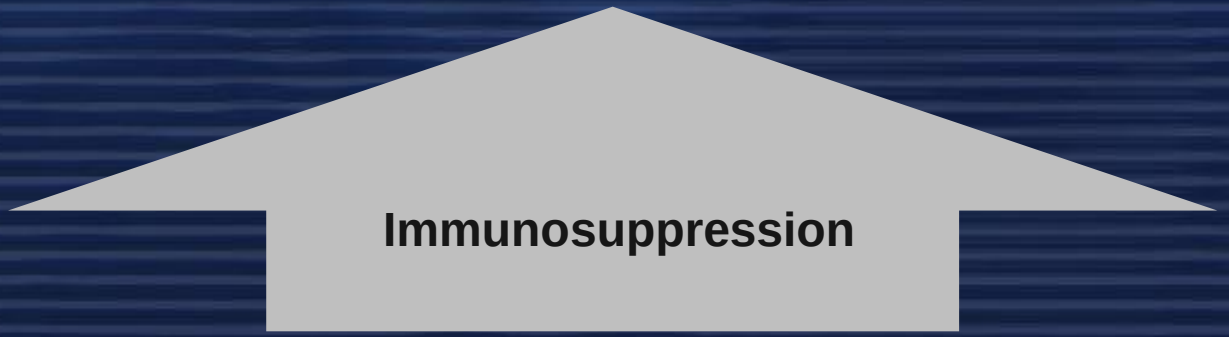
CEMO/INCA
1991 - 2012

PUVA for Chronic GVHD



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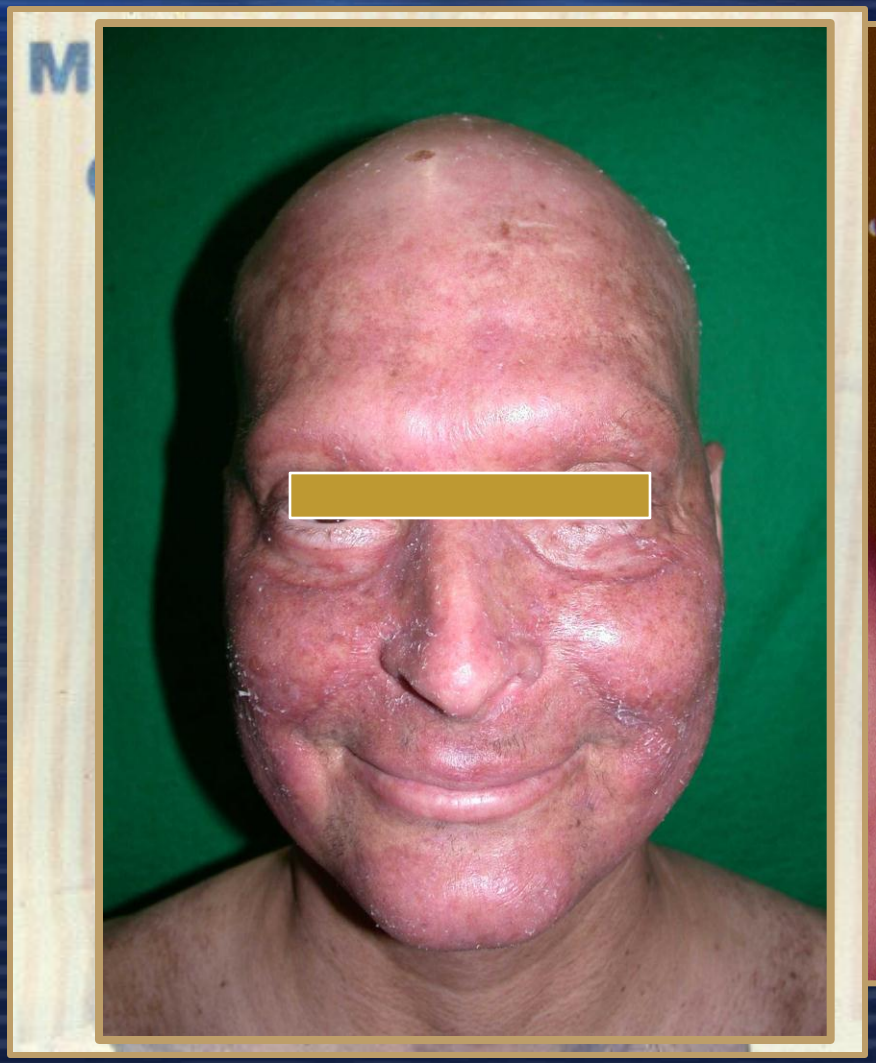
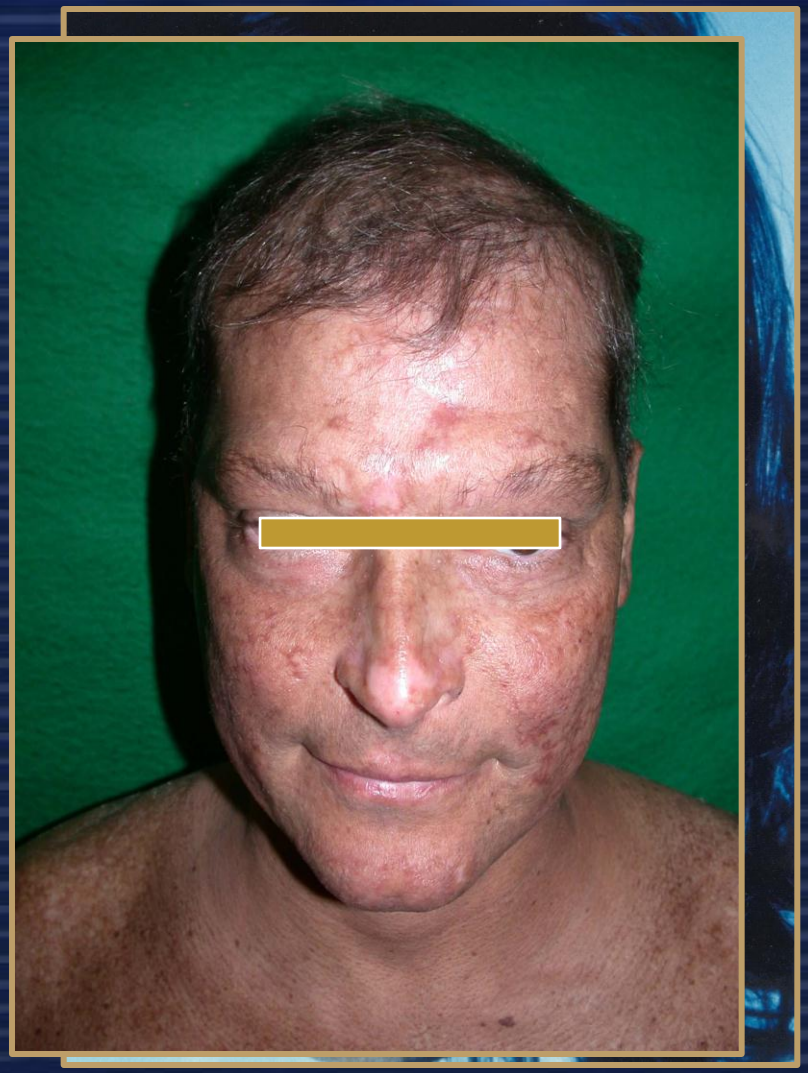
Results PUVA cGVHD

Before

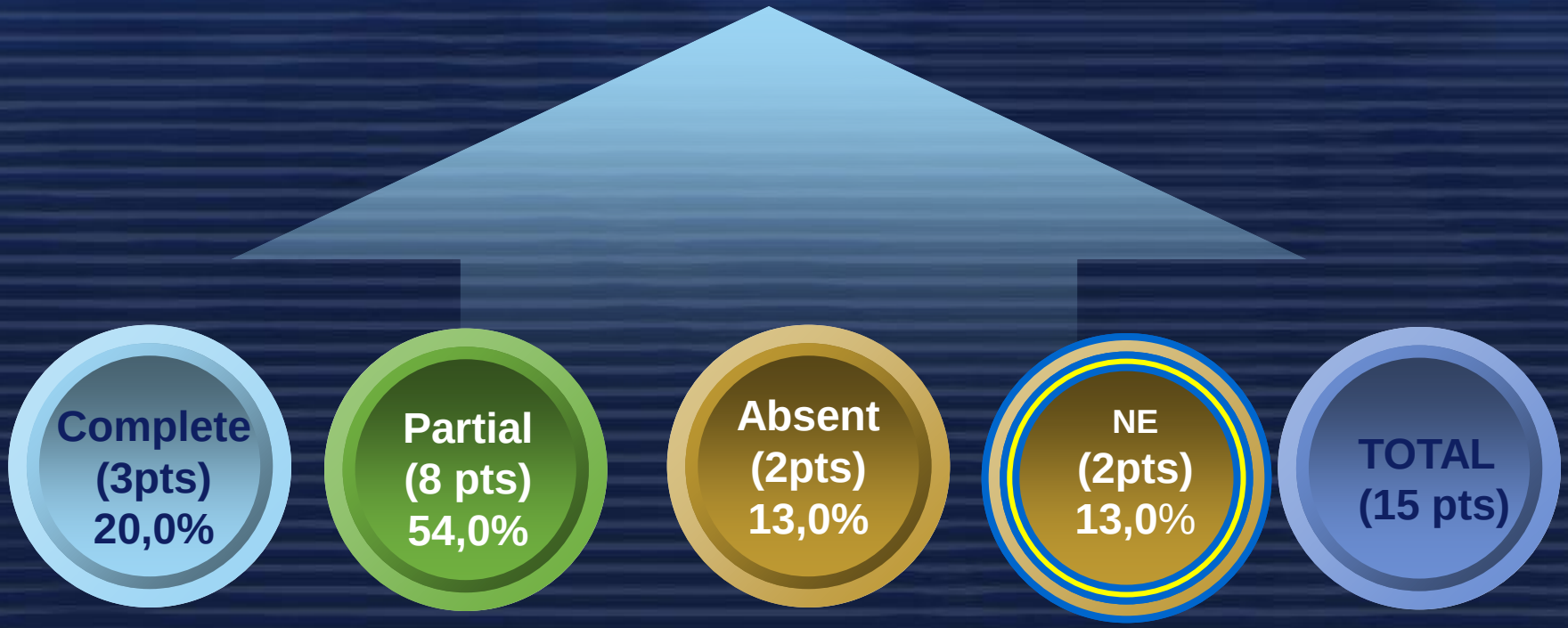


After



CEMO/INCA
1991 - 2012

UVBNB for cGVHD



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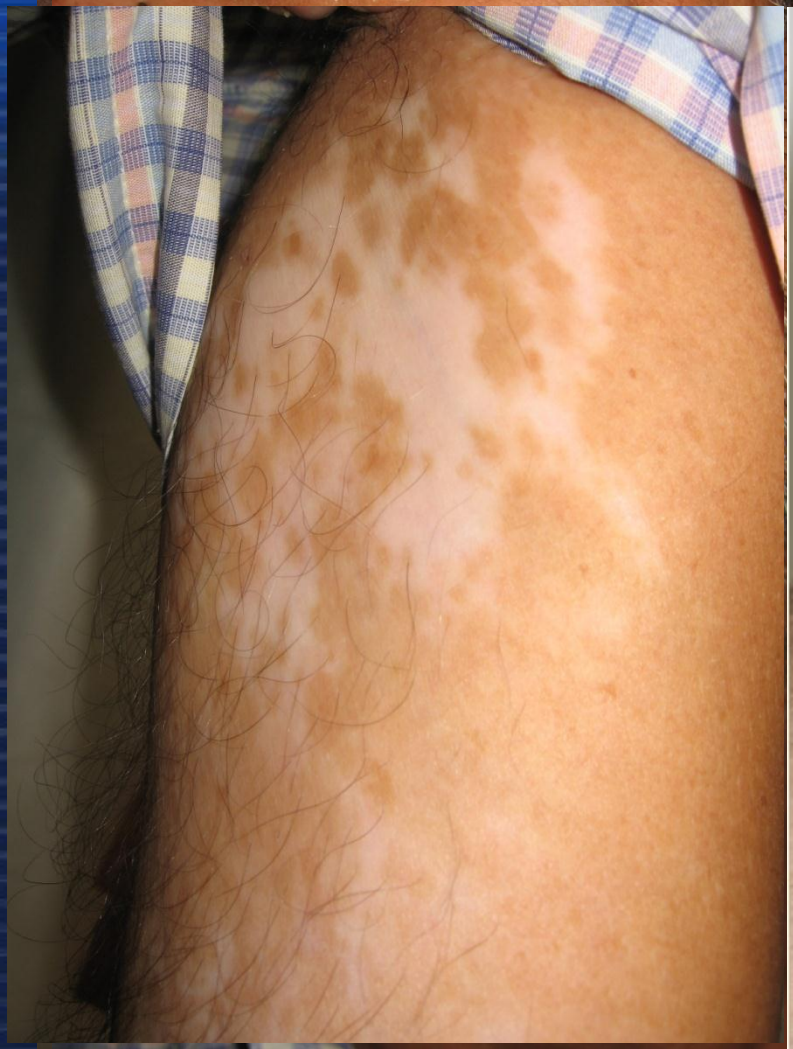
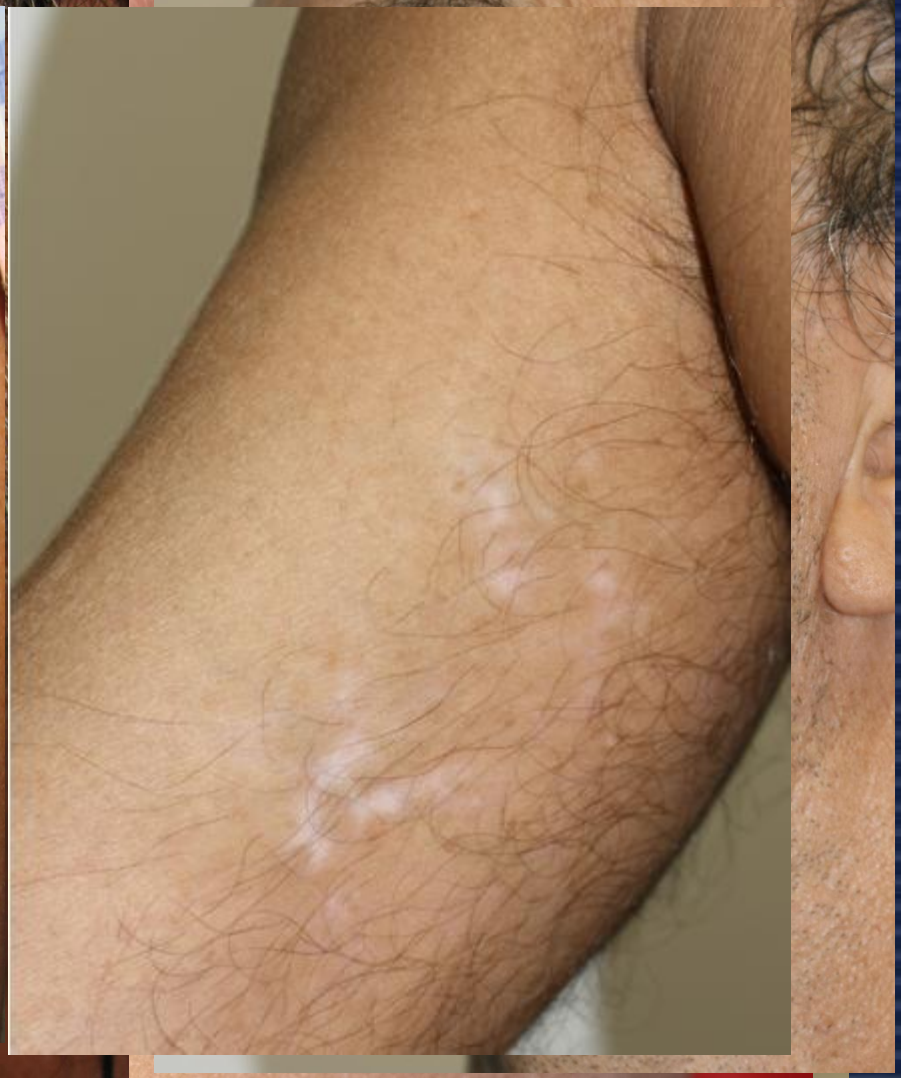
UBV-NB cGVHD



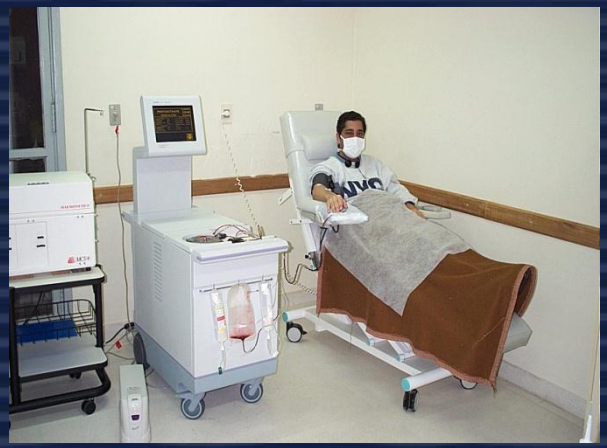


Extracorporeal Photopheresis

Centro de Transplante de Medula Óssea

Instituto Nacional de Câncer

Min. da Saúde



Extracorporeal Photopheresis
Definition

- **ECP is based on the exposition of peripheral blood mononuclear cells to *8-metoxipsoralen* (8-MOP) photoactivated after *Ultraviolet A* irradiation followed by treated cell product infusion.**

- **After this interaction, 8-MOP linked to DNA bases will promote a cell apoptosis process.**

- **Photochemotherapy basis- *PUVA***

Reprinted From

The New England
Journal of Medicine

VOLUME 316 FEBRUARY 5, 1987 NUMBER 6

TREATMENT OF CUTANEOUS T-CELL LYMPHOMA BY EXTRACORPOREAL PHOTOCHEMOTHERAPY

Preliminary Results

RICHARD EDELSON, M.D., CAROLE BERGER, PH.D., FRANCIS GASPARRO, PH.D., BRIAN JEGASOTHY, M.D., PETER HEALD, M.D., BRUCE WINTROUB, M.D., ERIC VONDERHEID, M.D., ROBERT KNOBLER, M.D., KLAUS WOLFF, M.D., GERHARD PLEWIG, M.D., GLYNIS MCKIERNAN, R.N., INGER CHRISTIANSEN, R.N., MARTIN OSTER, M.D., HERBERT HONIGSMANN, M.D., HUBERT WILFORD, M.D., EVA KOKOSCHKA, M.D., THOMAS REHLE, M.D., MARITZA PEREZ, M.D., GEORGE STINGL, M.D., AND LILIANE LAROCHE, M.D.

Extracorporeal Photopheresis
Indication

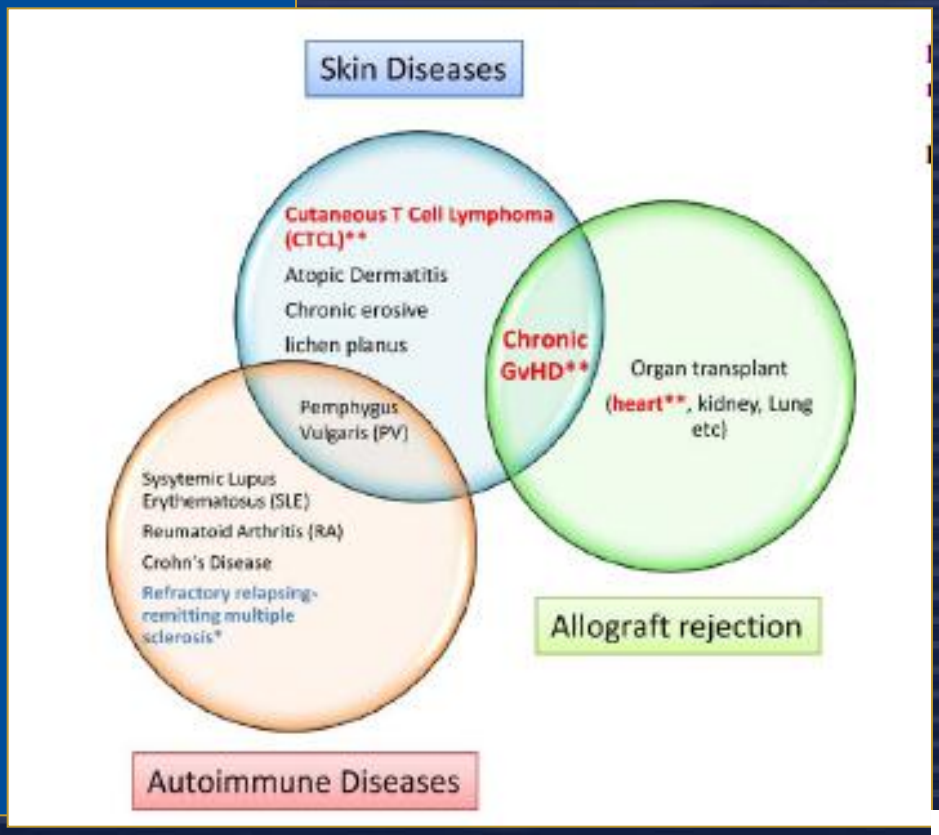
Resultados comprovados
Linfoma cutâneo de células T:Síndrome de Sézary(FDA)
Doença enxerto-contra-hospedeiro crônica

Interessante do caso de falha do tratamento habitual
DECH Aguda
Líquen plano erosivo
Dermatite atópica
Dermatoses bolhosas auto-imunes
Rejeição de transplantes de órgãos

A avaliar
Lupus eritematoso sistêmico
Dermatopolimiosite
Esclerose em placas
Diabetes insulino-dependente
Prevenção da rejeição de órgão
Artrite reumatóide
Infecção pelo HIV
Doença de Crohn

Controverso
Esclerodermia sistêmica

A. Maeda / Journal of Dermatological Science 54 (2009) 150–156



Extracorporeal photochemotherapy

Akira Maeda *

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, 1-Kawasumi,

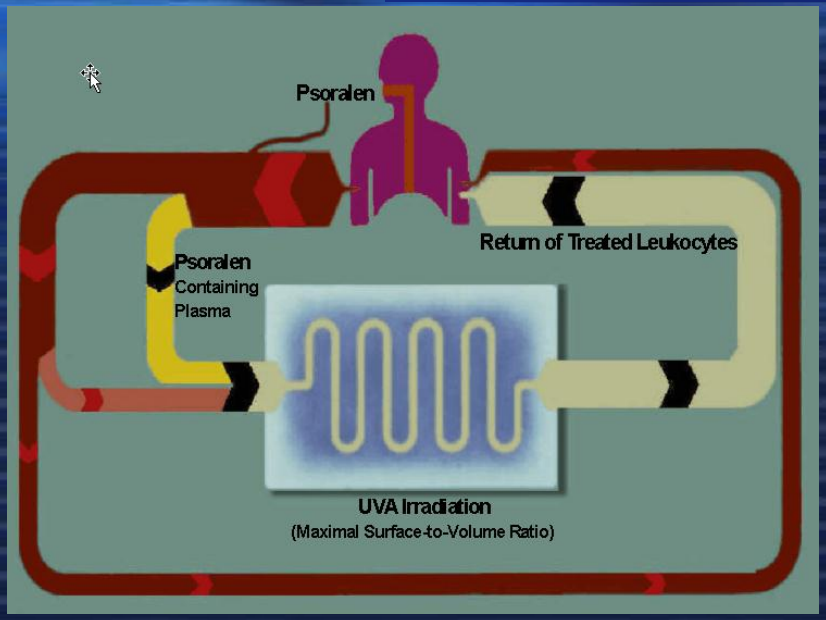
Journal of Dermatological Science 54 (2009) 150–156

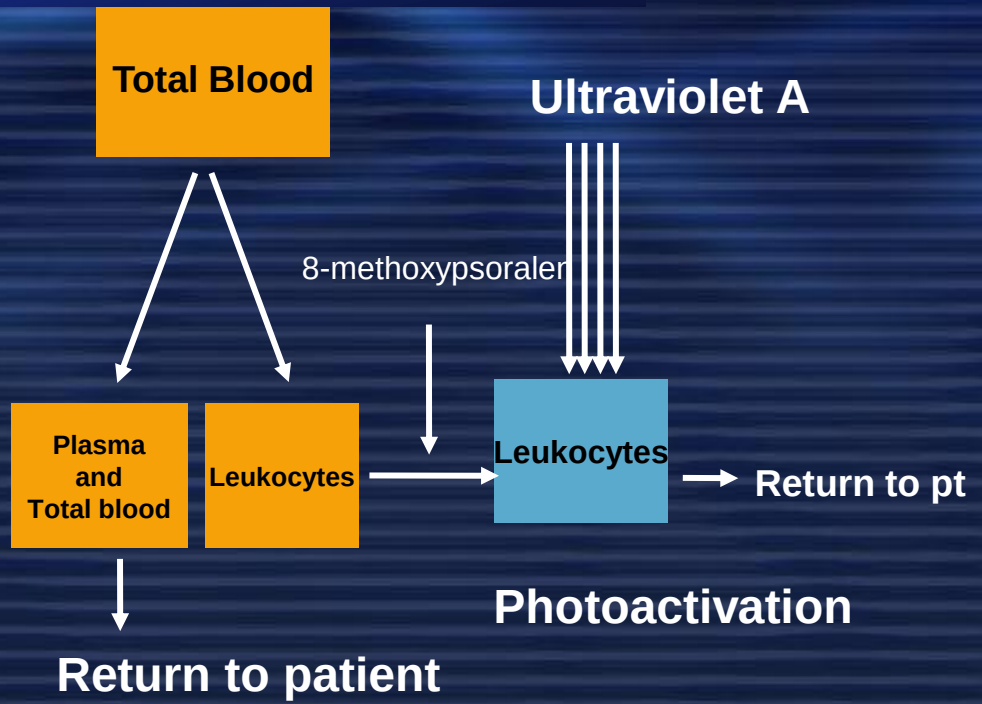
Table 1
Ongoing and recruiting clinical trials of extracorporeal photopheresis.

Condition	Treatment	Clinical trial	Study design	Progress
Extensive cGvHD	ECP with TH9402 (drug) and theralux (device)	Phase I/II	Randomized, open label, dose comparison, parallel assignment	Completed*
GvHD	ECP	Phase II	Non-randomized, open label, single group assignment	Ongoing
Cutaneous T-cell lymphoma (CTCL)	Bexarotene + ECP	Phase I/II	Non-randomized, open label, single group assignment	Completed**
cGvHD	ECP + standard therapy	Phase II	Randomized, single blind, active control, parallel assignment	Ongoing***
Rheumatoid arthritis	ECP	Phase II	Randomized, double-blind, placebo control, parallel assignment	Ongoing
CTCL stage1A, 1B, 2A	ECP	Phase IV	Non-randomized, open label, historical control, single group assignment	Recruiting
Acute GvHD	ECP	Phase II/III	Randomized, open label, active control, parallel assignment	Recruiting
Allogeneic stem cell transplantation	ECP + pentostatin + total body irradiation	Phase II	Randomized, open label, active control, parallel assignment	Recruiting
Non-small cell lung cancer	ECP + transimmunization	Phase I	Toxicity/feasibility study	Recruiting
HIV infections	ECP	Phase I	Non-randomized, open label, active control, single group assignment	Recruiting
GvHD	Etanercept + ECP	Phase II	Non-randomized, open label, single group assignment	Not yet recruiting

* Results were presented by Mielke et al. [14].
** Results were reported by Dernierre et al. [40].
*** Results were reported by Flowers et al. [31].

Extracorporeal Photopheresis
Procedure





Phase 1- Colection: 200-400ml Total Blood

✓Centrifugation of Total blood

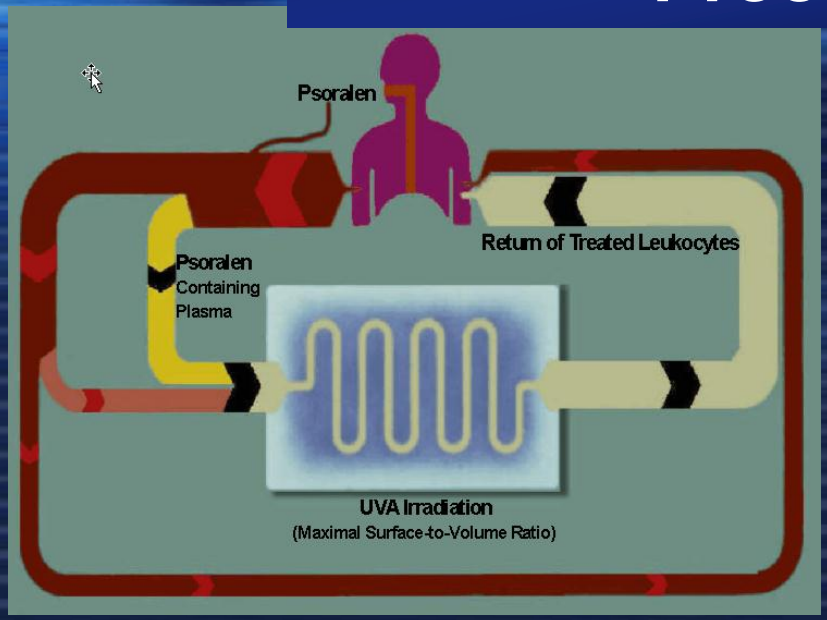
✓Leukocytes (buffy coat) separated and concentrated

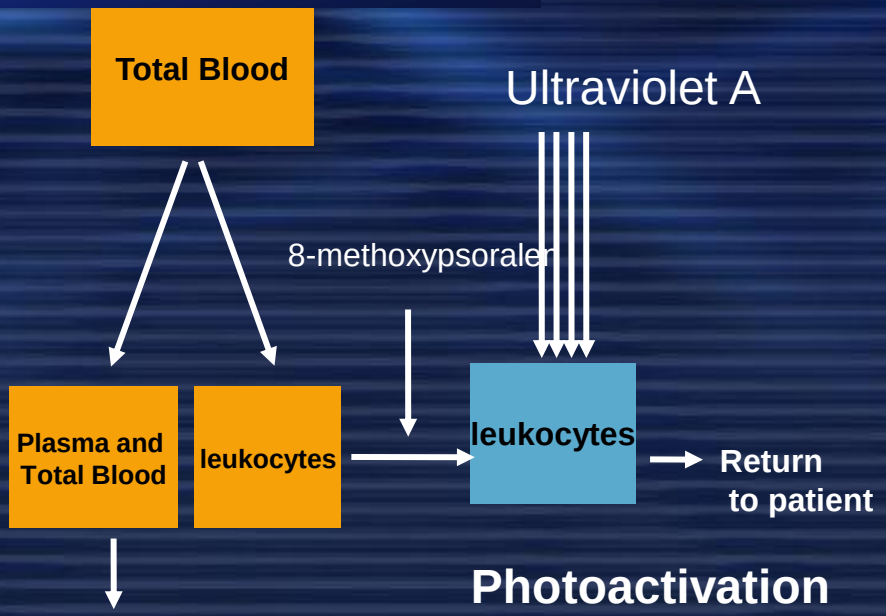
✓3-6 cicles repeated

Each cicle:

- Leukocytes concentrated and storaged (bag)
- Plasma + total blood – return to patient

Extracorporeal Photopheresis
Procedure





Phase 2- Photoactivation

❖Oral- 8-MOP 2 hours before ECP (nausea, GI symptoms, oral absortion variable)

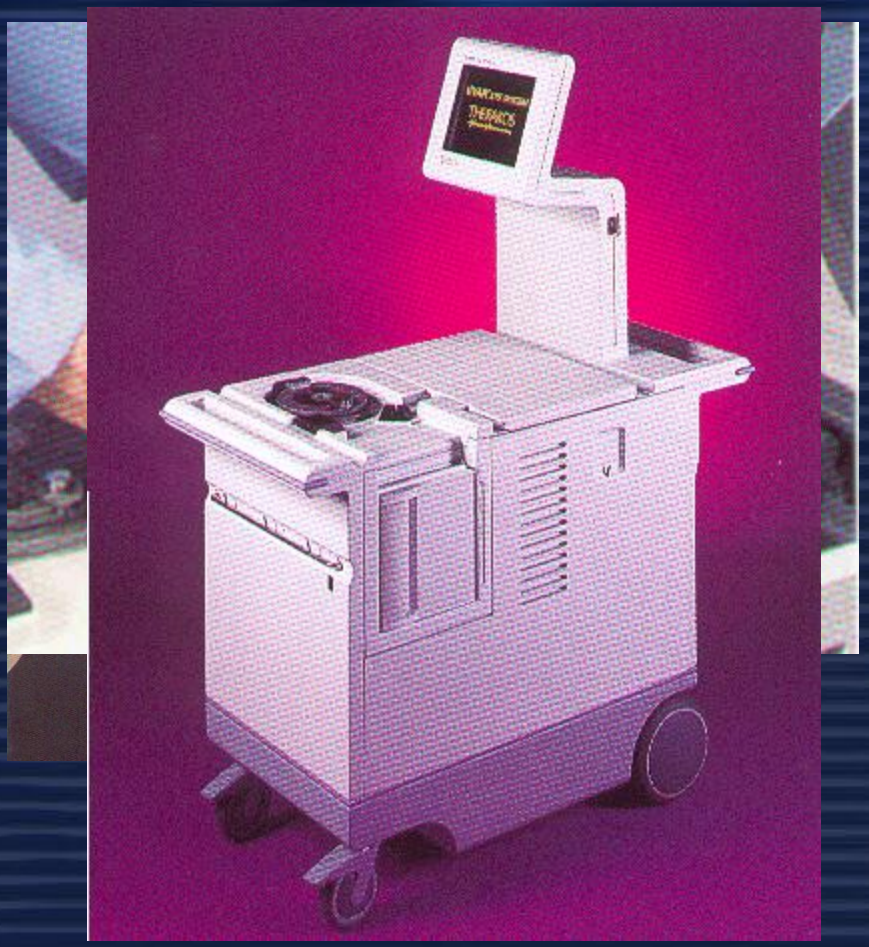
❖Injected- 8-MOP (UVADEX) injected
In the bag w/ conc. **leukocytes** previous to UVA irradiation (100-200ng/ml).
Product through **Photoactivation chamber** w/ UVA lamps (exposition time - variable)

Phase 3 - Reinfusion

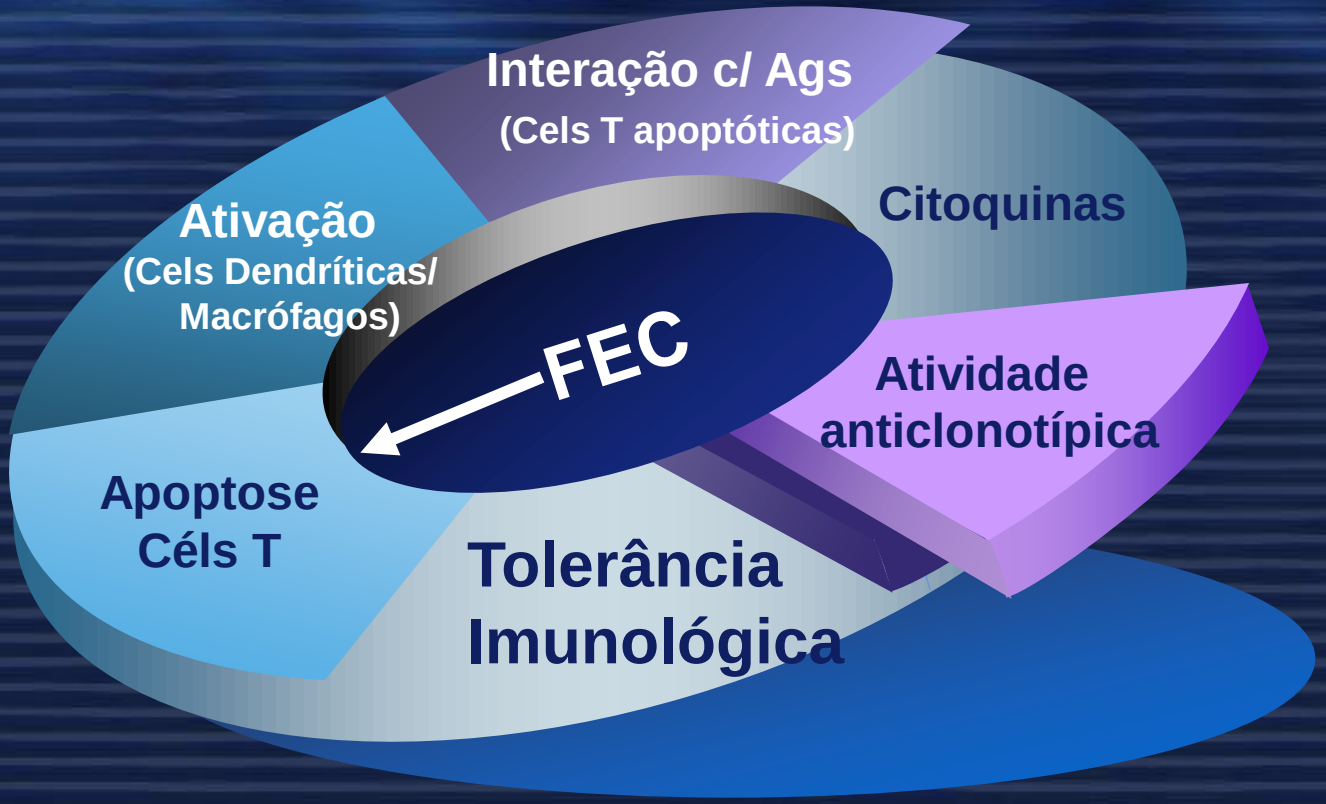
✓Volume - total + 500ml
✓Time / procedure total:150-240min
✓Venous access descontinued

Photopheresis System UVAR ®

- **Equipment UVAR**
- **Kit for Blood circulation (closed system)**
- **Photoreceptor®**
  Photoactivation chamber
- **Photosette-A ® UVA irradiation source**
- **Kit for centrifugation pediatric bowl**



Mechanism of Action
Extracorporeal Photopheresis

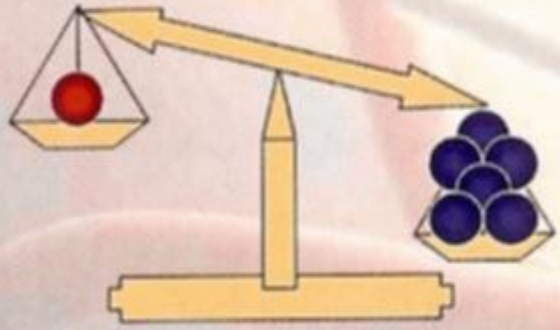


Immunological Homeostasis

Fight infections

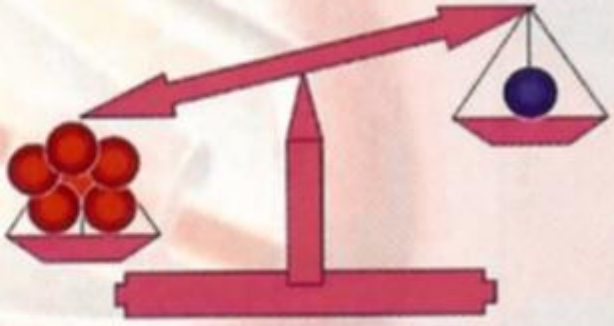
Inhibit autoimmunity

Immune System Fails



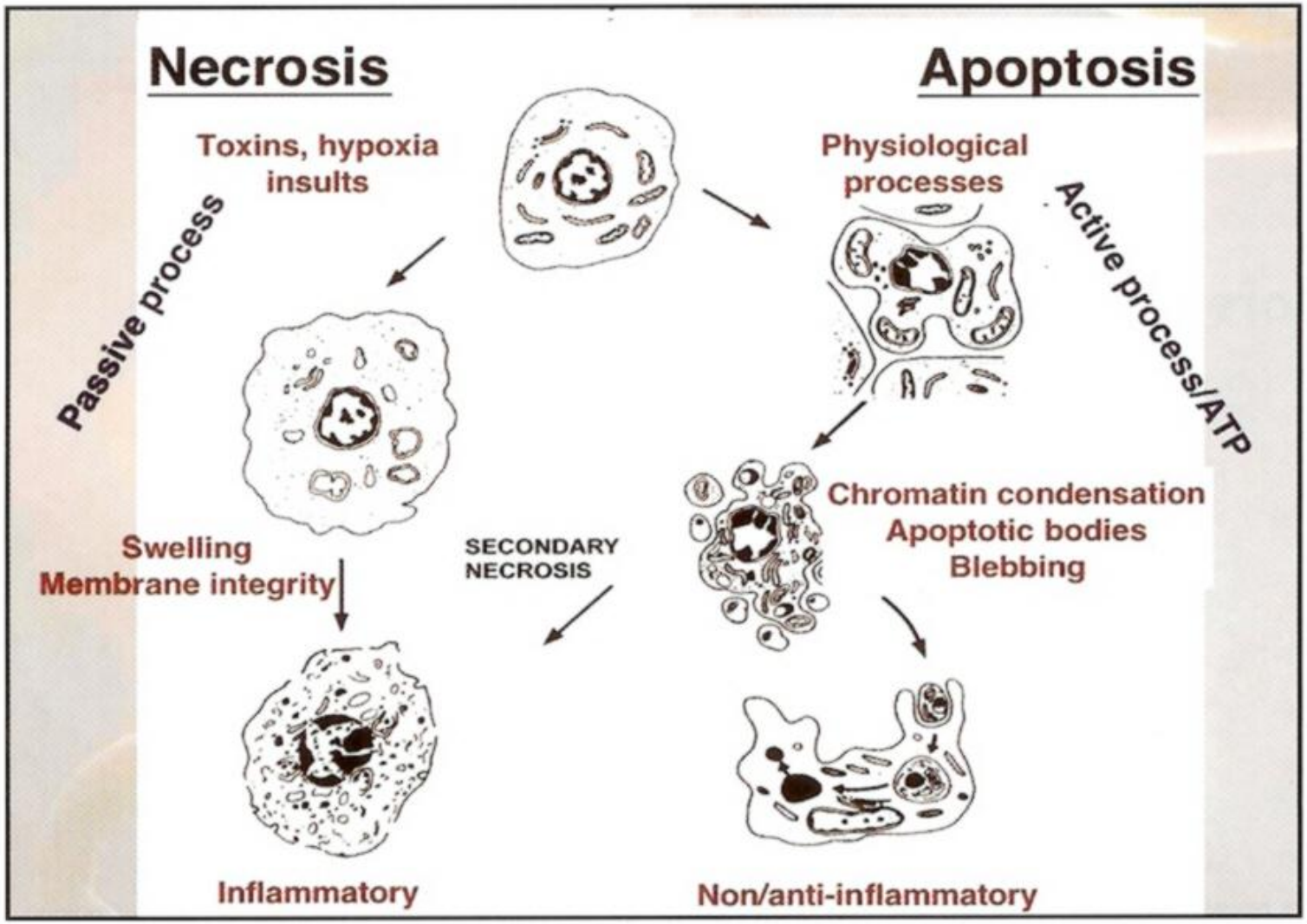
Immunodeficiencies, Cancer

Immune System Over-reacts

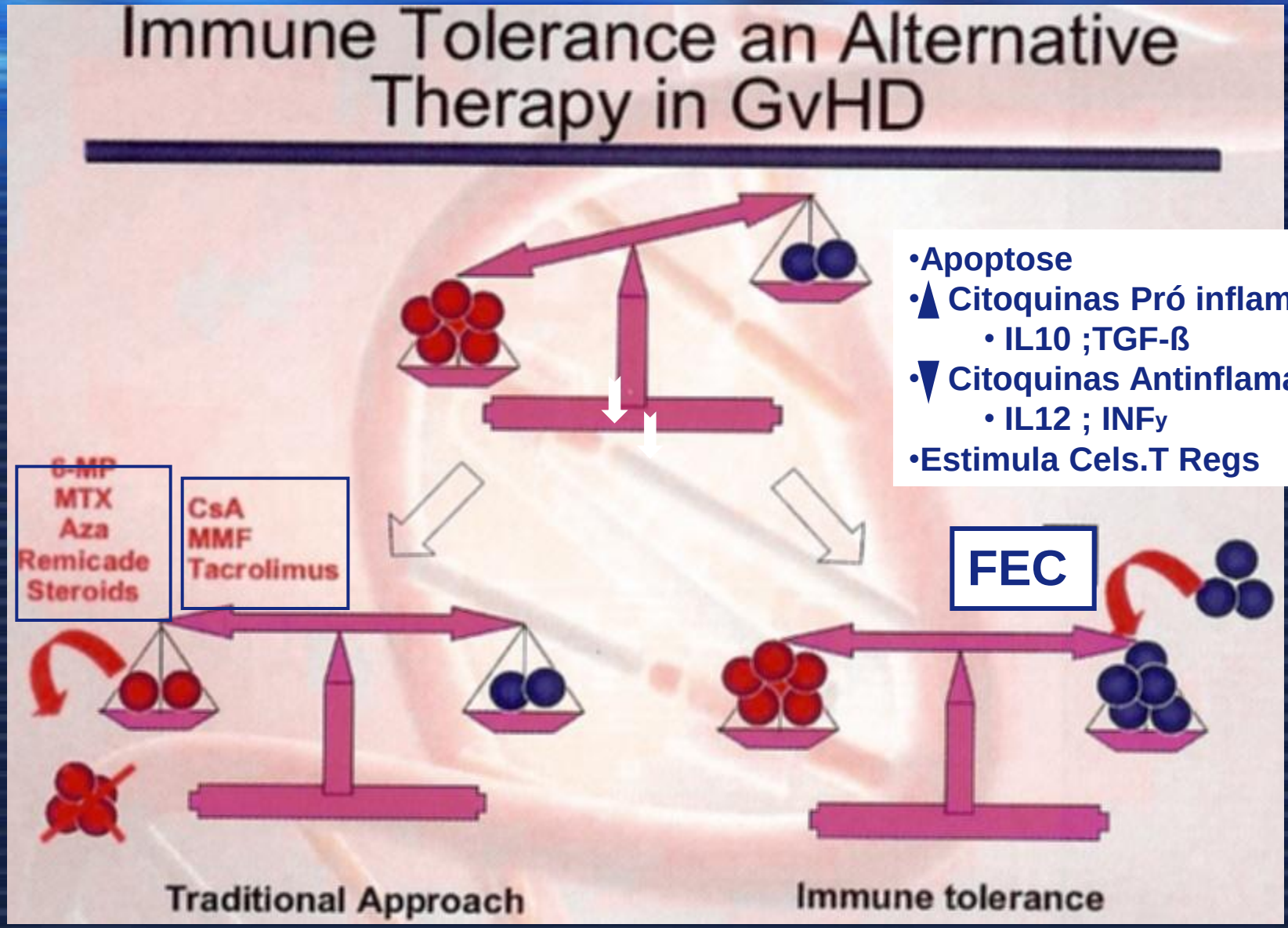


Autoimmune, alloimmune
GvHD, Transplant rejection

Peritt . D – IBMTR 2005


Necrosis
Apoptosis
Toxins, hypoxia insults
Physiological processes
Passive process
Active process/ATP
Swelling
Membrane integrity
SECONDARY NECROSIS
Chromatin condensation
Apoptotic bodies
Blebbing
Inflammatory
Non/anti-inflammatory

Immune Tolerance an Alternative Therapy in GvHD



- Apoptose
- ▲ Citoquinas Pró inflamatórias
  - IL10 ;TGF-ß
- ▼ Citoquinas Antinflamatórias
  - IL12 ; INFy
- Estimula Cels.T Regs

Extracorporeal Photopheresis and Chronic GVHD

Extracorporeal Photopheresis and Chronic GVHD

A Multicenter Prospective Phase II Randomized Study of Extracorporeal Photopheresis for Treatment of Chronic Graft-versus-Host Disease.
Blood. 2008 .112:2667-74

Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V, Bacigalupo A, Kolb HJ, Bouzas L, Michallet M, Prince HM, Knobler R, Parenti D, Gallo J, Greinix HT.

95 Pacientes com DECHc refratária ou corticóide – dependente:

- **Terapia imunossupressora convencional x FEC + imunossupressão;**
- **Sem complicações infecciosas;**
- **Grupo FEC: média de 50% de redução de corticoide e melhora tx sobrevida;**
- **RC e RP maior no grupo FEC.**

I Reunião da SBTMO de Diretrizes Brasileiras em Transplante de Células Tronco Hematopoéticas (TCTH)

DECH Crônica

- Coordenador: **Luis Fernando Bouzas**
- Colaboradores:

Marcia de Matos Silva
Rita de Cássia B.Tavares
Maria Claudia Rodrigues
Afonso Celso Vigoritto
Maria Elvira P. Corrêa
Vaneuza Funke
Vergílio Coulturato
Mair Pedro de Souza
Marcos Mauad

GEDECH
Brasil - Seattle

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Sistema de Graduação baseado em evidências para suporte da DECHc

Categoria	Definição
Força da Recomendação:	
A	Deveria sempre ser oferecida
B	Deveria geralmente ser oferecida
C	Evidência de eficácia é insuficiente para dar suporte a recomendação a favor ou contra, ou evidência de eficácia talvez não compense os efeitos adversos ou os custos da abordagem.Opcional.
D	Moderada evidência de falta de eficácia ou por efeitos adversos que recomendem contra a utilização. Não deveria geralmente ser oferecido
E	Grandes evidências de falta de eficácia ou por efeitos adversos que recomendem contra a utilização.Não deveria nunca ser oferecido

Sistema de Graduação baseado em evidências para suporte da DECHc

Qualidade da evidência que suporte a recomendação:	
I	Evidência de ≥ I estudo controlado, randomizado
II	Evidência de ≥ I estudo clínico bem desenhado sem randomização de um *cohort* ou estudos de análise caso controle(preferência para estudo que contenham mais de 1 centro) ou de múltiplos casos ou resultados dramáticos de estudos não controlados
III	Evidências de opiniões de especialistas baseadas em estudos clínicos descritivos

Conclusion

- Em face da multiplicidade de manifestações, do grau de acometimento, da combinação de sítios envolvidos e da disponibilidade de agentes terapêuticos em cada centro, **o tratamento de resgate de DECHc dependente ou refratária a corticosteróide costuma ser individualizado**, o que dificulta a realização de estudos prospectivos controlados, com tamanho amostral suficiente para definições de resposta, e o estabelecimento de diretrizes.
- Sugerimos que estes casos sejam **protocolados em estudos multicêntricos** e recebam abordagem multidisciplinar.
- **A terapia de resgate ideal ainda não está definida**.

- Early indication for ECP if available in the Center, for cutaneous or mucosal cGVHD as secondary therapy.

- As alterações músculo-esqueléticas parecem responder bem ao **uso de rituximab, e o papel do methotrexate** nestes casos, como alternativa de menor custo, precisa ser mais bem definido.
- Na DECHc com envolvimento visceral **o tratamento deve ser dirigido ao órgão mais afetado**, por exemplo, MMF e/ou tacrolimus para fígado, anti-TNF-α ou sirolimus para intestino e altas doses de metilprednisolona e rituximab para pulmão.

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Consensus Conference on Clinical Practice in Chronic GVHD: Second-Line Treatment of Chronic Graft-versus-Host Disease

Daniel Wolff,[1] Michael Schleuning,[2] Stephanie von Harsdorf,[3] Ulrike Bacher,[4] Armin Gerbitz,[5] Michael Stadler,[6] Francis Ayuk,[4] Alexander Kiani,[7] Rainer Schwerdtfeger,[2] Georgia B. Vogelsang,[8] Guido Kobbe,[9] Martin Gramatzki,[10] Anita Lawitschka,[11] Mohamad Mohty,[12] Steven Z. Pavletic,[13] Hildegard Greinix,[14] Ernst Holler[1]

Biol Blood Marrow Transplant ■:1-17, 2010

- **Therapy: 2ª line for cGVHD**

- **Recommendation clinical evidence based:**
  - **Cost**
  - **≥ study randomized, appropriated controlled**
- **Response rates variable w/:**
  - **Protocols for ECP**
  - **Dose intensity**
  - **Number of cycles**
  - **Treatment time**

- **Recommendation C-1 Evidence II**
  - **Used as 2ª line justifyable and recommended**
- **Recommendation B Evidence I**
  - **Waiting for study results**
  - **Indication as 1ª line**
  - **Safety and maintenance of GVL effect (GVL)**

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Biol Blood Marrow Transplant ■:1-17, 2010

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 mucocutaneous 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

TAM indicates transplantation-associated microangiopathia; CIN, calcineurin inhibitor; cGVHD, chronic graft-versus-host disease; BO, bronchiolitis obliterans.

Extracorporeal Photopheresis and Chronic GVHD

The role of photopheresis in the treatment of graft-versus-host disease

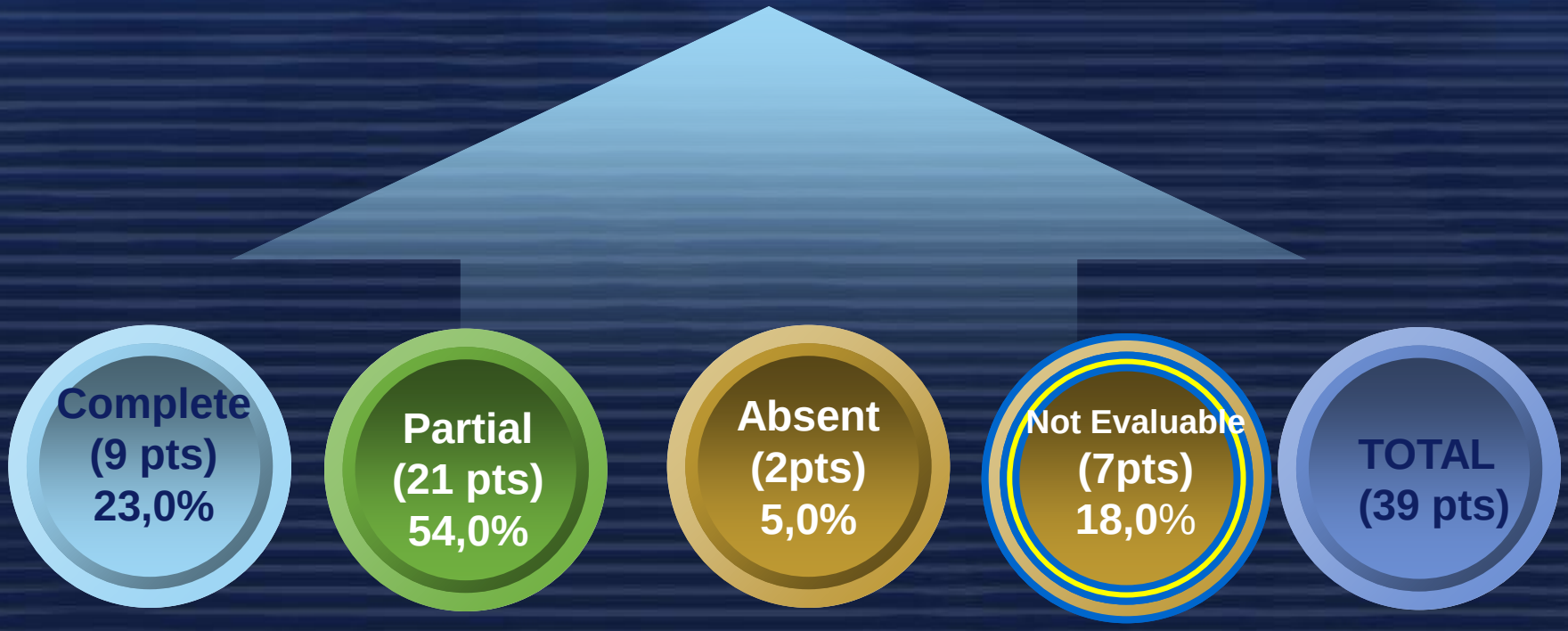
J. Klassen MD*

CURRENT ONCOLOGY—VOLUME 17, NUMBER 2 2010

- **Biomarkers could help to evaluate ECP efficacy**
- **3ª generation ECP equipment - Therakos Cellex - 75 a 100 min**

CEMO/INCA Experience
2000 - 2013

ECP for Chronic GVHD



Patients and methods
n=39

- Gender:
  - M - 21
  - F – 18
- Race:
  - W 28
  - B 06
  - M 05
- Disease:
  - ALL 05
  - AML 07
  - MDS 04
  - CML 13
  - CLL 01
  - NHL 03
  - HL 02
  - MM 03
  - NPH 01

- GVHD Prophilaxys
  - CSP 09
  - CSP MTX 28
  - TBI FLU 01
  - Tacrol MTX 01
- Organ
  - Skin
  - Liver
  - Mucosal
  - Lung
- Extension
  - Severe 37
  - Moderated 02
- GVHD Diagnosis
  - Prog 16
  - DeNovo 18
  - Overlap 05

Results

- **Access:**
  - **CVC 18**
  - **PV 21**
- **ECP:**
  - **r = 04 – 167**
- **AE:**
  - **CVC**
    - **Obst 07**
    - **CVT 01**
    - **Sepse 03**
  - **Other 02**
  - **No AE 26**

- Follow up
  - Death 14
  - Alive 25
- GVHD inactive 12
- GVHD active 02
- GVHD
  - ECP/PUVA 08
- Disc. CVC 03

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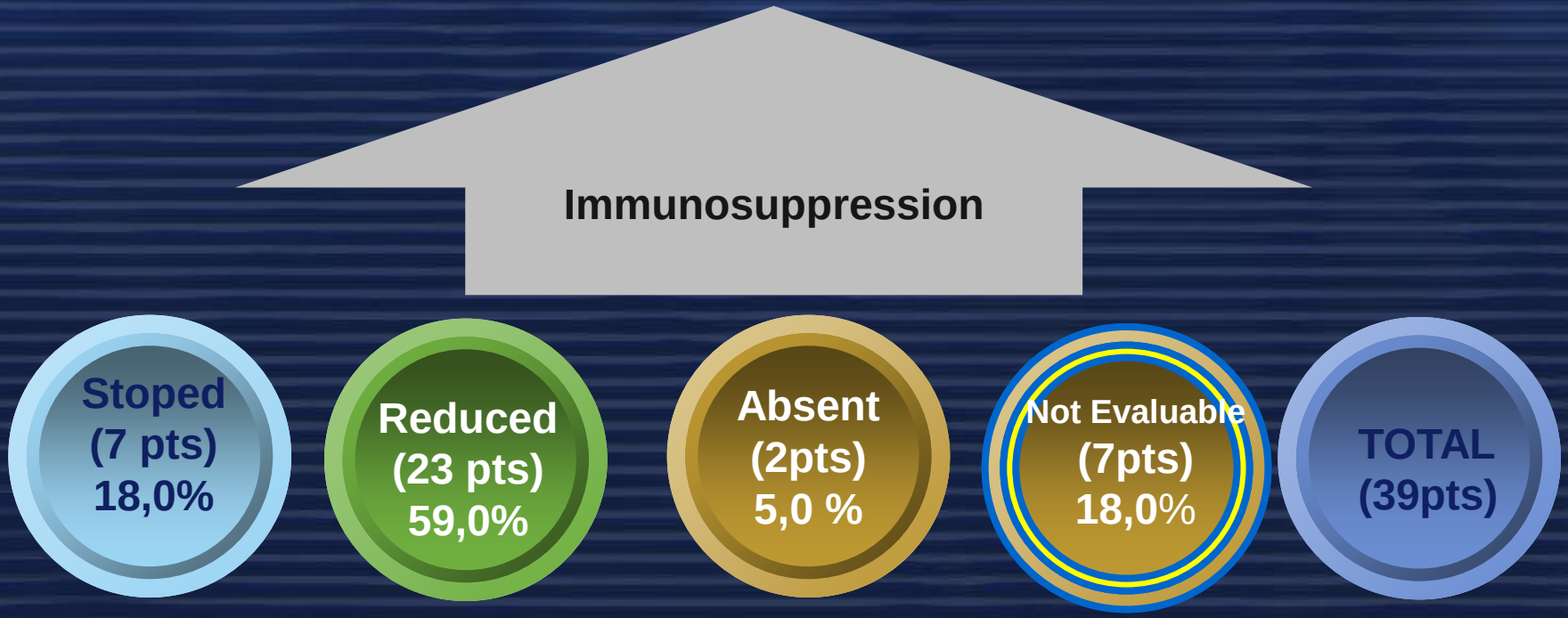
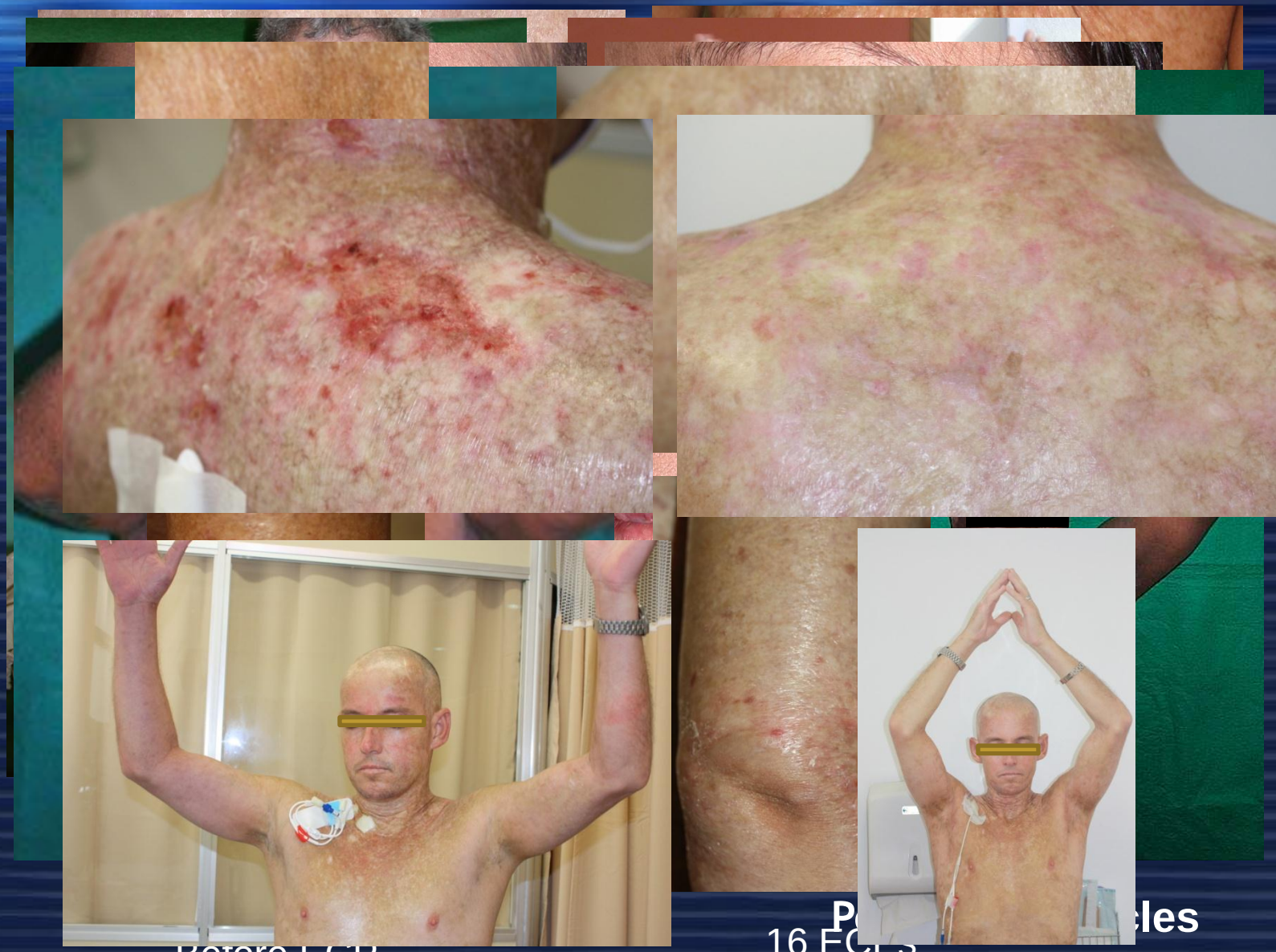
CEMO / INCA
2000 - 2013

ECP for Chronic GVHD



ECP for Chronic GVHD



Before ECP

Before ECP

16 ECPs

36 ECPs

Extracorporeal Photopheresis

Acute GVHD

Centro de Transplante de Medula Óssea - INCA

Role of Extracorporeal Photopheresis (ECP) in Treatment of Steroid-Refractory Acute Graft-verus-Host Disease

Hildegard T. Greinix,[1] Nina Worel,[2] Robert Knobler[3]

Biol Blood Marrow Transplant ■: 1-3 (2010)

Table 1. Comparison of Pilot Study [6] and Phase II Study [2] Using ECP for Second-Line Therapy of Steroid-Refractory Acute Graft-versus-Host Disease

	All	Pilot	Phase II
Number of patients	59	21	38
Median day of onset of aGVHD	17	19	17
Range	8-42	10-33	8-42
Median day of onset of steroids	19	21	19
Range	8-42	10-35	8-42
Grade of aGVHD at ECP			
II	36	10	26
III	13	6	7
IV	10	5	5
Median days of steroids prior to ECP	17	21	15*
Range	4-49	9-49	4-43
Med. cum. steroid dose first-line (mg/kg bw)	2.8	3.9	2.1†
Range	2-10.4	2-10.4	2-6.5
Median interval D0-start of ECP (days)	37	41	34‡
Range	14-70	20-70	14-69
Med. dose of steroids at start of ECP (mg/kg b.w.)	2.1	2.6	1.8§
Range	0.7-10.4	1.1-10.4	0.7-2.3
% complete resolution of aGVHD			
Grade II	86	100	85
Grade III	55	67	43
Grade IV	30	12	60
Skin	82	76°	86
Liver	61	67	55
Gut	61	25°	73
Best response after cycle (median)	4	4	4
Range	1-13	1-13	1-8
Best response after month (median)	1.3	1.7	1.2
Range	0.5-6	0.5-6	0.5-4.5
Med. days to D.C. steroids after start of ECP	55	53	56
Range	17-284	18-122	17-284
Med. steroid dose 4 weeks after start of ECP	0.9	1.1	0.7
Range (mg/kg b.w.)	0-5	0-5	0-2
Med. steroid dose 8 weeks after start of ECP	0.3	0.3	0.2
Range (mg/kg b.w.)	0-1.5	0-1.3	0-1.5

Med indicates median; b.w., body weight; cum, cumulative; D.C., discontinuation; aGVHD, acute graft-versus-host disease; ECP, extracorporeal photopheresis.

°Clarification: at the time of publication of the pilot study [6] 1 patient was still under ECP therapy, and thus reported as a nonresponder. In the comparison between the pilot study and phase II study [2] this patient had completed ECP therapy, and therefore the response rates for skin and GI involvement are different than originally reported in the pilot study.

*$P = .030$.

†$P = .0011$.

‡$P = .0028$.

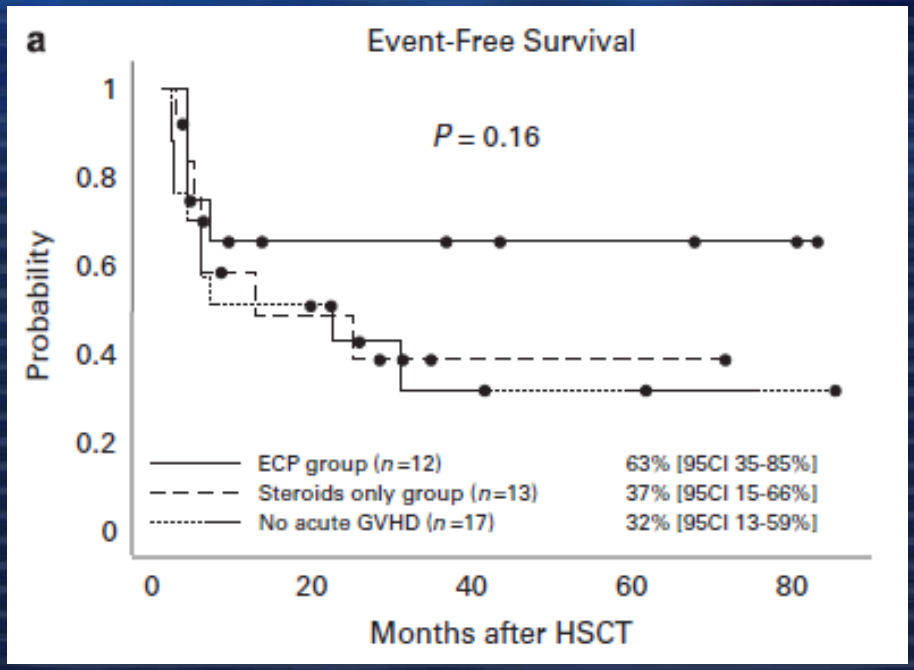
§$P = .010$.

Recommendation C / Evidence II

Extracorporeal photochemotherapy as second- or first-line therapy of acute GVHD?

Bone Marrow Transplantation (2010) 45, 963–965

E Merlin[1,2,3], C Paillard[1,2], E Rochette[1,2], A David[1,2], F Isfan[1,2], E Doré[1,2], F Deméocq[1,2,3] and J Kanold[1,2,3]



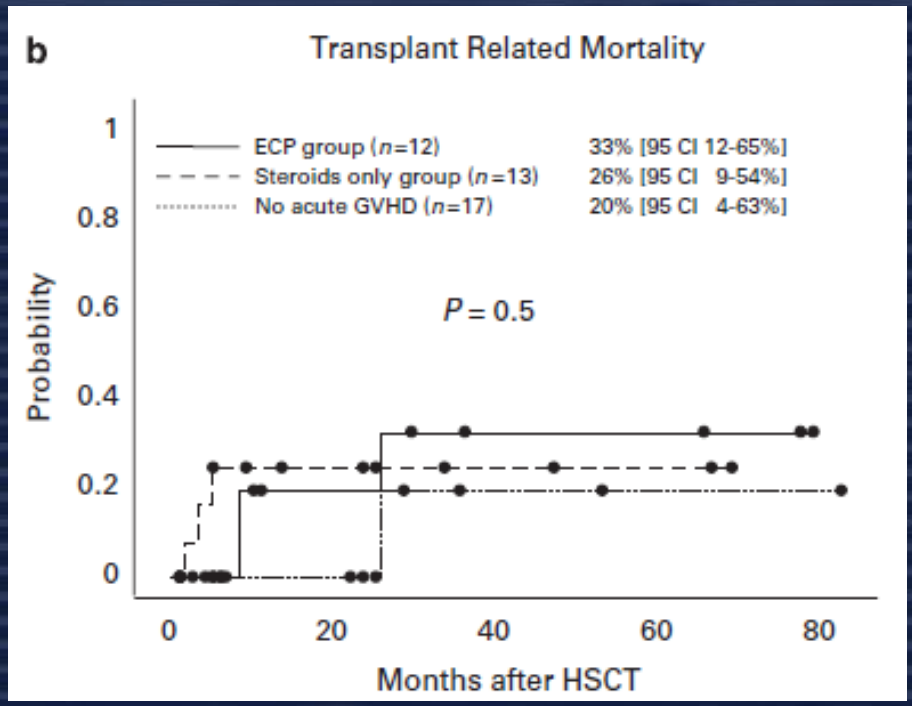


Figure 1 Outcome of patients treated with myeloablative allogeneic BMT for hematological malignancy depending on the features of acute GVHD. (**a**) EFS. Events were defined as relapse or extensive chronic GVHD. Patients without acute GVHD, patients responding to steroids without severe adverse events (steroids only group), patients treated with extracorporeal photochemotherapy (ECP) for steroid refractory or steroid-dependent acute GVHD or severe aGVHD responding to 'conventional treatment' but with intolerable treatment-related side effects (ECP group). (**b**) TRM. Log-rank test.

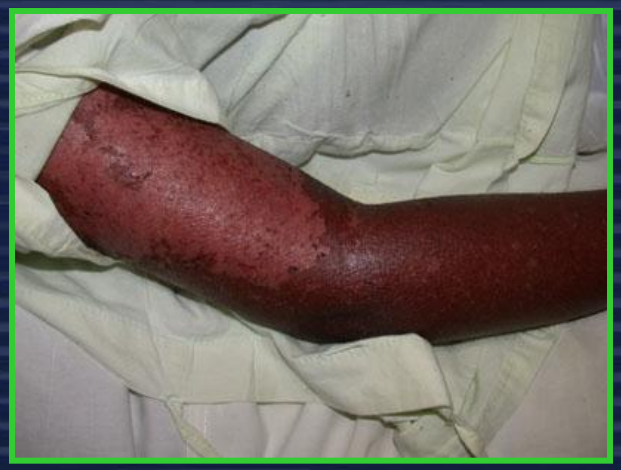
Extracorporeal Photopheresis

Acute GVHD

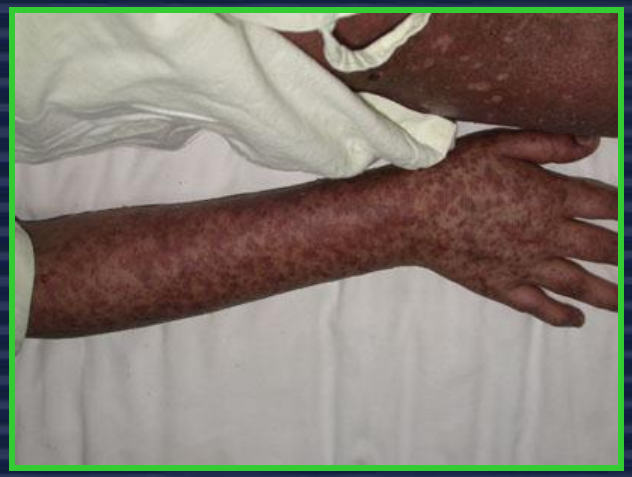
TQSA, 13a, LLA-T em 2ª remissão , TMO HLA-compatível(infusão 4,34 x 108 células nucleadas/Kg) após condicionamento com Cy/TBI. Profilaxia DECH:CSP/MTX

D+20-Lesões maculo-papulo disseminadas(DECHa grau III), fígado-BT=1,48(DECH-II).Tratado com basiliximab®/Prednisolona 2mg/Kg e Micofenolato

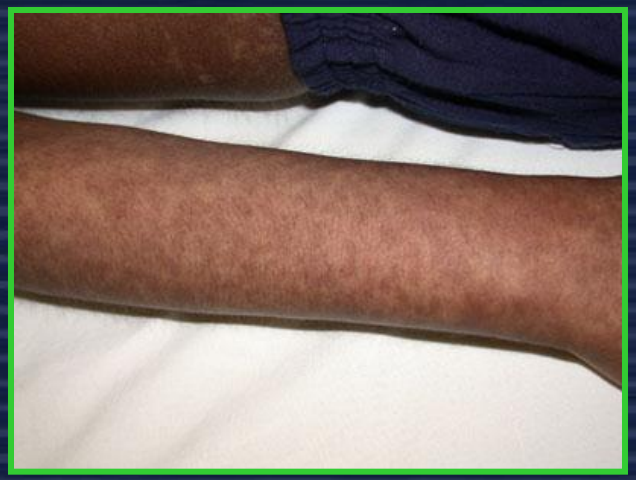
D+54- Evolução com eritrodermia com vesículas e bolhas(DECHa IV)



Before ECP



4 ECP



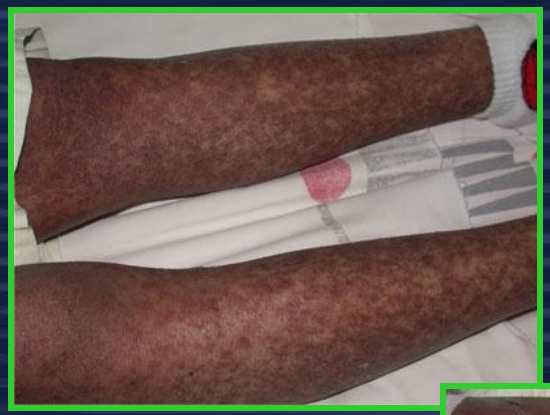
8 ECP

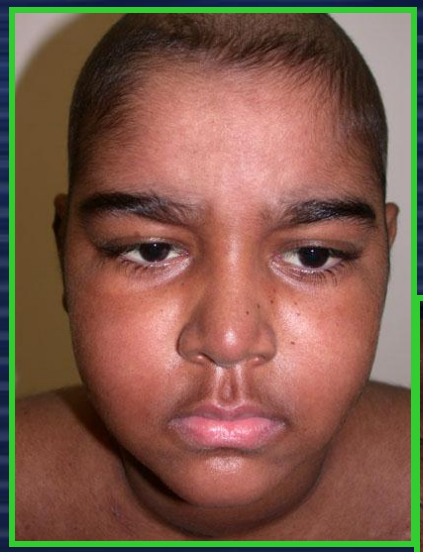
Extracorporeal Photopheresis and Acute GVHD

Results from CEMO – INCA (2000-2010)
N=9 PATIENTS

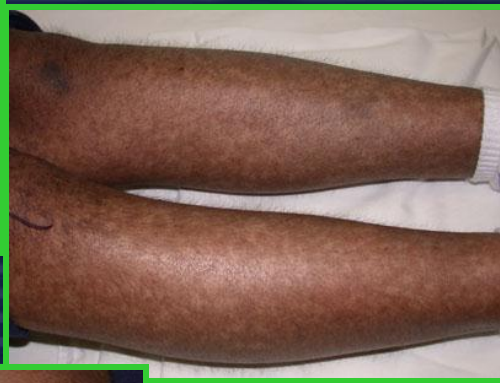
CR-5/9
NE-4/9(early death sepsis)

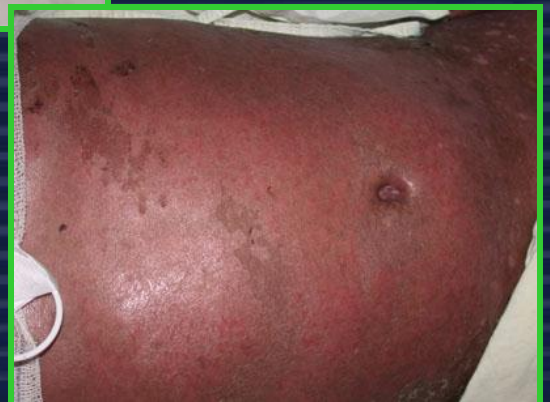
Before ECP

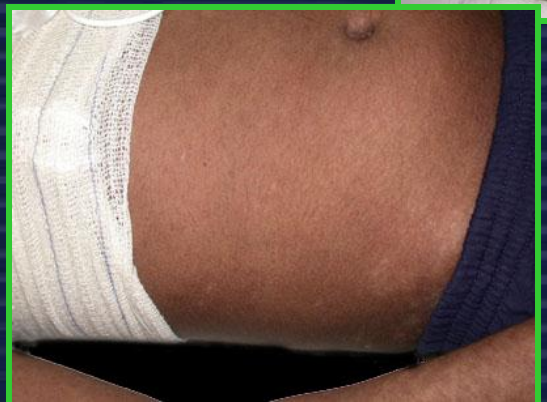




8 ECP







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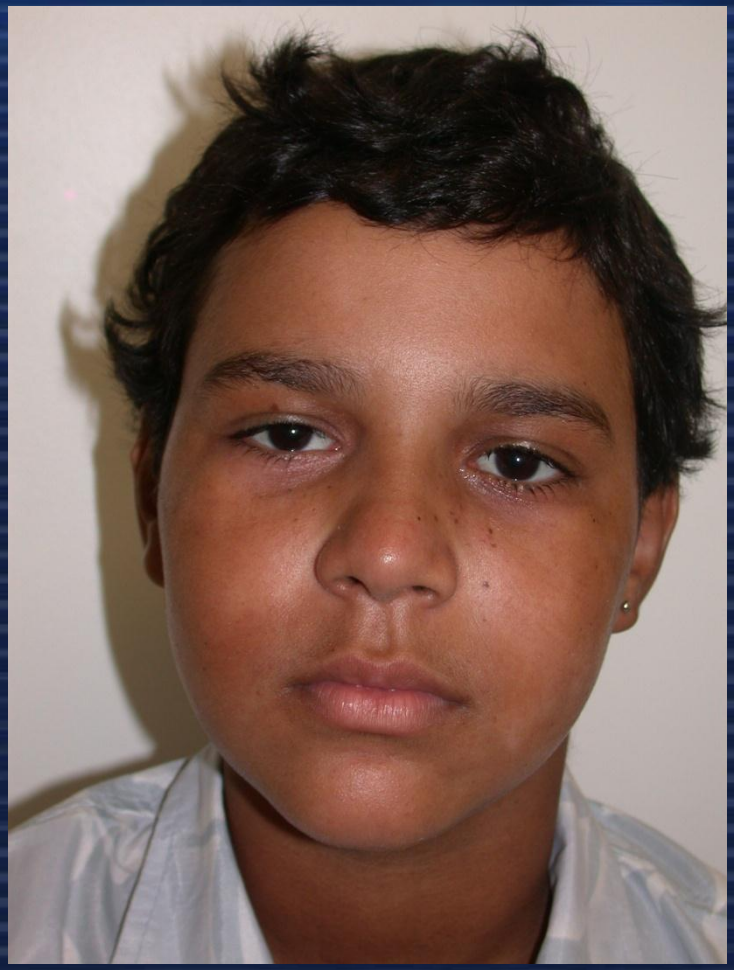
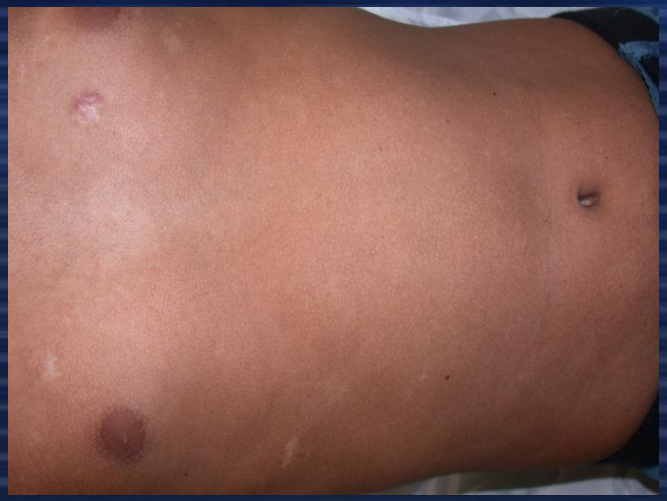
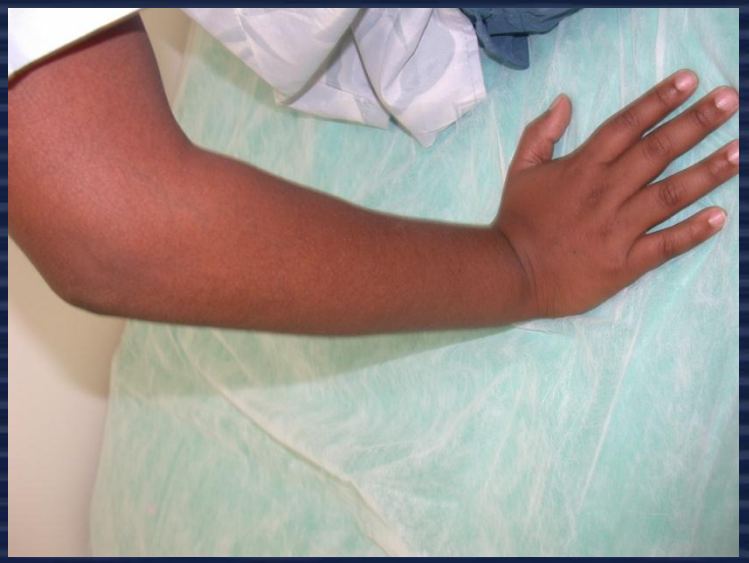
Extracorporeal Photopheresis and Acute GVHD

Without immunosupression after 2 years



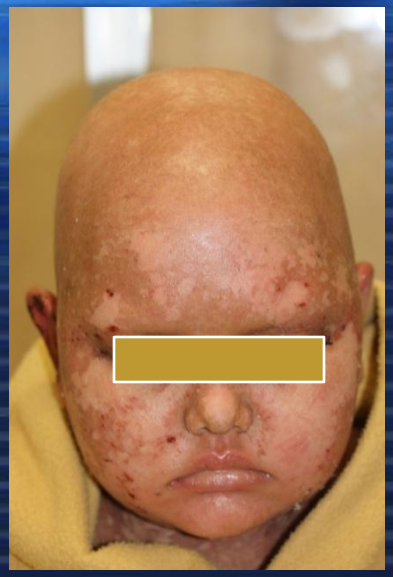
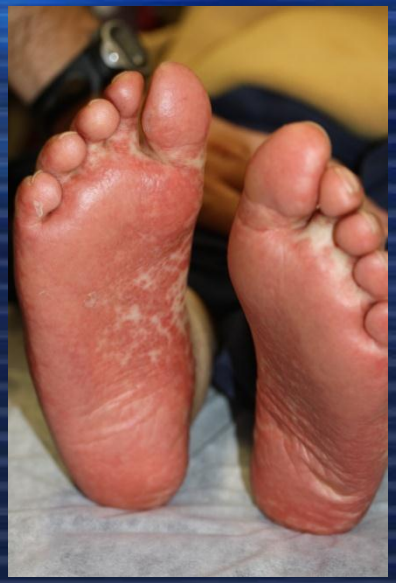
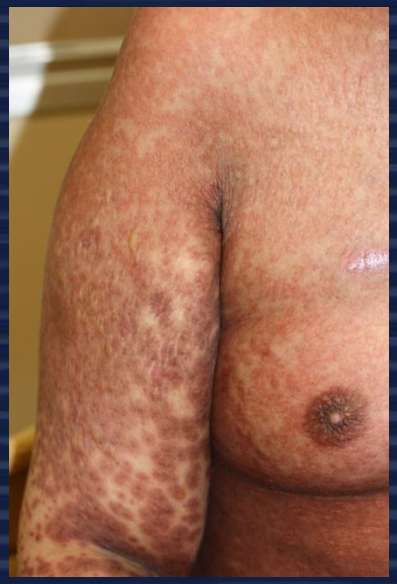
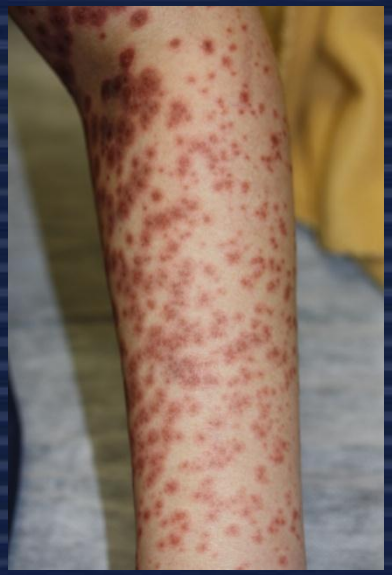
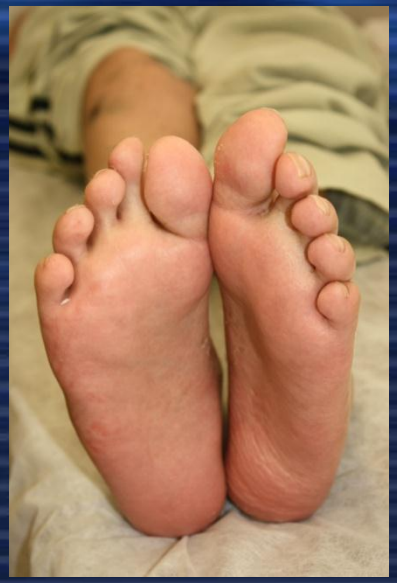
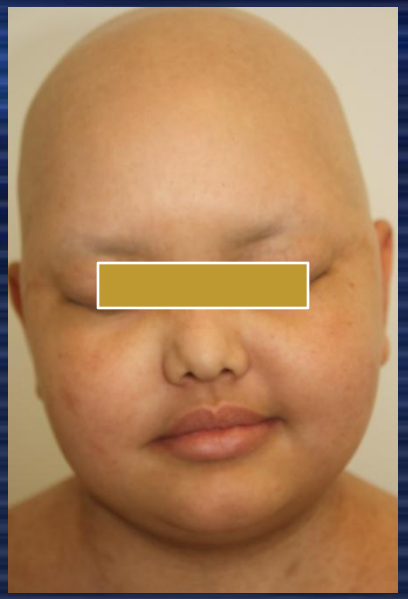
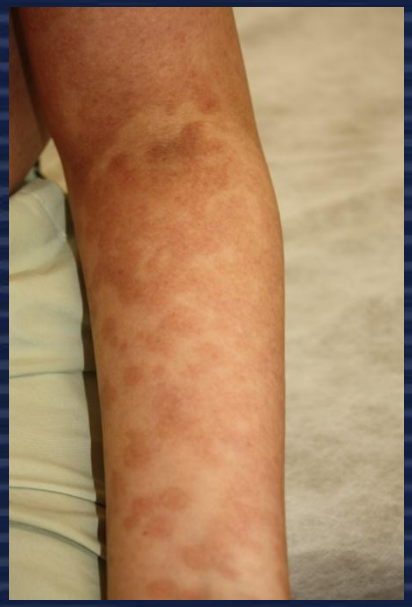
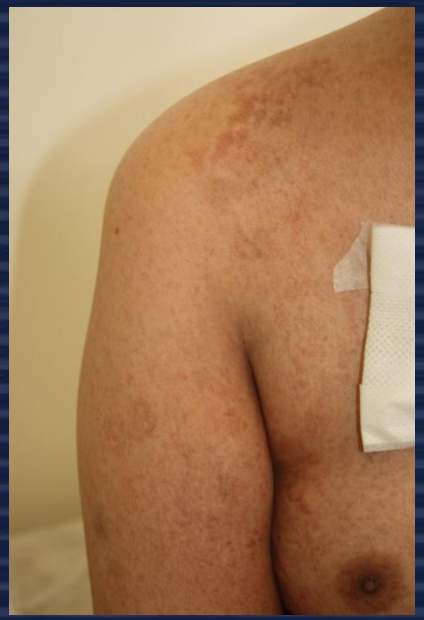




Pre ECP

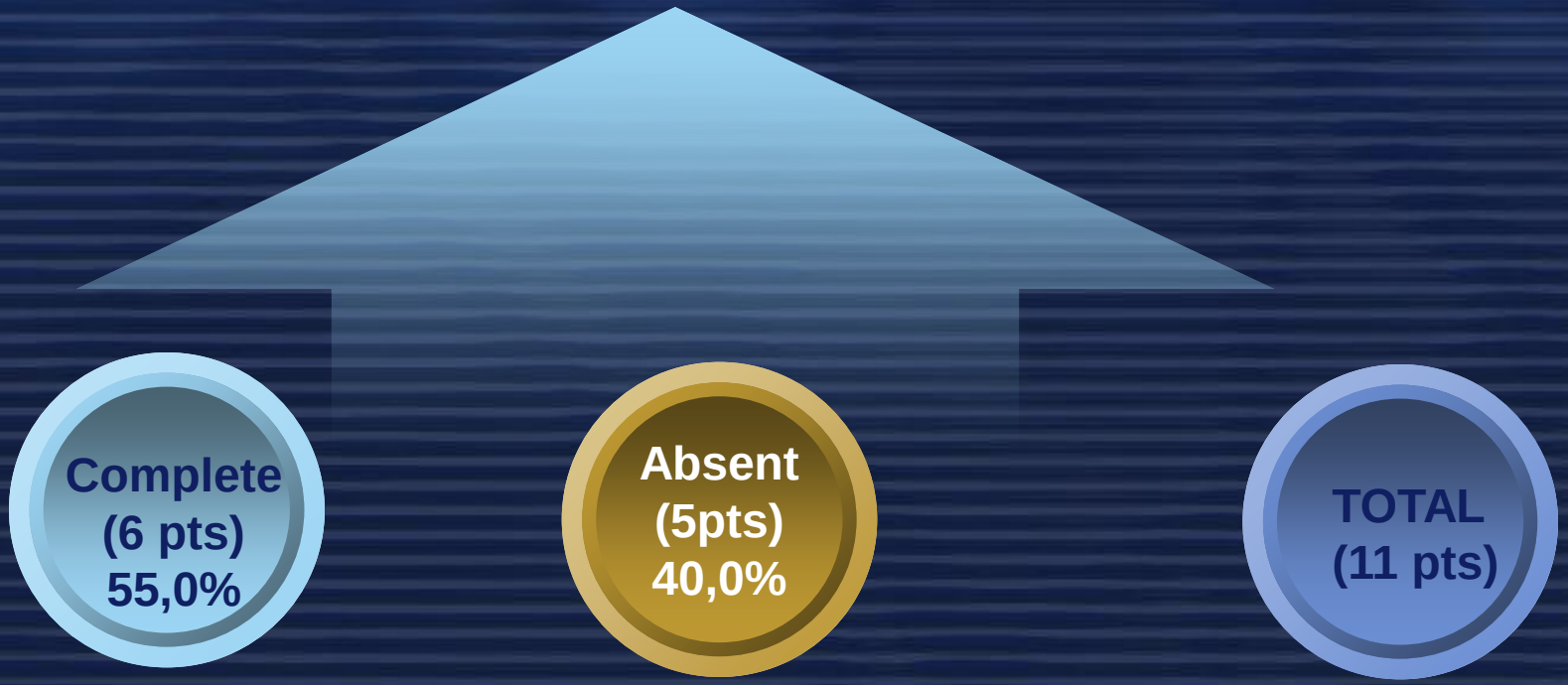
Extracorporeal Photopheresis and Acute GVHD

Post 8 ECP

ECP CEMO/INCA
2000 - 2013

ECP for Acute GVHD



Extracorporeal Photopheresis Multidisciplinary Team

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  - Luis Fernando Bouzas
  - Décio Lerner
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  - Marta Colares
  - Maria Claudia Moreira
  - Simone Maradei
  - Eliana Abdelhay
  - Hilda R. Diamond
  - Bernadete Gomes
  - Daniela Pinto
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  - Regina FM Fernandes
  - Flavia A de Oliveira
- *Patologia/INCA*
  - Sergio Romano
- *Fotodermatologia UFRJ*
  - Absalom L. Filgueira
- *Enfermagem Fototerapia*
  - Marcos Belo

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Obrigado!!!

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Ministério da Saúde