Dear Colleagues and Friends,

It is a great honor and pleasure to welcome you in Vienna to the 2012 annual clinically oriented meeting of the EORTC Cutaneous Lymphoma Task Force.

Our goal is to highlight important new developments in the areas of clinical and basic sciences as well as pathogenesis, diagnosis, and therapy of cutaneous lymphomas.

A major focus of this meeting will be to discuss and identify TARGETS FOR THERAPY IN CUTANEOUS LYMPHOMAS. For this purpose we welcome the active participation of all of you that will help us gain further insight into this highly promising, exciting and rapidly developing area of medicine and oncology.

As has become tradition the meeting includes oral and poster presentations of significance in the treatment and pathology of cutaneous lymphomas.

We wish you a fruitful and enjoyable meeting.

Robert Knobler, Franz Trautinger
Local organizers
EORTC CLTF 2012
TARGETS FOR THERAPY IN CUTANEOUS LYMPHOMAS
September 7-9, 2012
Vienna, Austria

LOCAL ORGANIZING CHAIRMEN:

Robert Knobler, M.D.
Assoc. Prof. of Dermatology
Lymphoma and Photopheresis Clinic
Department of Dermatology
Medical University of Vienna
Währinger Gürtel 18-20
1090 Vienna, Austria
Tel: +43 1 40 400 7807
Fax: +43 1 40 400 7808
email: robert.knobler@meduniwien.ac.at

Franz Trautinger, M. D.
University Professor
Department of Dermatology and Venereology, Landesklinikum St. Pölten
Karl Landsteiner Institute of Dermatological Research
Propst-Führer-Strasse 4
3100 St. Pölten, Austria
Tel +43-2742-300-11909
Fax +43-2742-300-11919
email: franz.trautinger@stpoelten.lknoe.at

LOCAL SCIENTIFIC & ORGANIZING COMMITTEE

Wolfgang Bauer
Lorenzo Cerroni
Johanna Eder
Ulrich Jäger
Constanze Jonak

Leonhard Müllauer
Hubert Pehamberger
Markus Raderer
Matthias Schmuth
Julia Valencak

MEETING COORDINATOR & SPONSORSHIP & EXHIBITION SALES CONTACT

Ursula Partsch-Brokke
Tagungsmanagement
A - 2560 Berndorf, PF 41
Tel/Fax: +43 (0)2672 88 99 6
email: office@tagungsmanagement.org

CONFERENCE VENUE

Austria Trend Parkhotel Schönbrunn
Hietzinger Hauptstr. 10-14, A - 1130 Vienna
Tel.:+43 (1) 87 804-0 | Fax: +43 (1) 87 804-3220
http://www.austria-trend.at/Parkhotel-Schoenbrunn
parkhotel.schoenbrunn@austria-trend.at
SCHEDULE

Friday, September 7  14:00 until 19:00
Saturday, September 8  08:30 until 18:30
Sunday, September 9  08:30 until 13:00

REGISTRATION  www.eortc-cltf2012.eu

Friday, Sept. 7: 11.00 Registration opens at Welcome Desk, Parkhotel Schönbrunn

REGISTRATION CATEGORY | UNTIL JULY 31, 2012 | AFTER AUGUST 1, 2012 | ON-SITE
--- | --- | --- | ---
EORTC members | €210 | €260 | €260
Non-members | €400 | €450 | €450
Accompanying persons | €100 | €100 | €100

Bank: Hypo NÖ Landesbank
Account name: Karl Landsteiner-Gesellschaft c/o Prim.Dr. Franz Trautinger
Account number: 3455037920
Bank code: 53000
IBAN: AT315300003455037920
BIC/SWIFT code: HYPNATWW

Advanced payment for the Congress must be received in order to confirm your registration. Once your payment has been accepted, a letter of confirmation will be sent to you via e-mail.

ABSTRACTS

An USB flash drive with an electronic abstract book in PDF-format will be provided to all registrants. The abstract book will also be available for free download from the congress webpage www.eortc-cltf2012.eu.

SOCIAL EVENTS

Sept. 7, 19:00  Welcome Reception at the Parkhotel Schönbrunn
Sept. 8, 20:00  Dinner at the Vienna City Hall

OFFICIAL LANGUAGE

The official language of the meeting is English. No simultaneous translation will be provided.

For more information about hotel accomodation, flights to Vienna, airport transfers, sightseeing tours, etc: http://www.austropa-interconvention.at/book/?lang=en
TARGETS FOR THERAPY IN CUTANEOUS LYMPHOMAS
EORTC-CLTF CLINICAL MEETING, Vienna, September 7-9, 2012

PROGRAMME

Friday, September 7, 2012

12.00  Registration at Welcome Desk
       Parkhotel Schönbrunn

12.00-13.30  EORTC closed business meeting

14.00-15.45  S01: Pathology and biology of cutaneous lymphomas I
             Chairs: M. Vermeer and P. Quaglino

         R. Willemze (Leiden) - 20 min

S01-02. Diagnosis of follicular B-cell lymphoma: new findings and their influence on therapeutic strategies.
         C. Massone, L. Cerroni (Graz) - 20 min

S01-03. Histopathologic criteria for the diagnosis of Sézary syndrome in differentiation from other erythrodermic skin diseases: an EORTC Cutaneous Lymphoma Group study of 101 cases.
         C.D. Klemke (Mannheim) - 20 min

S01-04. EORTC study on biomarkers for Sézary syndrome.
         S.E. Boonk, W.H. Zoutman, C.P. Tensen et al. (Leiden) - 20 min

S01-05. MicroRNA profiling of primary cutaneous large B-cell lymphoma.
         L. Koens, Y. Qin, W.Y. Leung, et al. (Leiden) - 20 min

15.45-16.00  Coffee break

16.00-17.45  S02: Pathology and biology of cutaneous lymphomas II
             Chairs: P.L. Ortiz Romero and S. Whittaker

S02-01. A bio-informatic approach identifies a high resolution genomic fingerprint characteristic for mycosis fungoides.
         M.S. van Kester, M. Borg, W.H. Zoutman, et al. (Leiden) - presented by C.P. Tensen - 17 min
S02-02. Regulation of cell survival in cutaneous T-cell lymphomas by microRNAs.  
V. Manfé, E. Biskup, A. Guldhammer-Skov, et al. (Copenhagen)  
- 17 min

S02-03. Phoshatidylinositol-3 kinase (PI3K)/serine/threonine protein (AKT) pathway in mycosis fungoides.  
E. Papadavid, P. Korkolopoulou, T. Papadaki, et al. (Athens)  
- 17 min

S02-04. Role of transcription factors in the pathogenesis of cutaneous lymphoma.  
C. Assaf (Krefeld)  
- 17 min

S02-05. Angiogenesis in cutaneous lymphomas.  
M. Felcht (Mannheim)  
- 17 min

17.45-18.00 Coffee break

18.00-19.00 Free communications I  
Chairs: R. Dummer and M. Marshalko

M. Battistella, D. Kottler, B. Crickx, et al. (Paris, Lyon, Nantes)  
- 8+2 min

FC-02. How big is your hand and should you use it to skin score?  
J. Scarisbrick (Birmingham), S. Morris (London)  
- 8+2 min

FC-03. Juvenile mycosis fungoides – cutaneous T-cell lymphoma with frequent follicular involvement.  
I. Amitay-Laish, D. Ben-Amitai, M. Feinmesser, et al. (Petach Tikva)  
- 8+2 min

FC-04. MiR-223 has reduced expression and slows cell growth in mycosis fungoides/ cutaneous T-cell lymphoma.  
L.Y. McGirt, J.A. Zic, C.M. Eischen (Nashville)  
- 8+2 min

FC-05. Mir-155 is involved in tumor progression of mycosis fungoides.  
E. Hodak, A. Barzilai, B. Gorovitz, et al. (Petach Tikva)  
- 8+2 min

FC-06. The role of versican isoforms in skin homing of Sézary cells.  
M.B. Karpova (Zurich), K. Fujii (Okoyama), O. Georgiev (Zurich), et al. - presented by M. Urosevic-Maiwald  
- 8+2 min

19.00 Welcome reception at the congress venue Parkhotel Schönbrunn
### Saturday, September 8, 2012

**08.30-09.45**  **S03: Targets for therapy I - “Cellular & molecular targets”**
*Chairs: W. Kempf, E. Berti*

- **S03-01.** Gene therapy for cutaneous lymphomas – light at the end of the tunnel.
  *M. Urosevic-Maiwald (Zurich)* - 18 min

- **S03-02.** Targeting IL21 in Sézary syndrome.
  *L. Van der Fits, J.J. Out-Luising, S. Commandeur, et al. (Leiden)*

- **S03-03.** Pharmacological induction of p53 as a therapeutic approach in mycosis fungoides.
  *C. Savorani, V. Manfé, E. Biskup, R. Gniadecki (Copenhagen)* - 18 min

- **S03-04.** Pre-clinical correlates of romidepsin sensitivity.
  *T. Trowe (San Francisco)* - 18 min

**09.45-10.00**  **Coffee break**

**10.00-12.15**  **S04: Targets for therapy II – “clinical targets”**
*Chairs: R. Willemze and C.D. Klemke*

- **S04-01.** Targeted therapies: past, present and future.
  *Y. Kim (Stanford)* - 20 min

- **S04-02.** Current status of combination therapies in mycosis fungoides/Sézary syndrome.
  *M. Beyer, D. Humme, W. Sterry (Berlin)* - 15 min

- **S04-03.** Folliculotropic mycosis fungoides: from histopathology to the clinic. Is there a need for a new T-score?
  *P. Quaglino, M. Novelli, R. Ponti, et al. (Turin)* - 15 min

- **S04-04.** Mechanisms of resistance of mycosis fungoides to liposomal doxorubicine (Caelyx®). A study linked to clinical trial EORTC 2012.
  *N. Martínez, V. Monsálvez, M. Sánchez-Beato, et al. (Madrid)* - presented by P.L. Ortiz Romero - 15 min
C. Delfino (Florence), A. Fabbri (Siena), V. Grandi (Florence), et al. - 15 min

S04-06. Mycosis fungoides: risk of second lymphomas or other primary malignancies.
P. Savoia (Turin) - 15 min

S04-07. Allogeneic stem cell transplantation after reduced-intensity conditioning in advanced stage mycosis fungoides and Sézary syndrome.
F. Onida, G. Saporiti, E. Tagliaferri, et al. (Milan) - 15 min

S04-08. Non-myeloablative allogeneic transplant with total skin electron beam therapy, total lymphoid irradiation, and anti-thymocyte globulin demonstrates graft-versus-lymphoma effect while absent nonrelapse mortality in mycosis fungoides and Sézary syndrome.
W.K. Weng, M. Krathen, R. Armstrong et al. (Stanford) - presented by Y. Kim - 15 min

12.15-12.30 Coffee break
12.30-13.00 Neil Smith memorial lecture
Chair: R. Stadler
Cutaneous lymphomas: between Scylla and Charybdis.
L. Cerroni (Graz)
13.00-14.00 Lunch
14.00-15.30 General assembly and clinical EORTC-trials
15.30-15.45 Coffee break
15.45-18.15 S05: Established therapies revisited
Chairs: M. Bagot and C. Assaf

S05-01. Cutaneous gamma-delta T-cells under physiologic and pathologic conditions.
G. Stingl (Vienna) - 20 min

R. Knobler (Vienna) - 15 min
S05-03. Treatment of advanced cutaneous T-cell lymphomas with non-pegylated liposomal doxorubicin – consensus of the lymphoma group of the Dermatologic Cooperative Oncology Group.
R. Stadler (Minden) - 15 min

S05-04. Non-mycosis fungoides guidelines
E. Olsen (Durham) - 15 min

S05-05. Tarado trial update.
R. Dummer (Zurich) - 15 min

S05-06. Bexarotene side effect management.
M. Weichenthal (Kiel) - 15 min

M. Krathen, S. Bashey, K. Wolpin, et al. (Stanford) - 15 min

FC-07. PUVA bath for follicular variant or early stage mycosis fungoides refractory to narrow band UVB.
F. Pavlotsky (Tel Hashomer), E. Hodak (Petach Tikva), D. Ben Amitay (Petach Tikva), et al. - 10 min

FC-08. UK consensus statement for bexarotene therapy in cutaneous T-cell lymphoma.
J. Scarisbrick, S. Morris, R. Azurdia et al. (UK Cutaneous Lymphoma Group) - 10 min

R. Cowan, S. Morris, J. Scarisbrick, et al. (UK Cutaneous Lymphoma Group) - 10 min

19.30 Shuttle bus departure from Parkhotel Schönbrunn
20.00 Dinner at the Vienna City Hall
Lichtenfelsgasse 2, 1010 Vienna
Sunday, September 9, 2012

8.30-10.30 **S06: A look beyond**
*Chairs: L. Papadavid and N. Pimpinelli*

**S06-01.** Novel non-myeloablative hematopoietic stem cell transplantation in mycosis fungoides/Sézary syndrome  
*Y. Kim (Stanford) - 20 min*

**S06-02.** A tribute to Warren L. Macaulay and CD30-LPD: Beyond the guidelines - critical and unsolved issues.  
*W. Kempf (Zurich) - 5+20 min*

**S06-03.** Open questions in phototherapy.  
*P. Wolf (Graz) - 20 min*

**S06-04.** Photodynamic therapy for folliculotropic mycosis fungoides: An open trial.  
*R. Gniadecki (Copenhagen) - 20 min*

**FC-10.** NRAS mutations in cutaneous T-cell lymphoma sensitize tumors towards treatment with raf inhibitor sorafenib.  
*J.P. Nicolay (Heidelberg, Mannheim), M.K. Kießling (Heidelberg), C.D. Klemke (Mannheim), et al. - 8+2 min*

**FC-11.** Peripheral neuropathy in mycosis fungoides/Sézary syndrome treated with brentuximab vedotin.  
*S. Bashey, M. Krathen, K. Sutherland, et al. (Stanford) - 8+2 min*

**FC-12.** Synergistic mechanism of histone deacetylase inhibitor and DNA methyltransferase inhibitor in cutaneous T-cell lymphoma treatment.  
*S. Rozati, P. Cheng, A. Fettelschoss (Zurich) - 8+2 min*

10.30-11.00 Coffee break

11.00-12.40 **Free communications II**
*Chairs: R. Knobler and F. Trautinger*

**FC-13.** Diagnostic micro RNA profiling in cutaneous T-cell lymphoma.  
*T. Marstrand (Ballerup), U. Ralfkiaer (Copenhagen), C. Glue (Copenhagen), et al. - 8+2 min*

**FC-14.** Expression and pathophysiological functions of T-plastin in cutaneous T-cell lymphoma.  
*E. Bégué, F. Jean-Louis, M. Bagot, et al. (Paris) - 8+2 min*

**FC-15.** Immunocytochemical p63 expression in primary cutaneous B-cell lymphoma, further evidence for pathogenetic heterogeneity.  
*Z. Shukur, P. Coates, J. Goodlad, et al. (London) - 8+2 min*
R.Y.P. Hunasehally, M. Ally, M. Rodriguez, et al. (London) - 8+2 min

M. Battistella, L. Michel, F. Jean-Louis, et al. (Paris) - 8+2 min

FC-18. Vascular endothelial growth factor (VEGF) expression in mycosis fungoides.
A. Pileri, C. Agostinelli, S. Righi, et al. (Bologna) - 8+2 min

FC-19. Human endogenous retrovirus type W envelope expression in mycosis fungoides provides new insights into cutaneous T-cell lymphomas.
P. Maliniemi (Helsinki), M. Vincendeau (Munich), J. Mayer (Saarbrücken), et al. - 8+2 min

FC-20. Notch1 signaling pathway activation study in cutaneous T-cell lymphomas.
F. Gallardo, R. Salgado, R. Garcia, et al. (Barcelona) - 8+2 min

L. Michel, F. Jean-Louis, E. Begue, et al. (Paris) - 8+2 min

FC-22. Secondary cancer and survival in mycosis fungoides or parapsoriasis: A Danish nationwide population based cohort study.
L.M. Lindahl, M. Fenger-Grøn, L. Iversen (Aarhus) - 8+2 min
Poster Session:
Posters will be on display during the whole congress.
The poster session is sponsored by:

P01 Leukemia cutis in acute lymphatic leukemia.
E. Geissler, F. Meiss, A. Schmitt-Graeff, et al. (Freiburg)

P02 Leukemia cutis as an initial manifestation of chronic myelomonocytic leukemia.
C. Duma, O. Inhoff, M. Hoffmann, et al. (Ludwigshafen)

P03 Mucosal head and neck stage IVB mycosis fungoides.
Ch. Mikropoulos, M. Tsui, M. Wain, et al. (London)

P04 Two cases of aggressive non-tumoral folliculotropic mycosis fungoides with pulmonary localization.
Brugière, Stefan, Dompmartin, et al. (Caen)

P05 Photopheresis plus PUVA for advanced mycosis fungoides. A demonstrative case.
H-M. Buenaventura, P-S. Yeray, M. Társila et al. (Las Palmas de Gran Canaria, Santa Cruz de Tenerife)

P06 Mycosis fungoides with central nervous system involvement: A review of six cases from a single institution and a review of the role of low dose whole brain irradiation as an effective palliative treatment.
A. Mirza, St. Morris, B. Wilkins, et al. (London)

P07 Analysis of lymphangiogenic markers in erythrodermic cutaneous T-cell lymphomas.
M.B. Karpova, K. Fujii, D. Jenni, et al. (Zurich, Okayama)

P08 Erythrodermic vs tumour-stage mycosis fungoides: clinical onset extracutaneous progression and survival. A multicenter retrospective study from the Italian group of cutaneous lymphomas.
P. Quaglino, N. Pimpinelli, E. Berti, et al. (Turin, Florence, Milan, Brescia, Rome, Bologna)

P09 Cutaneous tumour cell load correlates with survival in patients with Sézary syndrome.
N. Booken, J.P. Nicolay, C.-D. Klemke (Mannheim)

P10 Genomic alterations study in Sézary syndrome.
L. Corti, D. Fanoni, L. Venegoni, et al. (Milan)

P11 Retrospective review of extracorporeal photopheresis as monotherapy compared with extracorporeal photopheresis combined with other systemic biologic therapies in patients with Sézary syndrome.
S. Aguilar-Duran, SL. Morris, S. Whittaker, et al. (London)

P12 Folliculotropic mycosis fungoides.
U. Badstöber, M. Schmid (Vienna)

P13 Clonal heterogeneity in folliculotropic mycosis fungoides.
P. Mantaka, G. Trøen, P. Helsing, et al. (Oslo)
Folliculotropic mycosis fungoides: analysis of pilotropic T-cells.
O. Kontár, J. Csomor, N. Erős, et al. (Budapest)

Second neoplasm associated with primary cutaneous lymphomas.
M. Rodríguez-Vázquez, M. Luisa Martínez-Martínez, M.García-Arpa, et al. (Albacete)

The prevalence of primary cutaneous lymphomas at a dermatology referral center in Lower Austria.
J. Eder, A. Kern, M. Kitzwögerer, et al. (St.Pölten)

Cutaneous follicular helper T-cell lymphomas: a series of 6 cases highlighting new clinical-pathological aspects.
N. Ortonne, F. Kebir, D. Chatelain et al. (Créteil, Amiens, Paris, Carpentras, Caen)

Extranodal nasal-type natural killer/T-cell lymphoma mimicking refractory sinusitis in a 60-year-old-man.
H. Müller, B. Zelger, W. Willenbacher, et al. (Innsbruck, Graz)

Lymphomatoid papulosis associating massive eosinophilia and FIP1L1-PDGFRα fusion gene.
L. Curto, D. Sitjas, E. Llistosella, et al. (Barcelona)

Pecurisor blastic plasmacytoid dendritic cell neoplasia.
E. Berti, D. Fanoni, F. Novara, et al. (Milan, Pavia)

Indolent CD8+ lymphoid proliferation of acral sites: 7 cases including some atypical features.
D. Greenblatt, M. Ally, Z Shukur, et al. (London)

Two cases of blastic plasmacytoid dendritic cell neoplasm with exclusive skin localization treated with radiotherapy.
R. Piccinno, M. Caccialanza, E. Berti, et al. (Milan)

Primary cutaneous lymphomas at University Department of Dermatology and Venereology, Zagreb University Hospital Center, 2000-2010.
R. Čeovic, A. Pasic, J. Lipozencic, et al. (Zagreb)

t(8;9)(p22;p24)/PCM1-JAK2 Activates SOCS2/SOCS3 via STAT5 in cutaneous lymphoma cells.
S. Ehrentraut, S. Nagel, M.E. Scherr, et al. (Braunschweig)

withdrawn

BIOMED 2 multiplex T-cell receptor polymerase chain reaction protocol combined with heteroduplex analysis on Agilent bio-analyzer: interest in diagnosis of cutaneous T cell lymphoma.
C. Auzet, N. Bonnet, J.P. Dales, et al. (Marseille)

HSP 70 kDa protein 1A inhibits histone deacetylase inhibitor-induced apoptosis.
K. Fujii, N. Suzuki, T. Kaji, et al. (Okayama, Sapporo, Tokyo)

Ellipticine induced apoptosis in cutaneous T-cell lymphoma-importance of p53.
C. Savorani, V. Manfè, E. Biskup, et al. (Copenhagen)
Differential proteomic analysis in primary cutaneous marginal zone lymphoma.
V. Paulitschke, J. Eder, C. Jonak, et al. (St.Pölten, Vienna)

Recombinant anti-CD3-diphtheria toxin fusion protein in patients with cutaneous T-cell lymphoma.
Ch. Klade, J. Hodisch, O. Zahriychuk (Vienna)

Proteasome inhibition as a novel mechanism of the proapoptotic activity of gamma-secretase blocker I in cutaneous T-cell lymphoma.
M.R. Kamstrup, E. Biskup, V. Manfè, et al. (Copenhagen)

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma with Burkitt translocation and CD158K/KIR3DL2 expression.

Rituximab/Bendamustine combination therapy is an effective alternative in the treatment of primary cutaneous large B-cell lymphoma, leg-type, in elderly patients.
B. Arbacher-Stöger, R. Stadler (Minden)

Therapeutic attitude and evolution of a patient with T-cell-rich B-cell lymphoma.
C. Solovan, F. Baderca, S. Mohor (Timisoara)

Management of hyperlipidemia in cutaneous lymphoma patients treated with bexarotene.
U. Wehkamp, J. Becker, E. Geißler, et al. (Kiel, Würzburg, Freiburg, Erfurt, Ludwigshafen, Münster, Mannheim, Dresden, Tübingen, Zurich)

Ten years experience of bexarotene use and the regulation of plasma triglyceride levels by retinoid X receptor.
L.Väkevä, M. Robciuc, M. Jauhiainen, et al. (Helsinki)

Multiforme-like skin eruptions under bexarotene therapy in a patient with Sézary syndrome.
Christina Mitteldorf, Michael Tronnier (Hildesheim)

Positive impact of extracorporeal photopheresis on quality of life in patients with chronic graft-versus-host disease.

HIF-1α- mediated regulation of Th17/Treg balance in the skin of cutaneous T-cell lymphoma patients.
M. Alcántara-Hernández, F. Jurado-Santacruz, G. Pérez-Montesinos, et al. (Mexico)

Preceding, concurrent or sequential occurrence of various neoplastic lymphoproliferative disorders (NLPD) in patients.
V. Nikolaou, A. Economidi, E. Papadavid, et al. (Athens)

Mycosis fungoides cases mimicking various inflammatory dermatoses.
A. Economidi, V.Nikolaou, E.Papadavid, et al. (Athens)
TARGRETIN®
das selektive Rexinoid bei kutanem T-Zell-Lymphom

**Targretin® 75 mg Weichkapseln. Wirkstoff:** Bexaroten. 
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**Anwendungen:** 
Zur Behandlung von Hautmanifestationen bei Patienten mit CTCL im fortgeschrittenen Stadium, die auf mindestens eine systemische Behandlung nicht angesprochen haben. 

**Gegenanzeigen:** Überempfindlichkeit gegen Bexaroten oder andere Bestandteile, Schwangerschaft und Stillzeit, Patienten im gebärfähigen Alter ohne effektive Empfängnisverhütung, Vorgeschichte einer Pankreatitis, unkontrollierte Hypercholesterinämie oder Hypertriglyceridämie, Hypervitaminose A, unkontrollierte Schilddrüserkrankung, Leberinsuffizienz oder bestehende systemische Infektionen. 


**Spezifische Nebenwirkungen:** 
- Sehr häufig: Hypothyreose, Hyperlipämie, Hypercholesterinämie, exfoliative Dermatitis, Pruritus, Hautausschlag, Schmerzen, Kopfschmerzen. 
- Häufig: lymphomähnliche Reaktion, Lymphadenopathie, hypochrome Anämie, Gewichtszunahme, erhöhte GOT, erhöhte GPT, erhöhte LDH, erhöhte Kreatinin, Hypoproteinämie, Schwindelgefühl. 

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Wegen der möglichen Nebenwirkungen sind individuelle Dosisanpassungen angezeigt. 

**Verpackung:** Targretin® 75 mg Weichkapseln sind in Blisterpackungen von 30 Tabletten vorliegen. Jede Packung enthält 30 Tabletten in einer Blisterpackung. 

**Zulassungsinhaber:** Eisai Ltd., European Knowledge Centre, Mosquito Way, Hatfield, Hertfordshire, AL10 9SN, Vereinigtes Königreich. 

**Örtlicher Vertreter:** Teva GmbH, Graf-Arco-Str. 3, 89079 Ulm. Stand: April 2009.
S01-01
REPORT OF THE 2011 SH/EAHP WORKSHOP ON CUTANEOUS LYMPHOMAS AND THEIR MIMICS
Rein Willemze, MD.
Dept. of Dermatology, Leiden University Medical Center, Leiden, The Netherlands

In October 2011 the Society for Hematopathology (SH) and the European Association for Haematopathology (EAHP) organized a workshop on cutaneous lymphomas and their mimics in Los Angeles. The workshop attracted 431 participants from 28 different countries. Participants had submitted 322 cases for evaluation by the scientific committee. The program included, apart from invited lectures, six main sessions focused on: mycosis fungoides (63 submitted cases), cutaneous CD30-positive lymphoproliferative disorders (37 submitted cases), other CTCL, non-MF (95 submitted cases), cutaneous B-cell lymphomas (65 submitted cases), other lymphohistiocytic malignancies of the skin (34 submitted cases) and reactive lymphoproliferations of the skin mimicking cutaneous lymphomas (28 submitted cases). Of the 322 submitted cases 120 cases were scanned and placed on the workshop case server, which could be accessed by the participants via a web browser. Sixty of these 120 cases were selected for oral presentation.

In this presentation the discussions and conclusions of the different sessions are summarized. Novel findings, areas of special interest and diagnostic challenges emerging from the cases submitted to the workshop will be highlighted.

S01-02
Diagnosis of follicular B-cell lymphoma: new findings and their influence on therapeutic strategies
Cesare Massone, Lorenzo Cerroni
Department of Dermatology, Medical University of Graz, Austria

Primary cutaneous follicle center lymphoma (PCFCL) is the most common type of primary cutaneous B-cell lymphoma. It is defined as a proliferation of neoplastic follicle center cells with a follicular, follicular and diffuse, or purely diffuse pattern of growth. Patients usually present with large confluent plaques and tumors located mainly on the head and neck area or on the back. Recently, an unusual clinical variant characterized by inconspicuous, multiple miliary or agminated papules located predominantly on the head and neck area has been described. Histopathology in this variant is characterized by a follicular pattern of growth. In addition, clinicopathologic features of early lesions of PCFCL, diffuse type have been recently investigated. These lesions present with small solitary papules or plaques and minimal infiltrated erythema. Small papules may be observed far away from the main affected area, thus representing a problem when planning treatment, particularly radiotherapy.

Histopathologically, early PCFCL, diffuse type shows small perivascular and periadnexal aggregates of medium and large centrocytes admixed with variable numbers of small reactive lymphocytes, oftentimes simulating reactive infiltrates. Miliary-agminated PCFCL and early PCFCL, diffuse type represent pitfalls in the clinicopathologic diagnosis of PCFCL and should be properly classified by dermatologists and dermatopathologists.

S01-03
Histopathologic criteria for the diagnosis of Sézary syndrome in differentiation from other erythrodermic skin diseases: an EORTC Cutaneous Lymphoma Group Study of 101 cases
Claus-Detlev Kiemke1,†, Nina Booken1,†, Sergii Goerd1, Moritz Felcht1, Jan P. Nicolay1, Cyril Géraud1, Werner Kempf2, Chalid Assaf1, Nicolas Ortonne1, Maxime Batistella1, Martine Bagot1, Robert Knobler2, Pietro Quaglino2, Birgit Arheiliger3, Marco Santucci2, Patty Jansen10,†, Rein Willemze10,† and Maarten H. Vermeer10,†
1Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, Ruprecht-Karls-University of Heidelberg, Mannheim, Germany, 2Zürich, 3Krefeld, 4Crestell, 5Paris, 6Vienna, 7Turin, 8Minden, 9Florence, 10Leiden
†These authors have contributed equally to this work.

Erythrodermic patients are a diagnostic challenge regarding the clinical and histological differential diagnosis. 101 cases of erythroderma were collected by the EORTC CLTF histopathology group in order to describe diagnostic criteria. Skin biopsies from 3 different groups of erythroderma were investigated. Sézary syndrome (SS, n=54), erythrodermic mycosis fungoides (EMF, n=7) and reactive erythrodermas (RE, n=40; e.g. atopic dermatitis, psoriasis, drug eruptions etc.). The following criteria were evaluated during 2 histopathology workshops: epidermal and dermal changes, morphology of the infiltrate, immunohistochemical analysis of marker loss (CD2, CD3, CD4, CD5 and CD7), bystander infiltrate by stainings for CD8, FOXP3 and CD25 and expression of Ki-67, CD30, PD-1 and MUM-1. Then, the expert panel made a diagnosis based on histology and immunohistochemistry which was then correlated with clinical data including molecular biology data. The mean age for all 3 groups of erythroderma was 66 years. The male to female ratio was 1:1 (SS), 7:0 (EMF) and 4:7:1 (RE). Epidermal changes were seen in 86% (SS), 86% (EMF) and 80% (RE) of the cases. Pautrier microabscesses were found in 22% (SS) and 29% (EMF) of the CTCL skin biopsies and in none of the RE samples. All cases demonstrated an upper dermal infiltrate of lymphocytes which were admixed with large or small blasts in 35% (SS), 0% (EMF) and 15% (RE) of the cases, 59% (SS), 14% (EMF) and 10% (RE) of the samples showed an antigen loss for at least one of the T cell markers investigated. There was no difference in the bystander infiltrate (CD8+, FOXP3+ and CD25+ cells) between the 3 groups and none of the CTCL cases had FOXP3+ tumor cells. Also the expression levels of CD30, Ki-67, MUM-1 were similar for the 3 groups. There was no difference in the bystander infiltrate (CD8+, FOXP3+ and CD25+ cells) between the 3 groups and none of the CTCL cases had FOXP3+ tumor cells. Also the expression levels of CD30, Ki-67, MUM-1 were similar for the 3 groups. 74% of the SS samples (57% [EMF], 43% [RE]) had more than 50% PD-1+ lymphocytes in their skin infiltrate. Based on these criteria the workshop expert panel established a diagnosis of RE in 6% of the SS cases, 29% of EMF samples and 80% of biopsies from RE. A number of different histopathological and immunohistochemical criteria are required to differentiate between the different types of erythroderma investigated.
S01-04  
EORTC study on biomarkers for Sézary syndrome  
SE Boonk, WH Zoutman, CP Tensen, S Whittaker, M Bagot, D Klemke, A Ranki, P Quaglino, R Willemze, L van der Fits and MH Vermeer  
Dept dermatology LUMC, Leiden The Netherlands, on behalf of the EORTC study group.  
Sézary syndrome (SS) is an aggressive type of cutaneous T-cell lymphoma with a poor prognosis. Identification and quantification of tumor cells is often difficult. Several small, single center studies reported potential biomarkers for Sézary cells. However, these markers have not been evaluated in independent studies. In this prospective, European multicenter study we evaluate the diagnostic and prognostic value of (novel) markers in SS. We collected blood samples from SS patients and controls (benign erythroderma). Expression of potential biomarkers was evaluated on CD4+ cells on protein and mRNA level by flow cytometry and using a custom made qPCR platform, respectively. In addition copy number variation was assessed by qPCR. These results are correlated with clinical information at inclusion of the study and after 12, 24, 36, and 48 months follow up. During the first 18 months of this study, samples from 91 (SS) patients were collected. Aberrant expression of CD7, CD26, DNM3, EPHA4, GATA3, PL3, TWIST1 and STAT4 was confirmed. Also, alterations in copy number for MYC and/or MNT were confirmed in the majority of the samples. To evaluate the significance of these aberrancies as diagnostic and prognostic markers, we are currently correlating these results with clinical information. Further results will be presented in this presentation.

S01-05  
MICRORNA PROFILING OF PRIMARY CUTANEOUS LARGE B-CELL LYMPHOMA  
Leiden University Medical Center, Leiden, The Netherlands  
Aberrant expression of microRNAs is known to be pathogenetically involved in many diseases, including hematological malignancies. However, the presence and function of microRNAs in primary cutaneous large B-cell lymphomas (PCLBCLs) are not yet described. The two types of PCLBCL, primary cutaneous diffuse large B-cell lymphoma, leg type (PCBCL-LT) and primary cutaneous follicle center lymphoma (PCFCL) are characterized by an activated B-cell (ABC) genotype and a germinal center B-cell (GCB) genotype, respectively. By performing high-throughput next generation sequencing analysis, the microRNA profiles of frozen tumor biopsies from 11 cases of PCBCL-LT and 6 cases of PCFCL were established. Quantitative analysis for differential expression of microRNAs between the two tumor types was performed. For a selection of these microRNAs real-time qPCR on both internal and external validation groups was performed, along with a set of microRNAs known to be involved in the pathogenesis of nodal diffuse large B-cell lymphomas (DLBCLs). The sequence data showed 16 microRNAs that were differentially expressed between PCBCL-LT and PCFCL. However, 5 microRNAs commonly described to be differentially expressed between GCB and ABC type nodal DLBCL were not amongst them. Significantly higher expression of miR-9, miR-31, miR-129-2 and miR-214 in PCFCL compared to PCBCL-LT was confirmed by qPCR. These microRNAs are different from the ones previously described discriminating GCB from ABC type nodal DLBCLs.

S02-01  
A bio-informatic approach identifies a high resolution genomic fingerprint characteristic for Mycosis fungoides  
MS van Kester, M Borg, WH Zoutman, JJ Out, PM Jansen EJ Dreef, MH Vermeer, R van Doorn, R Willemze, CP Tensen  
Leiden University Medical Centre, Leiden, The Netherlands  
Mycosis fungoides (MF) is the most common type of primary cutaneous T cell lymphoma, consisting of skin-homing CD45RO+ effector memory T cells. To identify a high resolution genomic fingerprint characteristic for MF, we used a bio-informatic approach, involving meta-analysis of gene expression datasets available in the public databases combined with in house generated array data. Results were confirmed by quantitative PCR for a selection of transcripts in additional patient samples and relevant controls. With this method we identified a signature consisting of 989 aberrantly expressed genes, the majority (716 genes) statistically significantly higher expressed in MF compared to normal skin, inflamed skin and normal T cells, The signature mainly reflects the highly proliferative character of this T-cell malignancy illustrated by altered expression of many cell cycle and kinetochore regulators. It also gives an indication of the immunophenotype of the disease which appears to be dominated by the cytokines IL-10, IL-26 and IL-32, the chemokines CCL18, CXCL9, 10, 11 and up-regulation of the chemokine receptors CCR1, and 7. We identified over expression of RRM2, IDO1, TOP2A and CD74 in MF as possible therapeutic targets and identified GTSF1 and TRIP13 as novel diagnostic markers. Finally, the signature indicated loss of expression of the NF-kB inhibitor, NFKBIZ, which may explain the enhanced activity of NF-kB, a hallmark of MF.
MICRORNA PROFILING OF PRIMARY CUTANEOUS LARGE B-CELL LYMPHOMA

Evangelia Papadavid1,2, Penelope Korkolopoulou1, Theodora Papadaki1, Marina Siakantaris1, Vassiliki Nikolau1 Georgia Levidou1, Aphrodite Economidi1, Leonidas Marinos2, Angelica A Saetta2, Chatziandreou Ilenia3, Amanta Pysmt4, Efstratios Patsouris5, Christina Antoniou1.

1,2 Athens University Medical School, Cutaneous Lymphoma Clinics, 1st Department of Dermatology, A Sygros Hospital and 2nd Department of Dermatology, ATTIKON University Hospital
3 Athens University Medical School, 1st Department of Pathology
4 Department of HematoPathology, Evangelismos Hospital
5 Athens University Medical School, 1st Department of Internal Medicine, Laikon Hospital
6 Athens University Medical School, 2nd Department of Internal Medicine, Propaedetic, ATTIKON University Hospital

The serine/threonine protein kinase Akt, a downstream target of phosphatidylinositol 3-kinase (PI3K), has been shown to be involved in various cellular processes linked to tumorigenesis. PTEN protein, the product of PTEN tumor-suppressor gene, is a lipid phosphatase that limits the activity of PI3K pathway. PI3K plays a key role in growth signaling in a number of hematologic malignancies but its significance in Mycosis Fungoides (MF) has not been fully elucidated. We analysed immunohistochemically the expression of phosphorylated Akt (pAKT), p85 subunit of PI3K and PTEN in a panel of 54 samples (33 plaques and 21 tumors) from 50 MF patients clinical stages I-IV (T1-T2-T3). The immunoreactivity was expressed as histology (H) scores (the percentages of positive neoplastic cells multiplied by the staining intensity). The expression of these molecules was correlated with clinicopathological features as well as disease, progression-free, and overall disease specific survival (DFS, PFS, OS). Forty five cases were screened for activating mutations in exons 9,20 of PIK3CA and exon 4 of AKT1 by Real Time PCR-High Resolution Melting Analysis (HRMA), sequencing and/or Pyrosequencing. Cytoplasmic pAkt was recorded in 53/54 (97.1%) cases (H-scores 1-180 in positive cases), nuclear p85pAKT3 in 38/54 (70.3%) cases (H-scores 0.5-185 in positive cases) and cytoplasmic PTEN in only 25/53 (47.2%) cases with a low H-score of 1-35. Co-expression of pAKT and p85 was found in 37/54 (67.5%) cases and of all three molecules in 20/53 (37.7%) cases. PTEN was positively correlated with pAKT (R=0.2823, p=0.0406), when all samples were assessed inversely with clinical stage (p=0.0744). Tumoral MF cases displayed higher p85pAKT H-scores than plaques (p=0.0248). In univariate survival analysis increased pAKT H-score adversely affected OS (p=0.0198) along with CD30 (p=0.0004) and blood T cell clonality (p=0.0009) in patients with plaque MF whereas in tumor MF cases increased p85PI3K and lower PTEN expression portended a shorter OS (p=0.0485) and PFS (p=0.0612) respectively.

A PIK3CA mutation in exon 9 was detected by HRMA in one specimen (plaque stage). No mutations were identified in PIK3CA exon 20 or AKT1. Our findings implicate PI3K/AKT pathway in the aggressiveness of MF.

ROLE OF TRANSCRIPTION FACTORS IN THE PATHOGENESIS OF CUTANEOUS LYMPHOMA

Markus Möbs1, Anne Steininger2, Karl Köchert3, Marc Beyer1, Wolfram Sterry1, Michael Hummel1, Reinhard Ullmann1, Stephan Mathas1 and Chalid Assaf1,5

1 Department of Dermatology and Allergy, Skin Cancer Center Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany; 2Max Planck Institute for Molecular Genetics, Berlin, Germany; 3Hematology, Oncology and Tumor Immunology, Charité – Universitätsmedizin Berlin, and Max-Delbrück-Center for Molecular Medicine, Berlin, Germany; 4Institute of Pathology; 5HELIOS Klinikum Krefeld, Krefeld, Germany

Transcription factors are DNA-binding proteins involved in transcription processes in eukaryotes, by binding with high specificity parts of promoters or enhancers. They can thus regulate genes or complex networks by themselves. On this basis, alteration of a solitary transcription factor may lead to various cellular changes and also to neoplasia. A network of transcription factors, such as E2a, HD-2, NOTCH and PAX5 regulates lymphocytic development into B-, T-, NK- or plasmocytoid dendritic cells. Alterations of these genes via mutation or activation of inhibitors may lead to developmental disorders and also to malignant transformation. In our own investigations we recently identified the loss of E2A and subsequent MYC up-regulation as a common defect in Sézary syndrome (SS). In addition we could show that loss of E2A leads to upregulation of DELTEX, a regulator of the NOTCH-pathway, explaining the activated NOTCH1 signaling recently shown in cutaneous lymphoma.

Moreover, we could show that p53 signaling is non-functional in SS, which is the precondition of the observed MYC induced transformation in CTCL. In summary, our data demonstrate that alterations of transcription factors are essential in the pathogenesis of cutaneous T-cell lymphomas resulting in deregulation of a series of oncogenes and other transcription factors responsible for cell proliferation and transformation.

ANGIOGENESIS IN PRIMARY CUTANEOUS LYMPHOMAS

Moritz Felcht

1Dermatology, Venerology, and Allergy, University Medical Center Mannheim, Germany

Angiogenesis, the formation of a vascular network, represents a hallmark during cancer development and is regulated by a plethora of angiogenic molecules. Angiogenic factors are not only expressed by vascular cells but also by hematopoietic and even some lymphoma cells. This implies that lymphomatogenesis and angiogenesis are closely interconnected. Even more it suggests that angiogenesis and the factors of angio genesis are of key interest for the pathogenetic understanding of lymphomas. However, most studies have investigated angiogenesis in nodal lymphomas and only few analysed angiogenesis in primary cutaneous lymphomas. In nodal lymphomas the endothelium is characterized by aberrant genetic changes accompanied by lymphoma specific expression which also influences tumor cells from immune response. Most important in diffuse large B-cell lymphomas an angiogenic stroma correlates with an unfavourable outcome. In primary cutaneous B-cell and T-cell lymphomas (CTCL) increased angiogenesis has been observed. In CTCL angiogenesis involves blood as well as lymph vessels and increased angiogenesis correlates with advanced disease. The CTCL endothelium is characterized by aberrant protein expression with enhanced levels of matrix metalloproteinases and angiogenin. Therefore, it can be speculated that endothelial changes are essential for the pathophysiology of CTCL lymphomas. In summary, angiogenesis can be detected in cutaneous lymphomas. As lymphomatogenesis and angiogenesis are closely interrelated this seems worth for follow-up studies.
Our data support the polymorphic appearance of folliculotropic MF, highlighting the difficulties in differential diagnosis. The patients not only with patch/plaque stage but also with tumor-stage disease. Folliculotropic MF patients were classifiable as stage IA or IB, their survival was significantly lower than that of "classic" MF. Histopathologic clues included prominent (peri-)neck region and the seborrheic areas were the most frequently involved areas. Classic scaly erythematous patches involving the buttocks and the "bathing trunk" regions were found in 37% of patients. Clinical features included follicular hyperkeratotic papules, comedo-like lesions, nodules, cysts and alopecia. The head and
Mechanisms of resistance of Mycosis fungoides to Liposomal doxorubicine (Caelyx). A study linked to clinical trial EORTC 21012.

N Martinez (1), V Monsályez (2), M Sánchez-Beato(3), M Rodríguez-Pinilla(4), MA Piris(1), P Quagliino(5), JC Becker(6), R Dummer(7), M Karpova(7), JL Rodríguez Peralto(2), and PL Ortiz-Romero(2).

1: IFIMAV, Marqués de Valdecilla Hospital. Santander
3 Hospital Puerta de Hierro. Madrid
4 Clínica de la Concepción. Madrid
5 Clínica Dermatológica - Universita Di Torino
6 LHK-Universitätsklinikum Graz
7 University Hospital of Zurich

Pegylated Liposomal Doxorubicine (PLD) is an antineoplastic antibiotic with pharmacologic activity similar to Daunorubicine. The EORTC CLTF has recently completed a phase II clinical trial (EORTC 21012) in monotherapy for MF stages IIb to IVa. Our aim was to identify molecular markers of resistance to PLD in MF patients.

Fourteen patients enrolled in the EORTC 21012 had fresh frozen tissue, obtained just before treatment, during wash up period. All of them signed up informed consent for TR project linked to 21012 trial and for local tissue biobank. EORTC TRAC approved this study on 26/03/2011

RNA for gene expression profiles was extracted and hybridized on Human Gene Expression Microarrays (Agilent Technologies Inc., USA).

For analysis, patients were divided in responders (2CR+7PR) and non-responders (5 SD). Gene expression data were analyzed to obtain a molecular signature of response to PLD, using Babelomics 4.3.0.

A signature of 130 differentially expressed genes between responders and non-responders were selected (p<0.005) (84 overexpressed in responders’ group and 46 in non-responders’ group). Gene Ontology analysis revealed that these genes are mainly related with regulation of cell proliferation, cellular component movement, cellular transport, and endocytosis (Fatigo tool in Babelomics 4.3.0).

The results found in this study could help to elucidate the mechanisms of resistance to PLD and, when validated, a molecular signature could be used as a marker to determine which patients can get a benefit of a treatment with PLD.

Rituximab in combination with pegylated liposomal doxorubicin in DLBCL, leg type: results of a pilot study

C. Delfino (1), A. Fabbrì (2), V. Grandi (1), R. Alterini (3), N. Pimpinelli (1). Dept. of Critical Care, Medicine and Surgery - sections of Dermatology (1) and Hematology (3), University of Florence Med. School; (2) Haematology Unit, University of Siena, Italy.

Diffuse large B cell lymphoma, leg-type (DLBCL, LT) is a relatively rare primary cutaneous B cell lymphoma, which mainly affects elderly females. The recommended treatment of DLBCL, LT is systemic multi-agent chemotherapy, possibly associated with rituximab (anti-CD20 immunotoxin). Pegylated liposomal doxorubicin (peg-doxo) is a suitable candidate for its reduced cardiotoxicity and optimized cutaneous penetration. We report herein the preliminary results of a pilot study concerning the treatment of DLBCL, LT with the association of Rituximab and peg-doxo. We treated 11 patients with primary cutaneous B-cell lymphoma, including 3 patients with DLBCL, LT. Primary end points were overall response rate (ORR) and safety; disease free survival (DFS) and overall survival (OS) were secondary end points. The treatment schedule was: Rituximab (375 mg/m² i.v.) and peg-doxo (20 mg/m², i.v.) at days 1 and 15 every 28, for 2 cycles (induction phase). Consolidation phase consisted in recycling at day 1 every 28, for a total of 2 cycles. Overall, we experienced a 81% response (73% CR and 18% PR).

Interestingly all DLBCL, LT patients rapidly underwent CR already at the end of the induction phase, with a median relapse-free survival of 30 months. The combination of Rituximab and peg-doxo has preliminarily proven effective and safe in the treatment of DLBCL, LT.

ALLLOGENEIC STEM CELL TRANSPLANTATION AFTER REDUCED-INTENSITY CONDITIONING IN ADVANCED STAGE MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

Onida F1, Saporiti G2, Tagliabue1, E1, Annaloro C1, Corti L1, Grifoni F1, Olivares C1, Cortezelezzi A1, Berti E2
1 BMT Center-Hematology 1 and 2 Dermatology Unit, Fondazione Ca’ Granda IRCCS Ospedale Maggiore Policlinico, University of Milan and University of Milan-Bicocca, Italy

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) represents the only curative strategy for advanced stage mycosis fungoides (MF) and Sézary syndrome.

In our Institution, since 09/2000, 19 patients underwent allo-HSCT following reduced-intensity conditioning regimens. Graft-versus-Host Disease (GvHD) prophylaxis included cyclosporin A and mycophenolate mofetil. At the time of transplant all patients (13 males and 6 females; median age 50 years, range 27-66) had stage III/IV refractory MF (n=14) or refractory SS (n=5). Median time from diagnosis to HSCT was 48 months (range 13-252). Full donor chimerism was achieved in 88% of patients. Acute GvHD occurred in 10 patients (6 grade I-II and 4 grade III-IV), whereas chronic GvHD was observed in 7 (extensive in 2). Clinical remission (CR) was obtained in 11/18 evaluable patients. Seven patients died, 2 in CR (1 for sepsis; 1 for aGvHD) and 5 from progressive disease. With a median follow-up of 83 months (range 0-136), 12 patients are alive with a clinical CR maintained in 9. Molecular remission (mCR) was documented in 8 out of 9 patients. We conclude that RIC allo-HSCT is an effective strategy of cure in pts with MF/SS, suggesting an immunomodulated graft-versus-lymphoma effect in inducing and maintaining remissions.
S04-08
Non-Myeloablative Allogeneic Transplant with Total Skin Electron Beam Therapy, Total Lymphoid Irradiation (TLI) and Anti-Thymocyte Globulin (ATG) Demonstrates Graft-Versus-Lymphoma (GVL) Effect while Absent Nonrelapse Mortality in MF and SS

W-K Weng1, M Krathen2, R Armstrong3, S Arai2, K Sutherland4, RT Hoppe5, Y Kim7
1BMT; 2Cutaneous Onc; 3Rad Onc. Stanford Cancer Center, Stanford, CA, USA

Protective conditioning with TLI/ATG alters host immune profile to favor regulatory NK T cells that suppress GVHD by polarizing donor T cells towards secretion of non-inflammatory cytokine and promoting donor Treg cells.

In our phase II study, 15 patients have been transplanted to date; 6 MF, 9 SS with median age 63 years (range 20-73). All but two had stage IV; 9 with LCT. Median number of prior systemic therapies was 6 (range 3-12). 12/15 (80%) with CR; 12 mo PFS/OS rate, 68%/82%. Superior outcome in SS than MF (PFS, $p=0.022$; OS, $p=0.064$). Improved PFS was associated with >95% T cell chimerism ($p=0.022$). Observed nonrelapse mortality of 0%, grade II-IV aGVHD 1/15; cGVHD 1/15.

Minimal residual disease (MRD) was assessed using high-throughput sequencing of rearranged TCRβ CDR3 using solid phase PCR (Illumina GA2 system). Deep-sequencing allowed assessment of MRD with utmost sensitivity and specificity. Molecular remission was associated with durable clinical CRs and immune reconstitution of TCRβ repertoire.

Our findings demonstrate a successful utility of our novel protective conditioning in advanced MF and SS with meaningful GVL with encouraging safety profile. Furthermore, molecular remission by high-throughput sequencing of TCRβ may be predictive of a curative outcome.

S05-07
Brentuximab vedotin demonstrates clinical activity in mycosis fungoides and Sézary syndrome

Krathen M, Bashey S, Wolpin K, Sundram U, Adavni R, Hoppe R, Reddy S, & Kim YH. Stanford Cancer Center, Stanford, CA, USA

Introduction: Brentuximab vedotin (SGN-35) demonstrates significant responses in CD30-expressing malignancies, Hodgkin lymphoma and systemic anaplastic large cell lymphoma. In mycosis fungoides / Sézary syndrome (lower and more variable CD30 expression), it is unknown if brentuximab vedotin is effective and, if so, at what level of CD30 expression.

Methods: In this phase II, single-arm study, we explore the efficacy and safety of brentuximab vedotin in MF/SS with any level CD30 expression of tissue lymphoid cells by immunohistochemistry.

Results: Presently 17 patients are evaluable for response: 16 MF, 1 SS, 15 of 17 with stage IIB-IV. Median age 60y (20-88), prior systemic therapies 4 (1-15). Study follow-up time is ongoing and currently median 29 wks (6-47). Baseline CD30 expression: six subjects < 10%; ten, 10-50%; one, >50%. Objective responses noted in 13 (76%); median skin score (mSWAT) reduction of 65% (7-98%). Median time to response of 6 wks (3.0-18.0). Median progression free survival and duration of response not met. No clinical/pathological parameter was predictive of clinical response. Most related adverse events (AEs) in the study were grade 1 or 2, including peripheral neuropathy (76%), fatigue (65%).

Conclusions: Our exploratory study demonstrates significant clinical activity of brentuximab vedotin in MF/SS irrespective of tissue CD30 expression levels with mostly G1/2 AEs.

S06-02
A TRIBUTE TO WARREN L.MACAULAY AND CD30-LPD: BEYOND THE GUIDELINES – CRITICAL AND UNSOLVED ISSUES

Kempf W
Dept. of Dermatology, University Hospital Zürich, CH-8091 Zürich

Consensus recommendations for the management of primary cutaneous CD30-positive lymphoproliferative disorders (CD30+ LPD) including lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large-cell lymphoma (PCALCL) were elaborated by a multidisciplinary expert panel of the EORTC Cutaneous Lymphoma Group, the ISCL and the USCLC and published in 2011 (Blood 2011;118:4024 -35).

Several still unsolved issues beyond the recommendations are important for the future clinical trials and concepts for CD30+ LPD and include:

(i) Classification of CD30+ LPD: How many subtypes of LyP and ALC do we need? Expanding spectrum of lymphomas with CD30 expression: six subjects < 10%; ten, 10-50%; one, >50%. Objective responses noted in 13 (76%); median skin score (mSWAT) reduction of 65% (7-98%). Median time to response of 6 wks (3.0-18.0). Median progression free survival and duration of response not met. No clinical/pathological parameter was predictive of clinical response. Most related adverse events (AEs) in the study were grade 1 or 2, including peripheral neuropathy (76%), fatigue (65%).

(ii) Need for prospective clinical trials for traditional and widely used therapeutic strategies and for special circumstances, e.g. multifocal PCALCL and loco-regional lymphnode involvement in PCALCL and LyP

(iii) Documentation for response in clinical trials according to the criteria and endpoints defined in the recommendations. The concept of increased disease activity and definitions of progressive disease in LyP.

(iv) Identification of prognostic factors in CD30+ LPD prognostic factors.

(v) LyP associated secondary lymphoid neoplasms - terminology and prognosis.

(vi) Management of CD30+ LPD in immunosuppressed patients.

(vii) Management of CD30+ LPD in children.
**FC-01**

**Kimura disease: retrospective multicentric study of 25 French cases.**


*equal contribution

Pathology and Dermatology, Hôpital Saint Louis ; Hôpital Bichat ; Hôpital Pitie Salpêtrière ; Hôpital Henri Mondor ; CHU Caen ; Hôpitaux Lyon Sud ; CHU Nantes. France

**Introduction:** Kimura disease is a rare disorder of unknown etiology, mostly described in Far Eastern countries. Data in Western countries are lacking, especially regarding therapeutic modalities. A relation to IgG4-related systemic disorder has been hypothesized in the literature, regarding the fibrosing evolution of extranodal masses.

**Methods:** We reviewed 25 patients with Kimura disease diagnosed in France. We collected clinical, therapeutic and histopathological data. We performed IgG4, IgG and CD138 immunostainings, and EBER in situ hybridization.

**Results:** Patients were mostly male (62%), mean-aged 45.3 years (16-89). 73% patients had pigmented phototypes. 3 patients had renal involvement (nephrotic syndrome). Masses were present in the head and neck region in 89% patients.

Histopathological features were typical. Results regarding IgG4 expression and EBER are currently being completed.

**First treatment comprised surgery or oral corticosteroids with high complete response rate (100%, 90% respectively) but high relapse rate (42%, 50%).** Following lines comprised interferon-alpha, thalidomide, ciclosporin, acetytin, phototherapy, radiotherapy, pentoxifyllin, imatinib, cyclophosphamide, mycophenolate mofetil, methotrexate. Thalidomide, ciclosporin, and interferon-alpha seemed more efficient.

**Conclusion:** This study on 25 patients with Kimura disease is the largest one in a Western country and provides data regarding therapeutic modalities.


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**FC-02**

**HOW BIG IS YOUR HAND AND SHOULD YOU USE IT TO SKIN SCORE?**

J.Scaristbrick, J.Morris

1 University Hospital Birmingham. 2 St. Thomas’ Hospital London

Estimating body surface area(BSA) has been used to assess burns for decades using three methods: Palmer Method where palm SA=1%, Rule of Nines and Lund and Browder both divide body parts into percentage SA. The severity weighted assessment tool(SWAT) for mycosis fungoides(MF) uses Grid-Point Counting to assess BSA and scores patch=x1, plaque=x2,tumour=x3. A modified SWAT reported in the End Points Paper by Olsen used modified Lund and Browder with palm method.

In 2007 we conducted a Skin scoring Day where physicians and nurses were invited to a 2 hour lecture on skin scoring combining rule of nines and palm method. 6 live patients with various stages of MF were then scored by lecturer and attendees.

22 attendees produced 122 scores. The lecturers’ scores are shown compared to median score of attendees(range):

Patient1:73.6,50(26.4-99),Patient2:125.6,76.2(63-164),Patient3:50.7,57.7(17-91), Patient4:3.5,9.3(1.5-15.4),Patient5:4.7,15.9(4.2-25),Patient6:17.3,17.2(14-28). Of 22 attendees the trend for scoring above or below the lecturer’s was relatively constant for any individual. Hypopigmented MF(Patient5) had the widest range of scores whilst scoring of erythroderma(Patient2) produced least variation.

Even with a constant training method there is significant inter-user variability in skin scoring. Inconsistencies were reported as palm SA varies in different scoring system from 1%(palm method)-1.5%(Lund & Browder). Studies have found palmar SA to be nearer 0.8% resulting in overscoring. Constant scoring methods are required for future studies and should use the modified SWAT. Where possible the same scorer should score any individual.

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**FC-03**

**JUVENILE MYCOSIS FUNGOIDES – CUTANEOUS T-CELL LYMPHOMA WITH FREQUENT FOLLICULAR INVOLVEMENT**

*Amity-Lalish I,* Ben-Amitai D,* Feinmesser M,* Pavlotsky F,* Hodak E

Departments of Dermatology and Pathology, Rabin Medical Center; Unit of Pediatric Dermatology, Schneider Children’s Medical Center of Israel, Petach Tikva; Department of Dermatology, Sheba Medical Center, Tel Hashomer, Israel

Juvenile mycosis fungoides (MF) is uncommon. Data on folliculotropic MF (FMF) and MF with folliculotropism before age 18 years are scarce.

Records of 50 MF patients, (≤18 years old at clinicopathologic diagnosis), treated at our dermatology clinic during 1994 - 2011 were reviewed. Microscopy specimens with follicular involvement were reevaluated.

Atypical lymphocytes infiltrating the follicular epithelium were found in 27/50 patients. In 7/27 infiltration involved follicular epithelium only: in 20/27 folliculotropism combined with epidermotropism was noted. 17/27 had clinical findings of FMF, 16: stage IA-IIA, 1: stage IIB. In 4, FMF was the sole finding, 13 had combination with hypopigmented, psoriasiform, or classical lesions. Follicular lesions were located mainly on limbs and trunk, mostly hypopigmented alopecic patches on which follicular spiny papules were distributed. PUVA was given to 8 (3 systemic, 5 bath), 1 received electron beam for tumors, than PUVA + interferon alpha. Seven showed complete response, 2 are under treatment. Eight were given other skin-targeted therapies, only 1 responded completely.

We report the largest series of childhood MF, and the first to focus on follicular involvement, and FMF specifically, in this age group. The 34% rate of FMF in our young cohort is considerably higher than found in adults.
MiR-223 has reduced expression and slows cell growth in mycosis fungoides/cutaneous T-cell lymphoma
McGirt LY1, Zic JA1, Eichen CM2
1Medicine/Dermatology, and 2Pathology, Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA.

MicroRNAs (miRNA) are small, non-coding RNAs known to play a role in malignancy, and have altered expression in cutaneous T-cell lymphoma (CTCL). We hypothesized that the altered expression of miRNA in mycosis fungoides (MF) plays a role in oncogenesis or propagation of malignancy through effects on their target genes. Both MF and control skin biopsies, peripheral blood mononuclear cells (PBMC), and CTCL cell lines were evaluated for miRNA expression. We identified reduced expression of miR-223 in MF skin samples, which increasingly lessened as clinical stage advanced. MF PBMC had increased mRNA expression of the miR-223 target gene E2F1 (oncogenic transcription factor), whereas the CTCL cell lines had increased mRNA expression of the miR-223 target gene, MEF2C (oncogenic transcription factor), compared to controls. Overexpression of miR-223 in CTCL cell lines led to slowed cell growth with a corresponding reduction in its protein targets, E2F1 and MEF2C. The miR-223 inhibitor conversely resulted in increased cell growth and expression of its protein targets. Overall, miR-223 has reduced expression in MF/CTCL that leads to increased expression of oncogenic transcription factors and enhanced cell growth.

This study was supported through the Dermatology Foundation, American Cancer Society (IRG-58-009-51), and the Vanderbilt University Department of Medicine/Dermatology.

MiR-155 is involved in tumor progression of mycosis fungoides
Hodak E1,2, Barzlai A1, Gorovitz B1,2, Hirshberg A2, Rechavi G1, Amariglio A1, Jacob-Hirsch J1, Feinmesser M1, Moyal L1
Department of Dermatology1, Laboratory for Molecular Dermatology1 and Institute of Pathology2, Rabin Medical Center, Bellinson Hospital; Department of Dermatology1 and Cancer Research Center2, Sheba Medical Center, Israel

miR-155 is considered as an oncogenic miR which targets tumor suppressor genes. Recently miR-155 was found to downregulate the pro-apoptotic transcription factor FOXO3a in breast cancer. We sought to study the expression of miR-155 in early and advanced stages of mycosis fungoides (MF), and to investigate its relationship with the expression of FOXO3a.

Sections from biopsies of 23 MF patients with early stage, 20 with tumor stage and 15 with benign inflammatory diseases were studied for miR-155 expression as determined by real time qRT-PCR. Immunohistochemical staining was done for the detection of FOXO3a.

miR-155 was significantly up-regulated in tumors of MF as compared to lesions of early stage MF and inflammatory dermatoses. Using laser capture microdissection it was found that miR-155 was significantly higher in the lymphoma cells in advanced stage compared to the intraepidermal lymphoma cells in early stage. There was no difference in miR-155 expression between the intraepidermal and the dermal lymphocytes. A Significant inverse correlation was found between high miR-155 expression and low FOXO3a expression.

miR-155 is involved in the progression of early MF to tumor stage. The tumor suppressor gene FOXO3a might be a target of miR-155 in MF.

The role of versican isoforms in skin homing of Sézary cells
Karpova MB1, Fujii K1,2, Georgiev O3, Dummer R1, Urosevic-Maiwald M1
1Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland
2Department of Dermatology, Okayama University Graduate School of Medicine, Okayama, Japan
3Institute of Molecular Biology, University of Zurich, Zurich, Switzerland

Sézary syndrome is characterized by erythroderma, lymphadenopathy and the presence of neoplastic T lymphocytes, so called Sézary cells (SéCs) in the blood.

We performed microarray analysis on CD4+ SéCs, which were additionally sorted according to patient-specific TCR-Vb expression (Vb+). The effects of a candidate gene defined by this analysis were then tested on CD4+Vb+ SéCs from patients and cutaneous lymphoma (CL) cell lines.

We obtained expression profiles of clonal CD4+ T cells (Vb+) from patients and compared those to non-clonal CD4+ T cells obtained from the same patient (Vb-). We identified versican as the highest up-regulated gene in clonal CD4+Vb+ SéCs. Versican is a large chondroitin-sulphate proteoglycan and has four isoforms (V0-V3). Investigation of versican expression pattern revealed preferential expression of versican V1 isoform in the sorted SéCs from patients and also in the CL cell lines. Different cytokines influenced versican expression in a different manner. Further on, we assessed the effects of versican expression on the motility of CL cell lines to cytokines and chemokines and could show that versican V1 expression could modulate their motility.

Our experiments suggest a new factor that may regulate skin homing of SéC and we continue to work on this topic.
FC-07
PUVA BATH FOR FOLLICULAR VARIANT OR EARLY STAGE MYCOSIS FUNGOIDES REFRACTORY TO NARROW BAND UVB
Pavlotsky F (1), Hodak E (2), Ben Amiat D (3), Barzilai A (1) Phototherapy and Day Care Center, Department of Dermatology, Sheba Medical Center (1); Department of Dermatology, Rabin Medical Center (2); Pediatric Dermatology Unit, Schneider Children’s Medical Center (3), Israel

Today Narrow Band UVB (NB UVB) is frequently the preferred treatment for early stage Mycosis Fungoides (MF). However for UVB refractory and/or follicular cases PUVA is preferable. Oral PUVA is less suitable for patients with liver disease, cataract, children and those with an outdoor life style and/or occupation. PUVA Bath was not studied in this higher risk group and the aim of the present study was to summarize our experience in those patients.

Twenty six MF cases with an average age of 42.9 (8-82) years, including 11 NB UVB refractory early stage patients and 15 with follicular variant not eligible or reluctant for oral PUVA, were included in this retrospective analysis. All patients were treated twice weekly with 0.2mg/L 8MOP PUVA bath until clinical and/or histological remission, followed in some by gradual decrease to once monthly maintenance therapy.

Complete response was achieved in 71% after an average of 33 treatments followed by an average of 5-112 weeks maintenance with an average 180 J/cm2 cumulative dose.

In our experience PUVA bath is a good option for early stage MF refractory to NB UVB or for follicular MF cases not suitable for oral PUVA.

FC-08
UK CONSENSUS STATEMENT FOR BEXAROTENE THERAPY IN CUTANEOUS T-CELL LYMPHOMA
UK Cutaneous Lymphoma Group

Bexarotene is a synthetic retinoid and subclass of retinoids called rixenoids that selectively activate retinoid X receptors. It has activity in cutaneous T-cell lymphoma (CTCL) and isEMA approved since 1999 for treatment of the skin manifestations of advanced stage (IB-IVB) CTCL refractory to at least one systemic treatment.

In vivo bexarotene produces primary hypothyroidism which may be managed with thyroxine replacement. It also affects lipid metabolism typically resulting in raised triglycerides which requires prophylactic antilipid therapy. Effects on neutrophils, glucose and liver function also occur. Side effects are dose dependent and may be controlled with corrective therapy or dose adjustments.

Leaders from UK supraregional centres have produced a consensus statement after a series of meetings and review of the literature. The aim of this statement was to produce guidance on bexarotene dosing, monitoring pathways for lipids, thyroid function, glucose, creatinine kinase, liver function and blood count.

The statement provides detailed advice on bexarotene monitoring and dosing. It includes algorithms for a bexarotene dosing protocol and lipid management (including triple/quadruple therapy for hypertriglyceridaemia and hypercholesterolaemia) for use in the clinical setting.

Although prophylactic thyroxine and lipid lowering therapy have been discussed in previous papers none have provided comprehensive guidance.

This statement provides a useable bexarotene dosing schedule and monitoring protocol to enable bexarotene prescribers to deliver bexarotene safely at the optimal dose.

FC-09
An NCRI Phase II study of Gemcitabine and Bexarotene in the treatment of cutaneous T-cell Lymphoma (CTCL)
UK NCRI Cutaneous Lymphoma Group

Gemcitabine and Bexarotene are established single agents for the treatment of CTCL. We investigated this combination as part of a UK NCNR Phase II study.

A two-stage design was used, with a target response rate of ≥65%. Eligibility included Stages IIB to IVB patients who had failed skin directed therapy and ≥1 systemic therapies. Gemcitabine 1000mg/m² was given day 1 and day 8 every 21 days for 4 cycles. Bexarotene was started with Gemcitabine and at 12 weeks, responding patients continued on Bexarotene until disease progression or unacceptable toxicity.

Recruitment stopped following interim analysis of the first 35 patients. (clinical stages: 3 IIA, 10 IIB, 8 III, 14 IVA). 86% patients completed 4 cycles of Gemcitabine. 83% had dose delays, reductions or omission of Bexarotene during the first 12 weeks. Objective response at 24 weeks was 14% (PR 14%, SD 23%, PD 54%, not evaluable 9%) and at 12 weeks was 31% (PR 31%, SD 40%, PD 17%, not evaluable 11%). The median progression-free survival was 22.9 weeks and median overall survival was 91.9 weeks. Quality of life assessment showed a general improvement.

The overall response rate did not allow progression to the second stage of the study. However, patients experienced an improvement in quality of life.
miRNAs have a high diagnostic potential in CTCL. They distinguish CTCL from benign disorders with high specificity, sensitivity, and a classification accuracy of 95%, indicating that skin diseases can be diagnosed with > 90% accuracy. These miRNAs also distinguish malignant and benign lesions in an independent set of 50 patients. This confirms previous reports on miR-155 in CTCL. A q-RT-PCR-based classifier consisting of miR-155, miR-203, and miR-205 can analyze 103 patients with CTCL and benign skin disorders and validate differential expression of 4 out of the 5 miRNAs. The most induced- (miR-326, miR-663b, miR-711) and repressed- (miR-203, miR-205) miRNAs distinguish CTCL from benign disorders. MicroRNA (miRNA) profiling can discriminate CTCL from benign inflammation, and we study miRNA expression levels in 198 patients with cutaneous T-cell lymphomas (CTCL).

Peripheral neuropathy in MF/SS treated with brentuximab vedotin

Bashey S1, Krathen M1, Sutherland K1, Advani R1, Hoppe RT1, Kim YH1, and Nagpal, S2

FC-11 Stanford Cancer Center. 2 Stanford Neuro-Oncology. Stanford, CA, USA.

Brentuximab vedotin (BV) is a CD30-directed antibody-drug-conjugate where the cytotoxic component is monomethyl auristatin E, a microtubule inhibitor. In our phase II clinical trial evaluating the safety and efficacy of BV in mycosis fungoides/Sézary syndrome, we observed an overall response rate of 13/17 (76%). The most common adverse event was peripheral neuropathy (PN). We performed a sub-analysis to further characterize PN in our trial. Patients received BV every 3 weeks at 1.8 mg/kg; median duration of treatment was 7 cycles (2-12 cycles). Subjects with grade 2 PN required dose modification. Two subjects had a history of poorly controlled diabetes and ETOH use. 13/17 (76%) had PN by clinical examination. 8/13 (62%) and 4/13 (31%) experienced grade 1 and 2 PN, respectively. One subject developed grade 4 PN. Median time to PN was 12 weeks (6-21 wks). One subject's grade 1 PN resolved during trial. Two subjects with grade 2 PN improved to grade 1 following trial completion. At 24 weeks, 60% of patients did not have any resolution or improvement in neuropathy, median follow-up time 14 weeks (3-38 wks) from neuropathy onset. Four subjects required dose reductions. 6/17 (35%) withdrew from the trial due to any drug-related toxicity. 4/17 (24%) withdrew due to PN alone. Examination findings were consistent with a large fiber neuropathy. EMG confirmed an axonal neuropathy in 3 patients. In our cohort, BV caused a mixed sensory-motor axonal neuropathy similar to vincristine, another tubulin inhibitor; however, longer follow-up is needed to further assess its nature and duration.

Synergistic mechanism of histone deacetylase inhibitor and DNA methyltransferase inhibitor in CTCL treatment

Sima Rozati, Phil Cheng, Antonia Fettelschoss, Mitchell Paul Levesque, Reinhard Dummer.

Departments of Dermatology, Venerology and Allergology, University Medical Center Mannheim, Ruprecht Karls University of Heidelberg, Mannheim, Germany.

Curative modalities for Cutaneous T cell lymphoma (CTCL) have so far proven elusive and more treatment options are needed for patients in late stage disease. Therefore, there is still an immense need to find new therapeutic targets and drugs, that restrict the tumor burden and improve prognosis. The pathology of CTCL is at least in part based on resistance of these cells towards apoptosis. Recently, we have identified RAS mutations in late stage patients who showed significantly decreased overall survival compared to patients without mutations. RAS mutations have been shown to sensitize towards MEK inhibitors. Here, we show that the RAF inhibitor Sorafenib induces apoptosis in non-mutant CTCL cell lines and in primary cells from Sézary patients. NRAS mutations further sensitize towards Sorafenib-induced apoptosis in Hut78 cells. Vorinostat is an approved drug for CTCL therapy. Vorinostat, together with Sorafenib induces apoptosis in a synergistic manner in both, non-mutant and mutant cell lines. The cotreatment leads to a downregulation of the anti-apoptotic protein Mcl-1. Overexpression of Mcl-1 rescues apoptosis induced by Vorinostat and Sorafenib. Taken together, we conclude that Sorafenib might be a treatment option for non-mutant and mutant CTCL patients.

Diagnostic microRNA profiling in cutaneous T-cell lymphoma


NFAS mutations in cutaneous T cell lymphoma (CTCL) sensitize tumors towards treatment with Raf inhibitor Sorafenib

Jan P. Nicolay1, Michael K. Kießling1, Claus-Detlev Klemke1, Peter H. Kramer1, and Karsten Gülow1

German Cancer Research Center, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany.

Departments of Dermatology, Venerology and Allergology, University Medical Center Mannheim, Ruprecht Karls University of Heidelberg, Mannheim, Germany.

Cutaneous T-cell lymphomas (CTCL) are the most frequent primary skin lymphomas. Nevertheless, diagnosis of early disease has proven difficult due to a clinical and histological resemblance to benign inflammatory skin diseases. To address if microRNA (miRNA) profiling can discriminate CTCL from benign inflammation, we study miRNA expression levels in 198 patients with CTCL, peripheral T-cell lymphoma (PTL), and benign skin diseases (psoriasis and dermatitis). Using microarrays we show that the most induced- (miR-326, miR-663b, miR-711) and repressed- (miR-203, miR-205) miRNAs distinguish CTCL from benign skin diseases with > 90% accuracy. These miRNAs also distinguish malignant and benign lesions in an independent set of 50 patients with PTL and skin inflammation and in experimental human xenograft mouse models of psoriasis and CTCL. qRT-PCR analysis of 103 patients with CTCL and benign skin disorders validates differential expression of 4 out of the 5 miRNAs and confirms previous reports on miR-155 in CTCL. A q-RT-PCR-based classifier consisting of miR-155, miR-203, and miR-205 distinguishes CTCL from benign disorders with high specificity, sensitivity, and a classification accuracy of 95% indicating that miRNAs have a high diagnostic potential in CTCL.
miRNAs have a high diagnostic potential in CTCL. distinguishing CTCL from benign disorders with high specificity, sensitivity, and a classification accuracy of 95% indicating that analysis of 103 patients with CTCL and benign skin disorders validates differential expression of 4 out of the 5 miRNAs and the most induced- (miR-326, miR-663b, miR-711) and repressed- (miR-203, miR-205) miRNAs distinguish CTCL from benign.

Cutaneous T-cell lymphomas (CTCL) are the most frequent primary skin lymphomas. Nevertheless, diagnosis of early disease and Microbiology, University of Copenhagen, Copenhagen, Denmark.

Department of Dermato-Allergology, Gentofte University Hospital, Denmark; Department of International Health, Immunology LEO Pharma A/S, Ballerup, Denmark; Department of Biology, University of Copenhagen (UoC), Copenhagen, Denmark; Marstrand T., Ralfkiaer U, Glue C., Gniadecki R., Skov L., Odum N., Bashey S.

Peripheral neuropathy in MF/SS treated with brentuximab vedotin. Diagnostic microRNA profiling in cutaneous T-cell lymphoma FC-13 platform to identify biomarkers that could potentially be used in clinical studies evaluating the efficacy of these drugs in patients counteracts the loss of cell cycle control in CTCL more efficiently. The changes in IkB pathways was investigated by western blot.

The combination treatment showed a noticeable change of cell viability due to an increase in apoptosis and necrosis in a time consistent with a large fiber neuropathy. EMG confirmed an axonal neuropathy in 3 patients. In our cohort, BV caused a mixed improvement to grade 1 following trial completion. At 24 weeks, 60% of patients did not have any resolution or improvement in evaluation. 8/13 (62%) and 4/13 (31%) experienced grade 1 and 2 PN, respectively. One subject developed grade 4 PN. modification. Two subjects had a history of poorly controlled diabetes and ETOH use. 13/17 (76%) had PN by clinical peripheral neuropathy (PN). We performed a sub-analysis to further characterize PN in our trial. Patients received BV every 3

auristatin E, a microtubule inhibitor. In our phase II clinical trial evaluating the safety and efficacy of BV in mycosis Mcl-1 rescues apoptosis induced by Vorinostat and Sorafenib. Taken together, we conclude that Sorafenib might be a treatment NRAS mutations further sensitize towards Sorafenib -induced apoptosis in Hut78 cells. Vorinostat is an overall survival compared to patients without mutations. RAS mutations have been shown to sensitize towards MEK inhibitors. synergistic mechanism of histone deacetylase inhibitor and DNA methyltransferase inhibitor in CTCL treatment

Stanford Cancer Center.

Department of Dermatology, Venerology and Allergology, University Medical Center Mannheim, Ruprecht Karls University of

α2, β1, and β3 integrin staining was prominent and more intense in BCC's and MF. Fourteen cases of PCCL were labelled for PD-1, CXCL-13 and ICOS. Diffuse strong expression of PD-1, CXCL-13 and ICOS was consistent with a large fiber neuropathy. EMG confirmed an axonal neuropathy in 3 patients. In our cohort, BV caused a mixed improvement to grade 1 following trial completion. At 24 weeks, 60% of patients did not have any resolution or improvement in evaluation. 8/13 (62%) and 4/13 (31%) experienced grade 1 and 2 PN, respectively. One subject developed grade 4 PN. modification. Two subjects had a history of poorly controlled diabetes and ETOH use. 13/17 (76%) had PN by clinical peripheral neuropathy (PN). We performed a sub-analysis to further characterize PN in our trial. Patients received BV every 3

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Stanford Cancer Center.

Evaluation of Follicular T-helper Cells in Primary Cutaneous CD4+ Small/Medium Sized Pleomorphic T-cell Lymphomas and a Series of Inflammatory Dermatoses M Ally, RYZ Hunasehally, M Rodriguez, B. Martin, N Attard, A Attigalle, R. Verdolini, F Child, M Wain, S Whitaker, A Robson. St. John’s Institute of Dermatology, St. Thomas’ Hospital, London, UK

Primary cutaneous CD4+ small/medium sized pleomorphic T-cell lymphoma (CSMCL) is a provisional entity in the WHO-EORTC classification of cutaneous lymphomas. There is evidence to support a follicular T-helper phenotype in CSMCL, with expression of PD-1, CXCL-13 and ICOS by the atypical cells. We describe fourteen further cases of this entity and compare the expression of these immunophenotypical markers in these tumours with a series of forty inflammatory dermatoses (including 11 drug-related dermatoses, 10 eczema, 5 lupus erythematosus), 3 inflamed BCC’s and 1 case of solitary MF. All were stained for PD-1, CXCL-13 and ICOS.

All but one patient presented with solitary lesions on the head, neck and upper trunk; 1 patient developed multiple tumours. Biopsies revealed a dense nodular non-epidermotropic infiltrate of small to medium-sized atypical T-cells. Large cells constituted less than 30% of the infiltrate in all cases. Neoplastic cells had a CD3+/CD4+/CD8-/CD30- phenotype, with admixed CD8+ cells and numerous CD20+ cells. In the 8 cases tested, the Ki-67 fraction varied from 30-50%. Of 8 tumours analysed, TCR analysis was clonal in 5. Staging investigations performed in 11 cases were normal. All tumours regressed following treatment with topical steroids, excision or radiotherapy. All tumours widely expressed PD-1; and ICOS to a lesser extent. CXCL-13 stained fewer cells and was often less intense. Of the dermatoses, PD-1 and ICOS labelled lymphoid cells in all cases, albeit fewer than in the tumours, and CXCL-13 was negative in 32; PD-1+ cells were particularly numerous in comparison to the other markers. A rosette pattern of PD-1 expression was only identified in the CSMCL cases. There remains uncertainty about the appropriate nosological status of CSMCL, which some authors consider to be a "pseudolymphoma". The presence of atypical cells with a PD-1+/CXCL-13+/ICOS+ phenotype helps differentiate CSMCL from reactive infiltrates, and might account for the substantial B-cell fraction that characterises these tumours.
FC-17
EXPRESSION OF CD158K/KIR3DL2 BY SKIN-INFILTRATING CD30+ LYMPHOCYTES IN PATIENTS WITH CUTANEOUS ANAPLASTIC LARGE T CELL LYMPHOMAS. A FLOW CYTOMETRIC ANALYSIS.

Primary cutaneous CD30+ lymphoproliferative disorders (CD30+ LPDs) are the second most common form of cutaneous T-cell lymphomas (CTCLs) after mycosis fungoides (MF) and Sézary syndrome (SS). They represent a spectrum of diseases, including lymphomatoid papulosis (LyP) and anaplastic large-cell lymphoma (ALCL). We have previously identified several specific membrane markers, including CD158k/KIR3DL2, on T cells from patients with transformed MF or SS. The aim of the present study was to assess whether skin infiltrating CD30+ lymphocytes from patients with ALCL also express membrane CD158k/KIR3DL2 on their surface. Six patients with a diagnostic of ALCL were included in the study. The diagnostic relied on clinical, pathological and immunohistological analysis. Skin punch biopsies from tumor lesions were also performed for tumor cell isolation by enzymatic digestion and staining by four-color direct immunofluorescence for flow cytometric analysis. Skin-infiltrating lymphocytes were identified by cell size and through combination of gating techniques involving side scatter, forward scatter and CD3 expression using blood T cells for positive identification. The flow cytomeric analysis was considered positive for a neoplastic T-cell population if a discrete and homogeneous population of lymphoid cells was identified as CD30-positive cells that co-express CD3 or CD4 at their surface. Our results evidenced a CD158k/KIR3DL2 expression by the CD30+ lymphocytes isolated from tumor skin lesions in the six patients. The mean percentage of CD30+ cells expressing CD158k/KIR3DL2 on their surface was 49.85 ± 15.3 [min 15.2 – max 98.8]. None or very low (<2%) expression of CD30 or CD158k/KIR3DL2 was detected on circulating T cells of the six patients. These results clearly evidence an expression of CD158k/KIR3DL2 on CD30+ T cells in patients with ALCL, as previously reported for tumor T cells of SS patients.

FC-18
VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) EXPRESSION IN MYCOsis FUNGOIDES
Alessandro Pilieni1, Claudio Agostinelli2, Simona Righi2, Francesco Bacci2, Elena Sabattini2, Annalisa Patrizi1, Pier Paolo Piccatuaga3, Nicola Pimpinelli2 and Stefano A. Pilier4.
1. Section of Dermatology, Department of Internal Medicine, Geriatrics and Nephrologic Diseases, Bologna University School of Medicine, Bologna, Italy.
2. Department of Haematology and Oncological Sciences “L. and A. Seràgnoli”, Chair of Pathology and Haemolymphopathology Unit, Bologna University School of Medicine, Bologna, Italy.
3. Department of Dermatological Sciences, University of Florence Medical School, Florence, Italy.

High levels of vascular endothelial growth factor (VEGF) seem to herald a worse prognosis in mycosis fungoides (MF). The aim of our study was to assess possible differences in terms of VEGF expression between MF and normal T-cells. First, we compared VEGF mRNA levels in 63 MF cases and 20 samples of normal T-lymphocytes. Notably, significantly higher VEGF levels were found in MF. Second, we investigated whether the high VEGF expression in MF could represent a pathological attribute. To this end, we determined VEGF levels in normal CD4+ , CD8+ , HLA-DR+ and HLA-DR- T-cells, by showing higher values in activated T-lymphocytes irrespective of their CD4 or CD8 profile. Remarkably, the global gene expression profile (GEP) of MF turned out quite close to that of such subpopulation that was regarded as the normal counterpart of the disease. By focusing on the comparison between MF and activated T-lymphocytes, once again VEGF expression appeared significantly higher in the former. GEP results were supported by immunohistochemistry in routine sections from 18 MF cases. We demonstrated for the first time VEGF expression in MF cells, suggesting that the VEGF pathway may be implicated in MF pathogenesis and can represent a novel therapeutic target.

FC-19
HUMAN ENDOGENOUS RETROVIRUS TYPE W ENVELOPE EXPRESSION IN MYCOsis FUNGOIDES PROVIDES NEW INSIGHTS INTO CUTANEOUS T-CELL LYMPHOMAS.
Pilvi Maliniemi1, Michelle Vincendeau1, Jens Mayer2, Oliver Frank2, Sonja Hahtola3, Kirsi Niininen4, Leena Karenko5, Emilia Carlsson5, Francois Mallol1, Wolfgang Seifarth1, Christine Leib-Mösch1, and Annamari Ranki5.
1Department of Dermatology and Allergology, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland.
2Helmholtz Zentrum München, German Research Center for Environmental Health, Institute of Virology, Neuherberg, Germany.
3Department of Human Genetics, Medical Faculty, University of Saarland, and 4Medical Clinic III, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany, and 5Joint Unit Hospices Civils de Lyon-bioMéreux, Cancer Biomarkers Research Group, Centre Hospitalier Lyon Sud, Pierre Bénéte France.

Mycosis fungoides (MF) is the most common form of primary cutaneous T-cell lymphomas (CTCLs). Chromosomal instability is typical but the pathomechanism of MF is not known albeit e.g. underlying viral infections have been sought for. Human endogenous retroviruses (HERVs) are normal components of human genome but may be overexpressed in cancers. To explore the transcriptional activity of HERV sequences in the total of 34 MF and psoriasis skin samples, we used a retrovirus-specific microarray and quantitative PCR. Additionally a sequence analysis was performed to identify the active HERV loci. We identified a distinct, skin-specific HERV expression profile consisting of seven constitutively active HERV taxa. Strikingly, HERV-W showed clearly an increased expression in lesional skin of MF compared with the non-malignant from the same patient. Moreover, the active HERV-W loci were identified in 6q21 and 7q21.1, chromosomal areas harboring alterations typical for CTCL, too. Moreover, the latter locus codes for a viral envelope protein, syncytin-1, which we found expressed in MF skin lesion lymphocytes. Interestingly, we raise the serum from one patient showed antibodies against syncytin-1. We conclude that individual variability is a typical feature of HERV transcription but differences between lesional and non-malignant skin are significant. The expression of syncytin-1 offers new perspectives on the pathogenesis of CTCL.
NOTCH1 SIGNALING PATHWAY ACTIVATION STUDY IN CUTANEOUS T-CELL LYMPHOMAS

Notch1 is a transmembrane receptor that activates transcription. Notch1 participates in cell differentiation, proliferation and apoptosis and plays a direct role in normal T-cell development and clonal T-cell expansion of different haematological malignancies. Notch1 signaling represents an attractive target for new therapeutical strategies. Activation status of the Notch1 pathway in cutaneous T-cell lymphomas (CTCL) was studied. Eighteen mycosis fungoides (MF) and 10 primary cutaneous anaplastic large cell lymphoma (CD30+CTCL) samples were evaluated for: a) Expression and subcellular localization of Notch1 and Notch-ligands by immunofluorescence/immunohistochemical methods. b) MicroRNA expression profile by RNA microarrays searching for negative regulators of the Notch1 pathway c) Promoter hypermethylation analysis of Notch1-family miRNA targets. Obtained results were validated by qRT-PCR. Among different microRNAs that were downregulated in microarray screening, we identified mir200 family targeting Jagged1. mir200 downregulation was validated by qRT-PCR, and its effects were confirmed by the upregulation Hes1, the Notch1 target. We showed that Jagged1 is highly expressed in CTCL sections and Notch1 is active in infiltrating CD3+ cells. We failed to detect hypermethylation on Notch1-family-target miRNA indicating that epigenetic mechanisms are not responsible for Notch1 activation. Our results suggest that Notch1 activation may be implicated in the pathogenesis of MF and CD30+CTCL.

COMBINATION OF PLS3, TWIST, CD158K/KIR3DL2 AND NKP46 GENE EXPRESSION FOR THE DIAGNOSIS OF SEZARY SYNDROME.
Michel L, Jean-Louis F, Begue E, Bagot M, Benussan A.
Inserm U976. Department of Dermatology. Hôpital Saint-Louis. PARIS. FRANCE

Several molecular markers including T-palstin (PLS3), transcription factor Twist, CD158k/KIR3DL2 and Nkp46 (CD335) have been specifically identified in patients with Sézary Syndrome (SS), the erythrodermic and leukemic form of cutaneous T-cell lymphoma (CTCL). Our purpose was to investigate whether the expression profiling of these four genes by quantitative Real-time PCR (qRT-PCR) can be employed for the diagnosis of SS. A cohort of 81 patients with SS was investigated for tumor burden and mRNA expression quantification of PLS3, Twist, KIR3DL2, and Nkp46, in CD4+-purified T cells from blood samples using SYBR Green qPCR and specific primer pairs. CD4+-purified T cells from 12 healthy donors were studied as controls, with qRT-PCR mean values (±SD) of PLS3, Twist, KIR3DL2, and Nkp46 mRNA levels reaching 2.4±2.5, 6.6±8, 22.5±20.4, and 2.6±2.8, respectively. A respective threshold of 95% significance was set up at 5, 10, 25 and 50, and any value less than the respective threshold was considered as negative. As positive controls we used mRNA mean levels (±SD) detected in SS HuT-78 cell line cultures (n=3) with 128±65 for PLS3, 13155±3000 for Twist, 316±40 for KIR3DL2, and 7.3±1.9 Nkp46, respectively, as mRNA mean levels (±SD) in NK-purified cells (n=3) reaching 4.4±0.1, 0.5±0.15, 65±80.3, and 37±80.2, respectively. Our results demonstrated that qRT-PCR data accurately classified 100% of 81 SS patients with high blood tumor burden. CD4+-purified T cells from SS patients expressed PLS3, Twist, KIR3DL2, and Nkp46 mRNA mean levels (±SEM) of 706±133, 1440±292, 843±96, and 7.1±1.7, respectively. The accuracy was 100% in identifying these samples as SS patients since the four markers were detected in 20% CD4+-purified T cell samples, three ones in 53%, two ones in 20% and only one marker (Twist, PLS3 or Nkp46) in 7%. These results clearly demonstrate that gene expression profiling by quantitative PCR on a selected number of 4 critical genes can be employed for the molecular diagnostic of SS.

Secondary cancer and survival in mycosis fungoides or parapsoriasis: A Danish nationwide population based cohort study
L.M. Lindahl, M. Fenger-gren, L. Iversen
Department of Dermatology, Aarhus University Hospital

Data on incidence of secondary cancer and prognostic factors for survival in patients with mycosis fungoides (MF) and parapsoriasis are limited. Furthermore, it remains controversial whether parapsoriasis is a precursor of MF or should be considered as early MF. In this nationwide study we identified 368 patients with MF and 582 patients with parapsoriasis, without prior cancer history, from the Danish Cancer Registry (DCR) and the Danish National Registry. Data on secondary cancers were obtained from DCR and survival and causes of death from the Danish Civil Registration System and compared to the general Danish population. Standardized incidence ratio (SIR) for secondary cancers (excluding hematological cancers) was increased in patients with parapsoriasis (p=0.049), which was not observed in patients with MF (p=0.57). Survival was decreased in patients with MF, SIR 2.0 (95% CI 1.7-2.3), and parapsoriasis, SIR 1.3 (95% CI 1.1-1.6) compared to the general population. More than 5-years follow-up was a positive prognostic factor for survival in MF. Patients with parapsoriasis have increased SIR for secondary cancers and decreased survival indicating that parapsoriasis should be considered as early MF. Furthermore, more than 5-years follow-up is a prognostic factor for survival suggesting, that MF exists in an aggressive and an indolent form.
We carried out a retrospective review of patients diagnosed with Stage IV MF SS between 1971 and 2008.

We have identified a subgroup of patients with Stage IVB Mycosis Fungoides involving mucosal head and neck sites with a better response rate to treatment. The median survival post diagnosis of stage IVB was 4 years for the mucosal site patients and 0.76 years for the stage IVB other sites patients (log rank p = 0.03 HR 2.27 95% CI 1.08 to 4.8).

Stage IVB Mycosis Fungoides/Sezary Syndrome (MF/SS) (T1-4, N0-3, B0-2 and M1) has a poor prognosis. We report a subgroup of patients with a better response to treatment and improved survival.

We carried out a retrospective review of patients diagnosed with Stage IV MF SS between 1971 and 2008. 171 patients with Stage IV MF/SS were identified. 39 were Stage IVB. 21 had progressed from early stage IA/IB, and 11 from late stage IIIB-IVA. 31 patients had involvement of lung, liver, spleen, bone or CNS. 8 patients had biopsy proven mucosal head and neck involvement. (4 nasopharynx, 1 tongue and oropharynx, 1 nasopharynx and oropharynx, 1 epiglottis and 1 laryngopharynx) The stage at diagnosis in these 8 patients was stage IA/IB in 4 and stage IIIB/IV in 4. These 8 patients were treated with palliative external beam radiotherapy to the head and neck sites, 20 Gy in 10 fractions over two weeks. The overall response rate was 100%. 1 patient relapsed in the nasopharynx 3 years after initial treatment and was successfully retreated with radiotherapy. The median survival post diagnosis of stage IVB was 4 years for the mucosal site patients and 0.76 years for the stage IVB other sites patients (log rank p = 0.03 HR 2.27 95% CI 1.08 to 4.8).

We have identified a subgroup of patients with Stage IVB Mycosis Fungoides involving mucosal head and neck sites with a better prognosis. Radiotherapy is an effective palliative treatment for these patients.
P-04
Two cases of aggressive non-tumoral folliculotropic mycosis fungoides (FMF) with pulmonary localization
Brugière, Stefan, Dompmartin, Salaun, Comoz, Verneuil
Dermatology-Haematology-Pathology, University-Hospital-Caen
FMF, rare variant of mycosis fungoides (MF), is characterized by acniform lesions, comedones, and cysts. The visceral involvement is very rare. We report 2 FMF cases with pulmonary involvement.
A 63-year-old man had an interdigital intertrigo associated with head, back, comedonal plaques, abdominal ulcerated plaque, without erythroderma. Histology showed a non-tumoral FMF and flow-cytometric analyses detected a T-cell-population CD2+CD3+CD4+CD7+CD5+CD8-CD26+.
A 64-year-old man presented for one month an infiltration of the face, scalp alopecia areas, abdominal infiltrated plaques, with lymphadenopathy but no erythroderma. Histology showed a non-tumoral FMF with CD3+CD4+CD5+CD7-CD8- phenotype. Chest-CT-scan found an interstitial pneumonia.
Lymphocyte-immunophenotyping of skin, lymph node and bronchoalveolar-fluid using flow-cytometric analyses detected identical abnormal T-cell-population CD2+CD3+CD4+CD5+CD7-CD8-CD26-.
In the two patients, no Sezary-cells and T-cell clones were detected in blood.
In our patients, without erythroderma, skin tumoral-transformation, and leukemic phase detected, a lymphoma pulmonary localization was demonstrated. In case 2 with a very short disease course, concomitant lymphoma pulmonary lesions were present. These cases suggest an important aggressiveness of FMF variant, beside their therapeutic resistance.

P-05
PHOTOPHERESIS PLUS PUVA FOR ADVANCED MYCOSES FUNGOIDES. A DEMONSTRATIVE CASE.
Since 1987, extracorporeal photopheresis (ECP) is mainly recommended for patients with advance mycosis fungoides (MF) and PUVA is usually restricted for early stage disease. A 43-years-old man presented with a 1-year history of a progressive nodular eruption and generalized pruritus. Physical examination revealed red plaques and tumours on the scalp. Skin biopsy specimen showed epidermal and follicular infiltration by atypical lymphocytes and a dominant T-cell clone was demonstrated. Folliculotropic MF stage IIB (T3N0B0M0) was diagnosed. The patient was initially treated with PUVA + bexarotene (450 mg/day). After 6 months, several new lesions developed. An enlarged inguinal lymph node was biopsied showing dermatopathic changes (T3N1B0M0) and interferon-α was added to the treatment without clinical response. Despite monotherapy with vorinostat (400 mg/day) for 3 months, erythrodermic disease developed with blood involvement (T4N1B1bM0). After vorinostat withdrawal, ECP was initiated on a standard schedule with favourable haematological response after 3 months. However, cutaneous lesions only improved after three months of ECP + PUVA treatment. No significant adverse reactions were observed. This combined phototherapy approach (extracorporeal and skin directed therapy) may be an effective and safe option for patients with advance MF.

P-06
Mycosis fungoides with Central Nervous System involvement: A review of six cases from a single institution and a review of the role of low dose Whole Brain Irradiation as an effective palliative treatment
Dr Arafat Mirza, Dr Stephen Morris, Dr Bridget Wilkins, Dr Paul Fields, Dr Robert Marcus, Dr Fiona Child, Dr Natalie Attard, Prof Sean Whittaker
St John’s Institute of Dermatology, St Thomas’ Hospital, London, United Kingdom
Central nervous system (CNS) involvement with mycosis fungoides (MF) is rare with limited literature available to guide treatment.
We carried out a retrospective review of patients on the St John’s institute of dermatology database.
6 patients were identified, 4 patients with brain parenchymal and 2 with orbital involvement. Of the 6 patients identified 2 had the diagnosis confirmed on a brain biopsy. 3 patients received whole brain radiotherapy (WBRT) with partial response. 1 patient received high dose Methotrexate (MTX) with progressive disease and then had a complete radiological response to low dose radiotherapy. The high dose MTX was complicated by infection and renal failure. 1 patient with orbital involvement had a partial response to intra-vitreal MTX. The median survival from diagnosis of CNS involvement was 2.8 months.
The outcome of treatment of CNS involvement by MF is poor and prognosis is poor. Low dose WBRT may be an effective and less intensive approach to improve the quality of life in these patients.
Analysis of lymphangiogenic markers in erythrodermic cutaneous T-cell lymphomas

Karpova MB, Fujii K*, Jenni D, Dummer R, Urosevic-Maiwald M
Department of Dermatology, University of Zurich, Switzerland;
*Department of Dermatology, Okayama University Graduate School of Medicine, Okayama, Japan

Sézary syndrome (SS) is a leukemic, aggressive subtype of cutaneous T-cell lymphomas (CTCLs) characterized by the accumulation of malignant T-cells in the skin, as well as by blood and lymph node involvement. Lymphangiogenesis represents the de novo formation of lymphatic vasculature and has been associated with the occurrence of metastatic disease and poor prognosis. To date there are little or no data on the extent of lymphangiogenesis in SS or its counterpart erythrodermic mycosis fungoides (eMF).

We sought to evaluate lymphangiogenesis markers (LYVE-1, D2-40 and VEGF-C) in skin biopsies from patients with SS and eMF and to assess their dynamics during the disease course over several years.

We could show that the expression of VEGFR-3 was significantly higher in SS patients (p=0.0285) as compared to patients with eMF. LYVE-1, D2-40 and VEGF-C stainings showed similar tendency. Number of podoplanin (D2-40) expressing lymphatic vessels (p=0.025) as well as CD31-positive blood vessels (p=0.0065) correlated with the disease progression in SS patients.

We show for the first time a non-vascular pattern of VEGF-C and VEGFR-3 and their epidermal expression in erythrodermic CTCLs, suggesting their role in lymphocyte trafficking to the skin.

To summarize, we demonstrate the expression of several lymphangiogenic markers in biopsies of patients with SS and eMF implying ongoing lymphangiogenesis in these diseases.

ERYTHRODERMIC VS TUMOUR-STAGE MYCOSIS FUNGOIDES: CLINICAL ONSET PATHWAYS, EXTRACUTANEOUS PROGRESSION AND SURVIVAL. A MULTICENTER RETROSPECTIVE STUDY FROM THE ITALIAN GROUP OF CUTANEOUS LYMPHOMAS

Pietro Quaglino 1, Nicola Pimpinelli 2, Emilio Berti 3, Piergiacomo Calzavara-Pinton 4, Giuseppe Alfonso Lombardo 5, Serena Rupoli 6, Paola Savoia 1, Pierluigi Zinzani 7, Maria Grazia Bernengo 1.

1 Dermatologic Clinic, Dept of Biomedical Sciences and Human Oncology, University of Turin. 2 Department of Dermatological Sciences, University of Florence. 3 Dermatologic Clinic, University of Milano-Bicocca, Milan. 4 Institute of Dermatology, University of Brescia. 5 Istituto Dermopatico dell’Immacolata (IDI-IRCCS), Rome. 6 Institute of Hematology and Medical Oncology “L. e A. Seràgnoli”, University of Bologna.

Few data on large clinical series support the continued classification of tumour-stage MF at a stage below erythroderma. Retrospective review of 1,422 MF patients seen from 1975 to 2010 in 27 centres.

The majority of patients (77.9%) had stage I disease at diagnosis. Tumour-stage MF was diagnosed in 5.5%, erythrodermic MF in 6.8%. Erythrodermic patients had a male prevalence and elderly age. Erythroderma evolved more frequently from T1/T2 (13.9% and 28.2%) than T3 (<10%; p=0.013). Stage IIB showed a higher risk of node/visceral involvement (p=0.001), whilst stage III had a higher incidence of haematological involvement (p=0.05). No survival differences were found between erythrodermic and tumour-stage MF.

Erythrodermic and tumour-stage represent two alternatives pathways of MF evolution rather than sequential steps; the two forms show similar survival but different extracutaneous involvement (blood vs nodes/visceras) thus warranting different therapeutic approach.

Cutaneous tumour cell load correlates with survival in patients with Sézary syndrome

Nina Booken, Jan Peter Nicoley, Claus-Detlev Klemke
Department of Dermatology, Venereology and Allergology, University Medical Centre Mannheim, Ruprecht-Karls-University of Heidelberg, Mannheim, Germany

Sézary syndrome (SS) is defined by the triad of erythroderma, generalized lymphadenopathy and more than 1000 circulating Sézary cells/µl in the peripheral blood.

We screened the cutaneous lymphoma registry of our department for SS patients to identify clinical features of SS besides the defining criteria and to correlate them with disease survival. 24 SS patients were analyzed retrospectively. The mean age was 65 years with 62% male patients. The median follow-up time was 32.5 months with an estimated 5-year overall survival rate of 76%. All patients complained about itching and presented with palmoplantar keratoderma. 62.5% had nail involvement, 21% alopecia, 12.5% ectropion, 4% prurigo nodularis, 8% localized and 8% generalized skin tumours, including leonine facies. In addition, we diagnosed infections in 33% and also 33% had venous oedema. We identified cutaneous tumour cell load as a significant prognostic marker for SS. None of the other parameters were associated with disease specific survival.

Clinically SS is characterized by various presentations beyond erythroderma. The cutaneous tumour cell load in SS is strongly associated with outcome and survival. We could demonstrate a high risk for venous thromboembolisms in SS patients which might benefit from anti-coagulation therapies.
P-10
GENOMIC ALTERATIONS STUDY IN SÉZARY SYNDROME
Corti L, Fanoni D, Venegoni L, Onida F, Saporiti G, Berti E
Fondazione IRCCS Ospedale Maggiore Policlinico; Università degli Studi di Milano and Università degli Studi di Milano-Bicocca, Milan, Italy.

Sézary Syndrome (SS) is a cutaneous T-cell lymphoma characterized by erythroderma, lymphadenopathy and presence of neoplastic T-cells in skin, lymph nodes, and peripheral blood. Recent studies revealed chromosomal imbalances. The most frequent alterations were in chromosomes 8, 10 and 17.

We recruited 18 patients affected by primary SS showing a typical immunophenotype (CD4+/CD26−, CD7+/−) and clonal rearrangement of T-cell receptor beta and/or gamma chains.

We performed a whole genome array-based comparative genomic hybridization study on peripheral blood samples. As recurrent chromosomal alteration, we found Del17p13.1-p13.1 in 72% of cases, Amp17q11.2-25.3 (72%), Del10q11.21-q26.3 (56%), Del10p11.23-p11.21 (50%), Amp7q11.23 (50%), Amp8q24.3 (39%), Amp12q13.2 (39%), Amp19q13.2-q13.42 (39%).

We evaluated clinical presentation and outcome for all patients in correlation to the molecular data. No significant correlations were demonstrated.

Our results partially confirmed those reported by other studies about chromosomes 7, 8, 10 and 17. To the best of our knowledge alterations of 12q, 19p and 19q have never been described in SS patients. In 17q are located genes coding members 3 and 5 of the STAT family, while the involved region of 19p contains JAK3 gene. Phosphorylated JAK3 phosphorylates and activates STAT3 and STAT5. Activation of JAK/STAT signal transduction pathway leads to cell proliferation and anti-apoptosis. Our results suggest a role of JAK/STAT pathway in SS.

P-11
Retrospective review of Extracorporeal Photopheresis as monotherapy compared with Extracorporeal Photopheresis combined with other systemic biologic therapies in patients with Sézary Syndrome
Aguilar-Duran S1, Morris SL1, Whittaker S1, Child F1
1St John’s Institute of Dermatology, Guy’s and St Thomas NHS Foundation Trust

Extracorporeal photopheresis (ECP) is an effective treatment for Sézary Syndrome (SS). Retrospective studies have shown response rates of up to 63%. ECP can be used as monotherapy or combined with other systemic biologic agents and there is evidence to suggest that combination therapy is highly effective.

We report a single-centre retrospective study of patients with stage IV MF/SS who have had treatment with ECP. Overall response rate and progression free survival were assessed. Clinical information was collected from the patients’ medical records.

Data on fifty-seven patients was recorded. 35 patients had stage IVA1 and 22 had stage IVA2. The average duration of ECP treatment was 20.8 months. Forty-two patients (73.3%) were commenced on ECP monotherapy, however 15 (42.8%) had additional biologic therapies added. Fifteen patients were commenced on combined therapy (9 on dual therapy and 6 on triple therapy). Combined therapy included subcutaneous Interferon alpha, Bexarotene and Methotrexate. Overall partial/complete response was 49.1%. Mean Progression Free Survival (PFS) was 5.4 months. In patients receiving only ECP, mean PFS was 3.5 months compared with 6.7 months in patients with ECP combined with other systemic therapies (p=0.02).

In our study, patients receiving treatment with ECP combined with other systemic treatments had longer progression free survival rates than those on ECP as monotherapy.

P-12
Folliculotropic mycosis fungoides
Ursula Baßtöber, Martina Schmid
Department of Dermatology, Donauspital, Vienna

A 75-year-old male patient had been treated for fungal infection of the face with terbinafin during the previous 2 weeks. At initial presentation, erythematous plaques and nodules were located on the right cheek and in the neck area with scaling and crusting. Cervical lymph nodes were not enlarged. Non pruritic isolated eczematous lesions developed on the right cheek and in the neck area with scaling and crusting.

Differential diagnoses included chronic discoid LE, sycoisis barbae, cutaneous T cell lymphoma, lupus vulgaris, granulomatous rosacea and leishmaniasis. Fungal culture and herpes PCR were negative. Staphylococcus epidermidis and Enterococcus faecalis were cultivated from the lesion on the cheek. Blood sedimentation rate was elevated (72/102); CD4/CD8 ratio was elevated (10.5); biopsy chin and right nasolabial: Mycosis fungoides-associated follicular mucinosis, secondary finding Phytophthora colonization; biopsy left upper arm: pilottropic mycosis fungoides; bone marrow biopsy: normocellular; molecular biology: TCR - rearrangement (December 2009): tissue: beta and gamma chain positive, blood: negative, (June 2010): tissue: beta chain positive; CT neck, chest, abdomen: normal.

Diagnosis: CTCL stage T3 NO B0 M0 (classification according to ISCL / EORTC, 2007). Although lesions had increased initially with systemic antifungals electron radiotherapy was initiated for the face and neck area with a total dose of 30 Gray. A significant size reduction was achieved by irradiation. The lesions on the trunk responded well to PUVA therapy, which was stopped due to intolerance of 8- Methoxypsoralen (5-Methoxypsoralen was no longer available). Therefore we started treatment with Bexarotene (Targretin), 300 mg/ d, and finally 375 mg / d orally. Expected but subjectively asymptomatic side effects, such as hypothyroidism and hyperlipidemia were treated with levothyroxine 50 µg, as well as rosuvastatine 20 mg and fenofibrate 200 mg. Finally a rapid clearing of skin lesions could be achieved.
FOLLICULOTROPIC MYCOSIS FUNGOIDES: ANALYSIS OF PILOTROPIC T-CELLS


Folliculotropic mycosis fungoides (FMF) is an uncommon variant of MF with unique clinical and histological features. Investigations in FMF were carried out to better understand the pathomechanism of folliculotropism. In 13 cases with FMF the diagnosis was based on the characteristic clinical and histological features. Further immunohistochemical analysis was performed with CD3, CD4, CD5, CD7, CD8, CD30, PD-1, CXCL13, BCL6, CLA, CCR4, CCR10, FoxP3, CD1a, CD68, Ki-67 and nestin monoclonal antibodies. TCR γ gene rearrangement was studied by PCR method. Small lymphoid cells with cerebriform nuclei constitute the follicular infiltrate in all samples. Epidermotropism was observed in 4/13, syringotropism in 2/13 and mucinous degeneration in 8/13 cases. All cases were CD3+, CD5+, CD7+, CD30-, all but one were CD4+, and one CD8+. All cases showed clonal TCR γ gene rearrangement. The Ki67 proliferation rate was under 10%, CLA+ was 10-40%, FoxP3+ was 10-20% in 8/13 cases, CCR10 was focally and weakly expressed, CCR4 was negative in all cases. PD-1 positivity was found in increased in 7/13 cases. FMF demonstrates diverse clinical, histological and immunohistological characteristics comparing to classic MF. The tumor cells expressed follicular T-helper cell markers in majority of the samples. CLA seems to be significant in the trafficking of the tumor cells over against CCR4. FMF tumor cells’ characteristics may be related to unique homing in this rare manifestation.
P-16
THE PREVALENCE OF PRIMARY CUTANEOUS LYMPHOMAS AT A DERMATOLOGY REFERRAL CENTER IN LOWER AUSTRIA
Eder J., 1, 2 Kern A., 1 Kitzwürger M., 1 Sedivy R., 3 Trautinger P. 1, 2 1) Karl Landsteiner Institute of Dermatological Research, St. Pölten, Austria; 2) Department of Dermatology and Venereology, and 3) Institute of Clinical Pathology, Landesklinikum St. Pölten, St. Pölten, Austria

In this retrospective analysis we evaluated the prevalence and the clinical spectrum of primary cutaneous lymphomas (PCL) diagnosed and treated at the Department of Dermatology in St. Pölten, Lower Austria, between 2006 and 2012. The Department is a dermatology referral center providing secondary and tertiary care for a population of about 600,000. We identified 56 patients (pts; 17 females and 39 males) with ages at diagnosis ranging from 13 to 85 yrs and a median of 58 yrs. 43 pts (77%) had cutaneous T-cell lymphomas (CTCL) and 13 pts (23%) had cutaneous B-cell lymphomas (CBCL). 33 pts were classified as mycosis fungoides (MF; stages: IA n=17, IB n=8, IIA n=2, IIB n=8, III n=1). Large cell transformation was observed in 3 pts. Among pts with CTCL other diagnoses were Sézary syndrome (n=2), lymphomatoid papulosis (n=6), CD4+ small/medium sized pleomorphic T-cell lymphoma (n=1), and subcutaneous panniculitis-like T-cell lymphoma (n=1). CBCL was classified as follicle center lymphoma in 6 pts, marginal zone lymphoma in 4 pts, and diffuse large B-cell lymphoma, leg type, in 3 pts. Our data correspond well with the published annual incidence of PCL (0.5-1 per 100,000) and with the published distribution of separate disease entities. In conclusion, for sufficiently large populations it appears reasonable to provide specialized care for pts with PCL at centers with expertise in derma- oncology.

P-17
CUTANEOUS FOLLICULAR HELPER T-CELL LYMPHOMAS: A SERIES OF 6 CASES HIGHLIGHTING NEW CLINICAL-PATHOLOGICAL ASPECTS
Ortzone N, Kekri F, Chateaun D, Chaby G, Carlotti A, Lecaudrey-Hansen MH, Comoz F, Gaulard Pathology, Hôpital Henri Mondor, Créteil, France; Pathology, CHU d’Amines, France; Dermatology, CHU d’Amines, France; Pathology, hôtel Cochin, Paris, France; Pathology, Carpentras, France; Pathology, centre hopitalier de Caen, France.

A proportion of unclassified cutaneous T-cell lymphomas express follicular helper T-cell (TFH) markers and may represent a distinct sub-group among primary cutaneous T-cell lymphomas, recently termed primary cutaneous TFH lymphomas (PCTFHL). We reviewed 6 cases showing new clinical-pathological features. The patients had multiple nodules an ulcerated tumour or an erosion. A patient had an enlarged lymph node with partial involvement, another a polyadenopathy and 2 a leukemic component. Neoplastic epidermotropism was evidenced in 2 cases and large CD30+ T-cells in one. T-cell antigen loss was found in 3 cases (CD2 or CD5). One had a nodular infiltrate with follicular dendritic cells hyperplasia. The neoplastic T-cells were CD4+ with variable expression CXCL13, PD1, ICOS and BCL6 (<5% to over 50%), while CD10+ lymphocytes were rare (n=2). Plasma cells were present in 3 cases, with Kappa light chain restriction in one. Three had an EBV+ B-cell population, giving rise to an associated diffuse large B-cell lymphoma in two (skin and lymph node).PCTFHL have to be distinguished from the other cutaneous T-cell lymphomas that are known to express some TFH markers. Some are epidermotropic and they may give rise to an EBV+ DLBCL.

P-18
Extranodal nasoal-nasal type natural killer/T-cell lymphoma mimicking refractory sinusitis in a 60-year-old man
Hansgeorg Müller 1, Bernhard Zeiger 1, Wolfgang Willenbacher 2, Lorenzo Cerroni 1, Matthias Schmuth 1
1 Department of Dermatology, Innsbruck Medical University, Innsbruck, Austria; 2 Department of Hematology and Oncology, Innsbruck Medical University, Innsbruck, Austria; Research Unit of Dermatopathology, Department of Dermatology, Medical University of Graz, Graz, Austria

INTRODUCTION: Extranodal NK/T-cell lymphoma, nasal type, is an aggressive non-Hodgkin’s lymphoma subtype originating from peripheral T-cells or natural killer (NK) cells. Due to its rarity in European countries, the diagnosis is often missed at initial presentation, with its nonspecific symptoms misattributed to more common chronic diseases.

METHODS AND RESULTS: We report a 60-year-old white man who presented with uncontrollable acute exacerbation of chronic sinusitis despite antibiotic therapy for 3 months. Physical examination showed left-sided nasal deviation and obstruction, and diffuse swelling of the paranasal soft tissue. Imaging (CT, MRI) revealed no evidence of bone damage. The patient underwent endoscopic sinus surgery along with septoplasty that was followed by a revision surgery within one month due to persistence of symptoms. Histological examination of the resected tissue showed non-specific features of chronic inflammation. MRI and a repeated intranasal biopsy showed no evidence of malignancy. No long-term clinical improvement but the occurrence of nasal skin necrosis was observed under immunosuppressive therapy (Anakinra, Tocilizumab, methylprednisolone).

Histological assessment of a cutaneous excisional biopsy demonstrated a lymphoid infiltrate (CD3+, CD56+, TIA-1+, Granzyme-B+, EBER-ISH+) comprising small to medium-sized cells with irregular nuclei. 18F-FDG PET scan and bone marrow examination showed no further involvement (stage IE). The International Prognostic Index (IPI) was low risk (1 point; LDH 381 U/L).

Initial treatment for this locally advanced nasal-type NK/T-cell lymphoma consisted of a CHOP chemotherapy regimen plus Alemtuzumab and palliative plastic surgery of the destructed nasal tissue. Since no clinical response was observed after 5 cycles of chemotherapy, salvage chemotherapy (DHAP regimen) and radiotherapy were done. The patient has been selected to undergoing autologous stem cell transplantation.

CONCLUSION: Recalcitrant chronic sinusitis may be the initial presentation of nasal-type NK/T-cell lymphoma. A high index of suspicion, performance of repeat biopsies, and careful histological examination are crucial to prevent a delay in diagnosis.
LYMPHOMATOID PAPULOSIS ASSOCIATING MASSIVE EOSINOPHILIA AND FIP1L1-PDGFRα FUSION GENE

L Curto1, D Sitjas1, E Llistosella1, D López1, M García1, B Espinet2, L Florena2, F Gallado1, RM Pujol1

Departments of Dermatology1, Pathology2 and Cytogenetics3, Hospital del Mar. Barcelona.

Hypereosinophilic syndrome (HES) is a myeloproliferative disorder characterised by a sustained absolute eosinophil count > 1500/µl persisting more than 6 months without identifiable aetiology and organ damage. In some patients FIP1L1-PDGFR-alpha fusion protein has been detected.

A 25-year-old male presented a 2-year history of recurrent crops of and self-healing papules and ulcerated nodules on the trunk, extremities and oral mucosa. Histopathological and immunophenotypical features confirmed the diagnosis of lymphomatoid papulosis (LyP). Laboratory tests revealed massive peripheral eosinophilia (7900/mm3), elevated tryptase and vitamin-B12 serum levels. Bone marrow biopsy: hypercellularity with marked eosinophilia, atypical mast cells and reticulin fibrosis. CT scan showed splenomegaly. FIP1L1-PDGFR-alpha fusion gene was detected by FISH in peripheral blood cells. Treatment with imatinib mesilate was prescribed and a sustained response in both the abnormal haematological profile and LyP lesions was observed (follow-up period 6 months).

The association of LyP and HES secondary to FIP1L1-PDGFR-alpha has rarely been reported (3 previous reports). In two of such cases a complete remission of LyP lesions was noted after treatment with imatinib mesilate. The mechanisms implicated in such association remain obscure. A clonal T-cell population bearing the FIP1L1-PDGFR-alpha has rarely been identified in some HES cases. The possibility that such cells were responsible for induction of LyP lesions in patients with HES could be hypothesised.

PRECURSOR BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASIA

*Berti E, +Fanoni D, ^Novara F, +Onida F, ^Lucioni M.

*B full Prof. of Dermatology University of Milano-Bicocca,
+Fondazione Cà Granda IRCCS Ospedale Maggiore Policlinico Milan-Italy,
^Dept. of Human Pathology University of Pavia, IRCCS S.Matteo, Pavia.

Blastic plasmacytoid dendritic cell neoplasia (BPDCN) is an aggressive haematologic disorders showing localized or diffuse purpuric plaques and tumours, often with leukemic or systemic spread (median survival 23 months). We investigated 25 cases of BPDCN. We observed 2 familiar cases and the staging frequently showed a simultaneous visceral and leukemic involvement. We found a lower rate of bone marrow involvement in the group of patients with localized disease. Patients treated by CHOP regimen had shorter survival; while acute leukemia-type regimens, followed by stem cell transplantation, must be considered.

Two cases, with localized lesions, were treated by radiotherapy. Histologically, tumor cells show a blastic or pleomorphic cytomorphology with expression of CD4, CD45RA, CD56, CD123, TCL1 and CD2AP, except for some cases CD56 or CD4 negative or for 1 case showing CD3 positivity. Molecular analysis showed absence of TCR rearrangement and a peculiar set of chromosomal losses. Arrays-CGH studies confirmed that predominant genomic losses affected chromosomes 9 (71%), 13 (61%), 12 (57%), 5 (19%), 7 (19%), 14 (14%) and 15 (14%). The most frequent event was deletion of 9p21.3 (66%, 5 homozygous); long survivors never had homozygous loss. Loss of RB1 and CDKN1B locus were observed in 13 cases and of IKZF1/Ikaros in 5 of our patients.

INDOLENT CD8+ LYMPHOID PROLIFERATION OF ACRAL SITES: 7 CASES INCLUDING SOME ATYPICAL FEATURES


Department of Dermatopathology, St John’s Institute of Dermatology, St Thomas’ Hospital, London

Indolent CD8+ lymphoid proliferation is not currently recognised in the WHO-EORTC classification of cutaneous lymphomas. We describe seven cases, some with atypical features. Immunocytochemical and molecular studies were performed on all cases; four were stained for PD-1, CXCL-13 and ICOS. Four patients presented with solitary lesions on the ear or nose, two on the foot, and one developed multiple papules on the nose, arm and feet. Biopsies in five cases revealed a dense diffuse non-epidermotropic infiltrate of small to medium-sized atypical cells. In two cases there were Pautrier microabscesses. Neoplastic cells had a CD3+/CD8+/CD4-CD30-/TIA-1+ phenotype. Two cases were CD5- and a third CD5+. Granzyme B was positive in 20% of cells in one patient. All four cases tested were negative for PD-1, CXCL-13 & ICOS. The Ki-67 fraction was moderately high in 3 cases. TCR analysis was clonal in 5 cases, polyclonal in one and is awaited in the remainder. All tumours regressed following treatment with excision or radiotherapy. However, one patient has continued to develop new lesions.

This rare neoplasm presents a more variable clinical or histological pattern than originally described. Although it has been suggested to be a variant of cutaneous small/medium pleomorphic CD4+ T-cell lymphoma, the two are distinct.
TWO CASES OF BLASTIC PLASMACYTOID DENDRITIC CELL NEOPLASM WITH EXCLUSIVE SKIN LOCALIZATION TREATED WITH RADIOThERAPY

Piccinno R, Caccialanza M, Berti E, Onida F
Unit of Photoradiotherapy, Ouf Dermatology
Unit of Dermatology, University of Milano-Bicocca

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare haematological malignancy with common skin presentation. Since its usual aggressive behavior, chemotherapy and haematopoietic stem cell transplantation are considered the treatments of choice.

Two elderly male patients presented with a single cutaneous infiltrative plaque of the back. Histopathology revealed a BPDCN. Complete staging investigations excluded any extracutaneous involvement. The two men, poorly suitable for chemotherapy since their old age, were considered eligible for radiotherapy. Total dose administered was 30 Gy with complete remission of the skin lesions. The patients were strictly monitored and neither skin nor bone marrow relapses were observed after a follow-up of 7 months for the first patient, died following a brain hemorrhage, and of 25 months for the second, still alive.

Cytogenetic studies in BPDCN have shown that the deletion of 9p21.3 locus is the more frequent event and that homozygosis is associated to adverse prognosis. The arrays-CGH DNA analysis in our two patients demonstrated a monosomy 9 and the deletion of locus 12p13 in the first and a monosomy 10 and 12 and the deletion of locus 1q41-q44 and 22q12.1-q12.2 in the second.

The existence of a subset of the neoplasm with a better prognosis, potentially responsive to radiotherapy could be hypothesized, but needs further confirmation.

PRIMARY CUTANEOUS LYMPHOMAS AT UNIVERSITY DEPARTMENT OF DERMATOLOGY AND VENEREOLOGY, ZAGREB UNIVERSITY HOSPITAL CENTER, 2000-2010

Ceovic R, Pasic A, Lipozenic, Radman 1, Kostovic K, Rados J, Loncaric D

University Department of Dermatology and Venerology; Department of Hematology, University Department of Medicine, Zagreb University Hospital Center and School of Medicine, University of Zagreb, Zagreb, Croatia

Introduction: Primary cutaneous lymphomas (PCL) are defined as non-Hodgkin’s lymphomas (NHL) that present in the skin with no evidence of extracutaneous disease at the time of diagnosis.

Aim: Retrospective analysis of PCL patients treated during the 2000-2010 period.

Patients and methods: The study included 104 patients: 51 male patients aged 24-79 (mean age 51.5) and 53 female patients aged 33-91 (mean age 64). Mycosis fungoides (MF) was diagnosed in 82 (79%) patients. Other PCL types were diagnosed in 22 (21%) patients, as follows: cutaneous T-cell lymphoma other than MF in 10 and NHL B-phenotype in 6 (large B-cell lymphoma of lower extremities in 2 and small B-cell NHL in 4 patients). Patients with early stage MF (stages IA, IB and IIA) were treated with photochemotherapy (PUVA and Re-PUVA). Superficial radiotherapy was used in patients with pronounced plaque and tumor infiltrations. Patients with advanced MF stages or other lymphoma types were transferred to Department of Hematology, where they were treated with polychemotherapy.

Results: Complete remission was achieved in 16 (20%) and partial remission in 66 (80%) MF patients. The latter were closely followed up and readministered photochemotherapy (PUVA, Re-PUVA) and superficial radiotherapy as needed.

Conclusion: Early diagnosis of cutaneous NHL is of utmost importance. Nonaggressive dermatological therapy (PUVA, Re-PUVA and superficial radiotherapy) is effective in early stages of the disease. Full collaboration and team approach by dermatologist, hematologist, pathologist, oncologist and radiotherapist are necessary in the diagnosis and management of PCL.

t(8;9)(p22;p24)/PCM1-JAK2 Activates SOCS2/SOCS3 via STAT5 in Cutaneous Lymphoma Cells


Fusions of JAK2 with multiple partners occur in leukemia/lymphoma where they promote autonomous signalling. Affected entities are candidates for selective JAK/STAT inhibitor therapy.

We investigated JAK2-rearrangements in 200 peripheral T-cell lymphoma (PTCL) patients, and JAK2 signalling responses in cutaneous T-cell lymphoma (CTCL) cell lines. To identify downstream signalling effectors, siRNA was performed by lentiviral knockdown directed against JAK2 fusion mRNA, and gene expression changes investigated subsequently by realtime-PCR and western blotting.

We identified two patients with JAK2 rearrangements, confirming their rarity in PTCL. PCM1-JAK2 fusion was present in cell lines from a CTCL patient bearing (t(8;9)(p22;p24). PCM1-JAK2 cells expressed gene signatures combining JAK/STAT signalling with T-effector and autoimmune disease profiles and were conspicuously sensitive to selective JAK2 inhibitor (TG101348). Top targets of PCM1-JAK2 knockdown were upregulation of SOCS2 and SOCS3, and silencing of GATA3. Transcriptional inhibition by TG101348 mimicked PCM1-JAK2 knockdown, confirming JAK2 as the active moiety. Upregulation of SOCS2 and SOCS3 required activated pSTAT5 showing that neoplastic PCM1-JAK2 signalling resembles that of other JAK2 rearrangements.

Collectively, our data extend the paradigm of STAT5 activation by JAK2-translocations. We also identified the first JAK2-translocation cell lines, a resource for investigating JAK2 biology and therapeutics. Our data support investigation of SOCS genes, better known hitherto as tumor-suppressors, as JAK2 signalling effectors, prognostic indicators and potential therapeutic targets.
P-25
Poster withdrawn

P-26
BIOMED 2 multiplex T-cell receptor polymerase chain reaction protocol combined with heteroduplex analysis on Agilent bio-analyzer: interest in diagnosis of cutaneous T cell lymphoma
C Auzet¹, N Bonnet¹, JP Dales¹, MC Koeppel¹, J Gabert³, P Berbis¹
¹Department of Dermatology,
²Department of Pathology,
³Department of Molecular biology,
Hopital Nord, Université de la Méditerranée, Marseille, France
Molecular biology tools, allowing the detection of a dominant T-cell clonal pattern in skin biopsy, are useful in diagnosis of cutaneous T-cell lymphoma (CTCL), especially in early stages of the disease.
We assessed the diagnosis value of BIOMED-2 PCR assay combined with heteroduplex (HD) analysis on Agilent bio-analyzer in CTCL.
Clinical data and cutaneous samples obtained from consecutive patients with clinical suspicion of CTCL during a 4-years period were analysed with BIOMED-2 multiplex PCR and HD analysis by microcapillary electrophoresis on the Agilent 2100 bio-analyzer.
97 patients (23 CTCL and 74 benign inflammatory skin diseases) were included in the study. Specificity and sensibility of the Biomed-2 PCR method used was evaluated to 0.77 and 0.91 respectively. A monoclonal TCR gene rearrangement was observed in 69.5% of CTCL, 78.5% of mycosis fongoides and in 10.8% of BID. In CTCL, a trend to correlation between the detection of T-cell clonality and clinical staging was observed. Any dominant T-cell clone was noted in patients with parapsoriasis.
Our results are comparable to previous studies using Genescan screening and different separating method or primers. The good specificity of the method emphasizes its usefulness in diagnosis of CTCL.

P-27
HSP 70 kDa protein 1A inhibits histone deacetylase inhibitor-induced apoptosis
Fujii K, Suzuki N¹, Kaji T¹, Hamada T¹, Idogawa M², Kondo T³, Iwatsuki K¹
¹: Department of Dermatology, Okayama University, Okayama, Japan
²: Department of Medical Genome Sciences, Research Institute for Frontier Medicine, Sapporo Medical University, Sapporo, Japan
³: Division of Pharmacoproteomics, National Cancer Center Research Institute, Tokyo, Japan
To identify the possible targets to enhance the effects of histone deacetylase inhibitor (HDACi), we investigated the association between sensitivity against valproic acid (VPA) and proteomic features of the 33 lymphoid cell lines. We identified HSP 70 kDa protein 1A (HSPA1A) as the most upregulated protein in the VPA-resistant cell line groups, while its functional role in HDACi sensitivity remained largely unknown. First, we examined the combined effects of HDACi and a HSP 70 inhibitor, KNK437, on Jurkat cells. Treatment with 25 ug/ml of KNK437 alone did not have cytotoxic effects. In contrast, cotreatments with VPA and KNK437 resulted in considerable increase of annexin V-positive cells, compared with the treatments with VPA alone. KNK437 also significantly enhanced the apoptotic effects of vorinostat. Furthermore, HSPA1A overexpressed Jurkat cells were more resistant to VPA and vorinostat than control cell line. HDACi-induced apoptosis, detected by annexin V-staining, activation of caspase 3 and subG1 fraction, were markedly decreased in HSPA1A overexpressed cells, while reduction in mitochondrial membrane potential was observed. Thus, HSPA1A may protect against HDACi-induced apoptosis via mitochondrial pathway.
P-28
Ellipticine induced apoptosis in cutaneous T cell lymphoma - importance of p53
Cecilia Savorani, Valentina Manfé, Edyta Biskup, Vibeka Pless, Omid Niazi, Robert Gniadecki
Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark
In this work we explored the role of the tumor-suppressor p53 as possible therapeutic target in Mycosis fungoides (MF) and Sezary syndrome (SS), the most common types of cutaneous T-cell lymphoma (CTCL). Wild type p53 can be induced by the small molecule nutlin-3a, causing apoptosis. However, mutated p53 is resistant to nutlin. The aim of this project was to investigate whether mutated p53 can be activated in CTCL with ellipticine, a novel compound shown to be able to rescue mutant p53 transcription function.
We used CTCL cell lines with different p53 status: SeAx (SS cell line, mutated-p53 G245S), MyLa2000 (MF cell line, wildtype p53) and Hut-78 (leukemic CTCL, p53 deletion). As expected and previously reported (Manfé et al. J Invest Dermatol, 2012;135:1487) nutlin induced apoptosis and cellular senescence through a p53-dependent pathway only in MyLa. Ellipticine decreased cell viability by 30-45% in SeAx and MyLa in a time- and concentration-dependent manner. Expression of cleaved PARP by western blot analysis verified that apoptosis was the mode of cell death. No significant effect was observed in Hut. Combination of ellipticine with nutlin showed a synergistic activity in MyLa, but not in SeAx. p53 expression level increased after 5 pM ellipticine both in Myla and SeAx. However, neither p21 nor Bak expression were seen in SeAx. Transfection of SeAx with p53-siRNA reduced p53 but did not influence cell death. Thus, ellipticine is able to induce apoptosis in CTCL cells with mutated p53, but the mechanism of its action is at least partially independent of p53.

P-29
DIFFERENTIAL PROTEOMIC ANALYSIS IN PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA
Paulitschke V1, Eder J1, Jonak C1, Kunstfeld R1, Gerner C2, Trautinger F2
1) Department of General Dermatology, Medical University of Vienna, Austria; 2) Karl Landsteiner Institute of Dermatological Research, St.Pölten, Austria
Proteome profiling is an unbiased screening method with the potential to identify as yet unknown molecular mechanisms and biomarkers in human disease. This technique has not yet been applied in cutaneous lymphomas and we describe here initial results of the proteomic analysis in a primary cutaneous marginal zone lymphoma. Tissue was obtained from a cutaneous tumor of a 70-year-old male patient with primary cutaneous marginal zone lymphoma (pcMZL) and the whole sample was used for further analysis. Reference proteome profiles of fibroblasts, endothelial cells, and leukocytes were used for differential display of pcMZL specific proteins. Proteins were separated and identified by SDS page, proteolytic digest, nano-LC separation of peptides, and fragmentation analysis using an ion trap mass spectrometer. 30 proteins with a high specificity for the investigated tissue were identified. Among others these proteins included enzymes (Cathespin G, Lysozyme C), kinases (mitogen activated protein kinase 4, dual specificity protein kinase CLK3, tyrosin protein kinase BTK), cytokines (interleukin-18), proteoglykanes (decorin, osteoglycin), a DNA repair protein, and surface receptors (CD4, toll-like-receptor 4). These results provide the basis for further verification of the identified candidate proteins and for analysis for their relevance in the pathophysiology of pcMZL and related diseases.

P-30
Recombinant anti-CD3-diphtheria toxin fusion protein in patients with cutaneous T-cell lymphoma
Christoph Klade, Jurí Hodisch, Oleh Zahriychuk
AOP Orphan Pharmaceuticals AG
LAX-699 (recombinant anti-CD3-bi-single-chain-Fv-diphtheria toxin fusion protein) is a cytotoxic molecule produced consisting of a diphtheria toxin and two tandem sFv molecules derived from UCHT1 parental antibody. The action of LAX-699 occurs as a result of binding to the CD3 molecule on the cell surface, subsequent internalization, and enzymatic inhibition of protein synthesis leading to cell death. Phase I/II dose finding and explorative efficacy study has been initiated in patients with T-cell malignancies (both peripheral, PTCL and cutaneous, CTCL, T cell lymphoma), who have failed, were refractory or ineligible to approved treatment regimens. DLT has been defined as a drug-related non-hematologic toxicity of grade ≥3 severity or greater. MTD has been defined as the highest dose level yielding 0 to 1 out of 3 to 6 patients with a DLT. Dose levels of 20, 40 and 60 microG/kg were explored. Eleven CTCL patients are evaluable for response. Median number of previous treatments was 3 (range: 1-6). CTCL was in stage IB in 5, IIB in 4, IIIb in 1, and IV in 1; 2 complete remissions of 17 and 40+ months and 4 partial remissions of 1+ - 30+ months were observed. Drug-related toxicities were predominantly mild to moderate; most frequently, transient fever, chills, lymphopenia, transaminasemia, viremia, as also one case of severe vascular leak syndrome, occurred. The study drug has shown to be effective already in the dose finding Phase I setting. Dose escalation is ongoing. European phase Ib study is being planned to start late 2012.

P-31
PROTEASOME INHIBITION AS A NOVEL MECHANISM OF THE PROAPOPTOTIC ACTIVITY OF GAMMA-SECRETASE BLOCKER I IN CUTANEOUS T-CELL LYMPHOMA
Maria R. Kamstrup, Edyta Biskup, Valentina Manfé and Robert Gniadecki
Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Bispebjerg Bakke 23, Copenhagen-2400, Denmark
Notch signaling plays a pivotal role in the development of several hematologic malignancies. We have previously discovered that Notch1 is expressed on malignant T-cells in cutaneous T-cell lymphoma (CTCL) and is required for survival of CTCL cell lines. Notch can be inhibited by small molecule gamma-secretase blockers (GSI), which differ widely in their ability to induce apoptosis in CTCL. GSI I is very potent and reveal structural similarity to MG-132, a known proteasome inhibitor. Here, we demonstrate that in CTCL cell lines (MyLa, SeAx, JK, Mac1 and Mac2a) GSI I has proteasome blocking activity with potency comparable to proteasome inhibitors MG-132 and bortezomib. Activation of nuclear factor kB (NF-kB) is considered a crucial survival signal for CTCL and an important mechanism of action for proteasome inhibitors is inactivation of NF-kB. However, in this study we demonstrate an apparent activation of NF-kB after proteasome inhibition. Furthermore, we show that though the tumor suppressor protein p53 is induced during proteasome inhibition, it is dispensable for CTCL apoptosis since both SeAx cells, which harbor p53 mutations that attenuates its apoptotic capacity and HuT-78 cells, which have a deleted p53 gene, demonstrated potent apoptotic response. In conclusion, GSI I represents an interesting drug with dual mechanism of action comprising Notch and proteasome inhibition.
P-32
PRIMARY CUTANEOUS CD8+ AGGRESSIVE EPIDERMOTROPIC CYTOTOXIC T-CELL LYMPHOMA WITH BURKITT TRANSLOCATION AND CD158K/KIR3DL2 EXPRESSION
Ram-Wolf C1, Reguerre Y2, Rivet J3, Brice P4, Michel L5, Bensussan A6, Bagot M1.
Department of Dermatology1, Pathology2 and Hematology3, Inserm U9764, Saint Louis Hospital, Paris 7 University, Department of Hematology5, CHU d’Angers, Angers, France.

Primary cutaneous CD8+ epidermotropic cytotoxic T-cell lymphoma (CD8+ cytotoxic CTCL) is characterized by a very aggressive course and a poor prognosis. A 17 year-old man presented with diffuse papules and nodules of trunk and members in October 2009. Lesions were initially only cutaneous and spontaneously regressed. A cutaneous biopsy showed an atypical dense, dermal, very epidermotropic T lymphoid infiltrate, composed of medium and large CD3+, CD30-, CD8+, granzyme+ T cells. The patient was successively treated with interferon and targetin. Although initial efficiency, the disease progressed with occurrence of cutaneous tumors and adenopathies in September 2011. At that time, the disease was completely resistant to multiple lines of polychemotherapies and the patient died in January 2012. Cytogenetic analysis showed a t(8;14)(q24;q11) translocation, with juxtaposition of C-MYC-TCR alpha/delta, like Burkitt’s translocations. Flow cytometric analysis of T cells isolated from skin biopsy by enzymatic digestion and four-color direct immunofluorescence staining showed a strong CD158K/KIR3DL2 expression by all CD8+ lymphocytes isolated from the tumor lesion.

This case of CD8+ cytotoxic CTCL is completely unusual because of an initial indolent evolution simulating type D lymphomatoid papulosis. The secondary very aggressive course could be explained by the presence of a Burkitt-like translocation, which has never been reported in CTCL. Interestingly, it is the first time that the CD158k/KIR3DL2 receptor expression is described on malignant CD8+ cytotoxic CTCL. Thus, it could represent a potent biomarker and therapeutic target.

P-33
Rituximab/Bendamustine combination therapy is an effective alternative in the treatment of primary cutaneous large B-cell lymphoma, leg-type, in elderly patients
B. Arbacher-Stöger, R. Stadler
Department of Dermatology, Johannes Wesling Medical Centre Minden, Germany

Primary cutaneous large B-cell lymphoma, leg-type, is classified as a unique B-cell lymphoma in the WHO classification 2008 and associated with poor prognosis, especially for elderly patients with extensive involvement. According to international guidelines treatment comprises either radiotherapy or the combination therapy of rituximab and CHOP. However, the side effects associated with CHOP therapy, especially in elderly patients, could be life threatening. An alternative could be the less toxic combination regimen of bendamustine plus rituximab.

We report about three female patients, aged 80, 84 and 85 years, with extensive involvement of the right leg including the lower abdomen, the lower left leg, and the total right leg, partly with hemorrhagic appearance of the lesions. On day one the patients received 100 mg/m² bendamustine and 375 mg/m² rituximab and on day two 100 mg/m² bendamustine only. After 2 cycles of bendamustine plus rituximab all lesions dramatically regressed. 2 patients showed a complete remission after 3 cycles, 1 patient a partial remission. No major adverse effects were observed.

Bendamustine in combination with rituximab seems to be a safe and effective regimen for primary cutaneous large B-cell lymphoma, leg-type, in a group of elderly patients. Reference: Rigacci L et al., Bendamustine with or without rituximab for the treatment of heavily pretreated non-Hodgkin’s lymphoma patients: A multicenter retrospecive study on behalf of the Italian Lymphoma Foundation; Ann Hematol 2012 Feb 15 [Epub ahead of print]

P-34
THERAPEUTIC ATTITUDE AND EVOLUTION OF A PATIENT WITH T CELL-RICH B CELL LYMPHOMA
Caius Solovan, Flavia Baderca, Simona Mohor, Rodica Mihaescu
Department of Dermatology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania; Anatomopathology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania; Dermatology Clinic, County Hospital, Timisoara, Romania; Haematology, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania

Primary cutaneous T cell-rich B cell lymphoma is an extremely rare lymphoma and only few cases have been described in the english-language literature so far. We describe a 44 years old male patient presenting several red-purple, indurated, slightly boseleted surface tumor lesions, adherent to deep planes and disseminated on the trunk, arms and limbs. Histologic and immunohistochemistry findings were consistent with the diagnosis of T cell rich B cell diffused cutaneous lymphoma. The patient has followed a CHOP (doxorubicin, cyclophosphamide, vincristine and prednisone) treatment session and afterwards two R-CHOP (rituximab-doxorubicin, cyclophosphamide, vincristine and prednisone) treatment sessions, according to the WHO-EORTC protocol. Chemotherapy is well tolerated, and evolution in the first three sessions is favorable, reducing injuries in size. In literature, there are only a few cases regarding a systemic treatment of cutaneous B cell lymphoma with rituximab alone or in combination with chemotherapy, mostly in patients with relapsed disease with variable responses depending on histology and stage of disease. The patient will continue therapy until the completion of the six cycles, the prognosis being favorable due to the good response to chemotherapy after only 3 cycles.
P-35
MANAGEMENT OF HYPERLIPIDEMIA IN CUTANEOUS LYMPHOMA PATIENTS TREATED WITH BEXAROTENE


University Departments of Dermatology in *Kiel, 1Würzburg, 2Freiburg, 3Erfurt, 4Ludwigshafen, 5Münster, 6Mannheim, 7Dresden 8Tübingen, Germany and 9University Department of Dermatology, Zürich, Switzerland

Bexarotene is a retinoid X receptor specific retinoid registered for the treatment of cutaneous T-cell lymphoma (CTCL). Most commonly occurring side effects are hyperlipidemia and hypercholesterolemia. The average time for treatment response is 26 weeks. To achieve optimal treatment adherence an efficient side effect management is important.

From the Decog study network, 200 patients with various subtypes of CTCL were evaluated who have been treated with bexarotene. In addition to response evaluation the occurrence of side effects under bexarotene therapy and the respective management was evaluated comparing two differing side effect management strategies.

All patients were evaluated for the occurrence of serum lipid changes, graded by CTC-AE grades. Early treatment withdrawals, the maximum and cumulative dosage were calculated for both treatment strategies. Implementing a standardized lipid control management resulted in fewer grade III/IV adverse events and fewer treatment withdrawals than the original schedule. The introduction of standard algorithms for side effect management resulted in decreased rates of early treatment withdrawal. However the rate of dose limiting toxicity with respect to the proportion of patients who could tolerate bexarotene 300 mg/m² was not significantly affected.

P-36
Ten-year experience of bexarotene use and the regulation of plasma triglyceride levels by the retinoid X receptor

Liisa Väkevä, Marius Robciuc, Matti Jauhiainen, Christian Ehnholm, Annamari Ranki

Bexarotene is an oral retinoid that is currently used in the cutaneous manifestations of cutaneous T-cell lymphoma (CTCL). Retinoids belong to the steroid hormone family of molecules. The exact mechanism of action of bexarotene is unknown, but it binds to retinoid X receptors and induces dose dependent apoptosis of malignant T-cell lymphocytes. Literature on the efficacy, dosing and side effects of bexarotene is sparse. We have followed 37 patients with CTCL treated with bexarotene for 10 years. Bexarotene was equally effective as monotherapy or when combined with other treatment modalities, resulting in an overall response of approximately 75%.

The most common side-effect of bexarotene use was hypertriglyceridaemia. Elevated levels of triglycerides in plasma is an independent risk factor for the development of cardiovascular diseases. The mechanism of hypertriglyceridaemia is not completely understood. In rats, bexarotene elevates plasma triglyceride rich lipoproteins by inhibition of lipoprotein lipase (LPL) activity in the muscle. LPL is the rate limiting enzyme in the hydrolysis of plasma triglyceride rich lipoproteins. We have shown that the treatment of skeletal muscle cells with bexarotene inhibits LPL activity by upregulation of angiopterin-like 4 (Angptl4), a potent endogenous LPL inhibitor. Antibodies targeting Angptl4 have been used in mice to reduce plasma triglyceride levels. These antibodies applied to humans could benefit patients treated with bexarotene.

P-37
Multiforme-like skin eruptions under Bexarotene therapy in a patient with Sézary syndrome

Christina Mitteldorf, Michael Tronnier

Department of Dermatology, Venereology and Allergology, Klinikum Hildesheim GmbH, Hildesheim, Germany

We report about a 58-year-old female patient who has suffered from Sézary syndrome for three years. At the time of diagnosis the patient presented erythroderma with pruritus, hyperkeratosis of the palms and soles, generalized lymphadenopathy and fulfilled the diagnostic blood criteria.

We started an extracorporeal photopheresis (=ECP, one cycle every month) in combination with Prednisolone (to a maximum of 80mg/die) and Bexarotene (300 mg = 150 mg/m²/die). Bexarotene was given with the recommended co-medication L-Thyroxine and Fenofibrate. First, the therapy yield in a stabilization of the disease. Six month later the patient developed rapidly generalized multiforme-like skin lesions with scaling in the edges of the lesions, no purulatation. A skin biopsy confirmed the clinically suspected diagnosis of a drug reaction. Bexarotene therapy (including co-medication) was stopped and the dosage of Prednisolone was elevated. The skin lesions resolved in a complete remission within two weeks. Simultaneously, we initiated an interferon (INF) alpha therapy (9MIoE, 3 times a week), led to new skin eruptions with purulatation. Despite the absence of psoriasis in the patient’s history the diagnosis of psoriasis pustulosa was made by histology. We stopped INF and the eruptions healed completely. For further treatment of the Sézary syndrome we started a MTX therapy (20mg weekly). Under this therapy no new skin eruptions developed but only a moderate stabilization of her disease could be achieved. Because of the insufficient effect of the therapy and the uncertainty if the first described reaction was really due to Bexarotene or the co-medication, we decided to repeat this therapeutic approach. We started with Fenofibrate for one week without any skin eruptions and added Bexarotene later. After a few days the patient developed multiforme-like skin eruptions once again, which resolved spontaneously after discontinuation of the therapy.

We discussed two potential causes of the skin eruptions. On the one hand the patient could suffer also from pustular psoriasis triggered by Bexarotene or Fenofibrate and INF. This assumption is contradicted by a therapeutically effect of Bexarotene against psoriasis. Triggering of Psoriasis by Fenofibrate could not be excluded. On the other hand the patient could develop a real multiforme-like drug reaction under a therapy with Bexarotene and Fenofibrate, which was never reported before, but seems more likely in our view.
P-38
Positive Impact of Extracorporeal Photopheresis on Quality of Life in Patients with Chronic Graft-versus-Host Disease
FL Dignan 1,2, SA Aguilar 1, JJ Scarisbrick 1, BE Shaw 1,2, FJ Child 1
1 St John’s Institute of Dermatology, 2 The Royal Marsden NHS Foundation Trust, 3 University College London Cancer Institute, 4 University Hospital, Birmingham

Extracorporeal photopheresis (ECP) is recognised as a second-line treatment option for chronic graft-versus-host disease (GvHD). There are few reports of the effect of ECP on patients’ quality of life. We report a single-centre prospective study of patients undergoing fortnightly ECP. Response was assessed after six months of treatment using National Institutes for Health scoring criteria and reduction in immunosuppression. Patients completed a formal assessment of quality of life at baseline and after six months of treatment using the chronic GvHD symptom scale (cGvHD SS) and dermatology life quality index (DLQI).

Eighteen patients completed the cGvHD SS at baseline and after six months of ECP. The mean cGvHD SS was significantly lower after 6 months of ECP (22 compared to 36, p=0.012). Sixteen patients completed the DLQI at both time points. Baseline scores ranged from 0/30 to 15/30 with a median of 7/30. The mean score was significantly lower after 6 months of ECP treatment (3.4 compared to 6.9, p=0.009). 13/18 (72%) patients had a partial clinical response and 1 had a complete response. 9/15 (60%) patients receiving steroid therapy at baseline had a > 50% dose reduction. ECP may lead to an improvement in quality of life in patients with GvHD in addition to clinical response and reduction of immunosuppression.

P-39
HIF-1α-mediated regulation of Th17/Treg balance in the skin of cutaneous T cell lymphoma patients.
Alcántara-Hernández Marcela 1, Jurado-Santacruz Fermín 1, Pérez-Montesinos Gibrán 2, Peniche-Castellanos Amelia 3, Huerta-Yepez Sara 4, Bonifaz-Alfonzo Laura 4
1. Unidad de Investigación Médica en Inmunooquímica, Instituto Mexicano del Seguro Social
2. Doctorado en Inmunología, Instituto Politécnico Nacional
3. Hospital Dermatológico “Ladislao de la Pascua”
4. Servicio de Dermatología-Oncología, Hospital General de México
5. Unidad de Investigación en Enfermedades Oncológicas, Hospital Infantil de México “Federico Gómez”

Several types of lymphocyte differentiation have been reported in cutaneous T cell Lymphoma (CTCL), however it is not clear which CD4+ T cell response prevails and how does it affect the control or progression of the disease. Objective: To evaluate the fate of the CD4+ T cells present in the patients’ skin lesions as well as the role of the hypoxia inducible factor (HIF)-1α in the regulation of CD4+ T cell differentiation. Material and Methods: Skin biopsies from 39 patients diagnosed with CTCL were paraffin embedded or set in culture. The epidermis and dermis were separated and left untreated or treated with drugs that modulate HIF-1α activity. Cell suspensions were characterized and cytokines quantified by flow cytometry. Results: We found a Th17 dominant over T regulatory (Treg) profile in the CD4+ T cells of CTCL patients in which the expression of HIF-1α participates in the regulation of the Th17/Treg balance. Conclusions: We propose that the Th17/Treg balance mediated by HIF-1α could play an important role in the progression of the disease and this could have implication in the design of specific therapeutics.

P-40
Preceding, concurrent or sequential occurrence of various neoplastic lymphoproliferative disorders (NLPD) in patients with lymphomatoid papulosis: a case series.
Nikolaou V, Economidi A, Papadavid E, Marinos L, Stratigos A, Papadaki T, Antoniou C.
1. Lymphoma Clinic, “A Sygros” Hospital for Skin Diseases, University of Athens Medical School, Greece.
2. Hematopathology Department, “Evagelismos” Hospital, Athens, Greece.

Lymphomatoid papulosis (LyP) is a primary cutaneous CD30 positive lymphoproliferative disorder with an excellent prognosis. It has been reported that LyP may be associated with another type of cutaneous or systemic lymphoma in up to 20% of the cases. We analyzed a cohort of Greek patients, followed at “A. Sygros” Hospital Lymphoma Clinic, with histologically confirmed LyP, in terms of clinical, histological, immunohistochecmical and molecular findings, associated with a second NLPD. The group included twenty four patients (15 females and 9 males) with LyP followed up for a mean of 44.6 months (range 9-120 months). The mean age at diagnosis was 47 years. Ten patients had type A, 7 patients had type B and 4 patients had type C LyP. Two cases expressed a CD8+ immunophenotype with additional positivity for CD56 in one case. Three patients had regional LyP located on the forearm. Eight out of 24 patients (33.3%) were diagnosed with a second NLPD before (n=1), concurrently with (n=2) or after (n=5) the diagnosis of LyP. Mycosis fungoides (MF) was the commonest lymphoma (5 patients), followed by systemic non-Hodgkin lymphoma (2 patients with marginal zone lymphoma with transformation into a high grade diffuse large B-cell lymphoma and with peripheral T-cell lymphoma, respectively). One patient was diagnosed with coexistence of primary cutaneous anaplastic large-cell lymphoma and MF. There was one death, which occurred in a patient who had developed peripheral T-cell lymphoma one year after the diagnosis of MF. In our cohort the rate of development of a second NLPD was increased compared to the literature. These data emphasize the importance of regular follow up of all patients with LyP because of the potential association of the disease with various malignant lymphoproliferative disorders during its natural course.
P-41

Mycosis fungoides cases mimicking various inflammatory dermatoses

1 Economidi A, 1 Nikolaou V, 1 Papadavid E, 1 Marinos L, 1 Stratigos A, 1 Papadaki T, 1 Antoniou C.
2 Lymphoma Clinic, "A.Sygros" Hospital for Skin Diseases, University of Athens Medical School, Greece.
3 Hematopathology Department, "Evangelismos" Hospital, Athens, Greece.

Mycosis fungoides (MF) is a low-grade lymphoproliferative disorder and the most common cutaneous skin lymphoma. MF usually presents with erythematous macules with fine scale, that evolve into plaques and even tumors, after skin infiltration. In the past few years it has been called "the great masquerador", a title previously attributed to syphilis, since it can mimic more than 50 different clinical entities, especially in the early stages.

We present our clinic's experience on various cases of MF mimicking other inflammatory dermatoses including chronic classic or scalp psoriasis, alopecia areata, granuloma annulare. Since January 2001, 254 MF cases have been diagnosed and followed at the lymphoma clinic of "A. Sygros" Hospital for skin diseases. Biopsies from all cases have been submitted to the Hematopathology Department of "Evangelismos" Hospital, where, apart from the classic MF clinical types, histological, immunohistological and molecular findings established the diagnosis in 21 atypical cases (8.26% of the total cases), mimicking different skin diseases. Those included 11 patients with psoriasiform plaques distributed apart of the bathing suit area to the knees, elbows or scalp. One of those patients showed plaque stage large cell transformation after infliximab infusion. The rest of the cases included 2 cases of hypopigmented MF, 2 cases of ichthyosiform MF, 2 cases of alopecia areata like MF, 2 cases of MF accompanied by vasculitis, one case of granuloma annulare like MF and one case of sebhoareic dermatitis like MF. The atypical clinical cases of MF, although rare, can lead to misdiagnosis of the disease and inappropriate treatment. Clinicians should be aware of these unusual cases and biopsy every treatment resistant case of dermatologic disease.