Systemic therapies in CTCL

Tatyana Feldman, MD
Director,

T cell Lymphoma Program at JTCC

HUMC

Cutaneous Lymphoma

- CTCL
  - Mycosis Fungoides
  - CD30 Lymphoproliferative disorder – ALCL and LyP
  - Rare T cell lymphoma of the skin

Cutaneous B cell lymphoma

primary follicular

primary marginal zone

Goals of Treatment in advanced stage of MF

- Minimizing infections
- Relieving pruritus
- Improving skin appearance
- Improving quality of life

Threat of advanced CTCL

- Infection
- Transformation to Large T-cell Lymphoma
- Intense pruritus
- Social life interference

When is it appropriate to use systemic therapy

- When skin-directed therapy is not working
- When disease is advanced making skin-directed therapy unlikely to be successful (more advanced stage: tumors, ulcers, involvement of lymph nodes, Sézary syndrome)

What is systemic therapy

- Taken by other means than applied on the skin

Systemic therapy

- Biologic response modifiers
  - Interferons
  - Retinoid X receptor selective retinoids (rexinoids)
- Chemotherapy (alkylators, doxil, gemcytabine, methotrexate, pralatrexate)
- Immunotherapy
  - Pembrolizumab
  - Photopheresis
- Non-chemotherapy
  - HDACi (vorinostat, romidepsin)
  - Proteosome inhibitor (velcade)
  - IMID(lenalidomide)
- Targeted therapy
  - IL2-diphtheria toxin fusion protein(Ontak)
  - Drug-antibody conjugate(Brentuximab Vedotin)
  - Anti-CD52 antibody(Campath)

Bexarotene

- 94 patients , stage IIB-IVB
- ORR 45% (55% for higher dosing)
- Duration of response 299 days
- Side effects: hypertrygliceridemia with pancreatitis, hypothyroidism, headache

Duvic et al, JCO, Vol 19, 2001 May

Interferons

- IFN-alfa: OR 63% (CR% 15%) 3-6x10^6U qd-TIW, MTD 18x10^6U qd:
  - flu-like symptoms, depression

[1]Oncology 6:31, 1992 [2]J Clin Oncol 19: 376, 2001

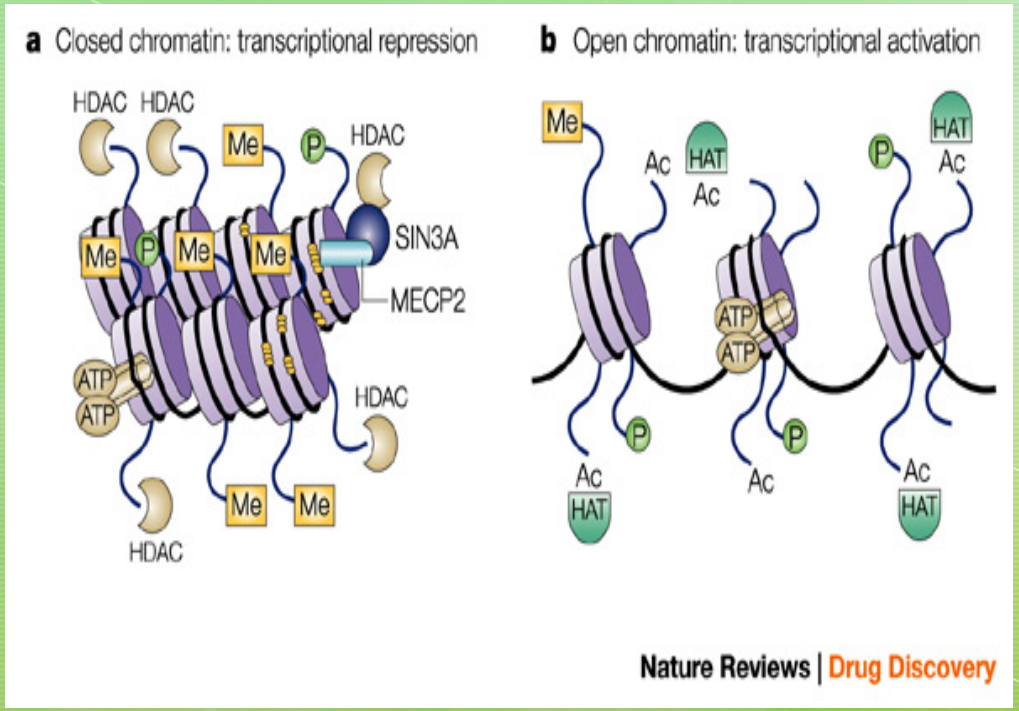
Ontak: denileukin diftitox

ALL CTCL
Stratified for CD25+ and CD25-
RR: 47% in CD25+
30% in CD25-
Duration of response more than 400 in negative and
More than 870 in CD25+

Can cause infusion reactions, swelling
Currently not available

Blood 06, Abstract #696

Histone deacetilation



Vorinostat: HDACi

33 patients on three schedules
No CR's
RR 31% and 33% in continuous groups
TTR 3.6 to 21.9 week (11.9 week)
Duration of response 9.4 to 19.4 (15.1 weeks)
Serious side effects in 37% (dehydration, thrombocytopenia, vomiting, anemia)
Administered as a tablet

Romidepsin: HDACi

- ORR 35%, Duration of response 15 mo, time to response 2 mo
- Control or pruritus up to 50%, long lasting responses
- Gastrointestinal side effects.
- Weekly dosing

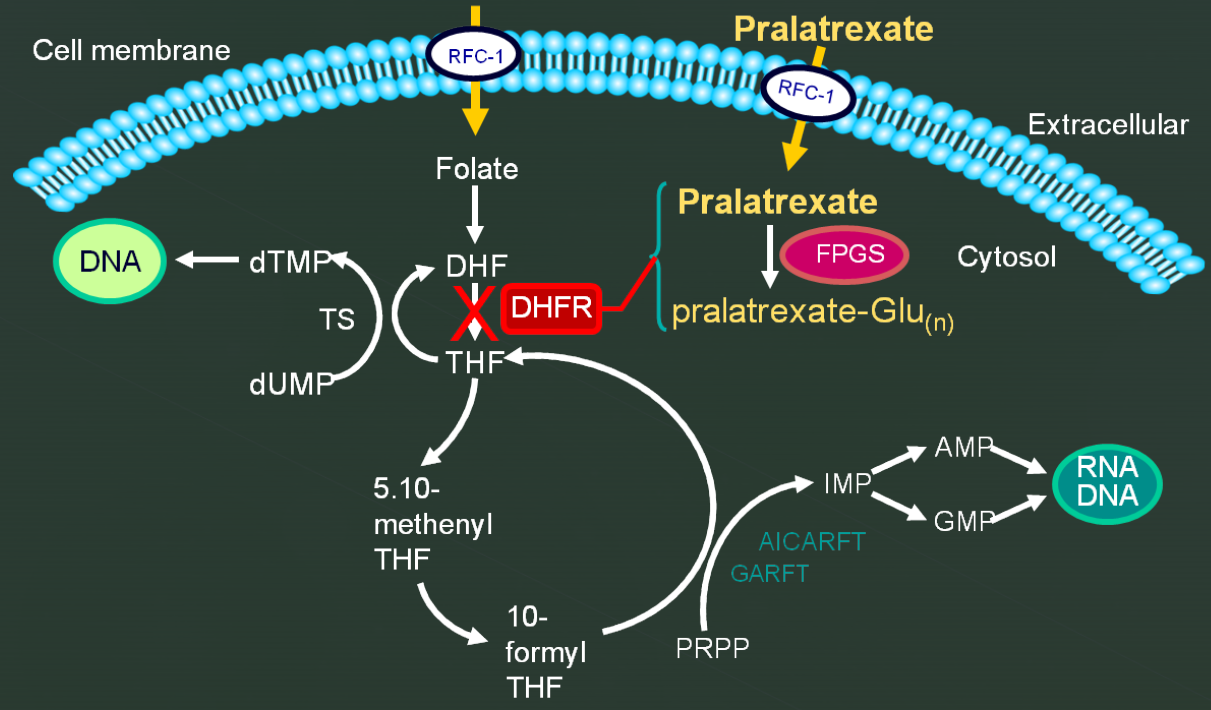
Campath-humanized IgG1 monoclonal antibody to CD52

- Two phase II studies:
- Lundin et al , Blood 2003
  - Campath 30 mg/m2 3xweek for 12 wks
    - **ORR > 50% (86% blood, 30% skin)**
      - Median PFS about 1 year
- Querfeld et al, Blood abstract#
- Cleared SS in 100%
- ORR 79%, CR 47%

- Infusion reactions, may cause severe infections

[3]Blood 101:4267, 2001 [4]Blood 94:902, 1999

Pralatrexate: Mechanism of Action



	DHFR inhibition K_i (pM)	Influx V_{max}/K_m	FPGS activity V_{max}/K_m
Pralatrexate	**13.4**	**12.6**	**23.2**
Methotrexate	**5.4**	**0.9**	**2.2**

> 10-fold Improvement in influx and polyglutamation

Phase II Study of Bortezomib in Refractory CTCL

- N = 15
- Bortezomib was given at 1.3 mg/m^2 IV push on days 1, 4, 8 and 11 every 21 days
- Patients were treated for up to a total of 6 cycles
- 12 patients were evaluable

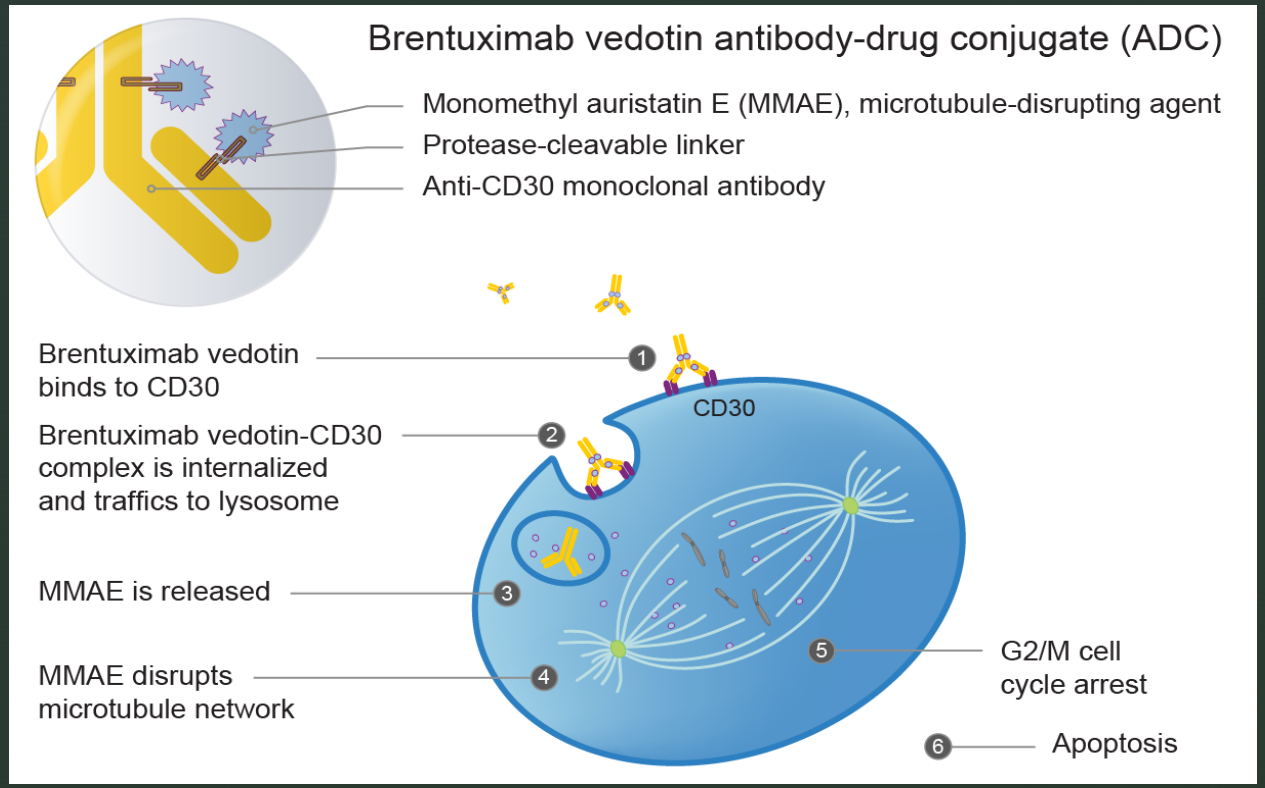
Results

- Efficacy
  - ORR = 8 (67%)
  - CR = 2
  - PR = 6
  - Median time to treatment failure = 9 months (range, 3-10)

- Small trial
- Diarrhea and neuropathy

Zinzani et al Blood 2006 vol 108 Abstract 2462

Brentuximab Vedotin

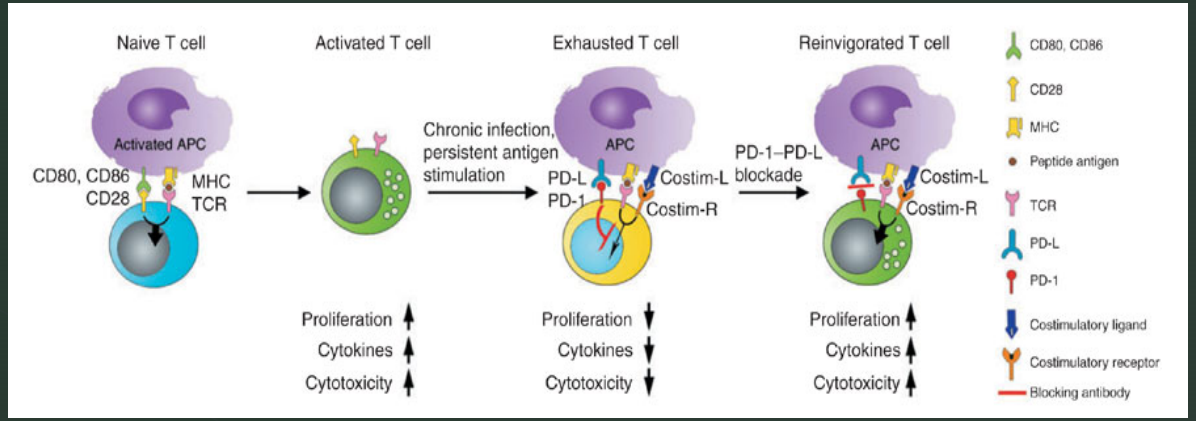


Younes A et al. *J Clin Oncol.* 2012;30(18):2183-2189

Adcetris: ALCL and CD30 positive MF

- 131 pts(97 with MF)
- ORR 60%, CR 19%, PFS 16mo
- Side effect: neuropathy
- Targeted therapy

Immunotherapy: Pembrolizumab



24 pts

Advanced stage

ORR 38%

Median PFS not reached

PFS at one year 69%

Ansell et al: N Engl J Med 2015; 372:311-319

Khodadoust, Blood 2016 128:181

Control of pruritus

- Successful disease treatment
- Systemic Prednisone
- Antihistamines, gabapentin, aprepitant, SSRi, naltrexon
- Minimizing colonization/treating infection of the skin
- Emollients

Infections

- Minimizing colonization of bacteria – staph
  - Skin culture
  - Mupirocin to nares
  - Hibiclens shampoo
  - Brief course of antibiotics
  - Suppressive antibiotics
  - Bleach bath

Identification of viral/fungal infections: shingles, Herpex simplex, candida.

Transformed MF

- More appropriate to use combination chemotherapy
- Allogeneic bone marrow transplant.

Conclusion

- Average responses for multiple existing medications: 30-40%
- Patient who achieved significant response may have it long-lasting
- We don’t know how to “match” patients with right medicine
- Need to develop novel therapies.