EARLY STAGE TREATMENT OPTIONS

THERESA PACHECO, MD

School of Medicine
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Theresa R. Pacheco, MD
Associate Professor
Department of Dermatology

GOALS

This activity is intended for patients and their families involved in the care of those with Mycosis Fungoides - Cutaneous T Cell Lymphoma (MF-CTCL).

The goal of this activity is to assess and summarize early stage treatment options of cutaneous lymphomas in clinical practice.

TREATMENT IN CTCL – MYCOSIS FUNGOIDES

There is no defined standard of care for early or late-stage disease in CTCL

Most cases of MF/SS are not curable, and many patients will require multiple therapies over time

NCCN® Practice Guidelines in Oncology – v.3.2007

Mycosis Fungoides/Sezary Syndrome
of the cutaneous T-cell lymphomas

Guidelines Index
NHL Table of Contents
Staging, MS, References

DIAGNOSIS

ESSENTIAL:
- Biopsy of suspicious skin sites
- Dermatopathology review of slides

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Immunohistochemical studies of skin biopsy[a] (CD2, CD3, CD4, CD5, CD7, CD8, CD26)
- Molecular study for T-cell receptor (TCR) gene rearrangements (assessment of clonality) of skin biopsy;[a] PCR methods
- Assessment of peripheral blood for Sezary cells (in cases where skin is not diagnostic, especially T4) including Sezary cell prep, flow cytometry and PCR for TCR gene rearrangement
- Biopsy of suspicious lymph nodes

→

WORKUP[b]

ESSENTIAL:
- Complete physical examination
  - Examination of entire skin: assessment of %BSA (palm plus digits ≈ 1%BSA) and type of skin lesion (patch/plaque, tumor, erythroderma)
  - Palpation of lymph node regions
  - Palpation of organomegaly/masses
- Laboratory studies:[c]
  - CBC with Sezary screen (manual slide review, "Sezary cell prep")
  - Sezary flow cytometric study (optional for T1); CD3, CD4, CD7, CD8, CD26 to assess for expanded CD4+ cells with increased CD4/CD8 ratio or with abnormal immunophenotype including loss of CD7 or CD26
  - TCR gene rearrangement of peripheral blood lymphocytes if Sezary Syndrome suspected
  - Comprehensive metabolic panel
  - LDH
- Imaging studies
  - Chest x-ray (in T1 or limited T2 where there is no indication of palpable adenopathy or blood involvement chest x-ray may be the only imaging study)
  - Neck/chest/abdominal/pelvic contrast-enhanced CT or integrated whole body PET/CT (≥ T2, large cell transformed or follicular MF, or with palpable adenopathy or abnormal laboratory studies)
  - Biopsy of suspicious lymph nodes (recommend assessment of clonality for all but particularly NCI LN 2-3) or suspected extracutaneous sites

USEFUL IN SELECTED CASES:[d]
- Bone marrow biopsy (not required for staging but used to document visceral disease in those suspected to have marrow involvement including B2 blood involvement and in patients with unexplained hematologic abnormality)

Stage IA	See Primary Treatment (MFSS-2)
Stage IB-IIA	See Primary Treatment (MFSS-3)
Stage IIB	See Primary Treatment (MFSS-4)
Stage III	See Primary Treatment (MFSS-5)
Stage IV	See Primary Treatment (MFSS-6)

[a]Pimpinelli N, Olsen EA, Santucci M, et al., for the International Society for Cutaneous Lymphoma. Defining early mycosis fungoides. J Am Acad Dermatol 2005;53:1053-1063

[b]See Revisions to the Staging and Classification of Mycosis Fungoides and Sézary Syndrome: A Proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Now in press in Blood 2007. Available as First Edition Paper, prepublished online May 31, 2007.

[c]Sezary syndrome (B2) defined by Sezary cell count ≥ 1,000/mL (Sezary cell prep) or expanded CD4+ cells with CD4/CD8 ratio ≥ 10, CD4+/CD7- ≥ 40%, or CD4+/CD26- ≥ 30% of lymphs in the presence of a positive clonal TCR gene rearrangement.

[d]Additional studies for related therapy: additional immunohistochemical studies - CD25, CD30 (targeted therapies), thyroid function studies (bexarotene therapy), lipid panel (systemic retinoid therapy).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT OF EARLY STAGE CTCL – MYCOSIS FUNGOIDES

Table II. Stage-related treatment options for refractory early-stage cutaneous T-cell lymphoma[a]

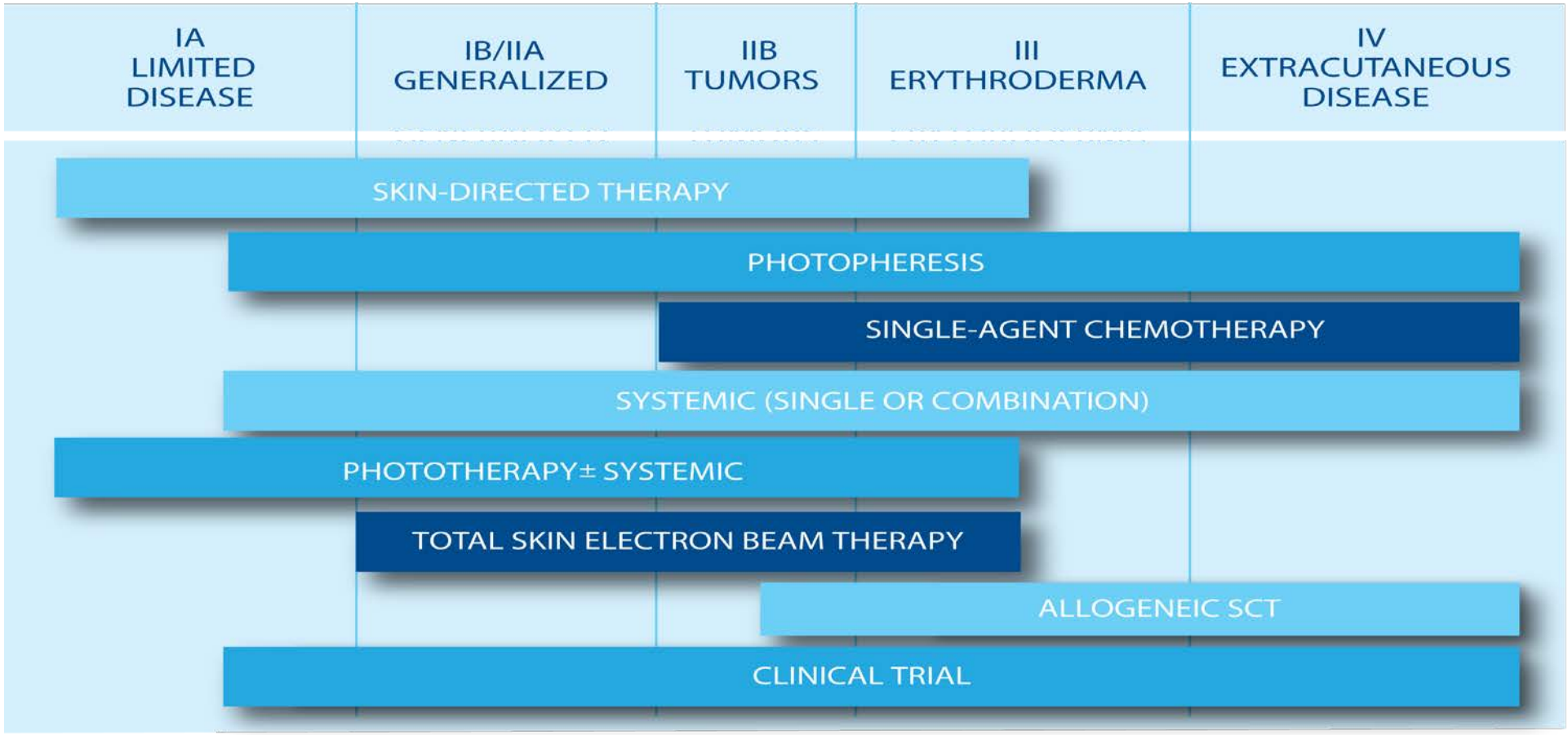
Stage	IA	IA	IB/IIA	IB/IIA
Clinical scenario	Unilesional	Limited patch-plaque (<10% of BSA)	Extensive patch	Extensive plaque
Treatment options	Topical corticosteroids Localized radiotherapy Topical chlormethine or carmustine Bexarotene gel	Topical corticosteroids Topical chlormethine or carmustine Bexarotene gel UVB (if only patches) PUVA PUVA + interferon-α Oral bexarotene ± PUVA	Topical corticosteroids (adjuvant only) Topical chlormethine or carmustine UVB (if only patches) PUVA PUVA + interferon-α Oral bexarotene ± PUVA Low-dose methotrexate	Topical corticosteroids (adjuvant only) Topical chlormethine or carmustine PUVA PUVA + interferon-α Oral bexarotene ± PUVA TSEB (only in specialized centers) ± adjuvant chlormethine Low-dose methotrexate

a Use of treatments lower in the column corresponds to increasing refractoriness of the disease.

BSA = body surface area; **PUVA** = psoralen + UVA; **TSEB** = total skin electron beam radiation.

American Journal of Clinical Dermatology- 2006

CURRENT CLINICAL MANAGEMENT OF CTCL DERIVED FROM NCCN PRACTICE GUIDELINES 2010



OVERVIEW OF CTCL – MYCOSIS FUNGOIDES

Skin Directed

- Topical corticosteroids

Topical chemotherapy
- Mechlorethamine (*Valchlor*)
- Carmustine (*BCNU*)

Topical retinoids
- Bexarotene gel (*Targretin* gel)

Phototherapy
- Narrow-band UVB (NBUVB)
- Psoralen with UVA (PUVA)

Radiation therapy
- Total-skin electron beam therapy (TSEBT)
- Site-directed radiation

Systemic

Vorinostat (ZOLINZA™)

Bexarotene capsules (*Targretin*)

Denileukin diftitox (*Ontak*)

Alemtuzumab (*Campath*)

Interferon-α

Extracorporeal photochemotherapy

Chemotherapy—single agent
- Chlorambucil (*Leukeran*)
- Cladribine (*Leustatin*)
- Fludarabine (*Fludara*)
- Methotrexate (*Trexall*, *Rheumatrex*)
- Gemcitabine (*Gemzar*)
- Pegylated doxorubicin (*Doxil*)
- Pentostatin (*Nipent*)

Combination chemotherapies
- CHOP, ESHAP, EPOCH

OVERVIEW OF SKIN DIRECTED TREATMENTS

Skin Directed

Topical corticosteroids

Topical chemotherapy
- Mechlorethamine (Valchlor gel)
- Nitrogen mustard (*Mustargen*)
- Carmustine (*BCNU*)

Topical retinoids
- Bexarotene gel (*Targretin* gel)

Phototherapy
- Narrow-band UVB (NBUVB)
- Psoralen with UVA (PUVA)

Radiation therapy
- Total-skin electron beam therapy (TSEBT)
- Site-directed radiation

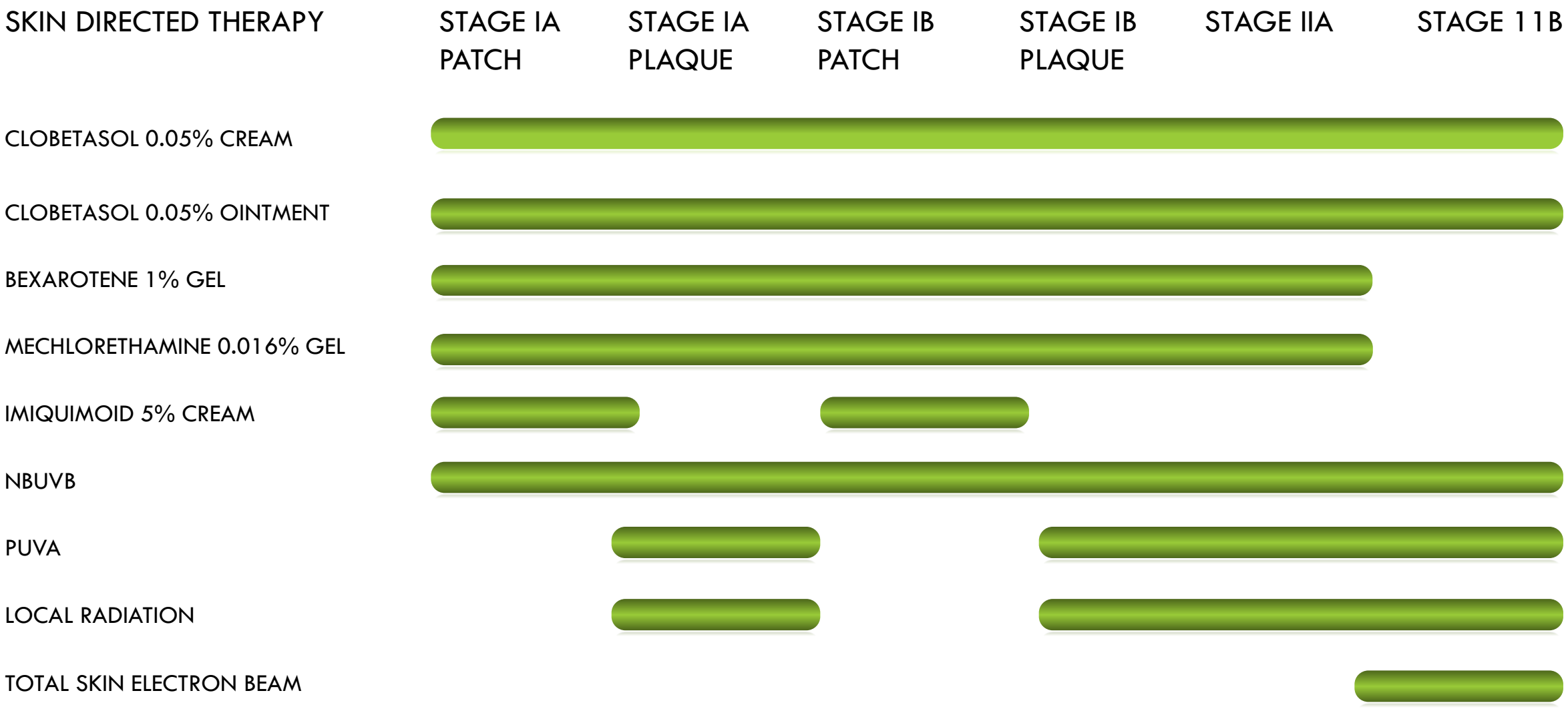
SKIN-DIRECTED THERAPIES ARE COMMON FOR EARLY-STAGE DISEASE

NCCN-suggested skin-directed therapy for CTCL	
Limited/localized skin involvement	**Generalized skin involvement**
Topical corticosteroids	Topical corticosteroids
Topical chemotherapy	Topical chemotherapy
Local radiation	Phototherapy
Topical retinoids	Total skin electron beam
Phototherapy	Extracorporeal photopheresis
Topical immune response modifier	Single-agent therapies

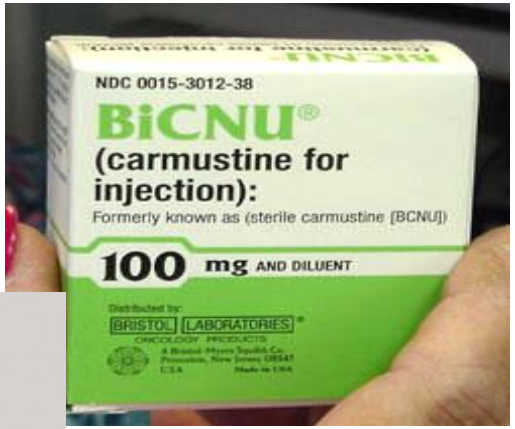
SKIN-DIRECTED THERAPIES ARE COMMON FOR EARLY-STAGE DISEASE

NCCN-suggested skin-directed therapy for CTCL	
Limited/localized skin involvement	**Generalized skin involvement**
Topical corticosteroids	Topical corticosteroids
Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)	Topical chemotherapy (mechlorethamine [nitrogen mustard], carmustine)
Local radiation (8-36 Gy)	Phototherapy (UVB, nbUVB for patch/thin plaques; PUVA for thicker plaques)
Topical retinoids (bexarotene, tazarotene)	Total skin electron beam (12-36 Gy) (reserved for those with severe skin symptoms or generalized thick plaque or tumor disease or poor response to other therapies)
Phototherapy (UVB, nbUVB for patch/thin plaques; PUVA for thicker plaques)	Extracorporeal photopheresis
Topical immune response modifier	Single-agent therapies (vorinostat; bexarotene; methotrexate)

SKIN-DIRECTED THERAPIES ARE COMMON FOR EARLY-STAGE DISEASE



SKIN-DIRECTED THERAPIES



CLASS I STEROIDS

Frequently used in early MF or an adjunct in more advance disease

T1 pts >90% response; T2 pts >80% response

- High potency (Class I) topical steroids under occlusion yield an the high response rate in early stage patients.

RXR RETINOID

Targretin (bexarotene) gel

- Targretin, the RXR selective retinoid, has been used in topical form.
- Bexarotene (Targretin): early stage MF (IA-IIA)
  - ORR 42-63% (58% response rate), CR-21%
    - The down side is the high incidence of irritant dermatitis (10-20%) and often requires concurrent use of topical steroids.

CHEMOTHERAPY – NITROGEN MUSTARD

Since its discovery of use in 1959, NM has been the most widely used topical (applied to the skin) chemotherapy in treating MF.

- Topical NM may be used as an aqueous (water)-based preparation, ointment-based preparation (mixed with Aquaphor), or as a propylene glycol gel-preparation.

- Mechlorethamine (*compounded*) ie: 1st line agent for patch/plaque stage
- T1 pts >93% response; T2 pts >72% response
- AE: contact hypersensitivities, hyperpigmentation, erythema, telangiectasias

TOPICAL CHEMOTHERAPY – NITROGEN MUSTARD

Mechlorethamine (*Valchlor*)

- New FDA-approved formulation
- 50-60% of VALCHLOR®(mechlorethamine) gel patients had an overall response compared with 46-48% of patients treated with compounded mechlorethamine ointment (comparator)

OFF-LABEL INDICATIONS FOR IMIQUIMOD

- Imiquimod is currently FDA-approved for treatment of external genital and perianal warts (1997), non hypertrophic actinic keratoses (2004), and superficial basal cell carcinoma (2004).
- Imiquimod has rapidly been recognized as a potential candidate for off-label use in over 60 conditions as presented in numerous case reports, letters, and small trials.
  - Imiquimod to rapidly and potently stimulate both innate and adaptive arms of the immune system.

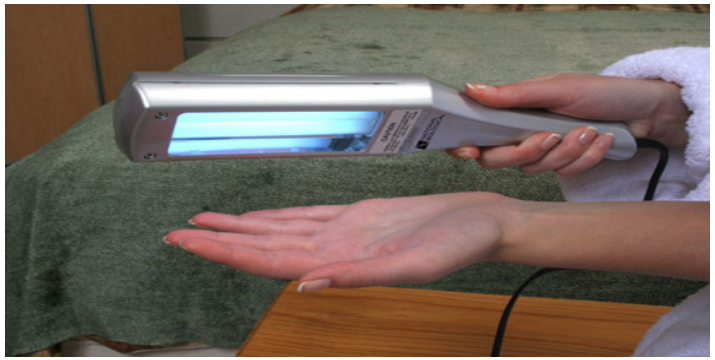
PHOTOTHERAPY – PUVA

PUVA may also be used as first-line therapy. It has a high rate of success, an 80% response rate.

- 1st line for early stage CTCL
- 85 pts with IA/IB: response of 95%
- IA-IIA, response in 80-90%, relapse common after tx or in maintenance therapy; disease progression cessation reported up to 43 months
- Beneficial in combination therapy (retinoids, INF-α)
- It will leave the damaged skin with an increased risk of skin cancer.

PHOTOTHERAPY – UVB

- Broadband (300-320 nm): 74% remission in stage I
- NBUVB (311-312 nm): 83% remission with early stage
  - NBUVB was made available in the USA in the 2000s for CTCL. UVB is effective, but mainly in patch stage disease.
    - It will leave the skin less damaged skin with an increased risk of skin cancer than PUVA.
    - It has become a favorite in early stage CTCL.



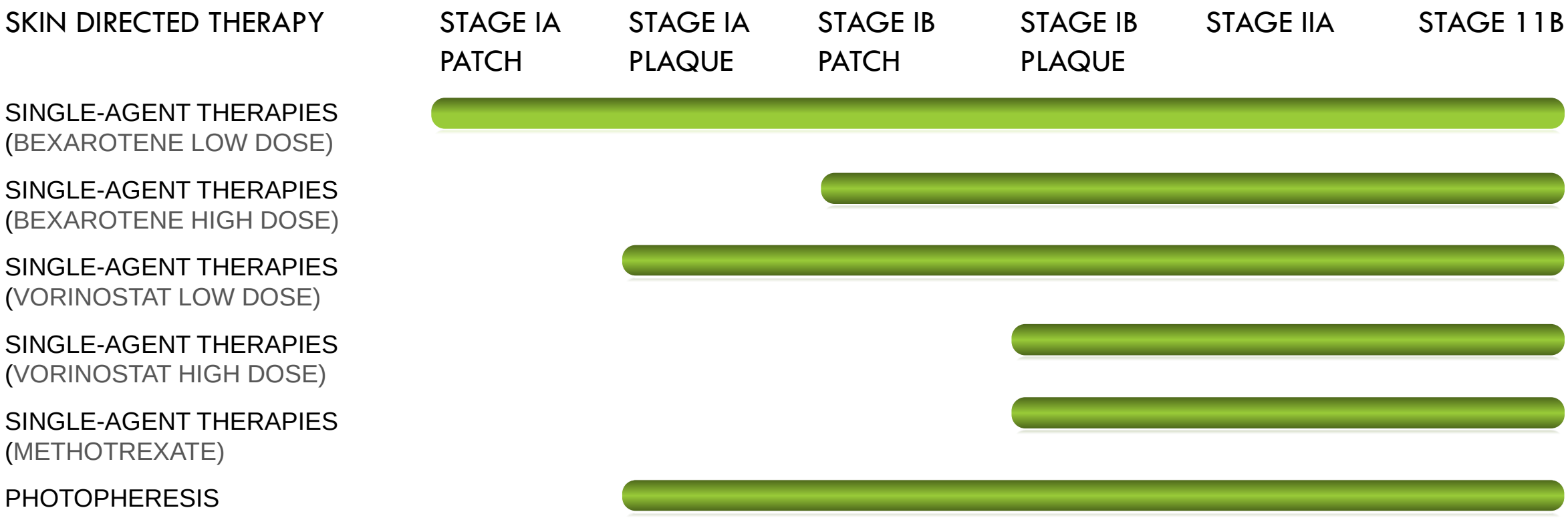
RADIATION THERAPY – ELECTRON BEAM

- Electron beam was developed in the 1950s for CTCL and is, therefore, the oldest treatment.
  - Highly effective in patients with skin-limiting disease but reserved for rapidly progressive or refractory disease
  - Energy of 4-6 MeV with total dose of 36 Gy over 8-10 weeks
  - T2-T3 disease- 75% ORR and 47% CR
  - AE: erythema, scale, hair loss, nails or sweat gland dysfunction
  - May consider local radiation for isolated tumors

SYSTEMIC THERAPIES CAN BE USED FOR EARLY-STAGE DISEASE

NCCN-suggested systemic therapy for early stage CTCL	
Limited/localized skin involvement	**Generalized skin involvement**
Extracorporeal photopheresis	Extracorporeal photopheresis
Single-agent therapies (vorinostat; bexarotene; methotrexate)	Single-agent therapies (vorinostat; bexarotene; methotrexate)

SYSTEMIC THERAPIES CAN BE USED FOR EARLY-STAGE DISEASE



CTCL – MYCOSIS FUNGOIDES SUMMARY

CTCL is a primarily indolent, heterogeneous group of NHL localized to the skin

CTCL is a primarily indolent, heterogeneous group of NHL localized to the skin

Disease stage influences the management of CTCL