Complete Summary

GUIDELINE TITLE

Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas.

BIBLIOGRAPHIC SOURCE(S)

Whittaker SJ, Marsden JR, Spittle M, Russell Jones R. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol 2003 Dec;149(6):1095-107. [67 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

On March 15, 2006, Ligand Pharmaceuticals and the U.S. Food and Drug Administration (FDA) notified healthcare professionals of changes to the WARNINGS section of the prescribing information for Ontak (denileukin diftitox), indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma. Loss of visual acuity, usually with loss of color vision, has been reported following administration of Ontak. While recovery was reported in some of the affected patients, most patients reported persistent visual impairment. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **
SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Primary cutaneous T-cell lymphomas (specifically, mycosis fungoides and Sézary syndrome)

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Dermatology
Family Practice
Internal Medicine
Oncology
Pathology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide evidence based guidance for the management of patients with primary cutaneous T-cell lymphoma

TARGET POPULATION

Patients with primary cutaneous T-cell lymphoma, specifically mycosis fungoides and Sézary syndrome

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Diagnosis

1. Skin biopsy
2. Blood counts
    - Total white cell
    - Lymphocytes
    - Sézary cell counts
    - Lymphocyte subsets, CD4/CD8 ratios
3. Human T-cell lymphotropic virus (HTLV)-I serology

4. Blood chemistry
    - Serum lactate dehydrogenase (LDH)
    - Liver function
    - Renal function
5. Computed tomography (CT) scan
6. Bone marrow aspirate or trephine biopsies
7. Immunophenotypic studies
8. T-cell receptor (TCR) gene analysis
9. Classification according to World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC) classification

Clinical Management

1. Central panel review of pathology
2. Patient review by multidisciplinary team

Treatment

1. Topical therapy
    - Corticosteroids
    - Mechlorethamine
    - Carmustine (BCNU)
    - Targretin (bexarotene) gel
    - Peldesine cream (considered but not recommended)
2. Phototherapy
    - Photochemotherapy (psoralen+ ultraviolet A [PUVA])
    - Broadband and narrowband UVB
    - High-dose UVA1 phototherapy
3. Radiotherapy
    - Low-dose, superficial orthovoltage radiotherapy
    - Whole body total skin electron beam (TSEB) therapy
4. Immunotherapy
    - Alpha-interferon
    - Interleukin-2 (considered but not recommended)
    - Gamma-interferon (considered but not recommended)
    - Cyclosporin (considered but not recommended)
5. Chemotherapy
    - Chlorambucil
    - Methotrexate
    - Etoposide
    - 2-deoxycoformycin
    - 2-chlorodeoxyadenosine
    - Fludarabine
    - Gemcitabine
    - Liposomal doxorubicin and gemcitabine
    - Multiagent chemotherapy
    - Allografts
    - Autografts
6. Monoclonal antibody therapy (fusion proteins)
    - Denileukin diftitox
7. Retinoids
    - Oral bexarotene (Targretin)

8. Extracorporeal photopheresis

MAJOR OUTCOMES CONSIDERED

- Treatment response rate and response duration
- Prognosis
- Side effects of therapy
- Disease free and overall survival
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

I: Evidence obtained from at least one properly designed, randomized controlled trial

II-i: Evidence obtained from well designed controlled trials without randomization

II-ii: Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one centre or research group

II-iii: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

IV: Evidence inadequate owing to problems of methodology (e.g. sample size or length or comprehensiveness of follow-up or conflicts of evidence).

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This guideline was generated by the U.K. Cutaneous Lymphoma Group (UKCLG) which is multidisciplinary and includes medical and clinical oncologists, haemato-oncologists, haematologists and dermatopathologists.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendation Grades

A. There is good evidence to support the use of the procedure.
B. There is fair evidence to support the use of the procedure.
C. There is poor evidence to support the use of the procedure.
D. There is fair evidence to support the rejection of the use of the procedure.
E. There is good evidence to support the rejection of the use of the procedure.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines are edited by the Therapy Guidelines and Audit Sub-committee (TGA) and subsequently returned to the task force for revision. The approved draft version is published in the quarterly British Association of Dermatologists (BAD) newsletter, and all BAD members are given the opportunity to respond, positively or negatively, but hopefully helpfully, within three months of publication. Finalised guidelines are approved by the TGA and the Executive Committee of the BAD and finally published in the *British Journal of Dermatology*.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Levels of evidence **(I-IV)** and grading of recommendations **(A-D)** are defined at the end of the Major Recommendations field.

Initial Assessment

- Repeated skin biopsies (ellipse rather than punch) are often required to confirm a diagnosis of cutaneous T-cell lymphoma (CTCL).
- Histology, immunophenotypic, and preferably T-cell receptor (TCR) gene analysis should be performed on all tissue samples (ideally molecular studies require fresh tissue).
- All patients (with the possible exception of early stage mycosis fungoides [stage IA] and lymphomatoid papulosis) should ideally be reviewed by an appropriate multidisciplinary team (MDT) for confirmation of the diagnosis and to establish a management strategy.
- Initial staging computed tomography (CT) scans are required in all patients with the exception of those with early stages of mycosis fungoides (stage IA/IB) and lymphomatoid papulosis.
- At diagnosis peripheral blood samples should be analysed for total white cell, lymphocyte, and Sézary cell counts, serum lactate dehydrogenase (LDH), liver and renal function, lymphocyte subsets, CD4/CD8 ratios, human T-cell lymphotropic virus (HTLV)-I serology and, preferably, TCR gene analysis.
- Bone marrow aspirate or trephine biopsies are required for CTCL variants (with the exception of lymphomatoid papulosis) and may also be appropriate for those with late stages of mycosis fungoides (stage IIB or above). **(Grade A/Level III)**

Histology

- The presence or absence of epidermotropism should be documented.
- The depth of the infiltrate should be noted.
- The morphology or cytology of the atypical cells and presence of large cell transformation, folliculotropism, syringotropism, granuloma formation, angiocentricity, and subcutaneous infiltration should be mentioned.
- Immunophenotypic studies should be performed on paraffin-embedded sections and include the T-cell markers CD2, CD3, CD4, CD8, B-cell marker CD20, and the activation marker CD30. Additional markers such as p53 may have prognostic significance in mycosis fungoides. Markers of cytotoxic function such as TIA-I, the monocyte/macrophage marker CD68 and natural killer (NK) cell marker CD56 may be useful for specific CTCL variants.
- Ideally all pathology results should be reviewed by a central panel (usually within cancer centres) as recommended for specialized pathology services.
- The histology, after correlation with the clinical features, should be classified according to an integration of the World Health Organization (WHO) and European Organization for Research and Treatment of Cancer (EORTC classification). **(Grade A/Level III)**

Prognosis

- Prognosis in mycosis fungoides (and clinical variants) is related to age at presentation (worse if >60 years), to the stage of the disease, and possibly to the presence of a peripheral blood T-cell clone; some mycosis fungoides clinical variants may have a better prognosis.
- In Sézary syndrome the median survival is 32 months from diagnosis.
- Primary cutaneous CD30+ lymphoproliferative disorders without peripheral nodal disease have an excellent prognosis (range 96-100% 5-year survival).
- The prognosis of other types of CTCL is generally poor with the frequent development of systemic disease. **(Grade A/Level IIii)**

Mycosis Fungoides and Sézary Syndrome

Also see Table below.

- Skin-directed therapy (topical therapy, superficial radiotherapy, and phototherapy) is appropriate treatment for patients with early stages of mycosis fungoides (stages IA-IIA) with the choice of therapy dependent on the extent of cutaneous disease and plaque thickness. **(Grade A/Level I)**
- Combined psoralen + ultraviolet A (PUVA) and alpha-interferon therapy can be effective for patients with resistant early-stage disease (stage IB-IIA). **(Grade A/Level IIi)**
- Patients with later stages of mycosis fungoides (stage IIB or higher) will require some form of systemic therapy. **(Grade A/Level IIii)**
- CTCL is a very radiosensitive malignancy and several fractions (2-3) of low energy (80-120 kV) superficial radiotherapy are appropriate for many patients. **(Grade A/Level IIii)**
- Chemotherapy regimens in advanced stages of mycosis fungoides generally achieve complete responses in the region of 30% but these are short-lived. **(Grade B/Level IIii)**
- Erythrodermic CTCL patients should be considered for immunotherapy and extracorporeal photopheresis (ECP), as responses to chemotherapy are generally poor. **(Grade A/Level IIii)**
- Total skin electron beam (TSEB) therapy is an effective treatment for stage IB and stage III mycosis fungoides but is not sufficient alone for stage IIB disease or those with significant haematological involvement. **(Grade A/Level IIi)**
- New agents such as bexarotene and denileukin diftitox offer important therapeutic alternatives which are currently being evaluated. **(Grade A/Level IIii)**
- In treatment-resistant cases of late stage disease, palliative radiotherapy and/or chemotherapy may produce a significant short-term benefit but the patient's quality of life should always be given priority. **(Grade B/Level III)**
- All patients and especially those with late stages of disease (>IIA) should be considered for entry into well designed randomized controlled clinical trials.

Table. Treatment of mycosis fungoides/Sézary syndrome

Stage	First line	Second line	Experimental	Not suitable
IA	SDT or no therapy	SDT or no therapy	Bexarotene gel	Chemotherapy
IB	SDT	alpha-interferon + PUVA, TSEB	Denileukin diftitox, bexarotene	Chemotherapy

Stage	First line	Second line	Experimental	Not suitable
IIA	SDT	alpha-interferon + PUVA, TSEB	Denileukin diftitox, bexarotene	Chemotherapy
IIB	Radiotherapy or TSEB, chemotherapy	alpha-interferon, denileukin diftitox*, bexarotene	Autologous PBSCT, mini-allograft	Cyclosporin
III	PUVA ± alpha-interferon, ECP ± alpha-interferon, methotrexate	TSEB, bexarotene, denileukin diftitox,* chemotherapy, alemtuzumab	Autologous PBSCT, mini-allograft	Cyclosporin
IVA	Radiotherapy or TSEB, chemotherapy	alpha-interferon, denileukin diftitox,* alemtuzumab bexarotene	Autologous PBSCT, mini-allograft	Cyclosporin
IVB	Radiotherapy, chemotherapy	Palliative therapy	Mini-allograft	

PBSCT, peripheral blood stem cell transplant; ECP, extracorporeal photopheresis; TSEB, total skin electron beam; PUVA, psoralen + ultraviolet A; SDT, skin-directed therapy including topical emollients, steroids, mechlorethamine, carmustine, bexarotene gel, UVB/PUVA, superficial radiotherapy. Stage III includes Sézary syndrome, although some cases of Sézary syndrome will be stage IVA. ECP is ideal for those patients with peripheral blood involvement.

*Not yet licensed in Europe.

Definitions:

Levels of Evidence

I: Evidence obtained from at least one properly designed, randomized controlled trial

II-I: Evidence obtained from well designed controlled trials without randomization

II-ii: Evidence obtained from well designed cohort or case-control analytic studies, preferably from more than one centre or research group

II-iii: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

IV: Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts of evidence)

Recommendation Grades

A. There is good evidence to support the use of the procedure.
B. There is fair evidence to support the use of the procedure.
C. There is poor evidence to support the use of the procedure.
D. There is fair evidence to support the rejection of the use of the procedure.
E. There is good evidence to support the rejection of the use of the procedure.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Consistent quality of care for patients with primary cutaneous T-cell lymphoma

POTENTIAL HARMS

- *Mechlorethamine*: The aqueous is relatively unstable, and the ointment base, which is more of an irritant than the aqueous solution, can cause irritant or allergic dermatitis in sensitized individuals.
- *Carmustine (BCNU)*: Hypersensitivity reactions occur less often (5-10%) than with mechlorethamine. All patients treated topically with BCNU should have regular monitoring of their full blood count; treatment is normally given for only a limited period, depending on the extent of the treated area (2-4 weeks for extensive areas) to avoid myelosuppression.)
- *Phototherapy*: Many patients will inevitably have a high total cumulative ultraviolet A (UVA) dose and the risks of nonmelanoma skin cancer are consequently increased for these patients.
- *Total skin electron beam (TSEB) radiation therapy*: Adverse effects include temporary alopecia, telangiectasia, and skin malignancies.
- *Denileukin diftitox*: Adverse effects include fever, chills, myalgia, nausea and vomiting, and a mild increase in transaminase levels. Acute hypersensitivity reactions occurred in 60%, invariably within 24 hours and during the initial infusion. A vascular leak syndrome characterized by hypotension, hypoalbuminaemia, and oedema was defined retrospectively within the first 14 days of a given dose in 25% of patients. Myelosuppression is rare. Five percent of adverse effects are severe or life threatening.
- *Bexarotene (Targretin)*: Side effects are transient and generally mild, but most patients require treatment for hyperlipidaemia and central (hypothalamic) hypothyroidism while on therapy.

- Chemotherapy: The numerous very significant severe side effects of chemotherapy are outside the scope of the guideline but include nausea, vomiting, diarrhoea, hair loss and cytopenias with consequent infections.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Mechlorethamine must not be used during pregnancy.
- Maintenance therapy with carmustine is contraindicated.
- Chemotherapy should not be used in patients with early stage IA, IB, or IIA disease.

Note: Refer to the original guideline document for detail and references.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists and the U.K. Cutaneous Lymphoma Group (UKCLG) and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not be necessarily deemed negligent.
- It is important that these guidelines are used appropriately in that they can only assist the practitioner and cannot be used to mandate, authorise, or outlaw treatment options. Of course it is the responsibility of the practising clinician to interpret the application of guidelines, taking into account local circumstances.
- Guidelines are inherently a fluid, dynamic process and will be updated on the British Association of Dermatologists (BAD) Web site on a regular basis.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

End of Life Care
Getting Better
Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Whittaker SJ, Marsden JR, Spittle M, Russell Jones R. Joint British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous T-cell lymphomas. Br J Dermatol 2003 Dec;149(6):1095-107. [67 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Dec

GUIDELINE DEVELOPER(S)

British Association of Dermatologists - Medical Specialty Society

SOURCE(S) OF FUNDING

British Association of Dermatologists

GUIDELINE COMMITTEE

U.K. Cutaneous Lymphoma Group (UKCLG)

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: S.J. Whittaker, St. John's Institute of Dermatology, St. Thomas' Hospital, London; J.R. Marsden, Department of Dermatology, Selly Oak Hospital, Birmingham; M. Spittle, Department of Oncology, Middlesex Hospital, Mortimer St; R. Russell Jones, Department of Dermatology, Ealing Hospital, Southall

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr Sean J. Whittaker has previously acted as an expert witness for Ligand Pharmaceuticals with regard to European licensing applications for bexarotene gel and denileukin diftitox.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Griffiths CE. The British Association of Dermatologists guidelines for the management of skin disease Br J Dermatol. 1999 Sep;141(3):396-7.

Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on April 19, 2005. The information was verified by the guideline developer on June 27, 2005. This summary was updated by ECRI on March 24, 2006 following the U.S. Food and Drug Administration (FDA) advisory on Ontak (denileukin diftitox).

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