Annals of Oncology 18 (Supplement 2): ii61–ii62, 2007
doi:10.1093/annonc/mdm040

Primary cutaneous lymphomas: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

incidence

The incidence of primary cutaneous lymphomas in the European Union reaches 1/100 000 per year. Primary cutaneous lymphomas originate in the skin and they are restricted to the skin. Secondary cutaneous lymphomas are manifestations of lymphomas of nodal or extranodal origin. Primary cutaneous lymphomas include various lymphoproliferative disorders: 65% are cutaneous T-cell lymphomas (CTCL), 25% are cutaneous B-cell lymphomas (CBCL), and the remaining 10% include rare subtypes.

diagnosis

Pathological diagnosis should be made according to the new World Health Organization/European Organization for Research and Treatment of Cancer classification. A surgical specimen providing enough material also for fresh frozen samples is preferred over punch biopsies. Reactive lymphatic processes have to be ruled out carefully, taking into account their possible clonal nature.

staging and risk assessment

History, clinical findings, laboratory parameters, and imaging techniques (ultrasound of abdomen and major lymph node regions or computed tomography scans) are necessary to exclude extranodal manifestations or an extranodal origin therapy. Prognosis is extremely variable depending on the exact subtype, origin, and stage of the lymphoma.

treatment plan

Due to the heterogeneity and rarity of the disease, most recommendations are not on the basis of high-level evidence. Treatment requires close cooperation with a center experienced in dermatology and oncology.

treatment of CTCL/mycosis fungoides/Sézary syndrome/CD30+ CTCL

Options in early stages are local treatment with topical steroids, Psoralen with UV-A irradiation (PUVA), and soft X-ray or electron beam irradiation. For more advanced stages, PUVA combined with retinoids [II, B] including bexarotene or interferon [III, B] may be considered before the use of chemotherapy such as chlorambucil, methotrexate (MTX), 2-chlorodeoxyadenosine, or combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) -like regimens. Denileukin difitox may be considered in refractory disease[II, B]. In CD30+ (mostly large cell) lymphoproliferative disease, low-dose MTX is the preferred systemic treatment (Bekkenk).

treatment of low-grade cutaneous B-cell (follicle center cell and marginal zone) lymphomas

Because of a usually excellent prognosis, overtreatment must be avoided [II, A]. Surgical removal alone may be adequate. Intralesional rituximab has been effective in single cases. Systemic rituximab is considered an adequate first-line therapy for disseminated primary indolent cutaneous lymphoma [III, A]. For secondary cutaneous lymphomas, therapy often has to be tailored mainly to the noncutaneous manifestations.

treatment of diffuse large-cell CBCL

Radiotherapy may be considered for isolated or grouped lesions [III, B]. Because of a less favorable prognosis, CHOP combined with rituximab is recommended in patients with widespread disease [II, A].

response evaluation

History and clinical inspection are recommended. Radiological examinations are only useful if extracutaneous manifestations were present at diagnosis or were clinically suspected [V, D].

follow-up

There is no proof that close monitoring with laboratory or radiological tests influences survival.

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via La Santa 7, CH-6962 Viganello-Lugano, Switzerland

Approved by the ESMO Guidelines Working Group: December 2006.

Table 1. WHO–EORTC classification of cutaneous lymphomas with primary cutaneous manifestations

	5-year overall survival
Cutaneous T-cell and NK-cell lymphomas	
Mycosis fungoides	88%
Mycosis fungoides variants and subtypes	
Folliculotropic mycosis fungoides (MF)	80%
Pagetoid reticulosis	100%
Granulomatous slack skin	100%
Sézary syndrome	24%
Adult T-cell leukemia/lymphoma	NR
Primary cutaneous CD30+ lymphoproliferative disorders	
Primary cutaneous anaplastic large-cell lymphoma	95%
Lymphomatoid papulosis	100%
Subcutaneous panniculitis-like T-cell lymphoma[a]	82%
Extranodal NK/T-cell lymphoma, nasal type	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified	16%
Primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma (provisional)	18%
Cutaneous γ/δ T-cell lymphoma (provisional)	NR
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)	75%
Cutaneous B-cell lymphomas	
Primary cutaneous marginal zone B-cell lymphoma	99%
Primary cutaneous follicle center lymphoma	95%
Primary cutaneous diffuse large B-cell lymphoma, leg type	55%
Primary cutaneous diffuse large B-cell lymphoma, other	50%
Intravascular large B-cell lymphoma	65%
Precursor hematologic neoplasm	
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)[b]	NR

EORTC, European Organization for Research and Treatment of Cancer; NR, not reached; WHO, World Health Organization.
[a]Restricted to lymphomas of α/β T-cell origin.
[b]On the basis of recent evidence suggesting derivation from a plasmacytoid dendritic cell precursor; this condition has also been designated as early plasmacytoid dendritic cell leukemia/lymphoma.

Table 2. Survival (%) in cutaneous T-cell lymphomas

Stage	IA	IB	IIA	IIB	III	IVA	IVB
At 5 years	96–100	73–86	49–73	40–65	40–57	15–40	0–15
At 10 years	84–100	58–67	45–49	20–39	20–40	5–20	0–5

literature

1. Rein Willemze, Elaine S. Jaffe, Günter Burg et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005; 105 (10): 3768–3785.
2. Grange F, Bekkenk MW, Wechsler J et al. Prognostic factors in primary cutaneous large B-cell lymphomas: a European multicenter study. J Clin Oncol 2001; 19: 3602–3610.
3. Bekkenk MW, Geelen FA, van Voorst Vader PC et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000; 95: 3653–3661.
4. Kaye FJ, Bunn PJ, Steinberg SM et al. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. N Engl J Med 1989; 321: 1784–1790.
5. Stadler R, Otte HG, Luger T et al. Prospective randomized multicenter clinical trial on the use of interferon-2a plus acitretin versus interferon-2a plus PUVA in patients with cutaneous T-cell lymphoma stages I and II. Blood 1998; 92: 3578–3581.
6. Duvic M, Hymes K, Heald P et al. Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results. J Clin Oncol 2001; 19: 2456–2471.
7. Fierro MT, Quaglino P, Savoia P et al. Systemic polychemotherapy in the treatment of primary cutaneous lymphomas: a clinical follow-up study of 81 patients treated with COP or CHOP. Leuk Lymphoma 1998; 31: 583–588.
8. Olsen E, Duvic M, Frankel A et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol 2001; 19: 376–388.
9. Kuzel TM, Hurria A, Samuelson E et al. Phase II trial of 2-chlorodeoxyadenosine for the treatment of cutaneous T-cell lymphoma. Blood 1996; 87: 906–911.
10. Heinzerling ML, Urbanek M, Funk JO et al. Reduction of tumor burden and stablization of disease by systemic therapy with anti- CD20 antibody (rituximab) in patients with primary cutaneous B-cell lymphomas. Cancer 2000; 89: 1835–1844.
11. Bekkenk MW, Vermeer MH, Geerts ML et al. Treatment of multifocal primary cutaneous B-cell lymphoma: a clinical follow-up study of 29 patients. J Clin Oncol 1999; 17: 2471–2478.

Coordinating author for the ESMO Guidelines Working Group: R. Dummer[1]

[1]Invited author, Department of Dermatology, University Hospital, CH-8091 Zürich, Switzerland