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Major achievements of the EORTC Cutaneous Lymphoma Task Force (CLTF)

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ABSTRACT

This article describes the achievements of the Cutaneous Lymphoma Task Force (CLTF) over the recent decade in their goal to optimize classification and response criteria and establish new treatment options for patients suffering from cutaneous T-cell lymphomas (CTCL). Collaborative work with the International Society of Cutaneous Lymphoma (ISCL) and the United States Cutaneous Lymphoma Consortium (USCLC) has led to publication of pivotal manuscripts proposing revised staging proposals for Mycosis fungoides (MF)/Sézary syndrome (SS) and also non MF/SS primary cutaneous lymphomas as well as the recent publication of a proposal for defining endpoints in MF/SS.

1. WHO–EORTC classification for cutaneous lymphomas

Primary cutaneous lymphomas often have a completely different clinical course and prognosis from histologically similar systemic lymphomas, which may involve the skin secondarily, and therefore require different types of treatment. For that reason, recent classification systems for non-Hodgkin lymphomas such as the European Organization for Research and Treatment of Cancer (EORTC) classification for primary cutaneous lymphomas and the World Health Organization (WHO) classification for tumors of hematopoietic and lymphoid tissues included primary cutaneous lymphomas as separate entities. In the EORTC classification, distinction was made between primary cutaneous lymphomas with an indolent, intermediate, or aggressive clinical behavior. The clinical validity of this classification has been confirmed by several large studies, including follow-up data of more than 1300 patients with a primary cutaneous lymphoma.

Although there was consensus between the EORTC and WHO classifications on the classification of most types of CTCLs, remaining differences between the two classification systems, in particular the controversy on the definition and terminology of the different types

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of cutaneous B-cell lymphoma (CBCLs), has resulted in considerable debate and confusion. During consensus meetings in Lyon, France (September 2003) and Zurich, Switzerland (January 2004), these differences were resolved by representatives of both classification systems, and a consensus classification was developed.[1] The WHO–EORTC classification for cutaneous lymphomas presented in this report may be considered as an important step forward.

This review will focus on primary cutaneous lymphomas and a few other conditions that frequently first present in the skin, such as $CD4^+/CD56^+$ hematodermic neoplasm (formerly also known as blastic natural killer [NK] cell lymphoma) and adult T-cell leukemia/lymphoma. Other neoplasms that may also first present in the skin in a minority of cases, such as precursor B-lymphoblastic leukemia/lymphoma and acute myeloid leukemia, and secondary cutaneous manifestations of systemic lymphomas, are not discussed. After a discussion of the two most controversial groups of cutaneous lymphomas that were defined differently in the original EORTC and WHO classification schemes, the main features of the different types of primary cutaneous lymphoma are presented.

The WHO–EORTC classification for cutaneous lymphomas presented herein may be considered as an important step forward. First, the development of this consensus classification will put an end to the ongoing discussion whether the EORTC or the WHO scheme can best be used, and is expected to contribute to a more uniform diagnosis and hence a more uniform treatment of patients with a cutaneous lymphoma. Second, major progress has been made in a better definition of some controversial groups of cutaneous lymphoma, in particular the group of primary cutaneous follicle center lymphoma PCFCL) and the group of CTCL other than mycosis fungoides (MF), Sézary syndrome (SS), and the group of primary cutaneous $CD30^+$ lymphoproliferative diseases (LPD). The new definitions of the groups of PCFCL, PCLBCL, leg type, and PCLBCL, other, will allow a more reliable distinction between indolent and more aggressive types of CBCL, and facilitate the decision whether radiotherapy or systemic chemotherapy should be selected as first choice of treatment.

Large multicenter studies are now required to validate the current proposals, and in particular to investigate the diagnostic and prognostic value of bcl-2 and Mum-1/IRF4 protein expression. The classification of CTCL other than MF, SS, and the group of primary cutaneous $CD30^+$ LPD is still difficult, as it requires accurate clinicopathologic correlation and a number of complementary techniques to arrive at a definite diagnosis. Subcutaneous panniculitis-like T-cell lymphoma (SPTL) (with an alpha/beta phenotype), extranodal NK/T-cell lymphoma, nasal type, and $CD4^+/CD56^+$ hematodermic neoplasm are now fairly well defined. However, considerable overlap is noted between cutaneous (and mucosal) GD-TCL and aggressive epidermotropic $CD8^+$ CTCL. The similarities in clinical presentation and pattern of dissemination between these conditions may reflect similarities in homing profile and biologic function of normal gamma/delta-positive T -cells and activated $CD8^+$ cytotoxic T cells, respectively. Apart from the group of SPTLs and the group of $CD4^+$ small/medium-sized pleomorphic CTCLs, these rare types of CTCL have a very poor prognosis and are generally resistant to conventional chemotherapy. More aggressive regimens, including allogeneic bone marrow transplantation, for patients with aggressive types of CTCL including advanced stages of MF and SS are currently under investigation. This article was one of the most highly cited articles published in *Blood* from 2005 through 2010.

In addition, consensus was reached between the International Society for Cutaneous Lymphomas (ISCL) and the EORTC CLTF about a new TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome.[2]

2. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome

Several reviews and guidelines on the management of mycosis fungoides and Sézary syndrome (MF/SS) have been published, however, treatment strategies for patients with MF/SS vary from institution to institution and no European consensus has yet been established. There are few phase III trials to support treatment decisions for MF/SS, and treatment is often determined by institutional experience. In order to summarize the available evidence and review 'best practices' from each national group, the EORTC CLTF met in September 2004 to establish European guidelines for the treatment of MF/SS. These recommendations reflect the best data available at the time the report was prepared.[3]

The report reviews the treatment regimens selected for inclusion in the guidelines and summarizes the clinical data for treatments appropriate for each stage of MF/SS. Guideline recommendations are presented according to the quality of supporting data, as defined by the Oxford Centre for Evidence-Based Medicine. Skin-directed therapies (SDT) are the most appropriate option for early-stage MF/SS and most patients can look forward to a normal life expectancy. Patients with advanced disease should be encouraged to participate in clinical trials and maintenance of quality of life should be paramount.

In early-stage MF, SDT represents the most appropriate therapy. Most patients will be able to achieve a short-term clinical response with recurrent disease for many years and, in the majority of cases, a normal life expectancy. Therefore, potentially toxic and

aggressive therapies should be avoided. Patients with more advanced stages of MF and patients with SS have a poor prognosis. In these patients, the absence of randomized, controlled trials results in a lack of sufficient evidence to provide a basis for a consensus. None of the therapies described so far have a documented impact on disease outcome. Thus, all patients with late-stage disease should be entered into appropriate clinical trials. As treatment of MF/SS is always palliative, maintenance of quality of life should be at the center of therapeutic strategies.

3. EORTC–International Society of Cutaneous Lymphoma (ISCL) and United States Cutaneous Lymphoma Consortium (USCLC) consensus recommendations for the treatment of primary cutaneous CD30-positive lymphoproliferative disorders (lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma) and for the management of cutaneous B-cell lymphomas

Various therapeutic regimens have been reported for primary cutaneous CD30-positive LPD, lymphomatoid papulosis (LYP) and primary cutaneous anaplastic large-cell lymphoma (PCALCL). International recommendations for the management of CD30+ LPD have not yet been established. W. Kempf, on behalf of EORTC CLTF, performed a systematic review of therapeutic studies in CD30+ LPD to assess response and relapse rates as well as outcome after treatment. Based on these data and the institutional experience of the EORTC Cutaneous Lymphoma Task Force, ISCL and USCLC members, consensus recommendations for CD30+ LPD were developed. [4]

Fifty-two reports on therapy in PCALCL including a total of 368 patients and 60 reports on therapy in LYP including a total of 585 patients were analyzed. Most treatment regimens have been reported in case reports or smaller retrospective cohorts studies. For solitary or grouped PCALCL lesions, both surgical excision (SE) and radiotherapy (RT) achieve complete response rates (CRRs) of at least 95%. Recurrences occur in approximately 40% of patients and are evenly frequent after both interventions. Non-interventional strategy with observation of the natural course may be justified at least for up to 8 weeks, since spontaneous regresssion of PCALCL lesions has been observed in 25% of the patients. CRR to multiagent chemotherapy as initial therapy was 85% and 62% for CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], vincristine [Oncovin], Predniso[lo]n). Relapses were observed in 43% of all patients treated with chemotherapy in general and in 70% of the patients treated with CHOP. In LYP, UV light therapy and systemic low-dose MTX result in reduction of the number of lesions with response rates ranging from 40% to almost 100%. Independent of the therapeutic approach, sustaining complete remission usually cannot be achieved and LYP tends to recur quickly after cessation of therapy. In addition, none of the therapies for LYP has been unequivocally proven to prevent LYP-associated second lymphomas.

Treatment of PCALCL should be tailored to the size and extent of tumoral lesions. SE and RT are best recommended as first-line therapy for solitary or grouped lesions. Non-interventional strategy with observation of the natural course may be justified at least for up to 8 weeks. For multifocal PCALCL low-dose methotrexate (MTX) is recommended. Multiagent chemotherapy is not indicated for multifocal PCALCL and should be reserved for patients with extracutaneous spread. For LYP with only a few lesions, abstention of active therapeutic intervention is a legitimate first-line approach. The best documented treatment regimens for patients with numerous or disfiguring LYP lesions are UV light therapy and systemic low-dose MTX. Overtreatment with aggressive and potentially harmful treatment modalities should be avoided. In regard to the lack of evidence for all reported therapies, prospective controlled and randomized trials are urgently needed to evaluate the effect of therapeutic interventions in CD30+ LPD.

EORTC/ISCL consensus recommendations were also given for the management of cutaneous B-cell lymphomas. It has been highlighted that low-dose radiotherapy rather than chemotherapy is the standard of care for low-grade PCBCL. [5]

4. Revisions to the staging and classification, clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome: a consensus statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the EORTC CLTF

Clinical trials in MF/SS have suffered from a lack of standardization in evaluation, staging, assessment, endpoints, and response criteria. Recently defined criteria for the diagnosis of early MF, guidelines for initial evaluation, and revised staging and classification criteria for MF and SS now offer the potential for uniform staging of patients enrolled in clinical trials for MF/SS. [6,7] These articles present consensus recommendations for the general conduct of clinical trials of patients with MF/SS as well as methods for standardized assessment of potential disease manifestations in skin, lymph nodes, blood, and visceral organs, and definition of endpoints and response criteria. These guidelines should facilitate collaboration among investigators and collation of data from sponsor-generated or investigator-initiated clinical trials involving patients with MF or SS.

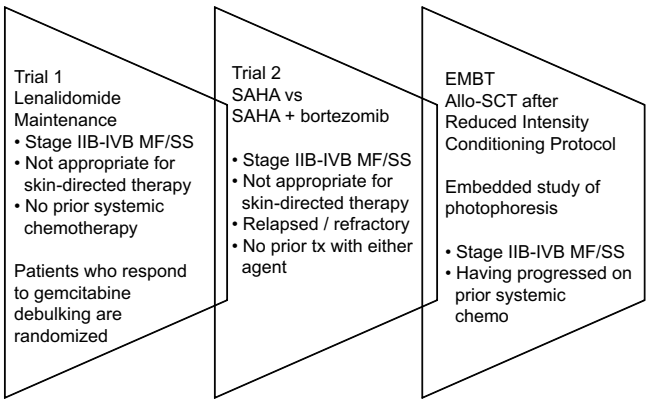

Fig. 1 – Eligibility criteria for platform.

5. The EORTC Cutaneous T-Cell Lymphoma (CTCL) Platform

The EORTC CLTF has recently successfully completed two clinical trials in CTCL (EORTC 21011/21012) which have been presented at the ASH Annual Meeting 2010 [8] and are now submitted for publication (21012) or are due for publication soon (21011). In an effort to target this rare disease more effectively, the CTCL platform has been designed by the EORTC CLTF to address critical unadressed questions to move forward the standards of care of CTCL in advanced-stage disease. It was built following a sequential approach. Following a European consensus defining the key clinical questions to improve disease control in CTCL, ideas regarding the biology of the disease and all possible emerging targets which may lead to a better understanding of the disease were explored. The candidate targets were selected and prioritized by their scientific and clinical relevance. The maturity and relevance of agents in development to tackle these pathways and targets were analyzed. Methodologically and statistically robust clinical trials were designed to allow the enrollment of patients through the evolution of their disease. Endpoints and translational research programs that could address and help identify mechanisms of action and clinical efficacy were also evaluated as to feasibility and scientific relevance. This comprehensive process led to the design of early phase randomized trials on solid scientific grounds with the use of innovative drugs.

Study protocol 21081 is a multicenter, randomized, open-label, phase III study and is suitable for patients who have not previously had other intravenous chemotherapy, and are therefore relatively treatment-naive. The accrual goal is 105 patients. The objective of this trial is to test the hypothesis that lenalinomide is able to increase progression-free survival in patients achieving a complete (CR) or partial (PR) response after standardized debulking treatment. A sister protocol, 21082, addresses patients who have had previous chemotherapy. Patients in this study will be randomized to receive the histone deacetylase inhibitor vorinostat alone or in combination with the proteasome inhibitor bortezomib. The primary objective of this trial will be to determine if the combination of bortezomib plus vorinostat is more effective than vorinostat alone in prolonging progression-free survival. The accrual goal is 189 patients. In both studies, validation of new proposed response criteria [4] is foreseen.

6. Conflict of interest statement

Matthias Karrasch, Baktiar Hasan, Denis Lacombe and Werner Kempf declare no conflicts of interest. Sean Whittaker consulted for and received honoraria from Genmab, received honoraria and research funds from Gloucester Pharmaceuticals and Cephalon, and received honoraria from Allos. Pablo Ortiz received travel coverage from Ferrer Farma SA and Isdin SA, and his institution received research funds from Ferrer Farma SA, MSD, J&J, Novartis, Biocryst, and Genmab. Robert Knobler consulted for and received honoraria and research funds from Therakos, and consulted for and received honoraria from Yupon. Martine Bagot consulted for and received research funds and travel reimbursement from Cephalon. Maarten Vermeer consulted for Millenium and received research funds from Cephalon. Reinhard Dummer received honoraria and research funds from Cephalon, research funds from MSD, and honoraria from Transgene.

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