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Cutaneous B-cell lymphoma : classification, prognostic factors and management recommendations

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Chapter 1.

General Introduction

Malignant lymphomas can involve the skin either primarily or secondarily. The term "primary cutaneous lymphoma" refers to various T-cell and B-cell malignancies that present in the skin without evidence of extracutaneous disease at the time of diagnosis. It is important to differentiate these primary cutaneous T-cell lymphomas (CTCL) and primary cutaneous B-cell lymphomas (CBCL) from their nodal counterparts, that can involve the skin secondarily, since they have a completely different clinical behaviour and prognosis and most often require different therapeutic approaches. Primary cutaneous lymphomas are the second most common group of extranodal lymphomas after the lymphomas of the gastrointestinal tract, with an estimated annual incidence of 1:100.000. While in systemic non-Hodgkin lymphomas the large majority is derived from a population of atypical B-cells, in the skin only 20-25% are CBCL; the remainder mainly consist of CTCL.[1] In the United States the reported incidence of CBCL is even lower, being approximately 4.5%.[2]

Until recently, there has been much controversy regarding the terminology and classification of CBCL, which may have come to an end with the publication of the WHO-EORTC consensus classification for cutaneous lymphomas.[3] In this classification three main types of CBCL are described: primary cutaneous marginal zone B-cell lymphoma (PCMZL), primary cutaneous follicle centre lymphoma (PCFCL) and primary cutaneous diffuse large B-cell lymphoma, leg type (PCLBCL, LT). In addition, a category of primary cutaneous diffuse large B-cell lymphoma, other (PCLBCL, other) was included.

This thesis includes a number of clinical, clinicopathologic and molecular studies in different groups of CBCL. The aims of these studies were (1) to validate the clinical and prognostic significance of the WHO-EORTC classification, (2) to identify and validate (new) diagnostic and prognostic markers, (3) to evaluate the clinical significance of current staging procedures and of a new clinical staging system in CBCL, (4) to evaluate the efficacy of radiotherapy in the treatment of different types of CBCL, and (5) to formulate consensus recommendations for the management of these diseases.

In this introductory chapter a brief historical overview of the classification of CBCL and a short description of the different types of CBCL as currently recognized in the WHO-EORTC classification, will be presented first. In addition, the background of the issues investigated in this thesis will be discussed.

Historical overview of the classification of CBCL

Until the early 1980's CBCL were not recognized as distinct disease entities. Malignant B-cell proliferations in the skin were considered invariably as manifestations of systemic disease and classified by systems used by hematopathologists for systemic lymphomas. Patients with a B-cell proliferation in the skin who showed a good clinical response to local treatment and had a favourable prognosis, were regarded as having a benign condition (so called pseudolymphoma).[4-7]

In the late seventies, the introduction of immunohistochemistry had a major impact on the diagnosis and classification of B-cell proliferations in the skin. By accepting monotypic immunoglobulin light chain expression on tissue sections of skin biopsies as golden standard for the diagnosis of malignant B-cell lymphoma, it became possible to distinguish between malignant B-cell lymphomas and reactive B-cell proliferations. Moreover, it became clear that B-cell lymphomas can be confined to the skin without any systemic disease being present. This simple distinction between primary and secondary cutaneous B-cell lymphomas proved extremely important. According to the criteria of the **Kiel classification**, that was in use in these days, most CBCL were classified as immunocytoma, centroblastic/centrocytic lymphoma, centroblastic lymphoma or immunoblastic lymphoma. Studies on well-defined groups of patients showed that these different types of CBCL had a highly distinctive clinical presentation and often another clinical behaviour and prognosis as compared to their systemic counterparts. These studies led to the delineation of distinct types of CBCL, which were however not recognized separately in the existing classification schemes used for nodal lymphomas, and were therefore often treated inappropriately. In 1994, Willemze and co-workers proposed a separate classification scheme for primary cutaneous lymphomas, thereby using the terminology of the updated Kiel classification to define distinct disease entities (see Table 1).[8] This proposal was extensively discussed within the EORTC Cutaneous Lymphoma Group (EORTC-CLG) and was formalised in 1997 with the publication of the **EORTC classification for primary cutaneous lymphomas**.[1] In this classification three main types of CBCL were distinguished: primary cutaneous immunocytoma, later called primary cutaneous marginal zone B-cell lymphoma (PCMZL), primary cutaneous follicle centre cell lymphoma (PCFCCL) and primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg). The distinction between the latter two groups was based on the observation that patients with tumours on the leg(s) had a much more aggressive clinical behaviour as compared to patients presenting with tumours on the head or trunk.[9]

In 2001 the **WHO classification for tumours of hematopoietic and lymphoid tissues** was published as a successor of the REAL classification.[10;11] This classification did not recognize CBCL as distinct disease entities. PCMZL was included in the broad category of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. PCFCCL with a (partially) follicular growth pattern, were classified as cutaneous

follicle centre lymphoma, which was considered as a variant of follicular lymphoma (FL), while PCFCCL with a diffuse growth pattern were classified as diffuse large B-cell lymphoma (DLBCL). The group of PCLBCL-leg was neither acknowledged as a distinct disease entity and was also classified as DLBCL. The classification of CBCL according to the different classification schemes is presented in Table 1.

The differences in terminology and definition of the three main types of CBCL between the EORTC and WHO classifications resulted in much debate and confusion.[12-15] The main point of discussion was formed by the group of PCFCCL. While this term resembles that of FL in the WHO classification, it is defined in a different way. FL denotes a neoplasm of follicle centre B-cells (a mixture of centrocytes and centroblasts), which has at least a partially follicular growth pattern.[11] FL is graded by the proportion of centroblasts, using a 3-grade system. The histological grade correlates with prognosis, with grades 1 and 2 showing an indolent clinical course, and grade 3 being more aggressive. The majority of FL is characterized by the presence of the characteristic chromosomal translocation t(14;18), resulting in overexpression of the anti-apoptotic protein Bcl-2.[16-19] In contrast, the term PCFCCL was introduced as an encompassing term for cutaneous lymphomas composed of cells with the morphology of follicle centre B-cells (centrocytes and centroblasts), regardless of their growth pattern.[20-23] Moreover, PCFCCL had an indolent clinical behaviour, irrespective of the proportion of centroblasts and thus, histological grading had no prognostic significance. In addition, PCFCCL generally showed no expression of Bcl-2 and the t(14;18) could only be identified in a small minority of cases.[24-26] However, because of the rarity of the disease, (hemato)pathologists were generally not familiar with this entity, and PCFCCL with a diffuse growth pattern were generally classified as DLBCL, leading to unnecessary aggressive treatment with multiagent chemotherapy.

To put an end to this ongoing controversy, in 2003 and 2004 consensus meetings were organized, in which representatives of the EORTC and the WHO systems succeeded to combine the best of the two systems and to reach agreement on a consensus classification, which was termed the **WHO-EORTC classification for cutaneous lymphomas.** In this classification four categories of CBCL were recognized, which will be discussed below and are summarized in Table 2.

CBCL in the WHO-EORTC classification for cutaneous lymphomas

Primary Cutaneous Marginal Zone B-cell Lymphoma (PCMZL), is an indolent lymphoma composed of small B cells including marginal zone (centrocyte-like) cells, lymphoplasmacytoid cells and plasma cells. The marginal zone cells express CD20, CD79a and Bcl-2, but are negative for CD5, CD10 and Bcl-6.[27;28] The plasma cells show monotypic cytoplasmic immunoglobulin light chain expression (kappa or lambda) on paraffin sections. This category includes cases previously classified as primary cutaneous

immunocytoma[29], cases of cutaneous follicular lymphoid hyperplasia with monotypic plasma cells[29;30] and rare cases of primary cutaneous plasmacytoma.[31] Clinically, PCMZL are characterized by red to violaceous papules, plaques or nodules preferentially localized on the trunk or extremities. They have a tendency to recur in the skin, but extracutaneous dissemination is exceedingly rare, which is reflected in the excellent 5-year survival rate of close to 100%.[29;32-35]

Primary Cutaneous Follicle Centre Lymphoma (PCFCL) is defined as a tumour of neoplastic follicle centre cells, usually a mixture of centrocytes (small and large cleaved follicle centre cells) and variable numbers of centroblasts (large noncleaved follicle centre cells with prominent nucleoli). It includes cases with a follicular, a follicular and diffuse and a diffuse growth pattern. The neoplastic follicle centre cells express CD20, CD79a and Bcl-6. CD10 is particularly observed in cases with a (partly) follicular growth pattern. Recent gene expression studies revealed that these PCFCL have the gene expression profile of germinal center B-cell (GCB)- like DLBCL.[36] Consistently, the neoplastic B-cells generally do not express Bcl-2, MUM-1 and FOXP1.[24;27;28;36-40] Clinically, PCFCL generally present with solitary or grouped plaques and tumours, preferentially located on the head or trunk.[20;22;23;41] Extracutaneous dissemination is uncommon and their prognosis is excellent, irrespective of the growth pattern or the number of blast cells (5-year survival of more than 95%).[20;22;23;38;40-42]

Primary Cutaneous diffuse Large B-cell Lymphoma, Leg Type (PCLBCL, LT) are diffuse large B-cell lymphomas with a predominance or confluent sheets of centroblasts and immunoblasts. These neoplastic cells express CD20, CD79a and, since PCLBCL, LT have the gene expression profile of activated B-cell (ABC)-like DLBCL, the great majority of cases strongly express Bcl-2, MUM-1 and FOXP1.[36] Bcl-6 is expressed in most cases, while CD10 is generally absent.[28;36;39;43-45] Characteristically, they present with tumorous skin lesions on the (lower) leg(s), but uncommonly can arise at other sites as well. The disease affects predominantly elderly patients, and females are more affected than males. These lymphomas often disseminate to extracutaneous sites and have an intermediate prognosis with a 5-year survival of approximately 50%.[9;43;46;47]

Primary Cutaneous diffuse Large B-cell Lymphoma, other (PCLBCL, other) is used for rare cases of primary cutaneous diffuse large B-cell lymphomas that do not belong to the group of PCFCL or PCLBCL, LT. These include morphologic variants, such as rare cases of anaplastic or plasmablastic lymphoma and intravascular large B-cell lymphomas presenting primarily in the skin. These latter entities are exceedingly rare and will not further be discussed in this thesis.

Table 1.

Classification of primary cutaneous B-cell lymphomas according to the Kiel classification, the EORTC classification, the WHO classification and the WHO-EORTC classification

Kiel classification	EORTC classification	WHO classification	WHO-EORTC classification
Immunocytoma	Primary cutaneous immunocytoma/ marginal zone B-cell lymphoma	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Primary Cutaneous Marginal Zone B-cell Lymphoma (PCMZL)
Centroblastic/ centrocytic or centroblastic lymphoma	Primary cutaneous follicle centre cell lymphoma	Cutaneous follicle centre lymphoma* Diffuse large B-cell lymphoma#	Primary Cutaneous Follicle Centre Lymphoma (PCFCL)
Centroblastic lymphoma Immunoblastic lymphoma	Primary cutaneous large B-cell lymphoma of the leg	Diffuse large B-cell lymphoma	Primary Cutaneous diffuse Large B-cell Lymphoma, Leg Type (PCLBCL, LT)

* Cases with a (partly) follicular growth pattern

Cases with a diffuse growth pattern

Outstanding issues

At the time the WHO-EORTC classification was published, there were still several outstanding issues requiring additional study.

First, the definitions of PCFCL and PCLBCL, LT in the WHO-EORTC classification imply that differentiation between PCFCL and PCLBCL, LT is determined above all by morphological criteria, namely the absence or presence of confluent sheets of centroblasts and/or immunoblasts (designated previously as cleaved cell versus round cell morphology[46]) and no longer by site (non-leg versus leg) as in the EORTC classification.[1;9;48] This implies that a proportion of patients classified as PCFCCL or PCLBCL-leg in the EORTC classification will be assigned to another prognostic category, which may have important therapeutic consequences. Recent studies suggest that this concerns 10-15% of PCFCCL and PCLBCL-leg, but exact data are not available.[49;50]

Second, recent studies also illustrated that the interpretation of the group of PCLBCL, other is defined in different ways. Some authors exclude rare Bcl-2 negative cases from the group of PCLBCL, LT and include them in the heterogeneous group of PCLBCL, other[49], whereas others include all cases with characteristic round-cell morphological features within the group of PCLBCL, LT, irrespective of Bcl-2 expression.[50]

Third, previous studies have suggested several clinicopathologic and immunophenotypical parameters with prognostic significance in patients with CBCL.[44;46;51-54] The most interesting findings were that strong expression of Bcl-2 is associated with an unfavorable prognosis in PCFCL cases with a diffuse growth pattern[44] and that inactivation of CDKN2A is a negative prognostic predictor in PCLBCL, LT patients.[55] However, most of these studies were based on cases classified according to older classifications systems, on mixed groups of patients or, as in the latter study, on only a small number of patients.

Therefore, in the study described in **Chapter 2** we reviewed clinical data and histologic sections of 300 CBCL patients included in the database of the Dutch Cutaneous Lymphoma Group (DCLG) who were originally classified by the EORTC classification, and reclassified all cases according to the criteria of the WHO-EORTC classification as well as those of the WHO classification. The aims were to (1) assess the clinical significance of this new classification; (2) determine the percentage of CBCL patients assigned to a different prognostic category when compared with the EORTC and WHO schemes; (3) define more precisely the clinicopathologic features and prognostic factor of the newly defined categories; and (4) establish more clearly which cases should be assigned to the group of PCLBCL, other.

In addition, in **Chapter 3** we aimed to confirm inactivation of CDKN2A as a prognostic marker for the group of PCLBCL, LT on a larger patient group. This study describes the results of an European multicenter study, conducted within the framework of the EORTC-CLG.

Staging of cutaneous B-cell lymphomas

The TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sézary Syndrome

Staging of cancer is important in the appropriate and effective care of patients. The goals of a staging system for cutaneous lymphoma are to offer a clinically reasonable basis for appropriate management, to predict prognosis, and to facilitate comparison of results among different therapies and different institutions. The most widely used staging system for lymphoma is the Ann Arbor system, which was first introduced as a staging system for Hodgkin lymphoma in 1971.[56;57] Although its utility for the staging of other lymphomas has been challenged, it is still the primary means for classifying patients with non-Hodgkin lymphomas (NHL).[58] The Ann Arbor system is primarily an anatomical assessment of disease with modifications by presence or absence of systemic symptoms. However, it does not distinguish consistently between patients with different prognoses. Thus, in 1993, the International Prognostic Index was established to supplement the Ann Arbor staging to aid in the treatment decision or stratification of patients in clinical trials for patients with lymphoma.[59] However, the Ann Arbor system has a number of shortcomings, especially when staging lymphomas that arise primarily in extranodal sites such as the skin. In primary cutaneous lymphomas, the initial stage according to the Ann Arbor system would either be IE (if single skin site) or IVD + (if multiple skin sites), thus disproportionately or inappropriately placing high number of patients in the highest stage, resulting in unnecessarily aggressive treatments.

The TNM classification system is the most widely used means for classifying the extent of nonlymphoid malignant disease. An adjusted TNM + B (blood) system has been in use for nearly 30 years to stage patients with mycosis fungoides (MF) and Sézary

syndrome (SS), both forms of CTCL[60], and this system has recently been revised and updated.[61] However, this system is not appropriate for staging of other forms of primary cutaneous lymphomas. Therefore, representatives of the International Society for Cutaneous Lymphomas (ISCL) and EORTC-CLG recently published a consensus proposal for a TNM classification system applicable to all types of primary cutaneous lymphomas other than MF/SS.[62] This proposed TNM system is primarily meant to document extent of disease in a consistent matter, thereby facilitating comparison of studies at different institutes. Studies investigating the applicability of this TNM system on a group of CBCL have not been performed. Moreover, the prognostic significance of this proposed system for CBCL was unknown. In the study described in **Chapter 4** we therefore tested its clinical applicability on the large group of CBCL which were reclassified according to the WHO-EORTC classification as described in **Chapter 2**, and evaluated its prognostic relevance for the group of CBCL. In addition, these results were compared with the scoring of disease extent as used by the Dutch Cutaneous Lymphoma Group (DCLG) since many years.

Bone marrow examination in the staging of cutaneous B-cell lymphomas

Ever since the first introduction of a separate classification for primary cutaneous lymphomas, it was recognized that a diagnosis of true primary cutaneous lymphoma can only be made after adequate staging investigations have been performed. These include a thorough physical examination, laboratory studies, imaging techniques and a bone marrow biopsy (BMB). However, in the paper introducing the TNM staging system for primary cutaneous lymphomas other than MF and SS, described previously[62], it was for the first time suggested that bone marrow examination was recommended, but not required in indolent types of primary cutaneous lymphoma, including PCMZL and PCFCL. However, in most clinical practice guidelines for NHL, unilateral trephine BMB are part of the routine work-up in all patients with (a suspicion of) NHL. Moreover, the recommendation that a BMB is not required in indolent types of CBCL is confusing, as studies describing these PCMZL and PCFCL as indolent lymphomas, required negative staging procedures, including a negative BMB.[3]

Studies on the frequency of bone marrow involvement in this specific group of patients have never been performed. In the study described in **Chapter 5** we evaluated the frequency of bone marrow involvement in a large group of patients with histological skin features consistent with a marginal zone lymphoma (MZL) or follicle centre lymphoma (FCL), in order to determine whether our current policy to perform a BMB in all patients with a histological diagnosis of cutaneous MZL or FCL should be maintained.

Treatment of primary cutaneous B-cell lymphomas

It is generally recognized that PCMZL and PCFCL are indolent types of CBCL, which should not be treated primarily with systemic chemotherapy, and that PCLBCL, LT is characterized by a more unfavourable prognosis, justifying more aggressive therapeutic approaches. In recent years various new therapies for the treatment of CBCL, like rituximab and interferon alpha, have become available, supplementing traditional therapies like, surgical excision, local radiotherapy (RT), systemic multiagent chemotherapy or combinations of the latter two. However, the most appropriate therapy for each of the newly defined entities remains to be determined.

RT is the most widely applied and best known treatment in CBCL. Already in 1951 Crosti described seven cases of "reticulohistiocytoma of the dorsum" that were markedly sensitive to radiation therapy.[63] This entity is nowadays classified as PCFCL. Previous studies have shown that RT is a suitable treatment for both PCFCL as well as PCMZL, and perhaps also for PCLBCL, LT presenting with solitary or localized skin lesions.[23;41;42;64;65] However, data from the literature regarding efficacy and relapse rate show a wide variation.[41;42;64;66-69] Moreover, these studies are all based on cases classified according to the EORTC or WHO schemes, and it might be expected that a number of cases would be assigned to a different prognostic category, using the WHO-EORTC classification. These observations prompted us to evaluate the results of RT as initial treatment in a large group of CBCL classified according to the WHO-EORTC classification. The aim of this study, described in **Chapter 6**, was to define remission, relapse and survival rates of these newly defined groups after treatment with RT, and to establish for which patients this is a safe and effective treatment.

In summary, with the advent of the WHO-EORTC consensus classification for cutaneous lymphomas in 2005, uniform terminology and classification for this rare group of neoplasms was introduced. However, staging procedures and treatment strategies still varied between different cutaneous lymphoma centres, which may be due to the fact that consensus recommendations for the management of CBCL have never been published. Following the results of **Chapters 4-6** and based on an extensive literature review and discussions among experts in the field of cutaneous lymphoma, collaborating in the EORTC-CLG and the ISCL, we formulated consensus recommendations for the management of the three main groups of CBCL, which are described in **Chapter 7**.

Aims and outline of the thesis

The studies presented in this thesis have aimed to address outstanding questions regarding the classification, prognostication, staging and treatment of CBCL.

Chapter 2 investigates the clinical applicability of the WHO-EORTC classification on a group of 300 patients with CBCL and determined the percentage of patients that was assigned to a different prognostic category using this classification as compared to the previously used EORTC and WHO classifications. Furthermore, clinicopathologic features and prognostic markers for the new WHO-EORTC categories and more precise criteria for the group of PCLBCL, other are defined.

Chapter 3 investigates if previously reported findings of inactivation of the CDKN2A gene as a prognostic marker can be confirmed on a large group of PCLBCL, LT and aims to further fine-map the aberrations found in this region by using MLPA.

Chapter 4 evaluates the clinical applicability and prognostic significance of the newly proposed TNM classification system for primary cutaneous lymphomas other than MF and SS on a group of 300 CBCL patients classified according to the new WHO-EORTC criteria and in addition, compares this classification system with the system used by the Dutch Cutaneous Lymphoma Group.

Chapter 5 investigates the frequency of bone marrow involvement in patients presenting with skin lesions that show histological features suggesting an indolent type of cutaneous B-cell lymphoma and evaluates whether the current practice to perform bone marrow biopsies in all these patients should be maintained.

Chapter 6 retrospectively analyzes the results of radiotherapy in a large group of CBCL classified according to the WHO-EORTC classification and establishes for which groups of patients this is a safe and effective treatment.

Chapter 7 provides a review concerning consensus recommendations for the management of CBCL, which were based on an extensive literature study and discussions among a broad panel of dermatologists, haematologists and (radiation) oncologists involved in the treatment of CBCL patients.

Chapter 8 summarizes and discusses the findings described in the preceding chapters.

Table 2.

Clinicopathologic features of the three main groups of primary cutaneous B-cell lymphomas recognized in the WHO-EORTC classification.

	Primary cutaneous marginal zone B-cell lymphoma	Primary cutaneous follicle centre lymphoma	Primary cutaneous diffuse large B-cell lymphoma, leg type
Clinical features	• solitary or multiple papules, plaques or nodules preferentially localized on the trunk or extremities • frequent cutaneous relapses • rarely extracutaneous dissemination	• solitary or grouped tumors presenting on the head or on the trunk • cutaneous relapses in 20% • extracutaneous dissemination in 5-10%	• solitary or multiple tumors presenting mainly on the leg(s) and rarely at other sites • frequent relapses and extracutaneous dissemination
Histopathology	patchy or diffuse infiltrates composed of small B-cells, including marginal zone (centrocyte-like) cells, lymphoplasmacytoid cells and plasma cells	follicular, follicular and diffuse or diffuse infiltrates composed of neoplastic follicle center cells , usually a mixture of centrocytes and variable numbers of centroblasts	diffuse infiltrates with a predominance or confluent sheets of of centroblasts and immunoblasts
Gene expression profile	Not applicable	Germinal centre B-cell (GCB)-like	Activated B-cell (ABC)-like
Immunophenotype	monotypic cIg, CD79a+, Bcl-2+, CD5-, cyclin D1-, Bcl-6-, CD10-, MUM-1+ (on plasma cells)	monotypic sIg or absence of sIg, CD20+, CD79a+, Bcl-6+, CD10+/-, Bcl-2-, MUM-1-, FOXP1- /(+/-)	monotypic sIg and/or cIg, CD20+, CD79a+, Bcl-6 +/(-), CD10-, Bcl-2+, MUM-1+, FOXP1+
Prognosis	5-year survival: 99%	5-year survival: 95%	5-year survival: 55%

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