Observations Regarding Hairy Cell Leukemia and Chronic Lymphocytic Leukemia Within the Proposed New Classification of Lymphoid Neoplasms

To the Editor:

In their proposal for a new classification of lymphoid neoplasms Harris et al. indeed simplify lymphoma classification to a list of pathologically defined disease entities. From a clinician’s viewpoint the purpose of a lymphoma classification is to support treatment decisions. Thus, the proposal from the International Lymphoma Study Group can be used only by comparing it regularly to the Kiel classification (in our region) to decide whether aggressive combined chemotherapy is justified or if the disease is a low-grade non-Hodgkin’s lymphoma (NHL), regarded to be incurable in the majority of cases.

Within the classification by Harris et al, the admixture of chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL) and lymphoplasmocytoid immunocytoma is provocative and in view of the heterogeneity among these diseases it would seem better to leave them separated. Furthermore, recent results in the treatment of CLL (with fludarabin) for the first time suggest the possibility of a cure.

Thus the “available therapy” mentioned by the authors probably refers to prednisone and chlorambucil, and in the more advanced cases, COP (cyclophosphamide, oncovine, prednisone) or CHOP (cyclophosphamide, doxorubicin, oncovine, prednisone). Also, while fludarabin has been found to be very useful in PLL, there are not enough data on the treatment of lymphoplasmocytoid immunocytoma with the drug, making the distinction clinically necessary.

In the case of hairy cell leukemia (HCL), it should be emphasized especially from the pathologic point of view, that, although rare cases without bone marrow involvement have been published, it is the spleen that is always involved. This is important, as HCL is presumed to originate from the spleen. Though lymph node involvement is clinically indeed uncommon, recent data show that retroperitoneal lymphadenopathy is not unusual in HCL.

When describing the immunophenotype of HCL, the negativity of the B-cell marker CD21 as compared with its positivity on B-CLL cells seems worth mentioning. Monoclonal antibodies such as anti-Tac (CD25), HC-2, RAB-1, and B-ly-7 (now designated CD103) are directed against activation molecules present on hairy cells. Thus, the postulated normal counterpart of the hairy cell is an activated B cell, that is relatively well differentiated. Though CD103 is indeed an important marker in differentiating HCL from other B-cell leukemias such as prolymphocytic leukemia (PLL) or CLL, it is less useful than HC2 in the differentiation of HCL from the HCL variant and from the splenic lymphoma with villous lymphocytes. Also, in rare cases of typical HCL, the neoplastic cells were found to be T cells by cell surface marker and even by gene rearrangement studies. This implies the existence of HCL of T-cell origin.

Finally, if mentioning therapeutic options in HCL, the difference in the capability of the listed drugs to induce remission is important: it is generally recognized by now that interferon a does not induce complete remission and is not curative, whereas with 2-deoxycoformycin and 2-chloro-deoxyadenosine, a considerable proportion of patients reach complete remission and, potentially, cure. With the presumed pathogenetic role of the spleen in the pathogenesis of HCL in mind, residual splenic disease after successful treatment of HCL with interferon-a2b and splenic relapse in a HCL patient during bone marrow remission after 2-chloro-deoxyadenosine therapy are of utmost interest.

In conclusion, although advances in the treatment of certain low-grade NHLs (like CLL and HCL) are considerable, it undoubtedly remains necessary to wait for a modified lymphoma classification even after the publication of the proposal by Harris et al.

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Response

We appreciate the comments of Drs Meijer, van der Valk, de Bruin, and Willemze and Drs Demeter, Schmid, and Porzsolt concerning our recent paper, and would like to take this opportunity to respond.

We agree with the comments of Dr Meijer et al about the distinctive behavior of some extranodal lymphomas. This point was emphasized in our paper in discussions of extranodal marginal zone (MALT) lymphomas, thymic large B-cell lymphoma, intestinal T-cell lymphoma, angiocentric lymphoma, and anaplastic large cell lymphoma. In fact, we specifically discussed the differences in clinical behavior between primary cutaneous anaplastic large cell lymphoma and similar tumors arising in other sites, citing the work of these authors.1 We also raised the issue of the homing properties of lymphoid cells and their implications for the clinical behavior of lymphomas, in the context of marginal zone lymphomas. However, the relationship of homing receptors to the behavior of lymphomas remains theoretical, and we do not believe that it can serve as the basis for a lymphoma classification at this time.

We agree that the area of cutaneous lymphomas other than mycosis fungoides has been underemphasized in the literature on lymphomas, and that further study of these tumors and their relationship to nodal lymphomas is needed. It is possible that the distinctive behavior of some cutaneous lymphomas, such as immunocytoma and large B-cell lymphoma, may be a consequence of their cell type, rather than their location. These cutaneous tumors may well be examples of low-grade and high-grade B-cell lymphomas of MALT type, respectively, and therefore, different from nodal immunocytoma and large cell lymphoma.2,3 We do not think it is feasible to classify lymphomas strictly according to their site of involvement because many primary extranodal lymphomas may spread either to other extranodal sites or to lymph nodes, and primary nodal lymphomas may involve extranodal sites. Until there is proof that the same tumor in a different site is really a different entity, we choose to abide by the precept of William of Ockham—what some might contend we have already stretched to its limit—that "entities should not be multiplied unnecessarily."

Along the same lines, Demeter et al suggest that we should have considered B-cell prolymphocytic leukemia (B-PLL) and the Kiel category of lymphoplasmacytoid immunocytoma as distinct diseases from B-cell chronic lymphocytic leukemia (B-CLL). Although it may represent an oversimplification, we placed B-CLL and B-PLL in the same disease category, because they currently appear to represent a morphologic and clinical continuum, similarly to follicular lymphomas. In the French-American-British (FAB) classification, they are distinguished only by arbitrary cutoffs in prolymphocyte count, with an intermediate category of CLL-PLL.4 However, we agree that there are distinctive immunologic and genetic differences between most cases of PLL and typical B-CLL, suggesting that they should in fact be considered distinct disease entities.

With regard to the question of the Kiel category of immunocytoma, Lennert himself showed that the lymphoplasmacytoid type had both immunophenotypic and clinical features virtually indistinguishable from B-CLL,5 and different from the lymphoplasmacytic type. Lymphoplasmacytic immunocytoma is acknowledged in the Kiel classification to be identical to Waldenström's macroglobulinemia.6 Therefore, we found it surprising that the two types of immunocytoma were left lumped together in the updated Kiel classification, and believe that our decision to separate them and merge the lymphoplasmacytoid type with B-CLL is logical. Because the treatment results reported for immunocytoma in the Kiel classification will include two distinct diseases—B-CLL and Waldenström's—no conclusions can be drawn from them.

The comments of Demeter et al about hairy cell leukemia are interesting and informative, and provide support for our contention that each neoplasm needs to be treated as a distinct disease entity,
not simply considered low grade or high grade. Needless to say, a
detailed exposition of all the clinical and immunologic features of
each lymphoid neoplasm was beyond the scope of our review, and
additional markers and treatment options could have been mentioned
for many of the entities that we listed.

Finally, Demeter et al contend that our proposed classification
must be used together with another classification, such as Kiel, to
decide whether patients should be treated aggressively. We of course
agree that our classification can be used together with the Kiel classi-
fication or the working formulation, as we suggested in our paper.
However, clinicians should recognize that the grades in the Kiel
classification are not clinical prognostic groups; they are histologic
grades that were established based on morphologic criteria without
regard to treatment response or outcome. Indeed, some tumors classi-
fied as low grade, such as centrocytic lymphoma and many of the
peripheral T-cell lymphomas (lymphoepithelioid, angioimmunoblas-
tic type, T zone, and pleomorphic small cell) can behave in an
aggressive clinical fashion. Demeter et al should also note that
using the Kiel categories of low grade and high grade to determine
treatment would result in lumping together B-CLL, B-PLL, immuno-
cyctoma, and HCL as low-grade lymphomas—entities that these au-
thors seem to feel have important differences in response to treatment
and curability.

However, we strongly disagree that our classification can be useful
only in the context of other classifications to have clinical relevance.
First, we did describe in our paper the clinical behavior as it is cur-
tently understood for each entity, and inherent in those descriptions
are the factors that guide treatment according to current protocols.
Second, clinicians should demand more in a tumor classification than
simply "support [for] treatment decisions." They should demand that
pathologists define distinct disease entities, which will permit them
to develop optimal treatments. The current need to lump distinct
diseases into broad treatment categories is an acknowledgment of our
failure to date to find the best therapy for each disease. Despite their
call for broad prognostic groups, it is clear from their comments about
the lymphoid leukemias that Demeter et al agree in practice with
our basic principle of delineating and treating distinct disease enti-
ties.

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