T-cell/histiocyte-rich large B-cell lymphoma: review on pathologic diagnosis, current therapeutic options and new targets for therapy

J. Cornillie, T. Tousseyn, G. Verhoef

T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) is a rare variant of diffuse large B-cell lymphoma (DLBCL) with an aggressive behaviour. Clinically, THRLBCL affects a young, predominantly male population. Pathologically, it is characterised by fewer than 10% of large neoplastic B-cells in a background of abundant T-cells with or without the presence of histiocytes. Differentiating THRLBCL from other lymphoproliferative disorders can be difficult but is achieved by morphologic and immunohistochemical characterisation of the tumour cells in the appropriate stromal microenvironment. Despite these clinical and pathologic differences, treating THRLBCL is not different from treating stage-matched DLBCL and can result in a comparable outcome. Comparative studies, however, on outcome of THRLBCL and DLBCL are methodologically weak and include small numbers of patients. Recently, gene expression profiling showed a predominant role for a distinct host immune response in THRLBCL, leading to tumor tolerance. Targeting specific molecules responsible for this tumour tolerance could lead to novel therapeutic options.

(Belg J Hematol 2012;3: 128-133)

Introduction

Currently, T-cell/histiocyte rich large B-cell lymphoma (THRLBCL) is considered as a rare morphologic variant of diffuse large B-cell lymphoma (DLBCL), representing 1% to 3% of all B-cell lymphomas.[1] In current practice, standard therapeutic regimens for DLBCL are also applied for THRLBCL. Multiple study groups focused on comparing outcome between DLBCL and THRLBCL. Some studies showed comparable outcome,[2-4] another study suggested worse prognosis for patients with THRLBCL compared to DLBCL.[5] This dichotomy results in uncertainty about the best therapeutic options when THRLBCL is diagnosed. This review discusses the clinical and biological differences between DLBCL and THRLBCL and aims at formulating recommendations for optimal treatment of THRLBCL.

T-cell/histiocyte-rich large B-cell lymphoma

Clinical characteristics

Clinical features of patients included in four previously published clinical series on THRLBCL are shown in *Table 1*. According to these data THRLBCL affects a

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Key words: T-cell/histiocyte rich large B-cell lymphoma (THRLBCL); diffuse large B-cell lymphoma (DLBCL); Rituximab-CHOP; tumour microenvironment

Table1. Literature review on clinical characteristics of THRLBCL.

	Achten et al, 2002[5]	GELA study, 2003[2]	Aki et al, 2004[3]	El Weshi et al, 2007[4]
No. of patients	40	50	21	61
Study period, years	10	10	4	10
Male sex, %	72	88	57	70
Median age, years	49	47	46	30
Spleen involvement, %	60	60	52	43
Liver involvement, %	40	33	31	33
Bone marrow involvement, %	17	31	27	33
Raised LDH level, %	55	60	54	57
Ann Arbor stage, %				
I-II	18	19	29	34
III-IV	82	81	71	66

young population with a male predominance. In these series liver, spleen and bone marrow are the most common sites of extranodal disease in THRLBCL. These observations are in contrast with the clinical presentation of DLBCL, which generally affects older people with only a minor male predominance. Organomegaly and bone marrow involvement at presentation are unusual in DLBCL.[5]

Pathology

1. Diagnostic criteria

T-cell rich B-cell lymphoma (TCRBCL) was first described in 1988 by Ramsay et al.[6] Five cases, previously misdiagnosed as T-cell lymphoma, were found to have a large malignant B-cell population surrounded by non-neoplastic T-cells. In 1992 Delabie et al. introduced the term 'Histiocyte-Rich B-cell Lymphoma' describing six cases of T-cell rich B-cell lymphoma in which the neoplastic T-cell environment consisted of numerous reactive histiocytes.[7]

However, these definitions were applicable to a large variety of B-cell lymphomas, some of which presented as mild disease, while others rapidly progressed to end-stage disease. This observation led Achten et al. to suspect that not only TCRBCL but also other lymphomas are characterised by an infiltrate of reactive T-cells and that additional criteria had to be used to differentiate TCRBCL from other similar clinicopathologic entities. They evaluated sixty cases of TCRBCL over a period of ten years (1992-2002).[5] Through a morphologic and immunophenotypic examination of the samples they were able to define four diagnostic criteria for THRLBCL: (1) a diffuse or vaguely nodular pattern of the neoplastic infiltrate; (2) the presence of large neoplastic B-cells that do not express CD15 and that account for a minority of the total cell population; (3) a prominent background infiltrate, composed of both T-cells and non-epitheloid histiocytes; (4) minimal presence of small B-cells in neoplastic areas.[5] THRLBCL was recognized by the World Health Organization as a distinct pathologic entity for the first time in 2001, in the latest 2008 edition it was characterised by a limited number of scattered, large, atypical B-cells embedded in a background of abundant T-cells and frequent histiocytes.[8,9]

2. Immunohistochemical features of THRLBCL

Immunohistochemical analysis revealed that neoplastic B-cells in THRLBCL express CD20 and CD45, in contrast to Reed-Sternberg cells of Hodgkin lymphoma. These neoplastic B-cells only rarely express CD30 and do not express CD15.[10] Up to 50% of THRLBCL express Bcl-2, a known negative prognostic marker in DLBCL.[10,11] The non-neoplastic stromal environment is histochemically characterised by lymphocytes with a CD3+/CD5+ profile, which may be CD4+ or CD8+, and typically CD68+ histiocytes.[10]

3. Differential diagnosis

At low power examination, classical Hodgkin's lymphoma (cHL) can mimic THRLBCL as it is characterised by minimal neoplastic cells embedded in a reactive inflammatory stroma.[10,12] Neoplastic cells in THRLBCL can appear like Reed-Sternberg cells, as typically seen in cHL. Both entities, however, show an opposite immunohistochemical profile. In contrast to Reed-Sternberg cells, the neoplastic cells in THRLBCL are negative for CD15, rarely positive for

CD30 and always positive for CD45 and CD20. Based on this difference, Achten et al propose the combined use of CD15 and CD20 to differentiate between lymphocyte-rich cHL and THRLBCL.[12]
More difficult is the distinction between nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) and THRLBCL. THRLBCL macroscopically often has a diffuse appearance, but can also present with a nodular pattern in as much as 75% of cases, thus causing confusion with NLPHL.[12] In addition, the immunohistochemical pattern of the neoplastic cells in THRLBCL and NLPHL is identical. Differential diagnosis on a pathological basis has to rely on characteristics of the tumoral reactive environment. While in NLPHL reactive B-cells predominate, these are rare or absent in THRLBCL.[12] Also, rosettes of CD57+ T-lymphocytes often surround the neoplastic lymphocyte-predominant cells in NLPHL but remain absent in THRLBCL. CD21+ or CD23+ follicular dendritic cells are always partially present in NPLHL but are lacking in THRLBCL.[10]

Treatment and prognosis

In 2002, a study group from Leuven reported retrospectively on forty cases of THRLBCL over a period of ten years.[5] Therapy was heterogeneous and included different chemotherapy schemas, no patients were treated with Rituximab. The median treatment failure-free survival (FFS) and median overall survival (OS) were respectively five and thirty-one months.[5] Relapse after a complete remission was usually observed early in the course of the disease and few patients relapsed after three years. These observations led Achten et al. to conclude that THRLBCL is a very aggressive form of lymphoma that requires more aggressive therapeutic regimens. They propose high-dose chemotherapy followed by stem-cell transplantation as initial treatment.[5]

In 2003, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) published the first matched-control analysis to compare outcome after chemotherapy in a patient group with THRLBCL (n=50) compared to DLBCL (n=150).[2] In the THRLBCL patient population, complete remission was achieved in 63% compared to 77% in the DLBCL patient group. The 5-year overall survival (OS) and event-free survival (EFS) in the THRLBCL patient group were 58% ± 18% (mean ± SD) and 53% ± 16% respectively,

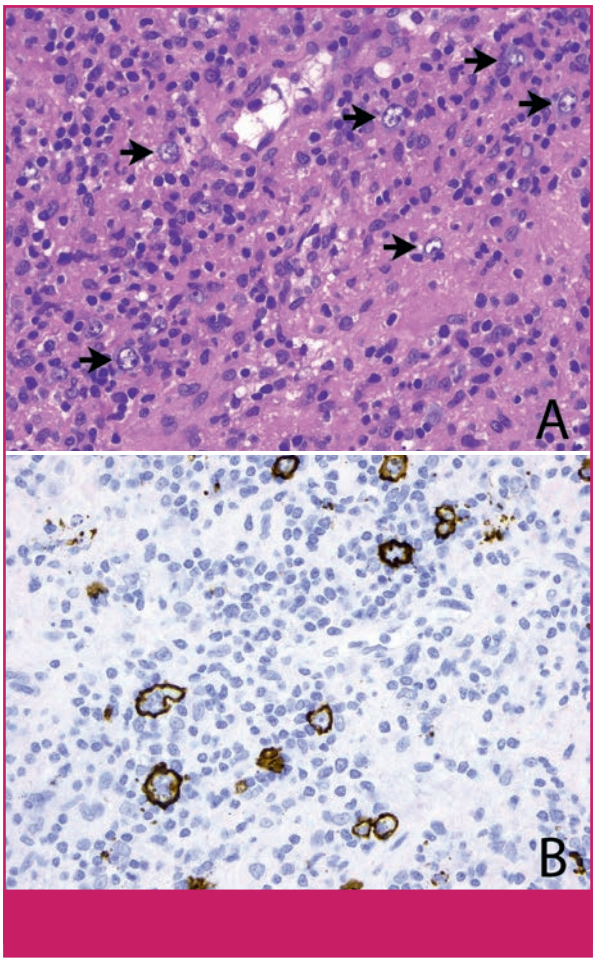

Figure 1. (A) High power magnification of a lymph node involved by sparse large neoplastic cells (arrows), in a background of non-neoplastic lymphocytes and histiocytes (Hematoxylin and Eosin, 400X). (B) The large neoplastic cells express the pan-B-cell marker CD20 (400X).

whereas in the DLBCL patient group OS and EFS were 58% ± 10% and 51% ± 10%.[2] These findings led the GELA study group to conclude that, despite a trend (P=0.06) toward better response to therapy for patients with DLBCL compared to THRLBCL, there is no statistical significant difference between the two groups in terms of overall survival and event-free survival. They conclude that no different therapeutic regimens were recommended.[2]

A Turkish study retrospectivelly selected twenty-one cases of THRLBCL from lymphoma samples diagnosed over a period of four years.[3] These were compared with fourty-three control patients with DLBCL. After CHOP chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone), 56% of patients with THRLBCL and 79% of patients

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No. of patients	40	50	21	61
Study period, years	10	10	4	10
CR, %	43	63	52	59
Median follow-up, months	22.5	39	17	22
OS, %	50	58	64	46
EFS, %	44	53	48	39

with DLBCL achieved a complete remision. Despite this difference in complete remision, sustained complete remision was achieved in all ten THRLBCL patients but only in twenty-seven of thirty-four DLBCL patients.[3] Consistent with the GELA study, Aki et al conclude that there is no need for specific therapeutic strategies for THRLBCL.

The most recent study concerning the management and outcome of THRLBCL is a retrospective study with a total study population of sixty-one cases of THRLBCL.[4] Fifty-nine patients were treated with CHOP chemotherapy, with additional Rituximab in ten patients. Complete remission (CR) was observed in 59% of patients. The amount of relapsers after CR in this study was 39%.[4] A possible explanation of this high relapse rate is the high rate of patients with stage IV disease included in this study.

Studies published on THRLBCL were retrospective, therapeutic strategies were heterogeneous and not properly defined and small patient populations were included. Also the introduction of new therapeutic options such as Rituximab makes it difficult to compare studies on outcome of THRLBCL. Only preliminary conclusions can thus be drawn and the need for better designed randomized, prospective, controlled clinical trials has to be emphasized.
Table 2 shows an overview of complete remission, overall survival and event-free survival in the studies publised on THRLBCL, using the 2001 WHO criteria as including criteria.

New targets for therapy

Antitumoral therapy is mainly focused on eradicating malignant cells. However, recently it became clear that not only the tumor cells, but also the tumoral microenvironment and particularly the tumor-host interaction plays a key role in the behavior of a malignancy.[13] Recently a tolerogenic host immune response was described in THRLBCL.[14] On ten cases of THRLBCL and ten cases of NLPHL microarray gene expression studies were performed. One of the genes being up-regulated and expressed at a higher level in THRLBCL was the gene encoding CCL8, a potent chemoattractant for histiocytes and macrophages. This may explain the histiocyte-rich microenvironment in THRLBCL. The gene encoding IFN-gamma was also found to be upregulated. IFN-gamma is known to play a key role in tumoral tolerance, activating the macrophages and histiocytes to produce tryptophane-degrading enzyme indoleamine-2,3-dioxygenase (IDO).[14,15] High levels of IDO suppress effector T-cells, promoting tumor immune tolerance.[15] The understanding of this distinct tolerogenic host immune response is important as it may lead to the identification of new therapeutic targets. The search for inhibitors of these enzymes resulted in the identification of 1MT, a competitive inhibitor of IDO.[13,15] Recent in vivo studies showed that tumor growth in rodents was slowed down using IDO-inhibitors.[16] In the future, further investigation is required to use CCL8, IFN-gamma or IDO as potential targets for therapy.
The development of immunohistochemistry led to the identification of tumor-specific antigens, which can be used as a target for therapy with monoclonal antibodies. Rituximab, a monoclonal chimeric antibody that targets the CD20 antigen on the surface of B-cell lymphomas, is included in the standard treatment for DLBCL and THRLBCL. Multiple new second-generation antibodies are being developed.[17] These are not chimeric, but humanised or 'fully' human antibodies. Human antibodies are believed to be less immunogenic than chimeric antibodies and this may result in less side effects as well as better sustained efficacy. Anti-CD22 antibody (Epratuzumab), anti-CD80 antibody (Galiximab) and anti-CD40

Key messages for clinical practice

1. T-cell/histiocyte-rich large B-cell lymphoma is a relatively newly recognized clinicopathological entity. It can be distinguished from diffuse large B-cell lymphoma by different clinical and pathologic features and is characterised by an aggressive behavior.
2. Treating THRLBCL identically as DLBCL with standard chemotherapy (Rituximab-CHOP) seems to result in a relatively comparable outcome. Therefore, first-line treatment of THRLBCL with R-CHOP is recommended until more evidence is published.
3. Several new therapeutic agents for aggressive B-cell lymphomas have emerged recently, attacking the malignant cells as well as the tumoral microenvironment.
4. In the future, gene expression profiling may result in individually adapted therapies.

antibody (Dacetuzumab) were also studied in DLBCL, but these could not prove superiority when compared to Rituximab.[17] Bevacizumab, which binds vascular endothelial growth factor, is a promising agent since DLBCL often is accompanied by important neo-angiogenesis. In clinical trials, however, the agent showed cardiac toxic effects without substantial benefit.[17] Development of antibody-toxin conjugates, which deliver a toxic agent selectively to malignant cells, are evaluated in phase 1 and 2 trials for B-cell non-Hodgkin lymphoma.[17]

Multiple well-described pathways in malignant lymphomas are potential targets for therapy. Fostamatinib disodium (FosD) is a tyrosine kinase inhibitor that attacks spleen tyrosine kinase, which is known to play a crucial role in B-cell lymphoma proliferation, growth and survival. In a phase I/II trial 22% of DLBCL patients responded to therapy with FosD.[17] Temsirolimus and everolimus inhibit m-TOR, an important kinase for cell growth in malignant lymphomas. Sorafinib, a multikinase inhibitor, is a promising agent already approved for treatment of advanced renal cell carcinoma and hepatocellular carcinoma. It shows in vitro effect on lymphomas but until now no clinical trials were designed to evaluate Sorafinib in malignant lymphoma.[18] Bendamustine activates a p53-dependent pathway leading to apoptosis of malignant cells. This therapy has recently been approved in Europe for treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL) and multiple myeloma.[18]

Conclusion

T-cell/histiocyte-rich large B-cell lymphoma is a relatively newly recognized clinicopathological entity. It can be distinguished from large B-cell lymphoma by different clinical and pathologic features and is characterised by an aggressive behavior. Based on the above reviewed study results, current practice of treating THRLBCL identically as DLBCL should be continued and recommended. This, however, does not rule out that further improvement could be obtained by investigation on new therapeutic targets. Over the last decade, a broad range of novel agents have been designed and these may play a role in the future managment of aggressive B-cell lymphoma and THRLBCL. In the future, gene expression profiling and immunohistochemistry will make it possible to identify an individual's lymphoma targets. These individualized targets may lead to optimal combinations of standard care together with drugs addapted to the specific characteristics of the malignant cells in an individual patient.

References

1. Pfreundschuh M, Trümper L, Kloess M, et al. Two-weekly of 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: results of the NHL-B1 trial of the DSHNHL. Blood 2004; 104(3): 626-33.

2. Bouabdallah R, Mounier N, Guettier C, et al. T-Cell/Histiocyte-Rich Large B-Cell Lymphomas and Classical Diffuse Large B-cell Lymphomas Have Similar Outcome After Chemotherapy: A Matched-Control Analysis. J Clin Oncol. 2003; 21(7): 1271-7.

3. Aki H, Tuzuner N, Ongoren S, et al. T-cell-rich B-cell lymphoma: a clinico-

pathologic study of 21 cases and comparison with 43 cases of diffuse large B-cell lymphoma. Leukemia Research 2004; 28: 229-36.

4. El Weshi A, Akhtar S, Mourad WA, et al. T-cell/histiocyte-rich B-cell lymphoma: Clinical presentation, management and prognostic factors: report on 61 patients and review of literature. Leukemia & Lymphoma 2007; 48(9): 1764-73.

5. Achten R, Verhoef G, Vanuytsel L, et al. T-cell/histiocyte-rich large B-cell lymphoma: a distinct clinicopathologic entity. J Clin Oncol. 2002; 20(5): 1269-77.

6. Ramsay AD, Smith WJ, Isaacson PG. T-cell-Rich B-Cell Lymphoma. Am J Surg Pathol 1988; 12: 433-43.

7. Delabie J, Vandenberghe E, Kennes C, et al. Histiocyte-Rich B-Cell Lymphoma. A distinct clinicopathologic entity possibly related to lymphocyte predominant Hodgkin's disease, paragranuloma subtype. Am J Surg Pathol 1992; 16(1): 37-48.

8. De Wolf-Peeters C, Delabie J, Campo E, et al. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymfoid Tissues. Lyon, France: IARC Press; 2008; 238-9.

9. Tousseyn T, De Wolf-Peeters C. T-cell/histiocyte-rich large B-cell lymphoma: an update on its biology and classification. Virchow Arch. 2011; 459(6): 557-63.

10. Abramson JS. T-cell/histiocyte-rich B-cell lymphoma: biology, diagnosis, and management. Oncologist 2006; 11(4): 384-92.

11. Gascoyne RD, Adomat SA, Krajewksi S, et al. Prognostic significance of Bcl-2 protein expression and bcl-2 gene rearrangement in diffuse aggressive non-Hodgkin's lymphoma. Blood 1997; 90: 244-51.

12. Achten R, Verhoef G, Vanuytsel L, et al. Histiocyte-rich, T-cell-rich B-cell lymphoma: a distinct diffuse large B-cell lymphoma subtype showing characteristic morphologic and immunophenotypic features. Histopathology 2002; 40: 31-45.

13. Muller AJ, Scherle PA. Targeting the mechanisms of tumoral immune tolerance with small-molecule inhibitors. Nature Rev. Cancer 2006; 6: 613-25.

14. Van Loo P, Tousseyn T, Vanhentenrijk V, et al. T-cell/histiocyte-rich large B-cell lymphoma shows transcriptional features suggestive of a tolerogenic host immune response. Haematologica 2010; 95(3): 440-8.

15. Löb S, Königrainer A, Rammensee H-G, et al. Inhibitors of indoleamine-2,3-dioxygenase for cancer therapy: can we see the wood for the trees? Nature Rev. Cancer 2009; 9: 445-52.

16. Hou D-Y, Muller AJ, Sharma MD. Inhibition of indoleamine 2,3-dioxygenase in dendritic cells by stereoisomers of 1-methyl-tryptophan correlates with antitumor responses. Cancer Res 2007; 67: 792-801.

17. Murawski N, Pfreundschuh M. New drugs for aggressive B-cell and T-cell lymphomas. Lancet Oncol 2010; 11: 1074-85.

18. Reeder CB, Ansell SM. Novel therapeutic agents for B-cell lymphoma: developing rational combinations. Blood 2011; 117(5): 1453-62.