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Treatment of lymphocyte-predominant Hodgkin lymphoma

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background

Lymphocyte-predominant Hodgkin lymphoma (LPHL) was first described as Hodgkin's paragranuloma by Jackson and Parker in 1944 [1]. Subsequently, a number of different terms such as lymphocytic-predominant Hodgkin's disease or lymphocytic and histiocytic-predominant Hodgkin's disease were used [2]. LPHL is rare, accounting for ∼5% of all Hodgkin lymphoma (HL) cases in western countries [3]. LPHL and classical HL (cHL) differ substantially in their histopathology and clinical cause. Histologically, LPHL can present with two distinct morphological patterns: nodular and diffuse. The nodular subtype is characterized by the presence of atypical lymphocytic and histiocytic (L&H) or popcorn cells that are embedded in a nodular background of small B lymphocytes and other reactive cells. In the diffuse subtype, the L&H cells are set against a diffuse background consisting mainly of reactive T cells. However, it remains controversial whether the diffuse subtype can be discriminated reliably. According to the current WHO definition, at least a partial nodular pattern is required for the diagnosis of NLPHL [4]. Compared with cHL, LPHL has been associated with less aggressive tumor growth and lymphadenopathy often preceding the diagnosis for many years [5]. Since the treatment of patients with LPHL results in complete remission (CR) in >95% of patients, the need for different treatment approaches particularly for early-stage patients has been questioned recently.

diagnostic procedures

Using a conventional histology only, nearly 50% of LPHL cases are misdiagnosed [6]. Differential diagnosis includes cHL, lymphocyte rich-cHL, non-Hodgkin lymphoma and reactive hyperplasia. Thus, immunohistology is required for the diagnosis of LPHL. L&H cells usually express CD20 and lack CD15 and CD30 which are the characteristic markers of cHL [7]. The differential diagnosis of NLPHL and related lymphomas is shown in Table 1.

Table 1. Differential diagnosis of LPHL and related lymphomas

	LPHL	CHL[a]	ALCL	TCRBCL
CD30	−	+	+	−
CD15	−	+	−	−
CD20	+	(+)	−	+
CD3	−	−	(+)	−
EMA	+	−	+	−

[a]Including LRcHL.

stage IA LPHL

The prognosis for this group of patients is extremely favourable with >95% achieving CR and excellent long-term outcome. Thus, different treatment modalities such as watch and wait, radiotherapy only, combined modality treatment or, more recently, the anti CD20 monoclonal antibody rituximab have been evaluated in this patient population. An analysis of stage IA LPHL in children treated within a French phase II study showed no difference in overall survival between those receiving surgical adenectomy only ($n = 13$) and those who had additional treatment ($n = 14$) [8]. However, only three of nine patients remained in CR after lymphadenectomy alone whereas 15 children not in CR after lymphadenectomy had a worse prognosis using watch and wait. Overall event-free survival was 90% with combined modality and 42% with watch and wait ($P < 0.04$). Thus, watch and wait cannot generally be recommended in stage IA LPHL patients. A more recent analysis by the German Hodgkin Study Group (GHSG) compared different radiation fields in 131 LPHL stage IA patients. Of these, 45 patients were treated with extended field (EF) radiotherapy, 45 patients had involved field (IF) radiotherapy and 41 patients received combined modality treatment (CM). With a median follow-up of 78 months (EF), 40 months (CM) and 17 months (IF), there were no significant differences between treatment groups with 98% (EF), 100% (IF) and 95% (CM) of patients reaching CR. With a median follow-up of 43 months, there were 5% relapses and only three patients had died. Thus, IF seems to be really effective and is being regarded as standard in this group of patients though longer follow-up is required [9].

treatment of advanced-stage LPHL

A comprehensive retrospective analysis of all LPHL patients compared with cHL patients was performed by the GHSG [10]. From a total of 394 LPHL patients, 63% were in early

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favourable stages, 16% were in early unfavourable stages and 21% in advanced stages. Overall, 87.5% of patients with LPHL and 81.7% of 7904 cHL patients achieved CR ($P = 0.0034$). Also for the subgroup of early favourable patients, there were significant differences in response (91.6% versus 85.9%; $P = 0.0145$). General risk factors for treatment failure as measured by freedom from treatment failure included advanced stage, low haemoglobin and lymphopenia (Table 2).

new approaches

Given that both the malignant L&H cells and the reactive background are strongly positive for the B-cell marker CD20, the chimeric anti-CD20 monoclonal antibody rituximab was evaluated in phase II studies in LPHL patients, demonstrating impressive activity even in those with multiple relapses [11, 12]. A recent update of the GHSG trial confirmed these earlier reports with 92% of patients alive and 50% progression free after a median observation time of 63 months [13]. On the basis of these provocative data, the GHSG has conducted a phase II study with standard-dose rituximab in stage IA LPHL patients. In addition, there are reports that rituximab might also be effective in cHL. Here, a combination of rituximab and ABVD resulted in event-free survival of 85% and overall survival of 88% [14]. Thus, our group is currently evaluating the additional use of rituximab in PET-positive advanced-stage cHL patients receiving eight cycles of $BEACOPP_{escalated}$.

Table 2. Multivariate analysis for freedom from treatment failure including international prognostic score and follicular lymphoma international prognostic index modified according to GHSG risk factors

Risk factor	LPHL	cHL
Male sex	0.8499	<0.0001
Age 45 years	0.3680	<0.0001
Advanced stage	0.0092	0.0098
Albumin <4 g/dl	0.8175	0.0762
Haemoglobin <10.5 g/dl	0.0171	0.0016
Leukocytes >15 000/μL	0.9894	0.0057
Lymphopenia[a]	0.0100	0.1546
Serum LDH > ULN	0.8571	0.6531
Three nodal areas	0.0703	0.0001
Elevated ESR[b]	0.5776	0.0098
Extranodal involvement	0.4525	<0.0001

[a]Lymphopenia <8% of white blood count.
[b]ESR 50 mm/h without B symptoms and 30 mm/h with B symptoms.
Abbreviations: cHL, classical Hodgkin's lymphoma; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; LDH, lactate dehydrogenase; LPHL, lymphocyte-predominant Hodgkin's lymphoma; ULN, upper limit of normal.

references

1. Jackson H, Parker F. Hodgkin's disease II. Pathology. N Engl J Med 1944: 231.
2. Lukes RJ, Butler JJ. The pathology and nomenclature of Hodgkin's disease. Cancer Res 1966; 26: 1063–1083.
3. Diehl V, Sextro M, Franklin J et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's disease: Report from the European Task Force on Lymphoma Project on Lymphocyte-Predominant Hodgkin's Disease. J Clin Oncol 1999; 17: 776–783.
4. Jaffe E, Harris NL, Stein H et al. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press 2001; 240–243.
5. Connors JM. Lymphocyte-predominant Hodgkin's lymphoma. In American Society of Hematology Education Program Book. Washington, DC: American Society of Hematology 2001; 187–190.
6. Thomas RK, Re D, Wolf J et al. Part I: Hodgkin's lymphoma—molecular biology of Hodgkin and Reed–Sternberg cells. Lancet Oncol 2004; 5: 11–18.
7. Anagnostopoulos I, Hansmann ML, Franssila K et al. European Task Force on Lymphoma Project on Lymphocyte Predominant Hodgkin Disease: Histologic and immunohistologic analysis of submitted cases reveals 2 types of Hodgkin disease with a nodular growth pattern and abundant lymphocytes. Blood 2000; 96: 1889–1899.
8. Pellegrino B, Terrier-Lacombe MJ, Oberlin O et al. Lymphocyte predominant Hodgkin's lymphoma in children: therapeutic abstention after initial lymph node resection—a study of the French Society of Paediatric Oncology. J Clin Oncol 2003; 15: 2948–2952.
9. Nogova L, Reineke T, Eich HT et al. Extended field radiotherapy, combined modality treatment or involved field radiotherapy for patients with stage IA lymphocyte-predominant Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin Study Group (GHSG). Ann Oncol 2005; 16: 1683–1687.
10. Nogova L, Reineke T, Brillant C et al. Lymphocyte-predominant and classical Hodgkin's lymphoma: a comprehensive analysis from the German Hodgkin Study Group. J Clin Oncol 2008; 3: 434–439.
11. Rehwald W, Schulz H, Reiser M et al. Treatment of relapsed CD20+ Hodgkin lymphoma with the monoclonal antibody rituximab is effective and well tolerated: results of a phase 2 trial. Blood 2003; 101: 420–424.
12. Ekstrand BC, Lucas B, Horwitz SM et al. Rituximab in lymphocyte-predominant Hodgkin disease: results of a phase 2 trial. Blood 2003; 101: 4285–4289.
13. Schulz H, Rehwald U, Morschhauser F et al. Rituximab in relapsed lymphocyte-predominant Hodgkin: long-term results of a phase 2 trial by the German Hodgkin Study Group (GHSG). Blood 2008; 111: 109–111.
14. Younes A FL, Goy A et al. Results of rituximab plus ABVD in 65 newly diagnosed patients with classical Hodgkin lymphoma: Improvement of event free survival in all International Prognostic Score groups Presented at 48th American Society of Hematology Annual Meeting, December 9–12, 2006, Orlando, FL. Abstract Book 2006 776a (Abstr 2742).