MODULE 1 - HODGKIN LYMPHOMA (HL)

HL: DISEASE DESCRIPTION

Let's begin with a description of HL.

Hodgkin lymphoma (HL), sometimes referred to as Hodgkin's disease, was first recognised by Thomas Hodgkin and Samuel Wilks in the first half of the 19th century.[1]

HL is a cancer of the lymphatic system. Since lymph nodes are distributed throughout the body[2], it can occur in almost any part of the body, but it commonly occurs in the lymph nodes of the neck.

This is an uncommon cancer with approximately 6,338 cases in men and 5,439 in women diagnosed in the EU each year.[3] The WHO classifies HL into two variants[2] :

- Classical Hodgkin lymphoma (CHL) comprises 95% of all cases
- Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), comprises 5% of all cases.

HL: MORPHOLOGICAL CHARACTERISTICS

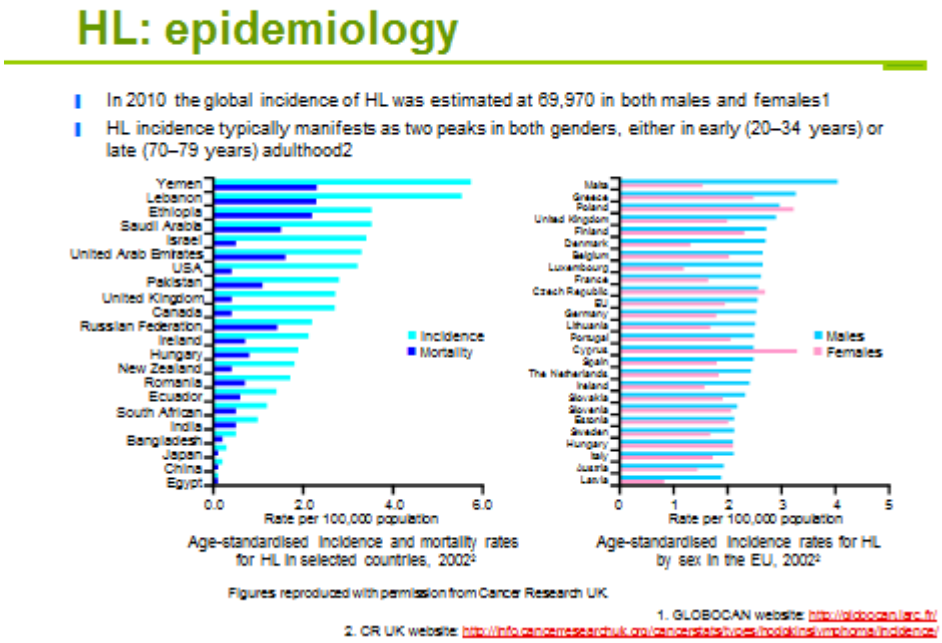
The two types of HL differ in their morphology, immunophenotype, and their microenvironment. [4,5] CHL is characterised by the presence of Reed-Sternberg (RS) cells.[4] NLPHL lacks RS cells and is instead characterised by the presence of popcorn cells, also known as lymphocyte predominant (LP) cells.[5]

Reed-Sternberg (RS) cells are thought to derive from naïve germinal centre (GC) B cells, while LP cells derive from antigen-selected GC B cells.[6] CD15 and CD30 are characteristic markers expressed by RS cells, while LP cells express CD20 and lack CD15 and CD30.[7] RS and LP tumour cells usually account for 0.1% to 10% of cells in tissue.[4]

HL: CHL

CHL is further subdivided into four subtypes, nodular sclerosis (NS), mixed cellularity (MC), lymphocyte rich (LR) and lymphocyte depleted (LD). This classification has been adopted by the World Health Organization (WHO).[8,9]

HL: EPIDEMIOLOGY



In 2010 the global incidence of HL was estimated at 69,970 in both males and females.[10] The graph on the left shows the age-standardised incidence and mortality rates for HL in selected countries around the globe in 2002.[10]

HL incidence survival rates are dependent on gender, race and age.[10]

It should be noted that in Western countries there is a clear bimodal age incidence in both genders with an early peak in young adults aged 20-34 years, followed by a second peak in older adults aged 70-79 years. In the Middle East and parts of Asia, the peak is more pronounced in early childhood.[10]

The crude incidence of HL in the European Union is 2.2/100,000 per year, the mortality 0.7/100,000 per year. The graph on the right shows the age-standardised incidence rate for HL by sex in the EU in 2002.[11]

Let's pause for a quick knowledge check. Answer the question on the screen and to see what you remember thus far.

KNOWLEDGE CHECK

What percentage of patients have CHL and what percentage of patients have NLPHL?

1. CHL: 95%, NLPHL 5%
2. CHL: 85%, NLPHL 15%
3. CHL: 75%, NLPHL 25%
4. CHL: 65%, NLPHL 35%

HL: SURVIVAL RATES

The improvement in 5-year survival rates for HL is unmatched in any other cancer type over the past four decades.[12]

The graph shows the UK HL mortality statistics trend in men and women from 1971 to 2007. You can see that in the UK, compared with survival in the early 1970s, the 10 year survival rate for 2010 was predicted to have increased from less than 50% to approximately 78%.[13]

In fact, in the UK and Wales, the 10-year relative survival for adults (15 to 99 yrs) diagnosed with HL was 49% between 1971–72. The survival rates increased to 77.9% by 2007.[13]

Since HL is a rare cancer with high cure rates, drug development is slow. No new HL drugs have been approved by the FDA in more than three decades.[12]

HL: PREDISPOSING FACTORS

The exact cause of HL is unknown, and most people who develop the disease do not have any particular risk factor. That said, some predisposing factors have been identified.[13]

One factor is age, with the highest risk of developing HL during adolescence and early adulthood.[13] Another factor is occupational exposure, including uranium radiation and smoking.[14] A third factor is childhood environment. Findings from one study related the susceptibility to young/adolescent HL to an aberrant cytokine response pattern that resulted from reduced microbial exposures in childhood. Viral infections with Epstein Barr virus (EBV)[15] and HIV[16], both of which affect the immune system are also predisposing factors for HL. EBV, is a ubiquitous human herpes virus. It was first thought to be involved in the pathogenesis of HL when it was detected in HL cells.

The incidence of HL is also known to increase in patients with HIV/AIDS.[16] This incidence has been reported to be higher in patients receiving HIV antiretroviral therapy.[17]

HL: CLINICAL PRESENTATION (1)

Patients with CHL typically present with asymptomatic lymph node enlargement, commonly in the neck.[18] Occasionally mass lesions may be found in other organs, such as the spleen, bone marrow, liver, bone or lungs.[19]

This screen shows the percentage of patients who have each of the most common manifestations of HL.

HL: clinical presentation (1)

- Patients with CHL typically present with asymptomatic lymph node enlargement, commonly in the neck[1]
- Occasionally mass lesions may be found in other organs, such as the spleen, bone marrow, liver, bone or lungs[2]

Common manifestations of HL	Occurrence
Lymphadenopathy	
Supradiaphragmatic	90%
Infradiaphragmatic	10%
Extranodal disease	
No extranodal extension	75%
Localised, contiguous with involved lymph nodes	10%
Disseminated (liver, lung, bone, bone marrow)	
Classical	15%
Nodular lymphocyte predominant	5%
B-Symptoms	35%

1. Gospodarowicz MK, Cancer J. 2009;15:138–42.
2. Connors JM, Cancer J. 2009;15:124–28.

The most common manifestation of HL in younger patients is the development of persistent, painless, firm (but not hard), supradiaphragmatic lymphadenopathy, typically in the neck. HL typically spreads in a predictable fashion from one set of lymph nodes to adjacent groups.[20]

HL: CLINICAL PRESENTATION (2)

The clinical presentation of CHL depends on the geographic region, age of the patient and co-infections, or diseases affecting the immune status of the patient.[21]

In developing countries clinical presentation may lack the bimodal age pattern[21] that is more evident in developed countries. Immunocompromised patients (with HIV), typically present with extranodal disease with B symptoms.[21] Clinical presentation has also been affected by other co-infections such as Epstein Bar Virus (EBV), that affect the immune status of the patient. Patients over the age of 60 often show subdiaphragmatic disease, mixed cellularity histology and B symptoms.[21]

The way that NLPHL presents clinically is somewhat different from how CHL presents. NLPHL is associated with less aggressive tumour growth and lymphadenopathy, usually preceding diagnosis for many years.[21,22] Other clinical characteristics of NLPHL include rare occurrence of systemic symptoms, and a low frequency of site-specific organ involvement.[23]

HL: STAGING

HL is defined by four stages that are based on the Ann Arbor staging system.[24]

At Stage I, HL is present in a single lymph node region, or there is localised involvement of single extralymphatic organ/site.[24]

At Stage II, there is involvement of ≥2 lymph node regions on same side as diaphragm or localised involvement of single associated extralymphatic organ/site and its regional lymph node(s). These

may occur with or without involvement of other lymph node regions on the same side of the diaphragm.[24]

At Stage III, there is involvement of lymph nodes regions on both sides of diaphragm, which may also be accompanied by localised involvement of an associated extralymphatic organ or site, by involvement of the spleen, or by both.[24]

At Stage IV, there is disseminated (multifocal) involvement of ≥1 extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.[24]

The stages are further described according to the presence of A, B, E or X symptoms. A means that no systemic symptoms are present. B means that the patient has unexplained fevers (>38°C), night sweats, unexplained weight loss (>10% body weight). E means that a single extra-nodal site is involved that is contiguous or proximal to the known nodal site. X is used to describe bulky disease and can also be applied to any stage of HL.[19]

HL: WORK UP AND DIAGNOSIS

A full history and physical examination is recommended for patients who may have HL. The patient's history may show the presence of B symptoms, pruritus and alcohol-related pain, HIV status, hepatitis B, hepatitis C, cardiac disease, pulmonary disease, or renal disease. The physical examination should include checking the peripheral lymph node area, liver, and spleen.[24]

Laboratory tests should include a complete blood count, LDH, liver function tests, and ESR. For a definitive diagnosis excisional biopsy of a lymph node is recommended, although a core needle biopsy may be sufficient.[24] If the biopsy is positive, additional tests may be performed, such as imaging, bone marrow aspiration, and histology.[25]

Imaging should include a CT scan and a PET-CT scan.

Immunohistochemistry is also recommended, particularly to determine if the patient has markers such as CD15 and CD30, both of which are expressed by RS cells).

HL: PROGNOSIS AND SURVIVAL

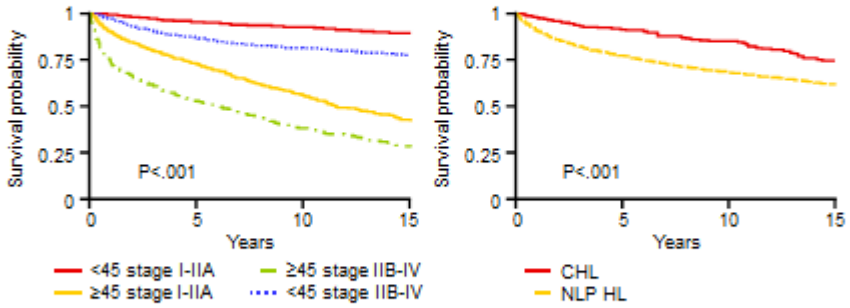
Survival of HL is influenced by age, histology, and stage of disease.[26]

The graph on the left shows survival information for patients who were diagnosed before the age of 45 and those who were diagnosed at or after the age of 45. For each age group, the graph shows the survival curve based on staging: Stage I–IIA versus Stage IIB–IV. Younger patients and those with Stage I – IIA have higher survival rates compared to patients 45 years of age and older, and those with stage IIB – IV disease.[26]

The graph on the right shows survival curves for CHL and NLPHL. As you can see, the survival curves differ for CHL and NLPHL, with the prognosis in NLPHL being better than for those with CHL.

HL: prognosis and survival

Survival rates in HL are influenced by age at diagnosis, histology and stage of disease



Survival curves by age at diagnosis (<45 yrs vs ≥ 45 years) and stage (Stage I–IIA versus Stage IIB–IV

Survival curves for CHL and NLPHL

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Shenoy P, et al. Adv Hematol. 2011;2011:725219. Epub 2010 Dec 16.

HL: PROGNOSIS (EARLY DISEASE)

A number of cooperative clinical study groups have identified risk factors which help determine prognosis in patients with early Hodgkin lymphoma. Unfavourable prognostic factors include age, histology, erythrocyte sedimentation rate (ESR), the presence of B (systemic) symptoms, mediastinal mass, and nodal sites.[27,28]

HL: PROGNOSIS (ADVANCED DISEASE)

The international prognostic system (IPS) is a seven-factor prognostic scoring system that predicts five-year rates of freedom from progression of disease and overall survival.[27] The International Prognostic Score (IPS) is based on a scale of 0 to 7, with higher scores indicating increased risk. It is the standard that is used for risk stratification of advanced stage HL.[27,28]

The IPS has been used to predict overall survival based on the number of prognostic factors in an individual. Prognostic factors include age, gender, staging, and certain laboratory values.[27]

HL: ELDERLY PATIENTS

Elderly patients over the age of 60 have a poorer risk profile compared with younger HL patients.[29]

These patients generally have poorer overall outcomes due to a number of factors.[29]

The factors include; biologically less favourable disease a lower tolerance for conventional chemotherapy due to severe treatment-associated toxicity, the need for lower-dose intensity treatment, and higher mortality during treatment.[29]

KNOWLEDGE CHECK

Let's pause for another knowledge check. Please read the question and select your answer.

What is the IPS?

1. International Position Staging
2. International Phase Scoring
3. International Prognostic System
4. International Passive Sets

HL: TREATMENT

Significant progress has been made with current regimens. More than 80% of patients with classical HL are cured by conventional therapy.[12,30] Therapy is based on disease stage and clinical presentation as well as additional prognostic factors.[25] Treatment typically involves polychemotherapy regimens that include chemotherapy with combinations of more than one agent.

HL: EARLY STAGE TREATMENT (1)

The European Society for Medical Oncology (ESMO) recommends the use of combined modality treatment (CMT) which is both chemotherapy and radiation therapy, as standard in limited stage HL.[25]

It recommends that patients receive two or three 28-day cycles of adriamycine, bleomycin, vinblastine, and darcarbazine (ABVD); followed by 30 Gy involved-field radiotherapy (IF-RT).

In the US, the National Comprehensive Cancer Network (NCCN) guidelines recommend the use of chemotherapy alone in certain cases, particularly in younger patients with favourable presentations of stage I-II non-bulky disease, especially if they experience prompt and complete response to the first 2 cycles.[24]

If using CMT, NCCN recommends using 4 cycles of ABVD, followed by 30 Gy RT. For patients with favourable disease, NCCN recommends 2 cycles of ABVD, followed by 20 Gy RT. Chemotherapy alone is also recommended in certain cases to avoid radiation induced toxicity.[31] Under these circumstances, NCCN recommends 2 cycles ABVD, followed by re-staging, followed by another 2 to 4 cycles ABVD.[24]

Stanford V treatment consists of doxorubicin (also known as 'Adriamycin'), vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone. It is recommended in stage I or II with non-bulky disease. When Stanford V is used, NCCN recommends 2 cycles over 8 weeks, followed by restaging. Consolidative irradiation should then be instituted within 3 weeks (30 Gy).[24]

HL: INTERMEDIATE STAGE TREATMENT

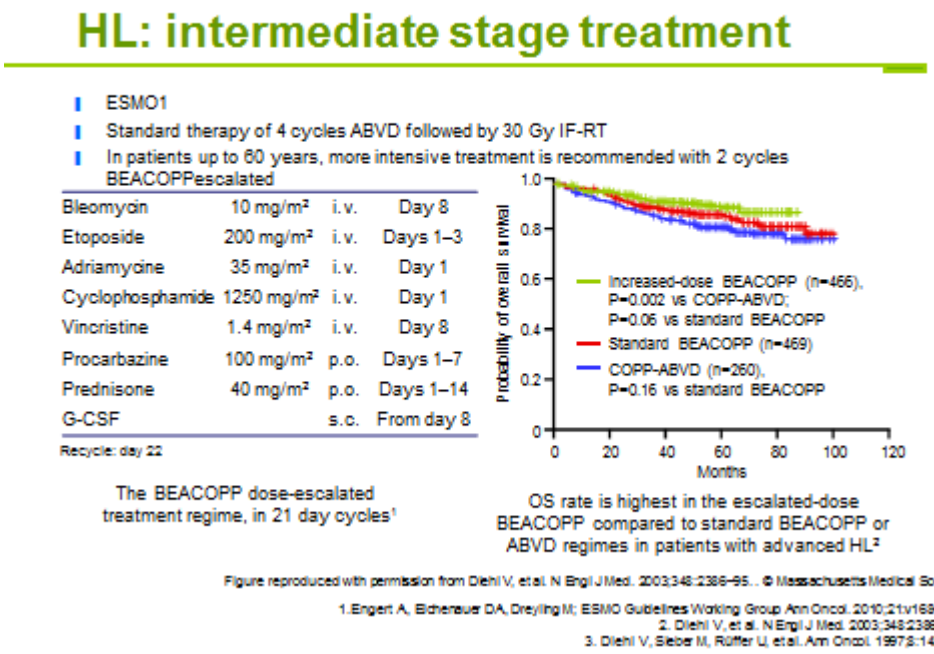
Intermediate stage disease, also referred to as stage I-II unfavourable disease, can be subdivided further into bulky or non-bulky.[25]

ESMO recommends a standard therapy of 4 cycles of ABVD, followed by 30 Gy IF-RT. In patients up to 60 years of age, ESMO recommends a more intensive treatment, consisting of 2 cycles of BEACOPP chemotherapy in escalated doses.[24]

The BEACOPP escalated regimen is mainly used in younger patients with advanced HL. It was developed to improve treatment results through dose escalation and time intensification.[31] BEACOPP consists of bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone. The BEACOPP dose-escalated treatment regimen is administered in 21-day cycles

In patients with advanced HL, the OS rate is highest in those who receive escalated-dose BEACOPP, compared to standard BEACOPP or to ABVD regimes.

The information on the screen reflects the ESMO guidelines, but there are also NCCN guidelines for intermediate stage HL.



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2. Diehl V, et al. N Engl J Med. 2003;348:2386–95
3. Diehl V, Sieber M, Rüffer U, et al. Ann Oncol. 1997;8:143–8.

NCCN guidelines recommend ABVD for 4 cycles followed by restaging. For patients who achieve complete or partial remission (CR or PR), 2-6 additional cycles of chemotherapy may be initiated.[24]

For patients who have non-bulky unfavourable disease with B symptoms, NCCN recommends 12 weeks of Stanford V and 30 Gy IF-RT. For patients who have non-bulky disease with other criteria for unfavourable disease, NCCN recommends 8 weeks of Stanford V and 30 Gy IF-RT. In bulky disease, the NCCN guidelines recommend 12 weeks Stanford V, followed by restaging and consolidative irradiation within 3 weeks (36 Gy to initial sites). [24]

HL: ADVANCED STAGE TREATMENT

Advanced stage HL is usually treated with chemotherapy only.

For patients up to 60 years old, ESMO recommends a chemotherapy regimen followed by localised RT of 30 Gy to any residual lymphomas. Chemotherapy may be either 6 or 8 cycles of ABVD every 28 days or 8 cycles of BEACOPP-escalated every 21 days. Chemotherapy should be followed by 30 Gy RT for residual lymphoma larger than 1.5 cm.[25] Treatment with BEACOPP escalated leads to superior freedom from treatment failure (FFTF) and overall survival (OS) rates, but is associated with increased toxicity.[24,25]

For patients over the age of 60, ESMO recommends 6-8 cycles of ABVD, followed by localised radiation of 30 Gy to the residual lymphoma. BEACOPP escalated is NOT recommended in elderly patients because increased toxicity has been observed in this age group.

NCCN guidelines are slightly different. They recommend 6 cycles of ABVD with restaging after 4 cycles. Two additional cycles are administered in patients with complete remission (CR) or partial remission (PR). Patients with bulky disease may have consolidative radiation therapy.[31]

Alternatively NCCN recommend the use of Stanford V for 12 weeks, followed by restaging. Consolidative irradiation should be instituted within 3 weeks (stage I–IIB, 30 Gy; stage II–IV, 36 Gy).[31]

The NCCN recommends escalated-dose BEACOPP for 4 cycles followed by restaging with PET. Additional cycles of escalated-dose BEACOPP may be required based on results from the PET scan and biopsy.[24]

HL: RELAPSED/REFRACTORY TREATMENT

Management of relapsed or treatment refractory to chemotherapy is dependent on the primary treatment used.[25] Autologous stem cell transplant (ASCT) remains a treatment of choice for patients with relapsed/refractory HL.[24]

Secondary therapy, also known as salvage therapy is recommended.[25,31] Salvage regimens such as DHAP (dexamethasone/high-dose ara-C/cisplatin) or IGEV (ifosphamide/gemcitabine/vinorelbine/dexamethasone) are given to reduce the tumour burden and mobilise stem cells before giving high-dose chemotherapy and ASCT.[31]

Disease relapse should be confirmed by biopsy.[25] For second-line/salvage therapy, there are a number of suggested regimens. ESMO guidelines recommend that most relapsed patients receive high-dose therapy (HDT) followed by ASCT.[25]

Low-risk patient who relapse after 2 cycles followed by RT should receive salvage treatment with intensive chemotherapy e.g. BEACOPPescalated Patients with localised late relapse should receive salvage RT only. There is no standard treatment for patients who relapse after high-dose chemotherapy and ASCT. These patients should be treated on a case by case basis.[24]

For patients with relapsed/refractory HL, the NCCN guidelines recommend biopsy, including bone marrow, and restaging.[24,32] There is no standard therapy for relapse in patients with initial IA to IIA who underwent chemotherapy. These patients should be treated individually. Potential treatment options for them include RT, second-line chemotherapy ± RT, and HDT/ASCT ± RT.

For patients with relapsed/refractory HL, NCCN guidelines recommend biopsy, including bone marrow, and restaging.

There is no standard therapy for relapse in patients with initial IA to IIA who underwent chemotherapy. These patients should be treated individually. Potential treatment options for them include RT, second-line chemotherapy ± RT, and HDT/ASCT ± RT. Brentuximab vedotin is an option for treatment of relapsed/refractory patients who failed treatment with HDT/ASCT or after at least 2 prior chemotherapy regimens regardless of HDT/ASCT eligibility.[24]

HL: CURRENT TREATMENT PARADIGM

The current treatment paradigm consists of a primary treatment involving ABVD, Stanford V, or BEACOPP ±RT. With progressive disease or a relapse, the patient is given second-line chemotherapy and possibly HDT/ASCT. Second-line therapy consists of several chemotherapy regimens such as C-MOPP, DHAP, ESHAP and ICE. The choice of ther regimen suited for the patient is based on factors like pattern of the relapse and prior regimens used.[24]

Also, some patients with minimal disease at relapse may be treated with HDT/ASCT without prior chemotherapy.[24]

For patients who relapsed despite 2 chemotherapy regimens, brentuximab vedotin is an option irrespective of eligibility for HDT/ASCT.[24]

Brentuximab is also an option for patients who had a relapse following HDT/ASCT or have been refractory to treatment with HDT/ASCT.[24]

KNOWLEDGE CHECK

Are you ready for the last knowledge check? Please read the question and select your answer.

What treatment does ESMO recommend for most relapsed patients with HL?

A. High-dose therapy followed by autologous stem cell transplantation
B. High dose therapy followed by allogeneic stem cell transplantation
C. Autologous stem cell transplantation followed by radiation
D. Allogeneic stem cell transplantation followed by radiation and/or high dose therapy

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