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Hodgkin lymphoma

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Abstract

Hodgkin lymphoma (HL) is a curable malignancy which shows a bimodal curve in incidence in economically developed countries; there is a putative association with Epstein–Barr virus. The WHO 2008 classification schema recognises two histological types of HL: the nodular lymphocyte predominant and the "classic" HL. The latter encompasses four entities: nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich. Most patients with HL present with asymptomatic superficial lymphadenopathy. The commonest sites of disease are the cervical, supraclavicular and mediastinal lymph nodes, while sub-diaphragmatic presentations and bone marrow and hepatic involvement are less common. Splenic involvement is usually concomitant with hepatic disease and systemic symptoms; extranodal presentations are quite rare. Systemic symptoms are present in ∼35% of cases. The stage of disease is defined according to the Ann Arbor staging system or its Cotswolds variant, and staging work-up includes physical examination, chest X-rays, chest and abdominal CT scan, and bone marrow biopsy. ^{18}FDG-PET (^{18}fluordeoxyglucose positron emission tomography) plays a central role in staging, response assessment and prognosis definition.

Classic HL usually spreads by contiguity within the lymphatic tissue network, with a late extension to adjacent and distant viscera. Mortality from HL has been progressively decreasing, as confirmed by the most recent 5-year survival figure of 81%. The list of putative prognostic factors in HL has been increasing, but most factors still require prospective validation. Some of these variables are used to stratify early-stage disease into "favourable" and "unfavourable" categories, with "unfavourable early-stage" being intermediate between "favourable early-stage" and "advanced-stage".

ABVD (adriamycin(doxorubicin), bleomycin, vinblastine, dacarbazine) combination chemotherapy followed by involved-field irradiation is the standard treatment for patients with early-stage HL, with a 5-year OS >95%. Several trials assessing less intensive approaches for patients with favourable early-stage HL are ongoing. More intensified combinations, such as the BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone) regimen, are being investigated, usually in patients with unfavourable early-stage HL and interim PET+. ABVD is the standard chemotherapy treatment also for patients with advanced disease. Although some evidence suggests that more intensive combinations provide better disease control, the inevitable increased risk of relevant late toxicity worries investigators. Consequently, there has been a shift towards investigating the innovative strategy of a more aggressive schedule for patients with ^{18}FDG-PET positive results after the first 2 courses of ABVD. High-dose chemotherapy supported by ASCT (autologous stem cell transplantation) is considered the standard of care in patients with HL which has relapsed after, or is refractory to conventional chemoradiotherapy, while allogeneic transplant is a suitable tool for patients with chemorefractory disease and patients failed after ASCT.

Keywords: Hodgkin lymphoma; ABVD; BEACOPP; Epstein–Barr virus; PET

1. General information

1.1. Definition

Hodgkin lymphoma (HL) is one of the few adult malignancies that can be cured in most instances. The salient feature of this lymphoma is the rarity (about 1%) of neoplastic elements in the cell population, whereas the overwhelming majority of cells are non-neoplastic, mostly consisting of T-lymphocytes [1]. Although the clonal B-cell origin of both lymphocyte predominant and "classic" HL was recently demonstrated [2], thus enabling the term 'Hodgkin disease' to be changed to 'Hodgkin lymphoma' [3], the pathogenic mechanisms of this lymphoma are still largely unknown.

1.2. Incidence

HL is an uncommon malignancy, with 7000–7500 new cases diagnosed annually in the United States of America. Most of these patients present with early stage disease. This malignancy displays a bimodal curve in incidence in economically developed countries. In economically underdeveloped countries, the overall incidence of HL is lower than in developed countries, with the exception of children under the age of 15, where a higher incidence is seen. There is only a mild increase in incidence throughout adolescence and young adulthood [4]. A difference in the distribution of histological subgroups occurs as well, since the incidence of nodular sclerosis is lower in underdeveloped countries.

1.3. Risk factors

The dual-peak incidence of HL supports the hypothesis that this malignancy may actually be a common result of two distinct pathogenic processes: an infectious agent of low infectivity may be related to the disease in young adults, while a mechanism shared with other lymphomas may account for the pathogenesis of HL occurring in the older age group [5]. The Epstein–Barr virus (EBV) genome has been detected in one third to one half of HLs occurring in patients without known immunodeficiencies [5–7], with the expression of latent membrane protein (LMP-1 and -2), EBERs (Epstein–Barr encoded RNAs), and EBNA (Epstein–Barr nuclear antigen) 1 in 30–50% of tumours [8]. Patients with infectious mononucleosis are at higher risk of developing EBV-associated HL [9] and this risk is also enhanced in subjects carrying HLA-A*01 [10]. However, the larger group of EBV-negative HL could still be regarded as an infectious-driven neoplasm in which the putative causative agent has not yet been detected [11]. Perhaps relevant to this controversy is the relatively obscure finding of an apparent elevated risk of HL in persons with systemic exposure to blood or blood products, such as intravenous drug users and haemophiliacs, who may be presumed to be HIV-negative. This could reflect the presence of undetected HIV infection, which has been well-established to lead to a substantially elevated risk of HL in all exposure groups [12–14]. In this context, much weaker putative candidate mechanisms include the deregulated immunity against foreign antigen(s). An altered B-cell response secondary to a virus infection, or some factors known to decrease or delay early exposure to infections, such as fewer siblings, single-family houses, early birth-order, and fewer playmates have been proposed as risk-increasing factors.

The role of HL as inherited disease remains to be defined. Nearly 40% of patients with HL seen at a tertiary care referral centre reported a first-degree relative with cancer; the incidence was significantly lower with respect to patients with NHL or CLL [15]. Six percent of these HL patients had a relative with a lymphoproliferative malignancy, with high rates of both HL and NHL in first-degree relatives. Substantial evidence suggesting that familial aggregation of lymphoproliferative disorders such as CLL and NHL has a significant genetic component is less clear in HL patients. However, the differences observed between CLL, NHL and HL indicate that the underlying biological predisposition may vary among the diseases, and is not merely an artefact of different age bands. Patterns of inheritance may provide some clues to pathogenesis. However, studies on familial HL are strongly limited by the unreliable validity of self-reported positive family histories of lymphoma. In fact, while familial HL reported by HL patients and controls is likely to be lymphoma, even in members of the extended family, it is unlikely to be HL per se [16].

2. Pathology and biology

2.1. Morphology

The updated 2008 WHO classification recognises two groups of histological types of HL: nodular lymphocyte predominant (LP), which includes about 5% of all HL cases, and the "classic" HL (cHL), which accounts for the remaining cases. In cHL, the following subgroups can be identified: nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich.

2.1.1. Nodular lymphocyte predominance

The lymph node architecture is usually effaced and, in most instances, without residual reactive germinal centres. This malignancy usually displays a nodular growth pattern, which may or may not be accompanied by diffuse areas; more rarely, a purely diffuse pattern may occur. At low power, nodular lesions are basically B-cell areas with nearby progressive transformation of germinal centres; these features can be further elucidated by means of CD20 and anti-CD21 investigation (a follicular dendritic cell marker). The neoplastic cells are large and characterised by vesicular, somewhat irregular and polylobated nuclei with small nucleoli and abundant cytoplasm. These cells, named lymphocytic and histiocytic (L&H cells) or "popcorn" cells, may occur in variable amounts, but they are never prominent and are often isolated, without any tendency to form dense aggregates.

The non-neoplastic background in lymphocyte predominant HL is mostly represented by small lymphocytes and a variable amount of histiocytes, which may focally form non-necrotising granulomas. When epithelioid histiocytes become numerous, the differential diagnosis with T-cell rich large B-cell lymphoma is difficult and requires additional investigations. Plasma cells, eosinophils and neutrophils are rarely seen [17]. This subtype may occur at any age, but it is more common in adult males. It is usually localised at diagnosis, and stage-IV disease with bone marrow involvement is rare. The mediastinum is usually spared, while peripheral lymph nodes, mainly cervical or inguinal nodes, are frequently involved. Importantly, deep-seated lymphadenopathies may occur as well (M. Ponzoni, personal observation).

2.1.2. Nodular sclerosis

This is the most common subtype of cHL, accounting for 75–80% of cHL cases. The salient feature of this entity is the occurrence of nodules of variable size separated by dense collagenous fibrous bands. These bands display typical green birefringence in polarised light, a cardinal feature which enables the distinction of nodular sclerosis from the lymphocyte depletion subtype; variable areas of coagulative necrosis are common. The pathognomonic element of cHL is the Reed–Sternberg (R–S) cell; this element is large, polynucleated and with prominent, basophilic nucleoli. Mononuclear variants of R–S cells include lacunar cells

and Hodgkin cells. In the nodular sclerosis variant, R–S cells are easily visible, but never prominent. Diagnosis of cHL can only be made when R–S cells occur within the appropriate background including small lymphocytes, plasma cells, eosinophils, neutrophils and histiocytes [18]. Nodular sclerosis more commonly affects adolescents and young adults, with a slightly higher prevalence in females. Mediastinal involvement is frequent and patients with nodular sclerosis cHL preferentially display upper thoracic disease that generally remains localised in lymph nodes and adjacent structures.

2.1.3. Mixed cellularity

In mixed cellularity HL, the infiltrate is diffuse or vaguely nodular, without band-forming sclerosis, although fine interstitial fibrosis may be present. R–S cells are more represented than nodular sclerosis. Patients are usually adults; males outnumber females, and the stage is frequently more advanced than in nodular sclerosis or lymphocyte predominant, involving lymph nodes, spleen, liver, or marrow.

2.1.4. Lymphocyte depletion

The lymph node architecture is completely effaced and predominantly represented by diffuse and dense fibrosis (not birefringent collagen). Necrosis may occur as well. Most of the residual cells are exclusively represented by R–S cells, while non neoplastic elements in the background are rare, if present. Overall, these features confer a "sarcomatoid" appearance to the lymph node architecture. Confluent sheets of R–S cells may occur and therefore constitute the "reticular" variant (or Hodgkin's sarcoma) [18]. The differential diagnosis between the "reticular" variant and anaplastic large cell lymphoma may be difficult, cHL requiring absence of ALK protein and absence of rearrangement of the genes which codify for T-cell receptor [19].

Lymphocyte depletion is the least common variant of cHL and occurs preferentially in elderly patients, and in non-industrialised countries. The most frequent presentations involve abdominal lymphadenopathy, or extranodal disease with spleen, liver and marrow involvement. The stage at diagnosis is usually advanced and the response to treatment is generally worse than in other subtypes [20].

2.1.5. Lymphocyte-rich

This subtype involves about 6% of HL cases [21]. There is a diffuse or focal, sometimes interfollicular involvement with a reactive cellular milieu, essentially represented by small lymphocytes, with very few, if any, neutrophils, eosinophils and plasma cells. Importantly, R–S cells are present, albeit infrequently, as well as some lacunar cells; both of them display the immunophenotypic/molecular properties of cHL (see below). Often, nodules show germinal centres and focal areas of fibrosis.

A lymphocyte-rich subtype, which was only recently introduced into the cHL classification [21], also demonstrates a characteristic clinical profile. It is characterised by late occurrence (i.e., patients older than 50 years of age), low aggressiveness, early stage at presentation, and involvement of subdiaphragmatic sites, whereas mediastinal or extranodal involvement, systemic symptoms and bulky masses are rare.

2.2. Immunophenotype

2.2.1. Lymphocyte predominance HL

L&H cells are typically CD45+ and B-cell-associated antigens (CD19, CD20, CD22, and CD79a)-positive, CDw75+, EMA+/− and CD15−. Bcl-6 is very often expressed in neoplastic cells. CD30 is usually absent, although it may occur in some instances, and with somewhat less intensity with respect to cHL. In paraffin-embedded material, immunoglobulin light chain restriction can sometimes be demonstrated [22]. J-chain has been shown in many cases [23,24]. Transcription factors PAX-5, Oct-2, PU.1 and the coactivator BOB.1 are almost constantly expressed [21]. Other recently introduced markers, such as HGAL, AID and centerin are expressed by L&H cells [25].

Small lymphocytes, present within the background of the nodules, are predominantly B cells. T-cells, which occur to a lesser degree, tend to form rosettes surrounding L&H cells and there is a relative prevalence of CD57+, MUM-1, PD-1+ (ref) small-sized elements. The microenvironment is completed by CD68+ histiocytes and a prominent meshwork of follicular dendritic cells, which is particularly evident within the nodules [21].

2.2.2. Nodular sclerosis, mixed cellularity and lymphocyte depletion

In paraffin-embedded material, R–S cells are intensively CD30+ (with its characteristic crispy membrane and/or 'dot-like' staining pattern), PAX-5+ (with a less intensive nuclear signal when compared to bystander small B lymphocytes), and CD45- (Table 1). CD15 is usually positive, but it should be taken into account that the rates of immunoreactivity of this marker may vary according to the employed clone [26]. Importantly, CD20 could be detected in about 30–40% of the cases of cHL; in most instances, this marker shows a less intensive signal with respect to T-cell rich diffuse large B-cell lymphoma and, importantly, a variable amount of R–S elements present within the same tissue are not reactive against this molecule. Other common markers of R–S cells include MUM-1 and, in about one fourth of cases, BLIMP1 [27]. T-cell antigens are reported in a small minority of cases. The prevalence is slightly higher in Japanese patients [28]. Importantly, many markers expressed in lymphocyte predominant lymphoma are absent in cHL; these markers include Oct-2, BOB.1, and CD45. The diagnosis is made on routine sections; however, immunophenotyping studies are essential for the diagnosis and are highly recommended.

2.3. Genetic and biological features

The putative normal counterpart of HL cells differ, falling into two main groups. In fact, L&H cells of lymphocyte

Table 1
Immunohistochemistry profile of Hodgkin lymphoma (HL), primary mediastinal large B-cell lymphoma (PMLBCL) and diffuse large B-cell lymphoma (DLBCL).

Marker	HL	PMLBCL	DLBCL
CD45	−/+	+	+/−
CD20	−/+	+	+
CD79a	−/+	+	+
PAX5/BSAP	+	+	+
BOB.1	−	+	+
Oct-2	−	+	+
PU.1	−	+	+
BCL-2	−/+	+	−/+
CD30	+	+/−	−/+
HLA-DR	+	+	
MAL protein	−/+	+/−	
BCL-6	−	+/−	−/+
MUM1/IRF4	+	+/−	+/−
CD10	−	−/+	−/+
CD21	−	−	−
CD15	+	−	−
CD68	−	−	−
T-cell markers	−/+	−	−

Updated from [25].

predominant Hodgkin disease could derive from a germinal centre B cell at the centroblast stage. This hypothesis is supported by the presence of rearranged immunoglobulin genes, detected either at DNA and mRNA level, as well as by the presence of ongoing mutations in the variable regions of immunoglobulin heavy chains [29]. R–S cells show somatic hypermutation of the variable region of immunoglobulin genes in almost all instances and, in a quarter of cases, non-sense mutations or deletions [30]. These characteristics favour the origin of R–S cells from pre-apoptotic germinal centre B cells [22].

Conceivably, the Hodgkin R–S cell orchestrates tissue derangement by recruiting immune bystander cells, such as non-neoplastic helper T lymphocytes, plasma cells, macrophages, mast cells, and eosinophilic granulocytes. R–S cells are frequently surrounded by a rosette of CD4+ T-lymphocytes of both the Th1 and the Th2 type. EBV-positive HLs show a shift towards Th1. Also regulatory T-cells may play a pathogenic role in cHL, since they could contrast the potential cytotoxic effect of CD8+ cells against R–S cells [22]. R–S cells arrange their survival and expansion through many cytokines and chemokines, which interact with the non-neoplastic surrounding microenvironment. Several pathways are constitutively activated in cHL, including NF-kB, JAK/STAT and aberrant expression of RTKs [22].

In addition, some findings suggest that EBV+ Hodgkin R–S cells originate from latently EBV-infected B cells. As with Burkitt's lymphoma, HL cells carry complete viral genomes in the form of multiple covalently closed episomal DNA. Molecular analysis revealed that viral genomes were clonal, suggesting that they have originated from a common proliferating precursor [31]. This argues against any role of virus replication in the establishment of the tumour cell. EBV positivity is correlated with mixed cellularity type and with non-mediastinal localizations, but there is no correlation with age or sex [6,32,33]. EBV infection is either only in the tumoural cells or in the surrounding cells [34]. Several studies have shown no difference in the prognosis of EBV+ and EBV− cHLs, while a more favourable outcome for patients with EBV+ HL has also been reported [35,36]. However, a poor prognosis associated with EBV infection in elderly patients has also been described [37].

Array-based comparative genomic hybridisation (aCGH) has been used to identify the genes involved in the pathogenesis of cHL. Comparison of serial analysis of gene expression libraries revealed consistent overexpression of 14 genes and downregulation of 141 genes in HL cell lines [38]. aCGH revealed gain of 2p, 7p, 9p, 11q and Xq and loss of 4q and 11q. Eighteen percent of the differentially expressed genes mapped to regions with loss or gain and a good correlation was observed between underexpression and loss or overexpression and gain of DNA. Remarkably, gain of 2p and 9p did not correlate with increased expression of the proposed target genes c-REL and JAK2. Downregulation of many genes within the HLA region also did not correlate with loss of DNA. FSCN1 and IRAK1 mapping at genomic loci (7p and Xq) that frequently showed gain were overexpressed in cHL cell lines and might be involved in the pathogenesis of classical HL. Overall, aCGH studies showed a 'loss of B-cell phenotype' and a downregulation of HLA gene expression in HL cell lines. More recently, an aCGH study demonstrated nonrandom DNA copy number alterations in the molecular karyotypes of cHL. Several recurring genetic lesions correlated with disease outcome [39].

Gene-expression profiling (GEP) studies have supported a strong relationship between cHL and primary mediastinal large B-cell lymphoma (PMLBCL) [40,41]. Over one third of the genes that were more highly expressed in PMLBCL than in other diffuse large B-cell lymphomas (DLBCL) were also characteristically expressed in cHL cells. PDL2, which encodes a regulator of T-cell activation, is the gene that best discriminates PMLBCL from other DLBCL and was also highly expressed in HL cells [41]. These studies identified a molecular link between classical HL and PMLBCL and a shared survival pathway. Of interest, the PMBCL subgroup was somewhat more related to the GC-like subgroup of DLBCL, than to the ABC-like subgroup of DLBCL, even though PMBCL was clearly distinguishable from both subgroups of DLBCL. PMLBCLs had low levels of expression of multiple components of the B-cell receptor signalling cascade, a profile resembling that of Reed–Sternberg cells of cHL. Like cHL, PMLBCL also had high levels of expression of the interleukin-13 receptor and downstream effectors of IL-13 signalling (JAK2 and STAT1), TNF family members, and TRAF1. Given the TRAF1 expression and known link to NF-κB, a nuclear translocation of c-REL protein has been demonstrated in almost all PMLBCLs cases.

3. Clinical presentations

Most patients with HL present with superficial adenopathy and are asymptomatic. The lymph node enlargement is usually painless, rubbery, matted, or discrete, and is most commonly located in the neck and supraclavicular areas. It is sometimes detected during a physical examination for other reasons. A presentation of mediastinal enlargement is common during routine chest X-rays. The commonest sites of disease are cervical, supraclavicular and mediastinal (over 50% of cases) nodes, while sub-diaphragmatic presentations are less common, and epitrochlear nodes, Waldeyer's ring, testicular, and gastrointestinal sites are uncommon. Abdominal nodal involvement is more common in older patients or when fever or night sweats are present. Bone marrow and hepatic involvement are uncommon. Spleen involvement is usually concomitant with hepatic disease and systemic symptoms. Systemic symptoms are present at diagnosis in about one third of cases, and among them fever is more common than night sweats and weight loss, whereas pruritus is rare and alcohol-induced pain is very rare. Pruritus does not constitute a systemic symptom, but it should be recorded, especially if generalised, if it is the cause of scratch lesions and if resistant to steroids [42]. Alcohol-induced pain is nearly diagnostic and consists of pain triggered by the ingestion of moderate amount of alcoholic drinks and localised in one of the anatomical deep sites involved by the disease.

Other rare clinical presentations, more commonly associated with advanced HL, are superior vena cava syndrome, acute spinal cord compression, central nervous system solitary lesion, Waldeyer's ring involvement, testicular masses, or intestinal occlusion.

4. Staging and restaging

4.1. Staging system and procedures

The standard staging system used for HL was proposed at the Ann Arbor Conference in 1971 [43], and partially modified at the Cotswolds Meeting in 1988 [43]. The staging system reflects both the number of sites of involvement and the presence of disease above or below the diaphragm, according to four stages of disease (Table 2).

Complete staging work-up for HL includes a detailed history, which records both presence and duration of possible systemic symptoms, an accurate physical examination, complete haematological and biochemical examinations (including erythrocyte sedimentation rate, serum alkaline phosphatase, renal function and liver function tests), chest X-rays, chest and abdominal computed tomography (CT) scans, skeletal X-rays when necessary, and bone marrow biopsy.

Bone marrow core biopsy, not aspiration, is useful. However, patients in clinical supradiaphragmatic stage I or II without B symptoms show a minimal probability of marrow involvement. Bone marrow biopsy is therefore considered particularly important in patients with B symptoms and/or clinical advanced stage and/or infradiaphragmatic presentation and in those with bone lesions, bone pain, hypercalcaemia, or an elevated serum alkaline phosphatase [44,45]. Whether it can be replaced in the future by ^{18}FDG-PET is still a matter of debate [46–48].

The sensitivity of ^{18}FDG-PET and PET/CT is higher than that of CT in order to identify both nodal and extranodal disease in primary staging [49–52]. The superiority of ^{18}FDG-PET or PET-CT over conventional CT staging is more evident for evaluating extra-nodal than nodal involvement [53]. ^{18}FDG-PET false-positives at diagnosis are around 2%, and some doubts arise about the risk of ^{18}FDG-PET upstaging, rather than downstaging, patients [53]. Although ^{18}FDG-PET may be superior to CT it is not yet considered the new standard staging imaging technique, however, prospective trials are useful in documenting its favourable impact on patient outcome [54,48]. The inclusion of ^{18}FDG-PET among initial staging procedures is in any case useful in order to compare the subsequent ^{18}FDG-PET results to allow better evaluation of both early and final responses to chemotherapy [55].

4.2. Molecular analysis of minimal residual disease

Application of tumour cell-specific rearranged immunoglobulin DNA sequences by single cell PCR allows for the identification of R–S cells in different tumour samples, including peripheral blood or bone marrow. Using these techniques, R–S cells were identified genetically in the peripheral blood of a patient with relapsed HL [56]. Interestingly, the tumour cells identified at relapse after years of clinical remission had identical genetic markers to those at first presentation [57]. This formal proof of minimal residual disease in HL could, in theory, be used to evaluate persistent molecular disease in patients in clinical complete remission as well as to detect contaminating cells in autographs, but its role remains a matter of investigation, and it is not useful for a routine clinical application.

4.3. Post-treatment evaluation

Restaging should include all the diagnostic procedures which were positive at time of initial staging. The evaluation of the response is complicated in HL by the frequent persistence of residual masses, mainly at mediastinum level. Residual masses can be due to fibrosis and they do not by themselves indicate active disease and increased risk of relapse. Until now, CT scans were the cornerstone for evaluating remission, but they cannot discriminate active disease from fibrosis. ^{18}FDG-PET is a more reliable instrument for the assessment of persistent active disease.

In 1999, an International Working Group (IWG) of experts published guidelines for response assessment and outcome measures of patients affected by both HL or non-Hodgkin Lymphoma [58]. These recommendations considered the possibility of unconfirmed or uncertain complete remission

Table 2
Ann Arbor staging system.

Stage I	Involvement of a single lymph node region or single lymphoid structure, such as spleen, thymus or Waldeyer ring (I), or a single extranodal site (IE).
Stage II	Involvement of two or more lymph node regions or lymphoid structures on the same side of the diaphragm (II) or localised involvement of an extralymphatic site (IIE). The number of anatomical regions involved should be indicated by a subscript (e.g., II_3). Mediastinal nodes are a single lymph node region.
Stage III	Involvement of lymph nodes regions or lymphoid structures on both sides of the diaphragm (III), or localised involvement of an extralymphatic site (IIIE), or spleen (IIIs) or both (IIIEs). Moreover, stage III_1 – characterised by splenic, hilar, coeliac or portal node involvement – can be distinguished from stage III_2 which presents para-aortic, iliac and/or mesenteric node involvement.
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement. Localised involvement of liver or bone marrow is also considered stage IV.
Extranodal disease:	Extranodal categorisation in stages I–III includes a single extralymphatic involvement by limited direct extension from an adjacent nodal site. Extranodal involvement should be identified by a symbol (M: marrow, L: lung, D: skin, H: liver, P: pleura, O: bone).
Systemic symptoms:	Fever >38 °C of no evident cause for 3 consecutive days, night sweats and unexplained weight loss >10% of body weight. Patients are divided according to the presence (B) or not (A) of these symptoms.
Bulky disease:	Palpable masses and abdominal masses (CT scan or MRI) are defined as "bulky" when its largest dimension is ≥10 cm. Mediastinal mass is defined as "bulky" on a posteroanterior chest radiograph, when the maximum width is ≥one-third of the internal transverse diameter of the thorax at the level of T_5–T_6 vertebrae.

(CR[u]), frequently used in cases of residual mediastinum mass. CR[u] defines patients in normal health with no clinical evidence of disease, but with persistence of some residual radiological abnormality at the site of previous disease, not consistent with the effects of therapy. Recommendations include the need to verify the uncertainty about completeness of remission 3 months later.

The widespread use of ^{18}FDG-PET as new cost-effective tool [59] for differentiating residual fibrotic masses from active persistent disease prompted a reassessment of initial IWG criteria [60]. In 2006, response criteria were revised with the inclusion in final restaging of ^{18}FDG-PET as a standard procedure [61]. These recommendations are nowadays the point of reference for post-treatment evaluation [62]. Guidelines for performing and interpreting ^{18}FDG-PET at the conclusion of therapy were established by a panel of nuclear medicine physicians, radiologists and haematologists/oncologists [63]. In these consensus recommendations, the following statements were included: a) ^{18}FDG-PET at diagnosis is not considered mandatory in order to asses final response; b) final ^{18}FDG-PET evaluation should not be performed before at least 3 weeks after chemotherapy and 8–12 weeks after radiotherapy (RT); c) visual assessment alone is considered adequate; d) positive uptake is defined according to specific rules. According to these criteria, post-treatment response is defined as summarised in Table 3.

4.4. Early response evaluation

^{18}FDG-PET was recently proposed by many authors as a new tool to predict therapy outcome at an early stage of treatment, usually after the first two courses of ABVD or BEACOPP chemotherapy (Table 4), as a surrogate test of chemo-sensitivity [64–68]. Patients already PET-negative after 2 courses of ABVD (PET2−) are candidates for an excellent prognosis, while those with residual or unchanged uptake (PET2+) show very poor outcomes. The opportunity to predict the final response to conventional therapy could be useful for introducing therapy tailored on the basis of early PET evaluation. However, there are as yet no data showing that altering treatment early on the basis of PET results improves patient outcome. Early PET evaluation is therefore considered investigational and it is recommended only within clinical trials and it should not yet be used to modify treatment strategy in daily routine practice [69,70].

4.5. Follow up evaluations

Following completion of therapy, clinical evaluations at 3–4 monthly intervals during the first and second year of therapy, at 6-monthly intervals in the third to fifth year and annually thereafter are recommended on a type R basis [71]. Patients in CR should receive a CT scan evaluation at least once a year for the first years after the end of treatment. Moreover, attention to secondary breast or lung cancers, monitoring the onset of cardiovascular disease and monitoring of thyroid function should be considered according to the type of prior chemotherapy and RT [71]. Particular caution is suggested for the use of ^{18}FDG-PET during the follow up after the end of treatment, due to the high incidence of false positive results, and so far ^{18}FDG-PET is not routinely recommended [60,69,71–73].

5. Prognosis

5.1. Natural history

In the majority of cases, the anatomical spread of HL occurs – initially and for variable length of time – mainly by contiguity and within the lymphatic tissue network, involving the adjacent lymph nodes first. Late in the course of the disease it can extend to the adjacent viscera and disseminate to the spleen, bone marrow, liver, bone, and other organs in a fashion somewhat resembling metastases from epithelial

Table 3
Consensus of the imaging subcommittee of International Harmonization Project in Lymphoma [63].

Complete remission	is the disappearance of all evidence of disease. In both patients with initial positive PET scan and those without an initial PET a residual mass of any size is permitted as long as it is PET negative. If the bone marrow was involved before treatment, the infiltrate must have cleared on repeat bone marrow biopsy.
Unconfirmed CR	has been eliminated.
Partial response	is defined as ≥50% decrease of the sum of the products of the diameters of up to six largest dominant masses. No increase should be observed in the size of other nodes, spleen or liver. Post-treatment ^{18}FDG-PET should be positive in at least one previously involved site. Bone marrow assessment, if positive before, is irrelevant for the determination of PR.
Stable disease	is defined as the absence of criteria needed to define both CR/PR and progressive disease. ^{18}FDG-PET should be positive at prior sites of disease with no new areas of involvement (CT and PET).
Progressive disease	includes one of the following situations: a) the appearance of a new lesion >1.5 cm in any axis (increased FDG uptake in a previously unaffected site should only be considered positive after confirmation with other modality, and therapeutic decision should not be taken solely on the basis of ^{18}FDG-PET); b) >50% increase of the sum of the product of the diameters of more than one node; c) >50% increase in longest diameter of a previously identified node >1 cm in short axis. Lesions should be ^{18}FDG-PET positive.

cancers. Left cervical node involvement is more common than right-sided and is more often associated with involvement of retroperitoneal lymph nodes. The mediastinum is not involved in 15% of patients with involvement of left cervical and retroperitoneal lymph nodes. This seems to suggest that HL sometimes does not spread by contiguity. Splenomegaly as the unique site of disease suggests that haematogenous dissemination to the spleen may be a part of the early course of this disease. Spread of disease to the splenic, hilar and retroperitoneal lymph nodes is then assumed. While splenic involvement is haematogenous, it is not necessarily an indicator of widespread, diffuse haematogenous disease as, in the past, regional irradiation associated with splenectomy frequently cured these patients. It is believed that the histological evolution of HL occurs with progressive loss of lymphocytes and an increase in the number of malignant cells.

Lymphocyte predominant disease often presents as solitary lymph node involvement. The disease progresses slowly,

Table 4
The most commonly used chemotherapy regimens.

ABVD	Drug	Dose (mg/m^2)	Day	Route	Frequency
	Doxorubicin	25	1, 15	IV	
	Bleomycin	10	1, 15	IV	
	Vinblastine	6	1, 15	IV	
	Dacarbazine	375	1, 15	IV	28 days
Stanford V					
	Doxorubicin	25	1, 15, 29, 43, 57, 71	IV	
	Vinblastine	6	1, 15, 29, 43, 57, 71	IV	
	Mechlorethamine	6	1, 29, 57	IV	
	Vincristine	1.4	8, 22, 36, 50, 64, 78	IV	
	Bleomycin	5	8, 22, 36, 50, 64, 78	IV	
	Etoposide	60	15, 43, 71	IV	
	Prednisone	40	qod for 12 weeks	Oral	
BEACOPP (basic)					
	Bleomycin	10	8	IV	
	Etoposide	100	1–3	IV	
	Doxorubicin	25	1	IV	
	Cyclophosphamide	650	1	IV	
	Vincristine	1.4	8	IV	
	Procarbazine	100	1–7	Oral	
	Prednisone	40	1–14	Oral	21 days
BEACOPP (escalated)					
	Bleomycin	10	8	IV	
	Etoposide	200	1–3	IV	
	Doxorubicin	35	1	IV	
	Cyclophosphamide	1250	1	IV	
	Vincristine	1.4	8	IV	
	Procarbazine	100	1–7	Oral	
	Prednisone	40	1–14	Oral	21 days

with fairly frequent relapses, which are rarely fatal. Late relapses have been reported to be more common than in other types of HL [74]. This may be associated with or progress to large B-cell lymphoma [75,76], while secondary low-grade non-Hodgkin's lymphomas can also occur. This is more frequently observed after lymphocyte predominant HL than after classical HL. Survival is long, with or without treatment, for localised cases.

The mortality of HL has progressively reduced over the last 30 years. In the 1950s, the mortality in the United States was 1.8 per 100,000, while in the early 90s it was 0.47 per 100,000. The most recent 5-year survival figure is 81% [77]. While this malignancy accounted for 30% of total lymphoma deaths in 1950, it accounted for only 6% in 1994. Untreated HL is rare today because both chemotherapy and RT are effective curative treatments. If the disease is left untreated, the course is brief, spanning 1–2 years with fewer than 5% of patients alive at 5 years.

5.2. *Prognostic factors*

The definition of prognostic factors and risk groups is still a matter for debate. A very long list of clinical, histopathological and laboratory parameters have individually been suggested to be of prognostic value [78–83]. Nearly all are more or less directly correlated with the amount of tumour present at diagnosis [84]. The measurement of the tumour burden on the serial slices of total body CT is a very powerful prognostic tool [85,86]. However, the increasing effectiveness of therapies requires periodic reevaluation of the actually important prognostic factors, with a remodelling of their hierarchical order [87].

The criteria of the Ann Arbor Conference [43] are internationally accepted as defining the two major prognostic groups of limited (early-stages) and advanced disease. Early-stages encompass stage I and II, while stages III and IV are included in the advanced disease group. Stage II with systemic symptoms (IIB) can be included in the group of either unfavourable early-stage disease (European Organization for Research and Treatment of Cancer – EORTC) or advanced disease (German Hodgkin's Lymphoma Study Group – GHSG), according to the policy of individual cooperative groups. The early-stage group is usually further subdivided into the two categories of "favourable" and "unfavourable" disease according to the presence or absence of other clinical and laboratory prognostic variables. The "unfavourable early-stage" group defines, therefore, a group whose prognosis is intermediate between "favourable early-stage" and "advanced-stage". Variables used to differentiate "favourable" from "unfavourable" early stages are not universally codified, but they are similar in EORTC and GHSG classification systems [88].

One or more of the following unfavourable prognostic features is needed to shift an individual patient in stage I or II from the category of "favourable" to that of "unfavourable" early stage in the EORTC and GHSG classifications:

- EORTC classification: bulky mediastinal mass; age ≥50 years; ESR ≥50 without B symptoms or ≥30 with B symptoms; ≥4 nodal areas.
- GSHG classification: bulky mediastinal mass; extranodal site; ESR ≥50; ≥3 nodal areas.

Seven prognostic factors (age ≥45 years, male sex, stage IV, serum albumin <4 mg/dL, haemoglobin <10.5 mg/dL, white blood cell count ≥15,000 x/L, and lymphocytes count <600 x/L) associated with a reduction of 7–8% in tumour control at 5 years have been identified in patients with advanced HL [89]. These variables are the basis for the construction of the International Prognostic Score (IPS). The number of factors present has been related to 5-year progression-free survival (PFS), which was 74% for patients with 0–2 unfavourable prognostic factors and 55% for those with 3 or more.

The identification of prognostic factors in patients with relapsed or refractory HL is confounded by the use of varied inclusion criteria in clinical trials. However, it would appear that relapses within the primary irradiated area, early relapses (first year) and chemorefractory diseases as well as poor performance status, mediastinal bulky disease, female sex, B symptoms, and extranodal disease at relapse are associated with a worse outcome [90–99]. Results are significantly better when the disease is still chemosensitive, and a second remission or at least a minimal disease status is reached before ASCT. Recent data show that ^{18}FDG-PET positivity after salvage debulking chemotherapy and before ASCT is probably the factor indicating the poorest prognosis in failed patients [100,101].

In patients with advanced-stage HL, the early response after 2 courses of ABVD chemotherapy, when evaluated with ^{18}FDG-PET scan, shows important prognostic significance [64–67]. It is considered to be similar to a test of chemosensitivity and it overrides all conventional prognostic factors, including IPS score. PET2-advanced-stage patients after 2 courses of ABVD are projected to achieve a 2-year PFS of >90%, while a 2-year PFS of <10% is expected in PET2+ patients. However, some concerns arise about the routine application of this technique in order to modify the treatment strategy for individual patients. First of all, the prognostic value of early ^{18}FDG-PET may be lower in patients treated with new regimens, such as escalated BEACOPP, which are more aggressive than ABVD [102]. Secondly, conventional criteria for ^{18}FDG-PET interpretation were not intended for interim analysis evaluation, but for end-treatment response assessment, and an important debate has arisen about how to evaluate the grey zone of "minimal residual uptake" [103]. International Workshops were organised and prospective studies are ongoing in order to reach a consensus on simple and reproducible criteria for ^{18}FDG-PET interpretation and to validate internationally the role of PET2 scans [104]. Several trials investigating ^{18}FDG-PET response-adapted therapy are ongoing (see Section 6.6), but until their results become available,

this prognostic factor is considered investigational and it is recommended only within clinical trials [69,70].

6. Treatment

6.1. Treatment of early-stage disease (stage IA–IIA ± IIB)

Primary ABVD combination chemotherapy (Table 4), followed by involved-field irradiation (IF-RT) is the standard treatment for patients with early-stage HL (type 1 evidence), with an overall survival (OS) >95% [105–108]. Even among patients with very favourable disease, according to the EORTC criteria [109], the use of RT alone was associated with an unacceptable relapse rate [110] and is no longer advisable. The superiority of the combined chemo-radiotherapy in comparison with extended-field irradiation (EF-RT) alone has been confirmed in diverse randomised trials [111–116].

The dose and the extension of irradiation field after primary chemotherapy is an important issue considering the risk of late morbidity related to combined treatment. Smaller fields and lower doses were progressively introduced to reduce the risk of death from second cancers [117,118], heart disease [119] and other complications. Several randomised trials using diverse chemotherapy regimens have all demonstrated that the extent of radiation can be safely reduced when chemotherapy is added [119–122]. No significant difference in survival has been observed among patients treated with IF-RT or EF-RT after ABVD [121] or COPP-ABVD [123,124]. This suggests that brief chemotherapy is able to eradicate all un-irradiated disease even when only IF-RT is used. Recent publications suggest a further reduction of IF-RT to involved-nodal irradiation (IN-RT) [125]. However, a randomised comparison between these techniques is not yet available and IN-RT is still considered an investigational technique.

The optimal radiation dose remains to be defined. According to the paediatric experience 20–25 Gy may be adequate in patients in CR after primary chemotherapy [126,127]; otherwise the classical doses of 30 Gy are still considered the standard treatment.

Whether early-stage HL can be treated with chemotherapy alone without any radiation is still an open question. Straus et al. randomised a group of patients to 6 courses of ABVD followed by IF-RT with 6 courses of ABVD alone [128]. After a median follow up of 5 years, there was no difference in PFS between the two groups, but patients with a bulky mediastinal mass were excluded from this study. In another randomised trial involving unfavourable early-stage patients without bulky disease, the combined modality treatment was superior to ABVD alone in terms of PFS, even though no differences were seen in OS [129]. Although a strategy of ABVD alone is considered a rational option in favourable early-stage patients [130], a recent meta-analysis shows that in patients with early-stage disease adding RT to chemotherapy improves both tumour control and OS [131]. Thus, a limited number of courses of ABVD chemotherapy followed by IF-RT is considered the best strategy on type 1 basis for the management of stage IA and IIA HL [71,108,132].

6.1.1. Treatment of favourable early-stage disease

The recently reported results of the HD10 trial are useful for informing the therapeutic approach for patients with favourable early-stage HL [133]. In this trial, four courses of ABVD were compared with two courses of ABVD and 30-Gy IF-RT was compared to 20-Gy IF-RT. No differences were seen in terms of freedom-from-treatment failure (FFTF) and OS according to the number of courses of ABVD or radiation doses, with actuarial rates of ∼90% in each arm. However, four courses of ABVD were more toxic than two, and 30 Gy were more toxic than 20 Gy. The authors have concluded that two courses of ABVD followed by 20 Gy IF-RT is an adequate and less toxic strategy for patients with favourable early-stage HL. This strategy can be considered at present the standard of care on type 1 basis for this group of patient, against which different combinations of chemo-radiotherapy can be compared. The impact on outcome of some less intensive strategies aimed at reducing acute and late toxicity is under study. A chemotherapy regimen less aggressive than ABVD is being assessed in the HD13 trial. Conversely, the use of the VBM (vinblastine, bleomycin, methotrexate) regimen [120,134] or its VbMp variant [135] is no longer recommended since it increased the risk of severe pulmonary toxicity and the need to deliver full doses of EF-RT. Omitting RT in selected patients with very favourable disease is another strategy under investigation, particularly, in patients with negative interim PET. Prolonged follow-up will be necessary to reach firm conclusions from these studies.

6.1.2. Treatment of unfavourable early-stage disease

ABVD chemotherapy followed by IF-RT is the most useful strategy in patients with unfavourable early-stage HL. In these patients, several chemotherapy regimens – potentially less toxic than ABVD – such as EBVM (epirubicin, bleomycin, vinblastine, methotrexate) EBVP (epirubicin, bleomycin, vinblastine, prednisone) or EVE (epirubicin, vincristine, etoposide), were assessed in large randomised trials and none were superior to ABVD in terms of FFTF or OS [136–138]. At present, four courses of ABVD followed by IF-RT 30 Gy is considered the standard of care on type 1 basis for this group of patients [112]. Whether more aggressive regimens (Table 4), such as BEACOPP baseline or BEACOPP escalated, in association with IF-RT can improve disease control in comparison with ABVD still is an open question. Final results of the HD11 trial have showed no difference between 4 courses of ABVD and 4 courses of BEACOPP baseline when they are followed by 30 Gy IF-RT. However, BEACOPP improves FFTF in comparison to ABVD if radiation doses are reduced to 20 Gy [139]. When comparing the best and least toxic arms of this four arm study, BEACOPP plus IF-RT 20 Gy might have the disadvantage of higher acute

toxicity, and a higher incidence of second myelodysplastic syndromes and infertility, while ABVD plus IF-RT 30 Gy might have the disadvantage of a potentially increased risk of secondary breast or lung cancer. Final results of the HD14 trial were recently presented [140]. This randomised trial compared 4 cycles of ABVD (arm A) or 2 cycles BEACOPP escalated followed by 2 cycles ABVD (arm B), both followed by 30 Gy IF-RT, in 1,655 patients with unfavourable early-stage HL. With a median follow-up of 42.4 months, there was a significantly better FFTF in the intensified arm (4-year: 89.3% vs. 94.7%; $p = 0.0001$), but without any difference in OS. Acute grade III–IV toxicity was more common in arm B (87% vs. 51%), but no differences in treatment-related deaths or secondary neoplasia rates were observed. German authors implemented BEACOPP escalated followed by ABVD and IFRT as new standard of care for early unfavourable HL in the follow-up study: the HD17 study.

6.2. Treatment of advanced-stage disease (stage III–IV ± IIB)

ABVD is also the standard chemotherapy for patients with advanced-stage HL, with a 10-year OS >50% [141,142]. More intensive combinations have been developed in the last decade to improve outcome. A weekly, seven-drug regimen, the Stanford V regimen (Table 4), with reduced cumulative doses of doxorubicin and bleomycin has produced a 5-year OS of 94% [143]. This regimen was originally designed to be used with a combined extensive IF-RT, which cannot be reduced without impairment of outcome [144]. The risk of late radiation-related adverse events is therefore a major problem with Stanford V. Two intensified combinations of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine regimens (BEACOPP baseline and BEACOPP escalated) have been developed to improve the outcome by escalating the dose intensity of the more effective drugs. The 10-year results of the randomised trial comparing the two modalities of BEACOPP regimens with alternating COPP/ABVD showed survival of 75% with COPP/ABVD, 80% with BEACOPP baseline and 86% with BEACOPP escalated, with a FFTF of 64%, 70% and 82%, respectively [145,107,146,147]. Some concerns are still present about BEACOPP-related toxicity, mainly acute haematological toxicity, secondary myelodysplastic syndromes and/or acute leukaemias, and infertility [148,149,147]. By contrast, infertility is not a problem with the ABVD regimen [150,151]. Moreover, the BEACOPP toxicity is particularly high and unacceptable in patients older than 65 years [152]. Two subsequent randomised trials have confirmed the superiority of BEACOPP escalated over ABVD in terms of disease control, but a difference in OS was not evident as a consequence of the salvage of ABVD failures with high-dose chemotherapy supported by autologous stem cell transplantation (HDC/ASCT) [153,154]. The superiority of BEACOPP over ABVD in terms of PFS is mainly evident in patients with a highly unfavourable presentation, such as those with IPS prognostic score ≥3 [153]. Considering that about 60–70% of patients with advanced disease can actually be cured with front-line ABVD alone with minimal toxicity, and that the rescue of ABVD failures is possible, the ideal would be to reserve BEACOPP escalated for patients with a very poor prognosis. Unfortunately, the IPS score is not a perfect predictor of ABVD response. However, the early response to the first two courses of ABVD evaluated with ^{18}FDG-PET seems to be a very good test for ABVD chemosensitivity. Many trials are therefore ongoing to evaluate the investigational strategy of an early shift to a more aggressive schedule for patients with ^{18}FDG-PET positive results after the first 2 courses of ABVD. Until the results of these trials are available, both the more aggressive and toxic BEACOPP and the less toxic ABVD can be considered rational options.

The consolidative role of IF-RT after full-dose chemotherapy in patients with advanced disease has been matter of debate for several years. The rationale for this strategy is based on the fact that relapse occurs in previously involved sites and often exclusively in lymph nodes, even in patients with advanced disease. In a first randomised trial, consolidation with IF-RT did not improve outcome in patients with advanced disease in CR after MOPP-ABV chemotherapy [155]. Conversely, a retrospective analysis of the impact of consolidation RT in patients registered in the UKLG LY09 randomised trial showed that the addition of RT was associated with significantly better PFS (5-year: 86% vs. 71%) and OS, suggesting that RT contributes significantly to the cure rate for advanced HL [156]. In a meta-analysis based on 1740 patients from 14 controlled adjuvant irradiation clinical trials [119], the addition of RT to chemotherapy was associated with an 11% improvement in tumour control but OS remained unchanged. The meta-analysis of studies comparing consolidation chemotherapy vs. consolidation RT showed that tumour control is similar in both groups while OS is 8% better in the chemotherapy-only patients because of fewer late treatment-related deaths. As a standard strategy on type 2 basis, consolidation IF-RT should be avoided in advanced HL, due to the potential for late morbid effects and the lack of a survival benefit demonstrated by randomised trials [157,158,155]. RT limited to the region of initial bulky disease or residual masses after effective chemotherapy is still an open question. Mediastinum irradiation after primary chemotherapy in patients with initial bulky mediastinal mass has been considered so far a required consolidation treatment. However, preliminary results of the HD12 trial show that radiation of initial bulk and residual masses after BEACOPP does not seem to be useful [159]. A useful new tool to tailor irradiation of residual masses is ^{18}FDG-PET evaluation at the end of chemotherapy. In the HD15 trial, patients with final ^{18}FDG-PET-negative residual masses were not irradiated and results showed 96% PFS [160]. However, some studies suggest that irradiation of initial bulky and residual PET negative masses are useful in patients treated with chemotherapy regimens less aggressive than BEACOPP [161,162]. Thus, RT of

initial bulk and residual masses is therefore still considered a standard treatment on type 3 basis when first-line chemotherapy is ABVD.

Consolidation with HDC/ASCT is an investigational approach in patients with HL in first CR after conventional first-line chemoradiotherapy. In spite of some encouraging early results [163], two subsequent randomised trials demonstrated that HDC/ASCT does not improve outcome in high-risk patients responding to front-line conventional chemotherapy [164,165].

6.3. Treatment of special categories of patients

6.3.1. Pregnant patients with HL

HL is one of the more frequent malignant conditions discovered during pregnancy, with concurrent pregnancy in ~3% of all patients with HL [166]. Efforts to determine the stage of disease in pregnant patients are somewhat restricted by the need to avoid CT scans and PET, but abdominal ultrasonography can be used to detect subdiaphragmatic disease. Overall, the clinical behaviour and prognosis of HL diagnosed in pregnant women are similar to those of nonpregnant women [167]. In general terms, treatment of pregnant patients with asymptomatic, early-stage HL should be deferred until after the second trimester. In fact, more than 50% of patients can continue pregnancy to term without treatment. If treatment is required, it is usually possible to control the lymphoma with single-agent chemotherapy, such as vinblastine or anthracycline, allowing the pregnancy to go to term [168,167]. The use of single agent vinblastine (6 mg/m^2) is associated with 75% ORR and normal infant delivery in most cases [169]. Patients who progress despite vinblastine can be treated with ABVD during the second or third trimester. Although RT should be avoided during pregnancy, recent advances in RT techniques have resulted in remarkably reduced risk of fetal complications [170], and, presently, it is relatively safe to irradiate patients with isolated supradiaphragmatic disease, with a whole body fetal dose ≤0.1 Gy.

If advanced HL is diagnosed during the first trimester, termination of the pregnancy should be considered followed by appropriate staging and polychemotherapy. Treatment should not be delayed during pregnancy if patient presents with B, bulky, subdiaphragmatic, or progressive HL after the first trimester. If treatment is required and the patient does not want a therapeutic abortion, the successful completion of pregnancy without fetal malformation is possible with ABVD or similar regimens [171]. There are no available data on the use of more intensive regimens such as Stanford V or BEACOPP in pregnancy.

6.3.2. HIV-positive patients

HL is one of the defining illnesses of the acquired immunodeficiency syndrome. Usually, HIV-positive patients with HL have mixed-cellularity or lymphocyte-depletion subtype, advanced and extranodal disease, and systemic symptoms. The availability of highly active antiretroviral therapy has dramatically improved outcome among these patients [172]. Today, HIV-infected patients with early-stage HL should receive the same treatment as HIV-negative patients with early-stage disease.

6.3.3. Elderly patients

Elderly patients, defined by chronological age, with HL represent a heterogeneous population in terms of life expectancy, morbidities, and functional status. Nearly 20% of HL patients are >65 years in some developed countries. In general, less than 10% of patients included in broad clinical trials are >60 years. The proportion of mixed cellularity histopathology and EBV-genome-positive tumours is higher in older adults. Five-year OS of patients 66–80 and >80 years is 58% and 26%, respectively. Older patients have lower remission rates, but PFS is less impaired. One reason for the relatively poor outcome in elderly patients is their susceptibility to the toxic effects of intensive therapy, and many have coexisting conditions that affect their ability to tolerate standard treatments. For example, elderly patients did significantly less well with EF-RT than with IF-RT; no such effect was observed in younger patients. Elderly fit patients younger than 65–70 years should be treated following the same modern therapeutic guidelines used in young patients. Even if elderly patients seem to benefit proportionally more than younger patients from the inclusion of doxorubicin in the treatment regimen [173], contraindications to use anthracycline should follow the well-known recommendations used in other lymphoma patients. In these cases, some regimens such as VBM appear advisable [174]. Thorough estimation of the individual patient's frailness/comorbidities to allow proper adjustment of treatment, thus saving patients from over/undertreatment, remains an important, but a rarely respected, recommendation.

6.4. Treatment of relapsed or refractory HL

The choice of salvage treatment in relapsed or refractory HL is strongly influenced by previous treatments and the duration of the previous response. HDC/ASCT is considered the standard of care on type 2 basis in patients with HL relapsed or refractory at conventional first-line chemoradiotherapy, while patients relapsed after RT as exclusive first-line treatment can be treated with ABVD (followed or not by IF-RT) on a type 3 basis. Patients with late relapse disease can be treated with a conventional dose combination, including the same previous regimen, with complementary RT to previously un-irradiated bulky sites [175]. Salvage treatment with intense chemotherapy regimens such as BEACOPP [176] or MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) [177] can be used successfully in patients with late relapse after front-line ABVD on a type R basis.

The advantage of HDC/ASCT in relapsed or refractory patients has been demonstrated in small randomised trials [163,178,179] and has also been suggested by many non-randomised studies [99,180–182]. HDC/ASCT can produce long-term DFS in 30–65% of selected patients with advanced relapsed disease, with a greater benefit among patients with a less favourable prognosis. In these studies, HDC/ASCT efficacy was related to the amount of primary therapy, presence of B symptoms, extent of disease at time of transplantation and the responsiveness to prior chemotherapy. Overall, these randomised trials are old studies that showed a significant impact in PFS, but no differences were shown in terms of OS, which seems to reflect the small number of patients and the possible bias due to the subsequent high-dose salvage treatment for non-transplantation arms.

Recently reported studies demonstrated that more than 60% of patients who have had a relapse after ABVD and about 30% of patients with initially refractory lymphoma can be reliably cured with HDC/ASCT [183]. A recently reported Italian randomised trial comparing BEACOPP vs. ABVD in patients with advanced disease HL showed that salvage HDC/ASCT could even cure patients with chemorefractory HL, offering a second chance at a cure to otherwise doomed patients [154]. In that trial, the use of salvage HDC/ASCT negated the initial PFS advantage in favour of BEACOPP (7-year: 85% vs. 73%; $p = 0.004$) resulting in similar OS (7-year: 89% vs. 84%; $p = 0.39$). Accordingly, patients with advanced-stage HL can be cured, with a lower risk of side effects, leukemogenesis and infertility, by using first-line ABVD followed by salvage HDC/ASCT in failed patients [184]. These observations underscore the full impact of reliably curative secondary treatment following the best choice of primary chemotherapy [184].

The best induction debulking regimen before HDC/ASCT remains to be defined since no randomised trials have been published comparing the efficacy and toxicity of available regimens. Several salvage regimens of different intensity, such as DHAP (dexamethasone, cytarabine, cisplatin) [98], ICE (ifosfamide, carboplatin, etoposide) [185], and IGEV (ifosfamide, gemcitabine, vinorelbine) [186] have showed good activity in reducing bulk disease, mobilising peripheral blood stem cells and evaluating chemosensitivity. Each of these regimens can be independently utilised as an individualised treatment based on a type 3 evidence.

Some authors suggest that residual positivity after debulkying chemotherapy and before ASCT detected by ^{18}FDG-PET is associated with poor outcome after a single ASCT [100,101]. In this set, a double ASCT procedure is feasible with acceptable toxicity and preliminary good results, but it should be considered as an investigational treatment option [187,188].

HDC supported by allogeneic stem cell transplantation seems to be a suitable clinical tool for patients with early relapsed or refractory HL, or for patients relapsing after ASCT. Until some years ago, transplant-related mortality of allogeneic transplantation represented a main limitation, reaching an overall rate of 40%. The recent advances in the field of transplantation, along with the introduction of non-myeloablative regimens and with an accurate management of the septic complications, increased the interest toward this approach [189,190]. A broad spectrum of evidence supports the existence of graft vs. HL (GVHL). Some studies showed a lower rate of relapse after allogeneic transplantation compared with ASCT and data from the EBMT (European Group for Blood and Marrow Transplantation) registry demonstrate a direct correlation between grade 2 and 4 graft vs. host disease (GVHD) and probability of recovery. Moreover, preliminary data suggest a direct anti-lymphoma activity exerted by donor's lymphocytes after allotransplant in cases of relapse [191,192].

Limited conditioning regimens before transplantation – introduced with the purpose of increasing GVHL and reducing myeloablation – have decreased the peritransplant mortality and allowed a better evaluation of the beneficial effects. A wide spectrum of reduced-intensity conditioning regimens has been proposed, the majority being based on fludarabine. The same goes for immunosuppressants following transplantation. Also, more homogeneous protocols on the use of DLI are advisable, according to the clinical features of disease, to the grade of GVHD and to immunosuppressant drugs.

At present, the estimated transplant-related mortality is about 20% and destined to decrease further [193]. A revision of the EBMT registry demonstrated the clinical efficacy of this procedure in HL, with 2-year OS of 47%, and a 15% peritransplant mortality [194]. Further EBMT studies have showed good results with reduced conditioning regimens [195], and a survival benefit in patients relapsing after ASCT, who had a donor and were allografted with a reduced conditioning regimen [196].

Response to debulking chemotherapy before allotransplant is an important prognostic factor [197], and ASCT following induction therapy might be useful in significantly increasing the proportion of patients in remission before allotransplant [198]. Accordingly, both double ASCT and ASCT followed by non-myeloablative allotransplant are promising strategies for very high-risk patients with relapsed or refractory HL, and they should be considered as investigational strategies in patients chemo-resistant before the first ASCT.

6.5. Treatment-related late complications and second tumours

The toxicity of chemotherapy is the major drawback to its widespread use. Early toxicity is usually manageable and of short duration. Conversely, late toxicity is often related to irreversible and sometimes life-threatening abnormalities. Alkylating agents may induce male and female sterility, but this is much less frequent in patients treated with ABVD-like regimens than alkylating-containing regimens, mainly BEACOPP [148–151]. Semen cryopreservation should be programmed into the treatment schedule for all men younger than 50 years. Over 50 years old, it is up to the patient and

his preference. A major problem concerns pre-puberal boys, who should be treated with non-gonadotoxic chemotherapy. Pulmonary fibrosis depends mainly, but not exclusively, on bleomycin use (1–6% of patients treated with ABVD); it is dose-dependent with a cumulative limited dose of bleomycin of 170 mg/m^2. However, this toxicity may appear even after a single dose of bleomycin. The addition of thoracic irradiation to bleomycin increases the risk of paramediastinal pulmonary fibrosis and cutaneous sclerosis.

RT is associated with unaesthetic modifications due to the disappearance of the fatty subepidermal tissues, mainly in the neck, and with skin sclerosis, xerostomia, hypothyroidism, oedema of the arm or thigh, amenorrhoea, and female sterility. Most severe non-tumoural late effects of RT are cardiovascular complications due to vascular obstructions (infarction and cardiac failure) and pericardiac sclerosis. Lung complications after mantle-field irradiation are often limited to paramediastinal fibrosis. In paediatric cases, where there is concern about the late effects on statural growth and thorax morphology, a dose reduction of radiation therapy to 20–25 Gy has been adopted in complete responders to primary chemotherapy. Fertility may be compromised in young women with infradiaphragmatic disease requiring pelvic irradiation. If the patient has no children, surgical ovarian displacement should be suggested. In this case, one ovary is moved to a median area just under the uterus, and the other is shifted out of the programmed RT field.

Secondary acute leukaemia and myelodysplastic syndromes are almost always fatal complications, often induced by alkylating agents [199]. Non-Hodgkin lymphomas is a complication of HL treatment [200–202] that should be distinguished from relapses by using excisional biopsy. The incidence of lung and breast cancer is higher than expected in patients irradiated with mantle field, and the risk of second cancers is increasing in proportion with intensity of RT and time after treatment [203,204,116,117]. In women treated with mediastinal RT, breast cancer develops at a younger age than the average, and regular breast screening is recommended. Other solid tumours arising within irradiated areas have been described [205–208]. The most appropriate screening methods, time of initiation and intervals between visits are currently uncertain and guidelines vary widely. There is a need to evaluate methods, benefits and costs of long-term follow-up, including the impact of breast cancer screening on mortality.

6.6. New active drugs and ongoing trials

Several investigational approaches are presently being tested in relapsed HL. Among others, Yttrium-labelled ferritin combined with HDC/ASCT [209], T cells against some antigens of EBV infused after HDC/ASCT [210], anti-CD30 antibodies-ricin A-chain immunotoxin [211], anti-CD25 antibodies-ricin A-chain immunotoxin [212], anti-CD16 × anti-CD30 bispecific monoclonal antibodies [213], and interleukin-2-diphtheria-toxin fusion toxin are being investigated [214]. Some histone-deacetylase inhibitors, such as panobinostat [215], and immunomodulators such as lenalidomide [216] are other interesting molecules under study alone or in association with conventional or HDC/ASCT [217].

Among new therapeutic options, attention is presently focused particularly on the potential role of rituximab, an anti-CD20 monoclonal antibody largely used in the treatment of B-cell non-Hodgkin lymphomas. It seems to be active, not only in CD20+ nodular lymphocyte predominant [218,219], but also in classical CD20 negative forms. The central hypothesis for using rituximab is that benign B lymphocytes in the lymph-node microenvironment promote survival of R-S cells. Consequently, targeting them by using rituximab may deprive neoplastic cells of survival signals and facilitate the action of chemotherapy [216,220]. Preliminary results of a phase II study combining rituximab with ABVD are encouraging [221], and randomised studies are ongoing (NCT00992030).

The development of novel therapies targeting CD30 is a major advance in the treatment of HL. Normal CD30 has a relatively restricted distribution on activated B-cells, T-cells and eosinophils thus making it a very attractive target in this disease. After an initial phase where several anti-CD30 antibodies showed considerable in vitro activity (i.e., the human Ig G1k antibody MDX-060, the human antibody 5F11, the humanised antibody XmAb 2513, the chimeric antibody SGN-30, the immunotoxin ki-4dgA), but modest clinical activity in patients with CD30-positive lymphomas (i.e., HL and anaplastic large cell lymphoma), more recently reported studies showed relevant clinical activity with some interesting molecules. Brentuximab vedotin (SGN-35) seems to be the more promising candidate. This agent is a conjugate comprising the antitubulin agent monomethyl auristatin E and a CD30-specific monoclonal antibody that has shown excellent activity both in cHL and anaplastic lymphoma. The phase I study evaluating this agent in relapsed or refractory CD30+ lymphomas included mostly patients with HL. The treatment was well tolerated with mostly grade 1 and 2 toxicity, mainly peripheral neuropathy [222]. A pivotal, phase 2 multicentre trial – recently reported in abstract form – addressed the efficacy and safety of SGN-35 in 102 patients with HL relapsed or refractory to ASCT [223]. Brentuximab vedotin 1.8 mg/kg was administered every 3 weeks for up to 16 cycles of treatment, resulting in tumour size reduction in 95% of patients and resolution of B symptoms in 83%, with manageable adverse events. This encouraging activity in heavily pretreated patients deserves to be confirmed in further trials. An ongoing randomised, placebo-controlled, multicentre phase 3 trial will assess the efficacy and safety of SGN-35 in patients with residual HL after ASCT (NCT01100502).

The chance to tailor subsequent treatment according to the results of PET scan after the first 2 courses of ABVD is an investigational strategy and many international trials focused on this topic are ongoing. Mostly, these trials try to determine if PET/CT imaging can be reproducibly and effectively

applied in the early assessment of response to chemotherapy and whether patients with a negative or a positive FDG-PET/CT scan after 2 courses of ABVD can be safely treated with a reduced or intensified therapy. Therapeutic intensity reduction in ongoing trials consists of excluding RT in early-stages (H10, HD0801), deleting some drugs from ABVD in advanced stage disease (CRUK-2007-006064-30), deescalating from BEACOPP to ABVD (AHL 2011) or reducing the number of courses (HD18). On the other hand, intensified treatment consists of including more aggressive regimens such as BEACOPP instead of ABVD (HD0607), adding rituximab (HD18) and early crossing to HDC/ASCT (HD0801) are also being investigated. In this context, and with the aim of reducing iatrogenic toxicity, the HD16 and the RAPID trials are assessing – with different designs – whether IF-RT avoidance in patients with favourable early-stage HL and PET negative after 2–3 courses of ABVD will result in non-inferior outcome with respect to conventional chemoradiation therapy. The HD17 will assess the role of PET in patients with intermediate risk HL, comparing 2 courses of BEACOPP escalated plus 2 courses ABVD followed by 30 Gy IF-RT irrespective of FDG-PET results after chemotherapy (control arm) vs. the same chemotherapy followed by 30 Gy IN-RT if FDG-PET is positive after chemotherapy or the same chemotherapy without RT if FDG-PET is negative after chemotherapy (experimental arm).

Conflict of interest

Authors have no conflict of interest to be disclosed.

Reviewers

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START METHODOLOGY

START is an evidence-based instrument. This means that statements on main clinical "options" are codified and accompanied by a codified "type of basis", as follows, according to a classification originally devised for the **START** project. The **START** Editorial team is glad to receive comments on this (please, address them to the START Secretariat). The background has been detailed in *Ann Oncol 1999; 10: 769-774.*

TYPE of OPTION

START provides the following diagnostic and treatment options. The "standard" and the "individualised" options are coupled with ranked types of basis,

- ***STANDARD ("standard", "recommended" [or "not recommended"])***
  This can be considered a conventional choice for the average patient.
- ***INDIVIDUALIZED ("suitable for individual clinical use")***
  This is not a standard option, but it can be a reasonable choice for the individual patient. The patient should be informed that the option is not standard and the decision must be shared with the patient.
- ***INVESTIGATIONAL ONLY ("investigational")***
  This is something which, in principle, can be offered to the patient only within a clinical study.

TYPE of BASIS for available options

START provides an appropriate basis for each clinical option. Types of basis are ranked in five levels.

- There is a widespread consolidated consensus. Randomised trials have not been carried out or have been inadequate, but the issue is settled without major controversy: currently, no (further) experimental evidence is felt to be needed
- ***"TYPE 1 evidence" (Randomised trial(s) available, strong evidence)***
  Consistent results have been provided by more than one randomised trials, and/or a reliable meta-analysis was performed. In some instances, one randomised trial can be considered sufficient to support this type of evidence. Further confirmatory trials do not seem necessary.
- ***"TYPE 2 evidence" (Randomised trial(s) available, weak evidence)***
  One or more randomised trials have been completed, but the evidence they provide is not considered definitive (their results are not consistent, and/or they are methodologically unsatisfactory, etc.). Some controlled evidence has therefore been provided, but confirmatory trials would be desirable.
- ***"TYPE 3 evidence" (External controlled comparisons available)***
  Evidence is available from non-randomised studies, with external controls allowing comparisons. Some uncontrolled evidence has therefore been provided, but trials would be desirable.
- ***"TYPE R basis" (Rational inference)***
  Little or no direct evidence from clinical studies is available. Yet clinical conclusions can be rationally inferred from available data and knowledge (e.g. by rationally combining pieces of information from published studies and observations; for a rare neoplasm, or presentation, through analogy with a related, more common tumour, or presentation; etc.). The inference can be more or less strong, and trials may, or may not, be desirable (although sometimes unfeasible).