Hodgkin's lymphoma: Belgian Hematology Society guidelines in diagnosis, treatment and follow-up

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SUMMARY

Hodgkin's lymphoma (HL) is a rare B cell malignant neoplasm affecting approximately 300 new patients in Belgium annually. This disease represents approximately 11% of all lymphomas and comprises two discrete disease entities: classical HL and nodular lymphocyte-predominant HL. In recent years, treatment of HL patients has changed tremendously due to the use of interim PET-CT scan and the appearance of new molecules. In this article, the diagnosis, staging, treatment and long-term follow-up of patients with classical HL are discussed.
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INCIDENCE AND EPIDEMIOLOGY

In 2015, approximately 300 new cases of Hodgkin's lymphoma (HL) were diagnosed in Belgium (Belgian Cancer Registry). HL has a bimodal disease distribution, with an increased incidence in patients in their teenage years and patients in their twenties and a similar increased incidence in patients who are older than 55 years.

The exact cause of HL remains unknown, but factors associated with an increased risk for HL include exposure to viral infections, familial factors and immunosuppression. Siblings of patients with HL have an increased risk for this disease.[1]

DIAGNOSIS AND STAGING

Patients usually present with supra-diaphragmatic disease. Abdominal or inguinal lymph nodes are less commonly involved. Most frequently, the disease involves regional lymph nodes, although extra-nodal disease can occur due to direct invasion by homological spread. Common sites that may be involved include the spleen, liver, lungs and bone marrow. Bone marrow involvement occurs in less than 10% of the newly diagnosed patients.

Patients are often asymptomatic. About 40% of them, especially in case of advanced disease, presents with constitutional symptoms: fever, night sweats and weight loss.

HL has the unique characteristic of clonal malignant Reed-Sternberg cells constituting only a minor part of the tumoral micro-environment. Small biopsy specimens may not include sufficient malignant cells. Therefore, an excision biopsy of the lymph node is mandatory to establish a definitive diagnosis.

A thorough anamnesis should be recorded including medical history, the presence of B symptoms and other disease associated symptoms (e.g. fatigue, pruritus and alcohol induced pain in the lymph nodes).[2,3]

An extensive blood examination including a full blood cell count, sedimentation rate and blood chemistry should be conducted, as well as a serological test for hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV).

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TABLE 1. Prognostic factors in early stage Hodgkin's lymphoma.

EORTC/LYSA classification	GSHG classification
bulky mediastinal mass	bulky mediastinal disease
age ≥50 years	extra-nodal site
ESR ≥50 without B symptoms	ESR ≥50
ESR ≥30 with B symptoms	≥3 nodal sites
≥4 nodal areas involved	
Presence of one or more of these risk factors indicates unfavourable disease.	

In female patients, human chorionic gonadotropin (HCG) testing, anti-Müllerian Hormone (AMH) testing and reproductive counselling is also advised.

Staging is performed by a PET-CT scan to be able to determine Ann Arbor classification. Bone marrow biopsy is no longer performed if staging includes a PET-CT scan because of the high sensitivity for bone marrow invasion of the PET-CT scan.[3,4]

PATHOLOGY

The disease is composed of two distinct entities: the more commonly diagnosed classical HL and the rare nodular lymphocyte-predominant HL. Classical HL includes the subgroups nodular sclerosis, mixed cellularity, lymphocyte depleted and lymphocyte rich.

In classical HL, the presence of Hodgkin and Reed-Sternberg (HRS) cells or their variants defines the disease. These cells are consistently positive for CD30 and CD15 and occasionally positive for CD20 and negative for CD45. The background cellular population determines the morphological sub-classification of classical HL.

Lymphocyte predominant (LP) cells are characterised by the expression of CD20 and CD45 but are lacking CD15 and CD30.

TREATMENT OF CLASSICAL HODGKIN'S LYMPHOMA

EARLY HODGKIN'S LYMPHOMA

Considering the good prognosis within this patient group, the aim is not only to cure but also to minimise treatment related toxicity. Therefore, there has been a trend towards reducing the dose of chemotherapy and decreasing the irradiation field and doses. Lately, several clinical trials investigated the possibility to tailor the treatment based on the results of the interim PET-CT.

Within the patient population with localised disease, there are two prognostic groups: favourable and unfavourable. Several prognostic factors, varying among different study groups, are used to define those subgroups (*Table 1*). Patients presenting with either one of these factors should be classified as unfavourable early stage Hodgkin disease (HD) and those with no risk factors can be considered as having favourable early stage HL.[3]

FAVOURABLE EARLY STAGE DISEASE

Patients with early favourable disease are generally treated with two to three cycles of adriamycin, bleomycin, dacarbazine and vinblastine (ABVD) followed by 20 Gy involved field radiotherapy (IFRT).

A large non-inferiority multicentre trial (HD 10 trial) randomised patients into four treatment groups with two or four courses of ABVD and 20 or 30 Gy IFRT. At a median follow-up of 7.5 years, there was no significant difference between four and two cycles of ABVD chemotherapy (five-year overall survival (OS): 97% *vs* 97%; freedom from treatment failure (FFTF): 93% *vs* 91%) or between 30 Gy and 20 Gy IFRT (five-year OS: 98% *vs* 97.5%; FFTF: 93% *vs* 93%). However, there were significant differences in major toxicity between four and two cycles of ABVD (grade ≥3 overall toxicity: 52% *vs* 33%) and between 30 and 20 Gy IFRT (grade ≥3 overall toxicity: 9% *vs* 3%).[6] This trial demonstrates that duration and intensity of the first line treatment can be reduced to two cycles of ABVD followed by 20 Gy IFRT.

Going further along the same direction there are currently trials being conducted to omit bleomycin in those good risk patients.

The German HD13 trial investigated the importance of

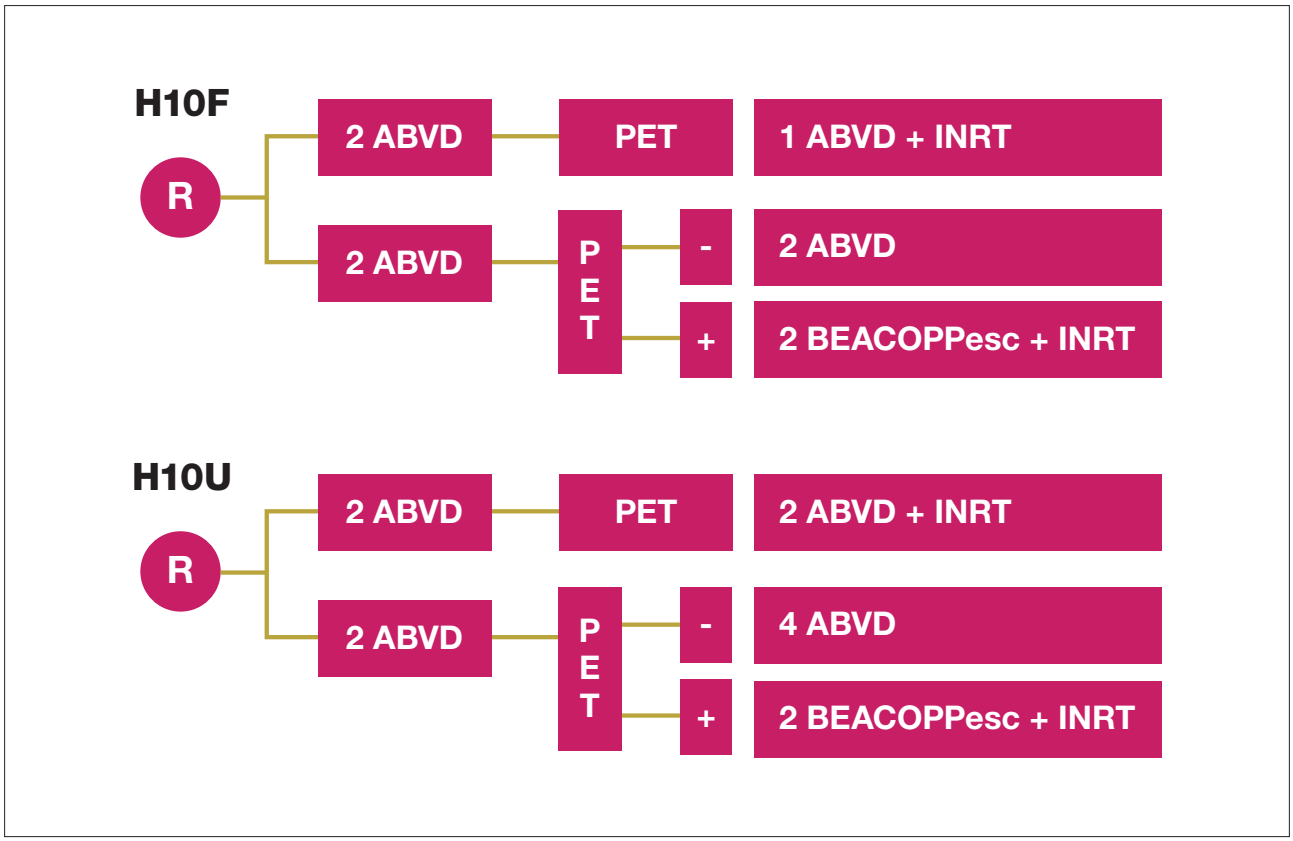

FIGURE 1. Trial design of the EORTC/LYSA/FIL H10 Trial.
ABVD: adriamycin, bleomycin, dacarbazine and vinblastine, BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, INRT: involved nodal radiotherapy.

bleomycin and dacarbazine within ABVD for patients with early stage favourable HL. Patients were randomly assigned to receive ABVD, AVD, ABV or AD. A significant lower FFTF in the patient groups treated without dacarbazine and/or bleomycin was observed at five years. Non-inferiority of AVD followed by 30 Gy IFRT could also not be established.[6] Currently, new trials are ongoing where brentuximab vedotin (BV) replaces bleomycin in the ABVD schedule.

Since an early PET scan predicts the outcome when the planned treatment is continued, contemporary trials have focused on optimising a combined modality strategy using early PET-CT scan as a guidance.[7,8]

The recently published EORTC/LYSA/FIL H10 trial addressed the question of omitting radiotherapy (RT) considering interim PET-CT scan results.[9,10] The first subgroup of patients had a favourable early stage HL (444 patients) and was treated with two cycles of ABVD, followed by a PET-CT scan. In the control group, the PET-CT scan was followed by a third cycle of ABVD and 30 Gy involved nodal RT (INRT). The investigational group was treated according to the result of the interim PET-CT scan. PET-negative patients received two more courses of ABVD and PET-positive patients were treated with two courses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (BEACOPPesc) followed by 30 Gy INRT (*Figure 1*).

In the PET-negative patient group, non-inferiority of ABVD alone could not be withheld. Intention to treat (ITT) and five-year progression-free survival (PFS) were 99.0% and 87.1% in the ABVD + INRT and ABVD only arms respectively, with a hazard ratio (HR) of 15.8 in favour of combined modality treatment. INRT should therefore still be offered to those patients. On the other hand, the overall excellent survival in both arms supports the consideration of INRT omission in selected patients.

In the PET-positive patients (favourable and unfavourable), a significant improvement (13.2%) of five-year PFS was reached in the experimental BEACOPPesc + INRT arm compared with continuation with ABVD + INRT. Even a benefit in OS of 6.7%, with a trend towards statistical significance, was observed. We do stipulate that the number of PET-positive patients with favourable HL was low (N=43).

The RAPID trial was a phase III trial including patients with a stage IA and IIA, non-bulky disease.[11] Patients with favourable and unfavourable disease were included. A 1:1 rando-

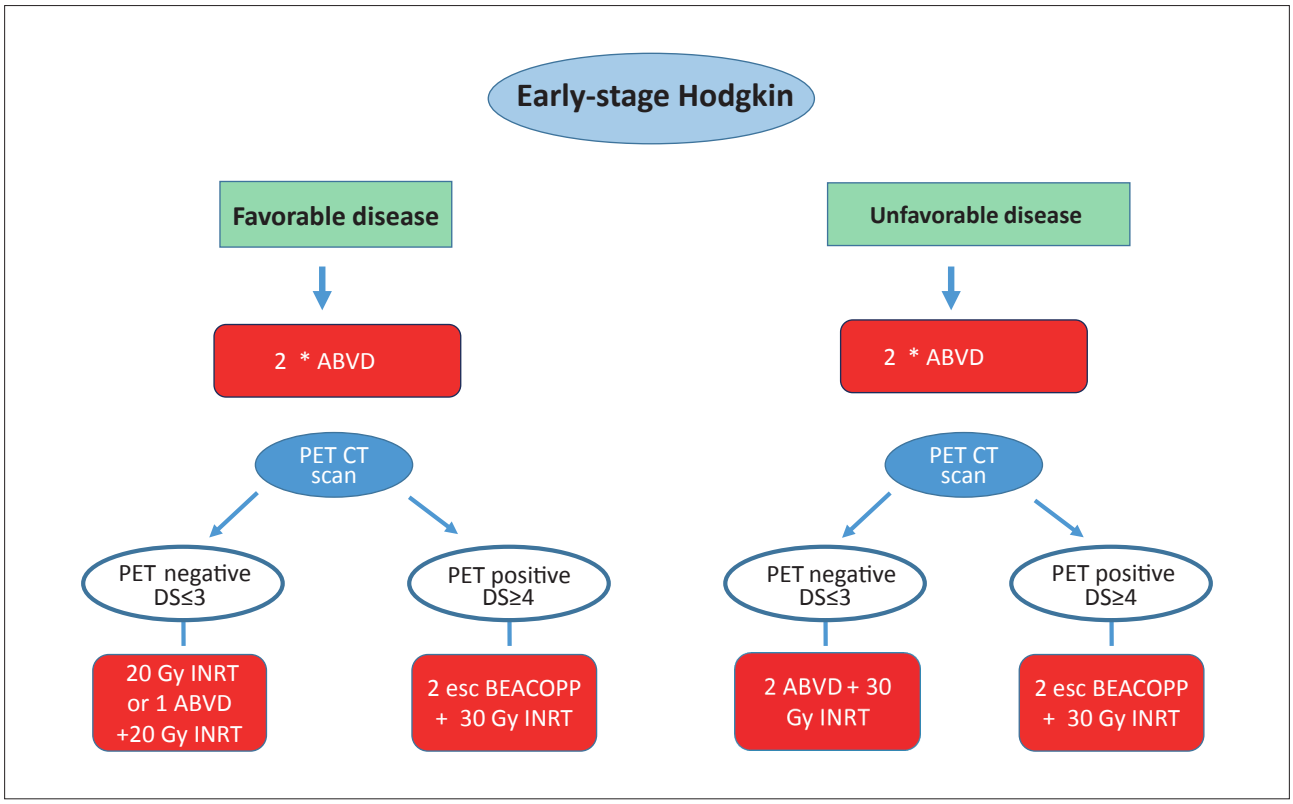

FIGURE 2. Treatment schedule early-stage Hodgkin's lymphoma.
ABVD: adriamycin, bleomycin, dacarbazine and vinblastine, BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, INRT: involved nodal radiotherapy.

misation was performed between no further therapy or IFRT for those who reached a negative PET-CT scan following three cycles of ABVD. Patients with a positive PET-CT scan after the third cycle of ABVD went on to a fourth and then received 30 Gy IFRT. No separate analysis was made for the favourable and unfavourable group (but bulky disease was excluded).

In the PET-negative group, there was no significant difference in the three-year PFS and OS. In the group with no further treatment, the three-year PFS was 90.8% and OS was 99.0%. In the RT group, this was 94.6% and 97.1% respectively. On the basis of a maximum allowable difference of seven percentage points, this study did not show non-inferiority of the strategy of no further treatment.

Omitting RT in this RAPID and H10 trial was thus associated with a trend towards higher treatment failure, but this did not translate into a lower OS. Whether long-term OS will finally be better in the non-RT group, due to less late toxicity, remains unknown.

A recently published sub-analysis of the GSHD HD10 and HD13 trial investigated the feasibility, toxicity and efficacy of ABVD and AVD in 287 older, (≥60 years) early-stage favourable HL patients. Grade III-IV adverse event rates were similar in patients receiving 2AVD and 2ABVD (40% and 39%, respectively), but considerably higher in patients receiving 4ABVD (65%). Bleomycin-induced lung toxicity was rare in patients receiving 2ABVD/AVD, but occurred in 7/69 (10%) of patients randomised to 4ABVD with three lethal events.[12]

Although no larger and other randomised trials are published, omission of bleomycin in patients ≥60 years of age can be advised if the interim PET-CT scan is negative.

RECOMMENDATIONS FAVOURABLE DISEASE (*Figure 2*)

Early PET-negative: 2-3 ABVD + INRT/IFRT 20 Gy.

Early PET-positive: 2 ABVD + 2 BEACOPPesc + INRT/IFRT 30 Gy.

EARLY STAGE UNFAVOURABLE DISEASE

Patients presenting with early unfavourable HL are generally treated with four cycles of ABVD followed by 30 Gy RT.

The final results of the HD11 trial have not shown a significant difference between four courses of ABVD versus four courses of BEACOPP baseline when followed by 30 Gy IFRT. Toxicity was higher in the BEACOPP group.[13]

In the German HD14 trial, patients were randomised between two times BEACOPPesc followed by two courses of ABVD or four cycles of ABVD, both followed by 30 Gy IFRT.[14] After a median follow-up of 43 months, FFTF was better in the intensively-treated group, however, without difference in OS.

A recently published retrospective trial showed no difference in disease control between patients treated with four or six cycles of ABVD, followed by RT. For patients receiving four and six cycles, the six-year OS was 100% and 97% (P=0.35), respectively, and the six-year freedom from relapse (FFR) was 100% and 98% (P=0.28), respectively.[15]

In the EORTC/LYSA/FIL H10 trial, patients with unfavourable disease were randomised between standard treatment consisting of four cycles of ABVD followed by 30 Gy INRT versus experimental treatment based upon early PET-CT scan after two cycles of ABVD.[10] Patients reaching an early negative PET scan went on to four additional cycles of ABVD, whereas in PET-positive patients, chemotherapy was upgraded to BEACOPPesc followed by 30 Gy INRT.

Analysis of the PET-negative patients demonstrated the five-year risk difference in PFS to be only 2.5% in favour of combined modality treatment versus chemotherapy alone. However, the difference seems less important in the favourable group, and non-inferiority of ABVD alone could not be declared as the upper bound of the 95% confidence interval (CI) of the estimated HRs exceeded the pre-set non-inferiority margins.

In the PET-positive group, as stated above, there was a significant improvement of five-year PFS in the experimental arm where treatment was switched towards BEACOPPesc and INRT.

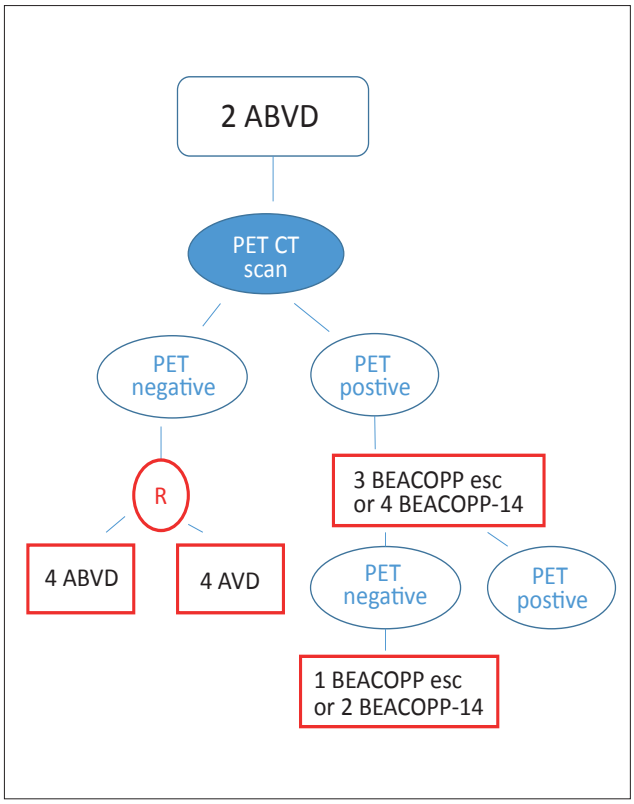

FIGURE 3. Design of the RATHL study.
ABVD: adriamycin, bleomycin, dacarbazine and vinblastine, BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, AVD: adriamycin, dacarbazine and vinblastine.

RECOMMENDATIONS UNFAVOURABLE DISEASE (*Figure 2*)

Early PET-negative: 4 ABVD + INRT/IFRT 30 Gy

Early PET-positive: 2 ABVD + 2 BEACOPPesc + INRT/IFRT 30 Gy.

ADVANCED HL

Advanced HL is usually treated with chemotherapy alone, with additional RT for patients with residual disease at the end of chemotherapy. Patients ≤60 years are classically treated with either ABVD (six cycles) or BEACOPPesc (six cycles), optionally followed by localised RT.[16,17] For patients >60 years, BEACOPPesc should not be used because of excessive toxicity and the increased rate of treatment-related mortality observed in this age group.[18]

For both BEACOPPesc and ABVD, several recent phase III randomised studies have shown that treatment should be evaluated after two cycles of chemotherapy by a PET-CT scan and that the result of this early PET scan should guide the management of subsequent treatment.

When ABVD is used, the RATHL study (*Figure 3*) has recently demonstrated that the omission of bleomycin is safe in cycles three to six in case of a negative interim PET scan (defined as a Deauville score (DS) ≤3) after two cycles of chemotherapy. This strategy should be considered especially in elderly patients and those at an increased risk for lung toxicity. This non-inferiority study was not able to exclude a PFS difference of >5% at three years.[19] The question of whether consolidating RT can be omitted in patients who have a negative PET scan after two and six ABVD cycles or at the end of chemotherapy has not been evaluated. In advanced HL patients who have a positive interim PET scan after two ABVD cycles (DS=4-5), the question of early intensification has not yet been evaluated in a randomised trial. However, several phase II studies have suggested that patients with advanced HL who have a positive interim PET scan (DS≥4 for RATHL and DS=3-5 for SWOG S0816 and HD0801 studies) have a better prognosis after switching

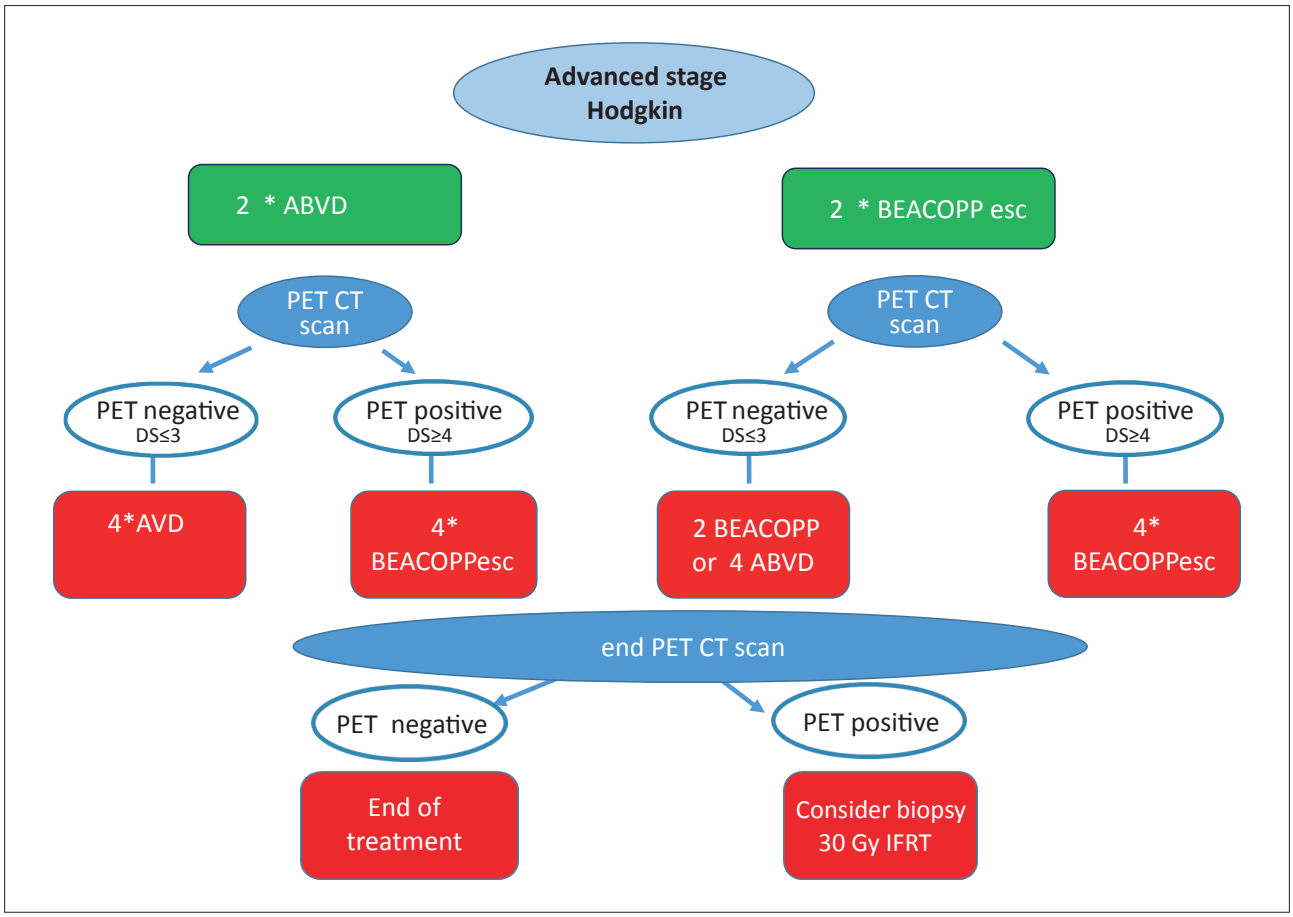

FIGURE 4. Treatment schedule for advanced-stage Hodgkin's lymphoma.
ABVD: adriamycin, bleomycin, dacarbazine and vinblastine, BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, AVD: adriamycin, dacarbazine and vinblastine, IFRT: involved field radiotherapy.

from ABVD to BEACOPP regimens than after continuation of ABVD.[19-21]

In patients that are initially receiving BEACOPPesc, the HD18 trial has shown that the treatment can be safely reduced to a total of only four cycles in case of a negative interim PET scan (DS≤2) after two chemotherapy cycles.[22] In the AHL2011 study, patients received two cycles of BEACOPPesc, and if the PET scan was negative (DS≤3), they were randomised between four BEACOPPesc (standard arm) and four ABVD (experimental arm) cycles. At the interim analysis, no difference was observed.[23]

In addition, RT can be restricted to patients with PET-positive residual lymphoma ≥2.5 cm after four and six cycles of BEACOPPesc.[17,22]

Four trials randomly comparing ABVD and BEACOPPesc have shown a superior tumour control and a non-significant trend towards a better OS with BEACOPPesc.[23-26] A network meta-analysis including 9993 patients also revealed a significantly better OS with BEACOPPesc when compared with ABVD. The survival benefit was 10% at five years.[27]

One phase III trial comparing ABVD versus AVD + BV has recently been completed and showed a modest 4.9% improvement of modified PFS in the AVD + BV arm.[28]

RECOMMENDATIONS (*Figure 4*)

1. Initial 2 ABVD
   - Early PET-negative: + 4 AVD
   - Early PET-positive: + 4 BEACOPPesc
2. Initial 2 BEACOPPesc
   - Early PET-negative: + 2 BEACOPPesc or + 4 ABVD
   - Early PET-positive: + 4 BEACOPPesc
3. Both initial ABVD or BEACOPPesc, end of treatment PET:
   - Negative: no further treatment
   - Positive: 30 Gy IFRT for PET positive residual lymphoma ≥2.5 cm

TREATMENT OF REFRACTORY OR RELAPSED CLASSICAL HL

Most patients are cured by modern treatment options containing a combination of chemotherapy with or without

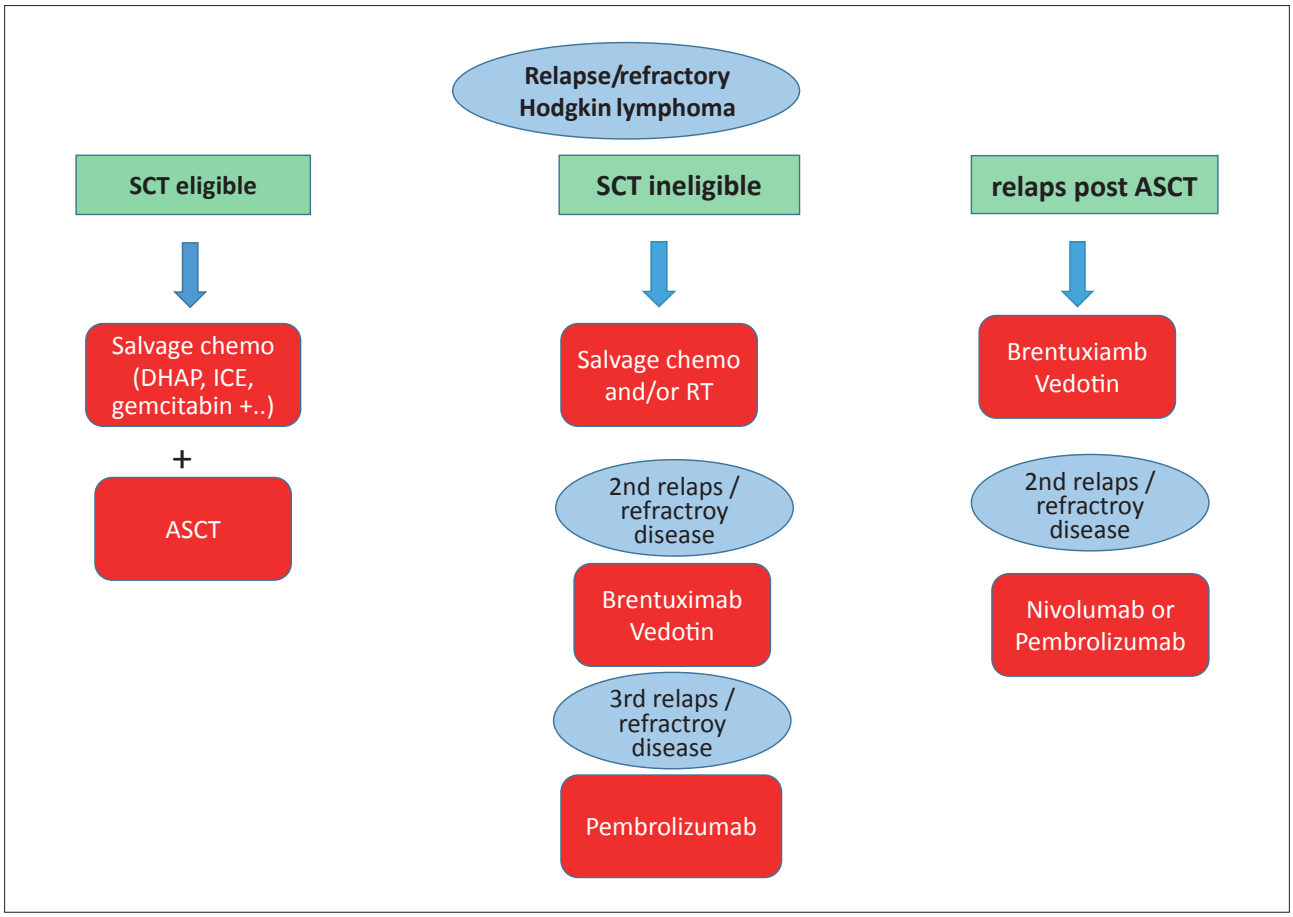

FIGURE 5. Treatment schedule for relapse/refractory Hodgkin's lymphoma.
SCT: stem cell transplantation, ASCT: autologous stem cell transplantation, RT: radiotherapy.

radiation treatment.

About 10-15% of patients with HL have refractory disease and 10-30% of patients experience a relapse (10-15% in patients with favourable characteristics, 15-30% in patients with unfavourable characteristics).

Relapse or recurrence is the presence of the disease at the prior disease sites and means new lesions after initial therapy and obtaining complete remission (CR). This occurs in one third of the patients (early relapse: <12 months, late relapse: ≥12 months). Progression after achieving a stable partial remission (PR) occurs also in one third of the patients. Refractory disease is when a CR or PR could not be obtained (one third of patients).

BIOPSY AND STAGING

Biopsy is required in most patients, especially in late relapse. A biopsy in the setting of early relapse and persistence of constitutional symptoms or measurable known radiographic abnormalities is probably not necessary. In the case of unusually resistant disease, a biopsy is necessary to exclude other diseases.[29]

Staging should include a PET-CT scan and the Ann Arbor 'RS' staging system. The subscript 'RS' is used to designate the stage at the time of relapse. A PET-CT scan should also be used to evaluate response after salvage therapy.[30] Prognostic factors include age, symptoms, stage, duration of first remission, extent of prior therapy and presence or absence of anaemia.

MANAGEMENT

Salvage chemotherapy and autologous stem cell transplantation

Most patients with refractory disease or first relapse (especially early relapse) are treated with intensive chemotherapy (DHAP, ICE or gemcitabine-containing combination therapy) followed by an autologous stem cell transplantation (ASCT) – in case of eligibility for ASCT – to obtain long-term disease control. Long-term survival is most likely if a CR is achieved. Intermediate risk patients (one of the following risk factors except refractory disease: early relapse, stage III/IV at relapse, relapse in previously irradiated site) who obtained a CR after salvage therapy will be treated with a single ASCT. A double transplantation can be considered for poor risk

patients (two or more risk factors) except for patients obtaining a CR after salvage treatment.[31,32]

In the era of novel molecules, performing a double ASCT might become a matter of discussion. Maintenance treatment with BV after ASCT was the subject of the AETHERA trial. PFS was significantly improved in patients in the BV group compared with those in the placebo group (HR 0.57, 95% CI 0.40-0.81; p=0.0013). Median PFS was 42.9 months (95% CI 30.4-42.9) for patients in the BV group compared with 24.1 months (11.5 not estimable) for those in the placebo group. This strategy might be an option for high risk patients after ASCT.[33]

For patients who are not eligible for ASCT (age, severity of comorbidity, etc.), the goals of therapy are prolongation of survival and/or palliation of symptoms. In patients with a first late, asymptomatic relapse (after several years) and localised disease, salvage chemotherapy with or without radiation is an alternative treatment strategy.[34,35]

Brentuximab vedotin after relapse ASCT or in refractory disease

For the 45% of patients who relapse or are refractory after ASCT, prognosis is dismal. Recently, in this patient group BV, an anti-CD30 antibody conjugated by a protease-cleavable linker to the microtubule disrupting agent monomethyl auristatin E induces CRs in 34% of patients and a PFS at five years of 52%. BV is approved in Belgium for the treatment of patients with HL after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for ASCT.[36,37]

Radiation therapy

There are no randomised trials showing a survival benefit for RT. However, RT may contribute to improved prognosis in special clinical scenarios for selected patients:

- late first relapse, localised, and asymptomatic in combination with salvage chemotherapy;
- consolidative RT for patients with bulky disease in PR after salvage therapy prior to ASCT, or residual disease after PSCT;
- RT for palliation without curative intent.

Checkpoint inhibition with PD-1 blockade in relapsed or refractory HL

Nivolumab, a programmed death 1 (PD-1) inhibitor is approved for patients with HL that relapsed or progressed after ASCT and post-transplantation BV. Sixty-six percent of patients obtained an objective response with 9% CR and 58% PR and with a median response duration of 7.8 months. Grade 3 adverse events with anti-PD-1 antibodies includes immune-related side effects (thyroiditis, adrenal or pituitary dysfunction, hepatitis, colitis and pneumonitis) but were quite rare.[38] Pembrolizumab, another PD-1 monoclonal antibody, is also recently approved for patients with progression after ASCT and BV and for patients who are ineligible for ASCT and have failed BV.

Both drugs can be used as a bridge to allogeneic stem cell transplantation, however, with a higher rate of transplant-related complications.

RECOMMENDATIONS (*Figure 5*)

1. First relapse:
   - SCT eligible: salvage chemo (DHAP, ICE, Gemcitabine based, etc.) followed by ASCT.
   - SCT ineligible: salvage chemo +/- RT.
2. Second relapse: brentuximab vedotin.
3. Third relapse: pembrolizumab.
4. Relapse post-ASCT: brentuximab vedotin or pembrolizumab/nivolumab.

ALLOGENEIC STEM CELL TRANSPLANTATION IN HODGKIN'S LYMPHOMA

Allogeneic haematopoietic stem cell transplantation (allo-HCT) can be curative in relapsed/refractory HL, but relapse rates remain high. A meta-analysis of allo-HCT studies that included 1850 patients reported a three-year relapse free survival of 31% and a three-year OS of 50%.[39] Reduced intensity conditioning (RIC) regimens, associated with lower rates of early post-transplantation morbidity and mortality, do not negatively influence the graft-versus-lymphoma effect.

A retrospective study of EBMT showed improvement of non-relapse mortality (HR 2.85; 95% CI 1.62-5.02) and OS (HR 2.05; 95% CI 1.27-3.29) in patients who received RIC regimens in comparison with myeloablative conditioning.[40]

The use of alternate donor sources (umbilical cord blood and haplo identical donors) is also feasible and safe, as reported in several retrospective reviews and case reports.[41,42]

There is some concern about the safety of PD-1-blockade therapy prior to and post-allo-HCT, regarding the risk of graft-versus-host-disease (GVHD).

LONG-TERM FOLLOW-UP

There are very few clinical trials or data available on the follow-up and monitoring of late effects in patients with HL after completion of treatment. Recommendations are mainly based on routine clinical practice and the recently published NCCN guidelines. The risk of late toxicity is also dependent on the treatment schedule that was used and may also be less with current treatment programs compared with those used >10 years ago.

In general, patients are followed by a haematologist during the

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Treatment should be PET-CT scan guided in early and advanced disease. In early stage HL, treatment can be reduced if the interim PET-CT is negative. In advanced disease, treatment can be started with either ABVD (adriamycin, bleomycin, dacarbazine and vinblastine) or BEACOPPesc and has to be adapted according to the results of the interim PET-CT scan.**
2. **In relapse/refractory disease, autologous stem cell transplantation remains the best option. In case of relapse post-autologous stem cell transplantation, brentuximab vedotin, pembrolizumab and nivolumab offer new therapeutic options. Allogeneic haematopoietic stem cell transplantation remains an option for eligible patients.**
3. **Long-term follow-up is important considering the late toxicities of the treatments.**

first five years to detect recurrence of the disease and then annually because of the risk of late complications. There is no consensus about the frequency of the follow-up, however, generally, patients are seen every four months during the first two years and every six months after that. Routine imaging is not advised.

Secondary cancers, cardiovascular disease, hypothyroidism, and fertility issues are the most serious late effects among long-term survivors of HL. The incidence of these late effects increases with longer follow-up time.[43]

SECONDARY CANCERS

Solid tumours, in particular lung and breast cancer, are the most common secondary cancers and most of them develop >10 years after treatment completion.

Annual breast screening (clinically, mammography, ultrasound or MRI, beginning no later than eight to ten years after therapy completion or at age 40, whatever occurs first) is recommended for women who have received mediastinal or axillary irradiation. Familial history should also be taken into account.

Women who received irradiation to the chest between 10 and 30 years of age are at very high risk for breast cancer, similar to women with BRCA1 or first/second line family members with breast carcinoma. In those women yearly MRI is advised.

A higher incidence of myelodysplasia and acute myeloid leukaemia (AML) is also seen in patients treated for Hodgkin. Particularly, treatment with the older schedules, such as MOPP, but also alkylating schedules, such as BEACOPP, are associated with a higher risk for myelodysplastic syndrome (MDS)/AML. A recent retrospective analysis of the German Hodgkin Study Group showed the diagnosis of AML/MDS in 0.9% of the patients at a median follow-up of 72 months. The median time to develop AML/MDS was 31 months. Patients who were treated with ≥4 cycles BEACOPPesc had an increased risk to AML/MDS when compared with patients treated with less than four cycles or no BEACOPP chemotherapy (1.7% *vs* 0.7% *vs* 0.3%; $P<0.0001$).[44]

CARDIOVASCULAR DISEASE

Mediastinal irradiation and anthracycline-based chemotherapy are the highest risk factors for developing cardiac disease. In a multivariate analysis, the patient's age at treatment, hypercholesterolemia, hypertension and RT dose to the coronary artery origins were identified as independent prognostic factors.[45]

Annual blood pressure monitoring (even in asymptomatic individuals) and aggressive management of cardiovascular risk factors (hypercholesterolemia, hypertriglyceridemia, glucose metabolism and obesity) are recommended. A baseline stress test or echocardiogram and carotid ultrasound (for patients treated with neck RT) should be considered at ten-year intervals after treatment completion.

HYPOTHYROIDISM

Abnormal thyroid function is reported in approximately 50% of long-term survivors who received neck or upper mediastinal irradiation. Thyroid function tests should be performed at least annually to rule out hypothyroidism, especially in patients treated with RT to the neck.

INFERTILITY

Chemotherapy combinations such as BEACOPPesc, especially after more than two cycles, may cause immediate and

permanent infertility in both men and women. ABVD on the other hand is only rarely associated with infertility. Because women who have received chemotherapy with alkylating agents and who maintain short-term fertility may experience premature menopause, this should be taken into consideration with respect to family planning. A fertility consult is advised before starting any treatment that may negatively influence fertility or in female patients with abnormal AMH levels. Sperm cryopreservation may be considered, and if the clinical setting allows postponing therapy, mature oocyte or embryo cryopreservation might be offered for young women where more than two cycles of BEACOPPesc might be necessary.[46,47]

PULMONARY TOXICITY

Bleomycin-induced pulmonary toxicity is well documented in patients with HL. The risk increases with higher cumulative doses of bleomycin and with additional risk factors such as older age, smoking, pulmonary irradiation and a history of lung disease.

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