POCKET GUIDELINE

Hematology

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

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Introduction

In 2018, the BHS lymphoproliferative working party reviewed the recent literature on diagnosis, treatment and follow up of Hodgkin's Lymphoma. The use of interim PET CT scan has changed our treatment approach, resulting in a more personalized treatment. In this way, treatment toxicity will hopefully be diminished. In addition we hope to augment the chances of patients to cure their disease. New treatments, such as brentuximab vedotin, nivolumab and pembrolizumab became available for patients with relapsing or refractory disease. I am confident that the near future will bring us more treatment possibilities to help our patients. The emerging role of PDL1 inhibitors in the treatment and their use in relation to allogeneic stem cell transplants will be interesting to follow.

On behalf of the BHS lymphoproliferative working party,

Vanessa Van Hende, MD, PhD, hematologist
AZ Nikolaas, Sint-Niklaas

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

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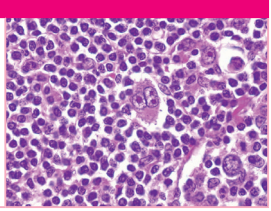
Presentation and symptoms

- bimodal age distribution
- often asymptomatic
- 40% presents with constitutional symptoms
- usually supradiafragmatic disease
- bone marrow involvement in < 10% of the newly diagnosed patients

Pathology

- Clonal malignant Reed Sternberg cells consitute only a minor part of the tumoral micro-environment
- Two distinct entities: classical and nodular lymphocyte-predominant Hodgkin's lymphoma
- Classical Hodgkin's lymphoma: 4 subtypes: nodular sclerosis, mixed cellularity, lymphocyte depleted and lymphocyte rich



Diagnosis

- An excision biopsy is mandatory
- Anamnesis: medical history, B-symptoms
- Physical examination
- Comorbidities
- Blood examination: full blood cell count, sedimentation rate and blood chemistry, serological test for hepatitis B virus, hepatitis C virus and human immunodeficiency virus (HIV)
- For female patients: human chorionic gonadotropin (HCG) testing, anti-Müllerian Hormone (AMH) testing
- PET-CT scan
- Reproductive counseling is advised

Staging

- Staging is performed by PET CT scan. Bone marrow biopsy is no longer necessary
- Staging by Ann Arbor classification: stage I - II: early disease, stage III-IV: advanced disease
- Early disease: favorable vs unfavorable (see *Table 1)*

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.	

EARLY STAGE DISEASE

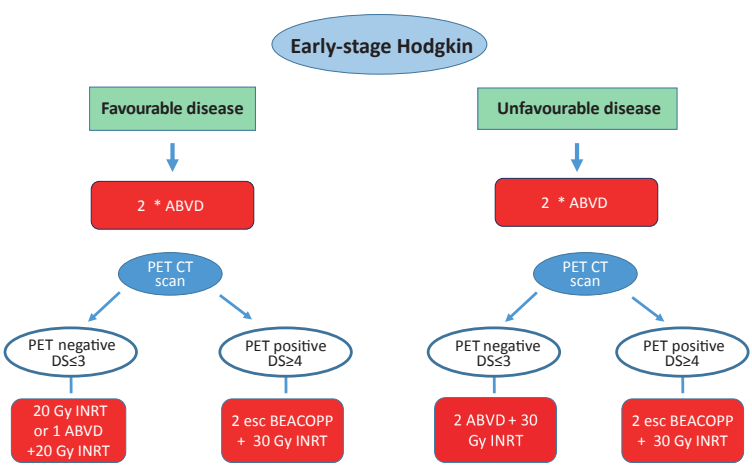
Recommendations favorable early stage disease

- Early pet-negative: 2-3 abvd + inrt/ifrt 20 gy.
- Early pet-positive: 2 abvd + 2 beacoppesc + inrt/ifrt 30 gy.
- 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 unfavorable early stage disease

- Early PET-negative: 4 ABVD + INRT/IFRT 30 Gy.
- Early PET-positive: 2 ABVD + 2 BEACOPPesc + INRT/IFRT 30 Gy.

Figure 1. Treatment schedule early-stage Hodgkin's lymphoma.

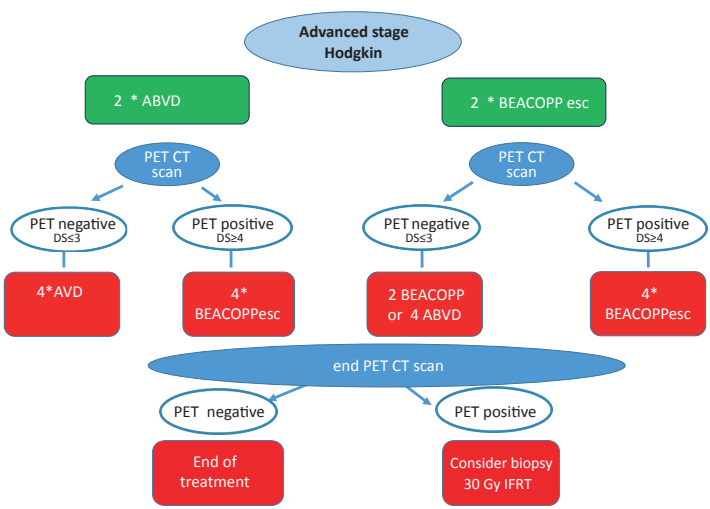


Omission of bleomycin in patients ≥60 years of age can be advised if the interim PET-CT scan is negative.
ABVD: adriamycin, bleomycin, dacarbazine and vinblastine, BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone, INRT: involved nodal radiotherapy

ADVANCED STAGE HODGKIN'S LYMPHOMA

Recommendations (see *Figure 2*)	
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

Figure 2. 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

MANAGEMENT OF RELAPSED / REFRACTORY HL

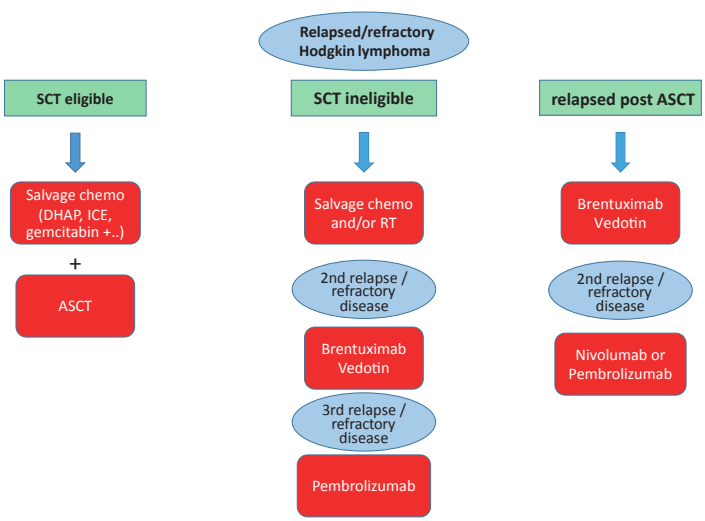
Biopsy and staging

- Biopsy is required in most patients, especially in late relapse.
- Staging by Ann Arbor classification.

Recommendations

1st relapse	• SCT eligible: salvage chemotherapy followed by ASCT • SCT ineligible: salvage chemo and/or RT
2nd relapse or 1st relapse after ASCT	• Brentuximab Vedotin
3rd relapse in ASCT ineligible patients	• Pembrolizumab
2nd relapse after ASCT	• Nivolumab or Pembrolizumab

Figure 3. Treatment schedule for relapsed/refractory Hodgkin's lymphoma.



SCT: stem cell transplantation, ASCT: autologous stem cell transplantation, RT: radiotherapy.

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.
- The use of alternate donor sources (umbilical cord blood and haplo identical donors) is also feasible and safe.
- 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

- 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.
- Secondary cancers, cardiovascular disease, hypothyroidism and fertility issues are the most serious late effects among long-term survivors of HL.
- 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.

Advised follow-up

- Annual measurement and aggressive management of blood pressure, lipid balance, weight, glucose metabolism.
- Annual testing for thyroid function.
- Annual breast screening (clinically, mammography, ultrasound or MRI), beginning no later than eigth to ten years after therapy completion or at age 40 (whatever occurs first), is recommended for women who have received mediastinal or axillary irradiation.
- Women who received irradiation of the chest between 10 and 30 years of age are at very high risk for breast cancer, similar for women with BRCA1 or first/second line family members with breast carcinoma. For those women, yearly MRI is advised.
- A fertility consult should already be offered before starting any treatment that may negatively influence fertility or for female patients with abnormal AMH levels.
- Be aware of pulmonary toxicity certainly with additional risk factors such as older age, smoking, pulmonary irradiation and a history of lung disease.

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.

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