

EHA-ISHBT Hematology Tutorial

Clinical Case – Session **Hodgkin's Lymphoma - Overview and Management**

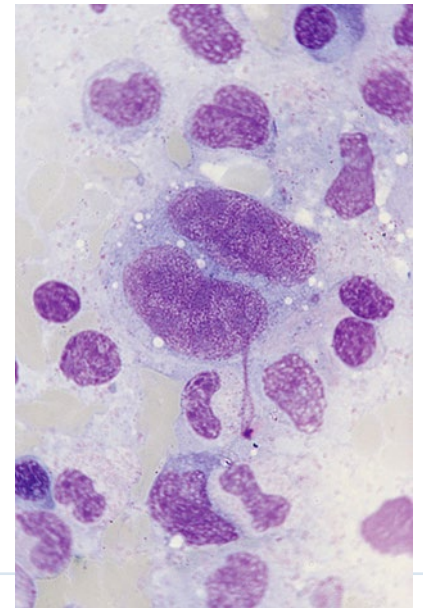
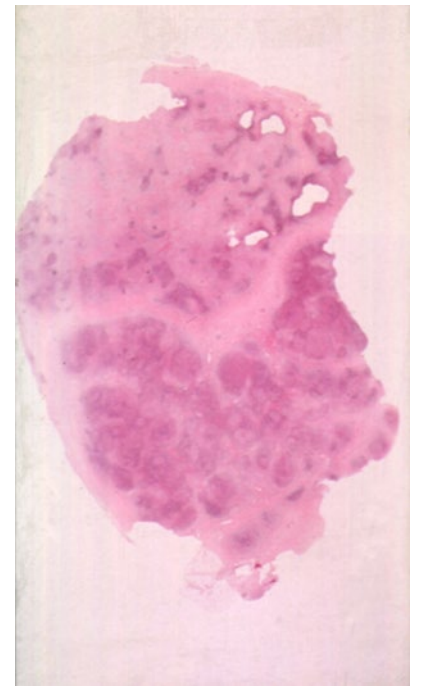
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| Clinical history

- A 26-year-old woman with a 2 months history of night sweats and itching was referred to a hematologist with cervical lymphadenopathy
- Lymph node biopsy was consistent with Hodgkin's lymphoma, nodular sclerosis type 1
- PET-CT showed bulky mediastinal (13x8 cm) and left cervical FDG-avid lymphadenopathy (3x2 cm)



Q1) Which of the following statements is true?

1. A bone marrow biopsy is needed to stage this patient
2. Erythrocyte sedimentation rate (ESR) is needed to determine into which prognostic group this patients belongs
3. This patient should be treated as having localised disease
4. This patients should be treated as having advanced-stage disease
5. There is no expert consensus as to whether this pattern of disease should be treated as localised or advanced

| Q1 - discussion

- Bone marrow biopsy is not considered necessary in newly diagnosed HL patients who have been staged with PET, because PET is more sensitive for detection of bone marrow disease
- This patient has bulky mediastinal-disease which puts her in the unfavorable prognostic group irrespective of ESR
- Patients with B symptoms and bulky mediastinal involvement are considered advanced-stage disease according to the German Hodgkin Study Group (GHSG), but not European Organisation for Research and Treatment of Cancer (EORTC) and Groupe d'Etude des Lymphomes de l'Adulte (LySA)

| Clinical history

- The patient received 1 cycle of ABVD
- Treatment was followed by significant nausea and vomiting
- B symptoms disappeared and the cervical lymph nodes regressed
- The patient refused further treatment

Q2) Which of the following statements is true?

1. Interrupting treatment is undesirable and may significantly worsen prognosis
2. The progression-free survival (PFS) of patients treated with ABVD and eBEACOPP in this setting is similar
3. AVD+brentuximab vedotin (Bv) is approved for treatment of stage II Hodgkin's lymphoma
4. ABVD and AVD+Bv have similar hematologic toxicity
5. eBEACOPP is more emetogenic than ABVD

| Q2 - discussion

- PFS of patients with localised-stage unfavorable or advanced-stage Hodgkin's lymphoma treated with eBEACOPP is significantly better than if they're treated with ABVD
- AVD+ brentuximab vedotin (Bv) is approved for front-line treatment of stage III and IV cHL
- AVD+Bv has more haematologic toxicity than ABVD and should (as eBEACOPP) be administered with G-CSF prophylaxis
- Dacarbazine is the most emetogenic drug in these regimens. Intensive anti-emetic prophylaxis is indicated with ABVD, AVD+Bv and BrECADD
- It is the general experience of physicians treating HL that interrupting therapy results in an outgrowth of resistant neoplastic clones, significantly reducing the chance of favorable outcomes

| Clinical history

- Six months later she presented with bilaterally enlarged cervical lymph nodes, predominantly on the left side, with night sweats and weight loss
- **Laboratory results:**
 - ESR- 52mm/hr, Hb- 111 g/L, WBC- $14.2 \times 10^9/L$, Lymphs- $6.0 \times 10^9/L$, albumin- 33.4 g/L
- **PET-CT**
 - Mediastinal lymph node conglomerate 19x11 cm, bilateral cervical lymph nodes 5x3 cm, bilateral axillary lymph nodes 2x1.3 cm, left pleural effusion 7-8 cm



Treatment

- **Six courses of eBEACOPP**
- *Treatment complications:*
 - 2 episodes of febrile neutropenia
 - 1 dose reduction because of thrombocytopenia
 - No need for treatment delay
- **PET-CT:** 3 weeks after the end of treatment
 - Mediastinal lymph node conglomerate 14x7 cm, Deauville 4
 - Left cervical lymph node 2x1 cm, Deauville 3, axillary lymph node 1x1 cm, Deauville 2
- **Radiotherapy 30 Gy to involved mediastinal nodes was administered**

Q3) Which of the following statements is NOT true?

1. Controlled studies have shown interim PET to be useful for **escalating** therapy in patients initially treated with **ABVD**
2. Controlled studies have shown interim PET to be useful for **escalating** therapy in patients initially treated with **AVD+Bv**
3. Controlled studies have shown interim PET to be useful for **de-escalating** therapy in patients initially treated with **eBEACOPP**
4. Radiotherapy to sites of localised PET+ disease can convert PR into CR
5. When evaluating PET results, Deauville 3 is considered negative and 4 positive

Relapse

- Two months later the patient presented at an unscheduled visit because of a palpable node in the right axilla (July 2017)
- Core needle biopsy – **Diagnosis: classical HL**
- **PET-CT:** left supraclavicular lymph node 3x1.8 cm, mediastinal mass 15x8 cm (PET-neg), right axillary lymphadenopathy 3x2.8 cm, supra-diaphragmatic lymph nodes 3.5x2.3 cm
- Metabolic and morphological progression
- **Bone marrow biopsy:** no tumor infiltration
- No B symptoms
- ESR- 21, Hb- 116 g/L
- **Refractory Hodgkin lymphoma**



Q4) How would you treat this patient now?

1. With a different standard-dose chemotherapy regimen (e.g. C-MOPP) followed by involved node radiotherapy
2. With Bv monotherapy
3. With a PD-1 inhibitors (PD-1i), e.g. pembrolizumab or nivolumab, as monotherapy
4. Using high-dose chemotherapy (with or without a newer agent) followed by autologous stem cell transplantation (ASCT) in case of PET-negative remission
5. With high-dose chemotherapy (with or without a newer agent) followed by ASCT only if there is a PET-positive partial remission

Third line treatment

- The patient received 2 cycles of DHAP+Bv
- *Treatment complications:*
 - 1x febrile neutropenia, required hospitalisation
 - Grade IV anemia, thrombocytopenia and neutropenia
 - Grade III mucositis
- *PET-CT:* no signs of metabolically active disease
- Stem cells were collected after the 3rd cycle
- Patient underwent ASCT after BeEAM conditioning
 - Gram positive sepsis
 - Diarrhoea
 - Hematological recovery on day +14
- Bv monotherapy was continued for a total of 16 cycles



Q5) Which of the statements below is correct?

1. Randomised studies have shown that the addition of Bv or a PD-1i to high-dose chemotherapy increases overall survival (OS)
2. Phase II studies suggest that the addition of Bv or a PD-1i to high-dose chemotherapy increases response rates and PFS
3. Bv-containing combinations have been shown to be superior to PD-1i-containing combinations
4. Bv maintenance after ASCT in high-risk patients should continue until progression or unacceptable toxicity
5. Regarding Bv maintenance, needing more than 2 lines of therapy to achieve remission does not qualify as high risk

| Q5 - discussion

- **No randomised studies** of high-dose chemotherapy ± newer agents in R/R HL have been performed
- Phase II studies consistently show that the combinations result in **superior response rates and PFS**, but there is no clear-cut advantage of either of the newer agents over the other
- As per study, Bv maintenance should be given for **up to 16 cycles**
- Risk factors fulfilling requirements for Bv maintenance after ASCT are:
 - primary refractory disease or early relapse
 - extranodal disease or B symptoms at relapse
 - need for more than 2 lines to achieve CR
 - not achieving CR prior to ASCT**

Q6) Which of the following statements regarding follow-up is NOT true?

1. This patient is at increased risk of developing heart disease and should be educated about appropriate life-style adjustments
2. This patient is at an increased risk of developing secondary malignancies and should start with breast cancer screening early
3. This patient needs regular imaging during follow-up
4. Methods to reduce infertility risk in female HL patients include use of GnRH analogues, oocyte and ovarian tissue cryopreservation
5. PD-1i and allogeneic stem cell transplantation have been shown to be effective in HL patients relapsing after ASCT and Bv maintenance

| Q6 - discussion

- Patients treated for HL are at increased risk of infertility, secondary malignancies and cardiac disease
 - Methods to reduce the risk of infertility, if needed, should be implemented before or at time of start of antineoplastic therapy
 - Patients should be warned about cardiac risk factors and educated on their reduction
 - In females, breast cancer detection programs should be started early
- Routine imaging does not improve outcome of relapsing lymphoma and should be avoided
- Both PD-1i and alloSCT (in responding patients) are useful in patients failing high dose chemotherapy, ASCT and Bv.

| Clinical history

- The patient is in continuous remission and well >6 years after ASCT
- She attends regular breast cancer screening examinations
- She performs regular physical exercise, watches her weight and does not smoke
- The patient refused GnRH analogue therapy at start of treatment
 - Not interested in progeny
- HL is a rare malignancy with 2, 3 or even 4 chances for cure!