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GUIDELINES FOR THE MANAGEMENT OF CLASSICAL HODGKIN LYMPHOMA
Early Stage Hodgkin lymphoma treatment pathway

All early stage Hodgkin lymphoma (including bulk)
Stratify into favourable (F) or unfavourable (U) using EORTC criteria. 1 or more of the following puts patient into unfavourable group

1) Age >50 years
2) 4 or more nodal areas assessed on PET/CT
3) Mediastinal/thoracic ratio equal or greater than 0.35
4) ESR >50 (or >30 if B symptoms)

Stage IIB with large mediastinal mass or extranodal disease should be treated as advanced disease

ABVD X 2

PET scan between days 22 and 25 of second cycle ABVD

PET negative
Deauville score 1-3
Favourable

PET positive
Deauville score 4-5
Unfavourable

Escalated Beacopdac X 2 plus ISRT 30 Gy

1X ABVD and 30 Gy ISRT
If patient very good risk ie 1 or 2 nodal areas then consider no further chemo and 20Gy IFRT (total 2 X ABVD plus 20Gy)
If long term toxicity of radiotherapy then a RAPID approach can be considered if iPET2 Deauville 1-2 (3 X ABVD)

2 XABVD and ISRT 30Gy
Or if no radiotherapy due to toxicity concerns 4 X AVD (omit bleomycin as per RATHL)

End of treatment PET scan 3 months if patient had radiotherapy, 6 weeks if chemotherapy alone.

Appointment with clinical oncologist for individual radiotherapy discussion during first 2 courses of ABVD
Early Stage Hodgkin lymphoma

Patients with stage I and II disease have an excellent prognosis and the treatment aim is to optimise disease control whilst minimising long term toxicities.

Optimal disease control is with combined modality therapy and for most patients this approach should be used. To guide the intensity of treatment required, patients are risk stratified as “early favourable” or “early unfavourable” using either the EORTC criteria or GHSG criteria which differ in terms of number of nodal sites and whether age above 50 is considered a risk factor.

### EORTC Criteria for Early Favourable Hodgkin Lymphoma

- No Large mediastinal adenopathy
- ESR <50 without B symptoms
- ESR <30 with B symptoms
- Age <50 years
- 1-3 lymph node sites involved

### EORTC 5 Nodal Areas

- CERVICAL
  - PRE-AURICULAR
  - UPPER CERVICAL
  - MEDIAN OR LOWER CERVICAL
  - POSTERIOR CERVICAL
  - SUPRACLAVICULAR

- AXILLARY
  - INFRACLAVICULAR
  - AXILLARY

### GHSG Criteria for Hodgkin Disease

<table>
<thead>
<tr>
<th>Early Favourable</th>
<th>Stage I or II without risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Unfavourable</td>
<td>Stage I or II A with ≥ 1 risk factors or Stage II B with risk factors C/D but not A/B</td>
</tr>
<tr>
<td>Advanced</td>
<td>Stage II B with risk factors A/B or Stage III or IV</td>
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### Risk Factors

- **A** Large Mediastinal Mass
- **B** Extranodal Disease
- **C** Elevated ESR
- **D** ≥3 nodal areas

Large Mediastinal Mass: >1/3 horizontal chest diameter

Elevated ESR: >50 without B symptoms or >30 in presence of B symptoms
Lymph node areas as defined by GHSG

- Area A: right cervical + right infra-/supra-clavicular/nuchal lymph nodes
- Area B: right cervical + right infra-/supra-clavicular/nuchal lymph nodes
- Area C: right/left hilar + mediastinal lymph nodes
- Area D: right axillary lymph nodes
- Area E: left axillary lymph nodes
- Area F: lymph nodes of the upper abdomen (spleen hilum, liver hilum, coeliacal)
- Area G: lymph nodes of the lower abdomen (spleen hilum, liver hilum, coeliacal)
- Area H: right iliac lymph nodes
- Area I: left iliac lymph nodes
- Area K: right inguinal + femoral lymph nodes
- Area L: left inguinal + femoral lymph nodes

All patients should be risk stratified as per the EORTC criteria. Following publication of the EORTC H10 trial (Andre et al JCO 2017) it is now recommended that a patient has a PET scan after 2 courses of ABVD and escalation of treatment considered if the interim PET scan is positive (Deauville 4 or 5).

Early Favourable Hodgkin Lymphoma

If a patient is early favourable (as per EORTC criteria) then they will have a total of 3 X ABVD and 30Gy IFRT.

There are 2 situations in which the treatment pathway does not follow an H10 approach. The first is in very good risk disease. These patients had previously only received 2 X ABVD and 20Gy IFRT and had an excellent outcome, 5 year freedom from treatment failure of 97% and 5 year overall survival (OS) 92%. If patients are early favourable as per GHSG criteria and achieve a Deauville score of 1, 2 or 3 after 2 courses of ABVD then they can proceed to 20Gy IFRT (Engert et al NEJM 2010; 363:640-653)

The second is when there is significant concern about the toxicity of radiotherapy for example women under 25 years of age with a radiation field involving breast tissue. In this situation a “RAPID” approach (Radford et al NEJM 2015; 372:1598-1607) could be considered for early favourable disease. If the patient achieves a Deauville Score of 1, 2 or 3 after 2 courses of ABVD then it is reasonable to give one final ABVD. Avoiding combined modality therapy will be associated with a reduction of PFS of 6% but if the patient is a candidate for salvage and the toxicity of radiotherapy is of significant concern then this approach can be considered for early favourable patients.

It is essential that clinical oncologists are involved in the treatment decisions and patient discussions.

Early Unfavourable Hodgkin Lymphoma

Patients with early unfavourable disease as per EORTC criteria they should receive 4 X ABVD with 30Gy IFRT. For patients who have widespread stage II disease it may be optimal to consider extended chemotherapy for this group with a RATHL approach instead of combined modality therapy.
Advanced Hodgkin Lymphoma

For patients with stage III and IV disease, the majority will be treated as per the RATHL protocol:

Baseline PET scan. (If bulk disease, patient should discuss the risk/benefit of consolidation radiotherapy with clinical oncologist during chemotherapy)

\[ \text{ABVD X 2} \]

\[ \text{PET scan day 22-27 of cycle 2 ABVD} \]

- **PET negative** (Deauville 1, 2 and 3)
  - 4 X AVD (remove bleomycin)

- **PET positive** (Deauville 4 and 5)
  - 4 X escalated BEACOPDac

**Bulk disease** (>10cm, or thoracic ratio at T5/6 >0.33) at diagnosis and radiotherapy to bulk planned

**No**

End of treatment PET scan 6 weeks post chemotherapy

**Yes**

PET scan 3 weeks post chemotherapy then radiotherapy to site of initial bulk disease (This decision should be made upfront at initial MDT, patient should discuss with Clinical Oncologist during chemotherapy as evidence is limited and mixed, RATHL and HD 0607)

End of treatment PET scan 3 months post radiotherapy

Stage IIIB with a large mediastinal mass or extranodal disease should be treated as advanced stage
Intensification of first line treatment with escalated BEACOPDac

The HD15 and HD18 trials show an improvement in PFS for advanced stage disease using escalated BEACOPP upfront however this is associated with more toxicity. A RATHL approach is a concern for patients who are iPET2 positive with a 3 year PFS of only 68%. At present this poor risk group cannot be identified upfront but subgroup analysis of RATHL has shown that patients with a higher IPSS score have an inferior PFS. RATHL : IPS 3 or more 75%, HD18 IPS 4 or more 89% 5 year PFS.

It may be reasonable therefore to consider an intensive approach for some patients with a Hasenclever index 3 or higher.

Escalated BEACOPDac is associated with significant toxicity in comparison to ABVD and should be given with caution to patients over 45 years of age. It is also associated with higher infertility when compared with ABVD and a risk/benefit discussion should be undertaken with the patient. The procarbazine has now been replaced with dacarbazaine (escalated BEACOPDac) in some UK centres (following extrapolation of paediatric data which shows reduced toxicity without loss of efficacy). These data will be audited.

Baseline PET scan

\[\text{Escalated BEACOPDac} \times 2 \text{ cycles}\]

\[\text{PET scan, Deauville 1,2,3}\]

\[2 \text{ cycles escalated BEACOPDac (Total 4 courses)}\]

\[\text{End of treatment PET scan 6 weeks post chemotherapy completion}\]

\[\text{Radiotherapy to PET positive sites unless progressive disease}\]

\[\text{PET scan, Deauville 4 and 5}\]

\[4 \text{ cycles escalated BEACOPDac (Total 6 courses)}\]
Hodgkin lymphoma in older patients

Compared with younger patients, patients over 60 years of age have significantly inferior outcomes, primarily due to reduced tolerability of treatment.

A recent analysis (Boll et al Blood 2016.127(18):2189-2192) of the German HD10 and HD11 trials focused on the over 60 subgroup. This showed that 2 cycles of AVD and ABVD were similar in toxicity but 4 cycles of ABVD was considerably more toxic to patients over 60 years of age. There was 10% bleomycin lung toxicity in this group, compared to 1% if only 2 courses of ABVD given.

It would be reasonable for early favourable disease for a patient under 65 and fit to have 2XABVD and 20Gy radiotherapy.

Early unfavourable disease or advanced disease should either be treated with AVD or VEPMEB (protocol used in SHIELD study, Proctor et al Blood 2012;119:6005-6015). Bleomycin should be removed if concerns about lung toxicity.

Each patient should be assessed on an individual basis for fitness for treatment but more than 2 courses of ABVD should be avoided in view of its associated toxicity.

Other options include DECC and CHLVPP (chlorambucil, vinblastine, procarbazine, prednisolone) although this is associated with an inferior response rate but it is less toxic for patients.
Management of relapsed classical Hodgkin lymphoma

A biopsy should be performed to confirm relapse and the patient staged with CT and PET.

Relapse greater than 5 years from initial disease could be treated as new disease.

If patient unfit consider radiotherapy, palliative chemo eg DECC/CHLVPP/, brentuximab if eligible or steroids for symptom control.

Patients who are fit should have salvage regimen (GDP, DHAP, IVE) there is no evidence that there is one salvage regimen that is better than others.

A CT scan should be done after 2 courses of first line salvage to ensure response (or earlier if concerns about response). A total of 3 courses should be given and then a PET scan 3 weeks after 3rd salvage. If PET negativity achieved then a BEAM auto performed.

If a patient achieves a complete metabolic remission (CMR) on PET prior to autograft then they will have an event free survival of >80% (Moskowitz et al Blood 2010;116,4934-4937) even if they require 2 lines of salvage treatment to achieve PET negativity. If first line salvage does not achieve PET negativity then second line treatment should be given.

Brentuximab vedotin can be given if the patient has had 2 prior lines of therapy. The patient should have a PET scan after 4 cycles and proceed to auto if CMR achieved. Review current Blueteq indication for maximum number of cycles, currently 10.

Allogeneic transplant should be considered if the patient has relapsed post autograft or has not achieved an adequate response to salvage chemotherapy.

Checkpoint inhibitors are currently available if a patient has relapsed but has previously had BV and an autologous stem cell transplant.
Patient fit for salvage chemotherapy?

Yes

Salvage chemo (rarely radiotherapy alone if limited disease)

Responding? (CT after 2 courses or earlier if clinical concern)

Yes

Complete 3 courses of first-line salvage

PET scan

PET negative

PET positive

Brentuximab vedotin or second line salvage chemotherapy

PET scan

PET negative

PET positive

Third-line salvage chemotherapy, brentuximab vedotin or salvage radiotherapy or checkpoint inhibitor as per NICE guidance

Disease response

Yes

Autograft

No

Allograft

Clinical trial or palliation (steroids, DECC)

No

Radiotherapy

Consider radiotherapy, depending on site of relapse

Radiotherapy appropriate

Yes

Options include brentuximab vedotin if eligible, DECC/CHLVPP or palliative steroids

No
Reduction of the late effects of treatment

Breast screening

Women treated with mantle irradiation aged under 35 years, or other irradiation which included breast tissue, are at increased risk of breast cancer from 8 years after treatment.

The clinical oncologists will indicate in the treatment summary whether a patient is at risk and the patient will be referred directly to a central BARD database or via their GP.

Thyroid dysfunction

Patients have a 30% chance of hypothyroidism after radiotherapy to the neck (greater if >30 Gy given). Annual thyroid function tests required.

Smoking cessation advice

Patients have 4-11 x the age-matched population risk of developing lung cancer. This “normalises” if they are non-smokers.

Malignant Melanoma

Risk increases to 5-8 x normal if the patient is exposed to sun burn.

Osteoporosis

Women and men both have decreased bone density. 10% of patients who have had combined modality treatment may develop osteoporosis.

References

- HD 0607 Gallamini et al JCO Jan 23 2018
Appendix

Deauville 5 point score
An internationally recommended scale for reporting of PET scans. The score is based on 2 visual reference points of the individual patient relating to FDG uptake.

- Deauville 1: No uptake
- Deauville 2: Slight uptake but below blood pool (mediastinum)
- Deauville 3: Uptake above mediastinal but below or equal to uptake in the liver
- Deauville 4: Uptake slightly to moderately higher than the liver
- Deauville 5: Markedly increased uptake in comparison to liver.

Deauville 1 and 2 relate to a complete metabolic remission and 4 and 5 probable disease or relapse. Deauville 3 is usually a negative score unless it is used in a “de-escalation” study such as the RAPID study when it is positive. A Deauville score of 3 in the RATHL study was negative due to the escalation nature of the protocol.

Bleomycin
The risk factors for bleomycin induced pneumonitis include:
- age over 40 years
- smoking and pre-existing lung disease
- Impaired renal function.

Patients receiving bleomycin should have baseline pulmonary function tests (PFTs) including TCLO. If respiratory symptoms or basal crepitations develop then the PFTs should be repeated and the bleomycin stopped if there is a greater than 10% reduction in TLCO. It should be used with caution in patients over the age of 60 years.

International prognostic index (Hasenclever Score)
Albumin <40 g/L
hæmoglobin < 10.5 g/dL
Male sex
Age ≥ 45 years
Stage IV disease
WCC> 15 x 10⁹/L
Lymphocytes < 0.6 x 10⁹/L

Score 1 point for each factor