Lymphoma Network of New Zealand

Classic Hodgkin Lymphoma Protocol

Classical Hodgkin Lymphoma

Includes; Nodular sclerosis, Mixed cellularity, Lymphocyte-rich, Lymphocyte-deplete

Note; lymphocyte predominant hodgkins is a separate entity refer to separate protocol

Review Histology, Present at lymphoma MDT, enrol in clinical trial if available, complete staging and prognostic score – refer below

Initial Investigations

Bloods; Full blood count, Na, K, Ca, PO_4, renal function, urate, liver function test, ESR (for early stage), albumin (for advanced stage).Consider HIV, hepatitis B and C testing and pregnancy test.

Imaging; PET CT scan or CT body+/-neck (CT if upstaging is not likely to change management or if delay to obtain PET clinically unacceptable)

Bone Marrow; Not required if PET undertaken or CT staged as Stage IA or IIA

Cardiac assessment: cardiac echocardiogram/gated heart scan if indicated for patients who are to receive an anthracycline.

Respiratory assessment; . Consideration can be given to undertaking a baseline CXR and/or respiratory function testing.

Fertility discussions . Consider referral to fertility associates and GNRH analogues esp if for BEACOPPesc > 4 cycles

Staging Ann Arbor (Cotswold modification) staging system

I	Involvement of a single lymph node or lymphoid structure (spleen, thymus, Waldeyer's ring)
II	Two or more regions on the same side of the diaphragm
III	Two or more regions on both sides of the diaphragm
IV	Involvement of extranodal sites (such as liver, lung or marrow) not due to direct extension from a nodal site
X	Bulky Disease ▪ 10 cm maximal dimension of a nodal mass, or ▪ Mediastinal mass > 1/3 internal transverse diameter of the thorax measured at the level of T5/6 intercostal space on PA CXR.
E	Involvement of a single extranodal site, adjacent to a known nodal site.
B	▪ Recurrent unexplained fever > 38º, or ▪ Recurrent unexplained drenching night sweats or unexplained weight loss (>10% from baseline in the previous six months).

Risk Stratification in Limited Stage Hodgkins

Treatment Group	EORTC/GELA	GHSG
Risk Factors	A) Mediastinal mass >1/3rd horizontal chest diameter B) Age ≥50 years C) ESR >50 without B symptoms, ESR >30 with B symptoms D) ≥4 nodal areas	A) Mediastinal mass >1/3rd horizontal chest diameter B) Extranodal disease C) ESR >50 without B symptoms, ESR >30 with B symptoms D) ≥3 nodal areas
Early Stage Favourable (Limited Stage)	Stage I and II without risk factors	Stage I and II without risk factors
Early Stage Unfavourable (Intermediate stage)	Stage I and II with ≥1 risk factor	Stage I and IIA with ≥ 1 risk factor, Stage IIB with risk factors C/D but not A/B,
Advanced Stage	Stage III/ IV	Stage IIB with risk factors A/B, Stage III/IV

Treatment of Limited Stage Hodgkin Lymphoma

Early Stage Favourable – Options;	Early Stage Unfavourable – Options;
2-3 ABVD + 20Gy IF RT (2ABVD – GHSG, 3 ABVD EORTC) if RT toxicity concerns consider 4 ABVD OR 2ABVD with interim PET, if PET positive reconsider RT Value of escalating therapy to escBEACOPP + IF RT on basis of positive interim PET is uncertain but may be of benefit.	4 ABVD + 30Gy IF RT 2escBEACOPP + 2ABVD + 20Gy RT (<60yr) if RT toxicity concerns consider 6ABVD or 2ABVD with interim PET, if PET positive reconsider RT Value of escalating therapy to escBEACOPP + IF RT on basis of positive interim PET is uncertain but may be of benefit.

Rationale for early stage disease

Combined Modality vs Chemotherapy Alone

In early stage disease, combined modality therapy provides maximal disease control (PFS superiror in RT groups by approximately 5% - UK Rapid). The disadvantage is the risks of cardiovascular events and development of secondary cancers. Given advances in radiation technology, these risks may be reduced in comparison with historical cohorts but it should be presumed that important risks persist.

Chemotherapy alone offers reduced long-term disease control in comparison to combined therapy. However, those who relapse may still be curable with salvage therapies.

Therefore in early stage disease, combined modality therapy is the current standard of care. However, for those at increased risk of toxicities from radiotherapy (eg young females with mediastinal disease), consideration can be given to chemotherapy alone.

Those failing to obtain a CR/Cru on CT (not PET) after 2 cycles appear to benefit the most from combined modality treatment (8yr PFS 88% vs 74%, OS 95% vs 91% (Hay et al Ann Onc 24; 3065-3069).

Interim imaging by CT PET may be considered on a case by case basis in those considered at increased risk of toxicities from radiotherapy to inform discussions on further management (currently not funded for this indication).

Number of cycles of ABVD and Radiotherapy Dose

Early Stage Favourable HD – The GHSG HD10 trial (ASH 2010 abstract 716) supports the use of 2 ABVD + 20Gy IF RT

Early Stage Unfavourable HD – The GHSG HD11 trial (ASH 2010 abstract 717) comparing baseline BeaCOPP x4, ABVDx4 with 20Gy, 30Gy IF RT, demonstrated 4ABVD should be followed by 30Gy IF RT and baseline BeaCOPP x4 should be followed by

20Gy IF RT.

ABVD vs BEACOPP in early stage unfavourable disease

ABVD x4 + IF RT 30Gy is widely considered the standard of care. More intensive approaches in those <60 years may be considered and is supported by the HD14 study which compared 2xescBEACOPP+ 2ABVD + 20Gy IF RT (HD14) – this regimen shows improved tumour control although no clear OS survival advantage. Acute toxicity is increased compared to ABVD but treatment related mortality is the same. (5yr PFS 89.1 vs 95.4, 5yr OS 96.8 vs 97.2%).

The use of interim PET to escalate from ABVD after 2 cycles on the baiss of a positive PET, to escBEACOPP is under study, to date H10 reports a favourable outcome to this approach (PET adapted vs standard therapy; 5yr PFS 91% vs 77%, 5 yr OS 96^ vs 89%), data from 50604 suggests this approach may not improve outcome)

Advanced Stage Hodgkin Management

Risk Stratification in Advanced Hodgkin Lymphoma (IPS)

Adverse Prognostic Factors	Number of Factors	FFP at 5 years (%)	OS at 5 years (%)
Age ≥ 45 years	0	84	89
Male	1	77	90
WCC ≥15,000 cells/µl	2	67	81
Lymphocytes <600 cells/µl or <8%	3	60	78
Albumin <40g/l	4	51	61
Haemoglobin <10.5 g/dl	≥5	42	56

IPS 0-3 or age ≥60	IPS ≥4 and age <60
6 ABVD + RT to initial bulk >5cm or residual mass	EscBEACOPP x 6 + RT to initial bulk >5cm or residual mass ≥2.5cm (consider PET directed) Or ABVD x 6 + RT to initial bulk >5cm or residual mass Or BEACOPP-14 x 8 + RT to initial bulk >5cm or residual mass ≥2.5cm (consider PET directed)

Advanced Stage Hodgkin Management Rationale

ABVD vs escBEACOPP

escBEACOPP has been used in patients <60 years of age and is associated with a higher response rate and freedom from treatment failure than ABVD and a 7-10% increase in OS at 5yrs (Meta AnalysisLancet Onc 2013 14;943-952). However, it is associated with significantly more toxicity. There is increased haematological toxicity, there is a 3% treatment-induced mortality, infertility in males and females is almost universal, and there is an increased risk of secondary neoplasms (cumulative risk of developing second malignancies at 10 years was 0.9%, 6.6%, with ABVD, BEACOPP (HD2000 Merli et al JCO 2016). The ability to salvage patients for fail first line therapy leads some to debate the role of more intensive first line strategies.

EscBEACOPP vs BEACOPP-14

HD15 demonstrates equal efficacy of 6xescBEACOPP and 8x BEACOPP-14. Both could therefore be considered as options. The toxicity profile favours 6xescBEACOPP.

Role of Radiotherapy

Studies using combined modality treatment for patients in complete response have failed to demonstrate an advantage to this approach.

However, radiotherapy to patients with incomplete response and initial bulk or even initial moderate bulk (>5 cm) is undertaken in many studies.

The ability of PET to guide the use of radiation to residual mass has been studied (HD15 ASH 2010 BEACOPP treated, Saveage et Al ASH 2015 ABVD treated). Early data suggests radiothereapy is indicated where residual disease is PET postive and can be deffered in those who are PET negative (even if initial bulk present)

Role of interim PET

PET negativity after 2 cycles of chemotherapy has been shown to be prognostic but its incorporation into changes in management remains the subject of ongoing trials but appear promising. The RATHL study investigating interim PET with de-escalation from ABVD to AVD is awaited.

Treatment in Elderly and those with poor performance Status

Treatment should be based on consideration of age and co-existing organ dysfunction .

For those not considered candidates for ABVD, ChlorVPP is an alternative.

For those not considered candidates for multiagent chemotherapy options include; Vinblastine weekly, Etoposide, Investigational agents via clinical trails or Radiotherapy

Relapsed Hodgkin Lymphoma

Relapses require confirmation by FNA or formal biopsy and restaging investigations

Adverse Prognostic Factors for Relapsed Disease

- Relapse <12/12 of initial therapy
- Extranodal disease
- B symptoms
- Less than CR or PET positivity to salvage chemotherapy
- The IPS has some prognostic significance

Relapse in transplant eligible

Salvage chemotherapy followed by autologous transplant, results in five year OS >50% in relapsed disease and >25% in refractory disease. The optimal salvage regimen is unknown - commonly used regimens include ICE, DHAP or IVE. The optimal transplant conditioning is unknown – commonly used regimens include BEAM, CBV. Radiotherapy to persistent mass or sites of previous bulk is commonly performed post-transplant, although there is no trial data to support this approach.

Chemotherapy sensitivity to salvage therapy is preferable. PET negativity post salvage and prior to proceeding to autograft is prognositic. Those failing to obtain a sufficent response prior to transplant need further discussion at MDTs/transplant meetings The standard of care for these patients is not certain. Consideration can be given to 2nd line salvage (GDP, Brentuximab (unfunded), tandem auto, tandem auto/allo.

In some patients with localized late relapse, salvage radiotherapy alone can be considered (Josting et al JCO 2005 23 1522-1529)

Relapse post autologous stem cell transplant

In young patients, consideration to allogeneic reduced-intensity SCT can be given. Early discussion with the transplant advisory committee is advisable. Chemotherapy sensitivity is required as patients with relapse that is refractory to additional chemotherapy do poorly. The transplant-related mortality is significant.

Relapse in transplant ineligible

options include the following; (used as single agents or in combination)

- Vinorelbine
- Gemcitabine
- ChlorVPP
- Vinblastine weekly
- Etoposide
- Brentuximab (not currently funded)
- Radiotherapy
- Investigational agents if available

In patients with very late relapses, repeat of prior therapy could be considered