London Health Sciences Centre
London Regional Cancer Program

Hodgkin's Lymphoma (HL)

Hematology Practice Guideline

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This guideline is a statement of consensus of the Hematology Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgment of the physician in the context of individual clinical circumstances to determine any patient's care or treatment.

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HODGKIN'S LYMPHOMA (HL)
Hematology Practice Guidelines

BACKGROUND

- HL accounts for only 15% of lymphomas
- Slight male predominance (1.3:1)
- Median age at diagnosis is 26
- Incidence of HL is bimodal
  - peaks in 3rd decade of life (age 20-29)
  - second smaller peak in patients > age 50
- HL typically presents as painless lymphadenopathy; usually begins in lymph nodes, spreads contiguously to adjacent lymphoid structures
- > 80% present with cervical lymph node involvement and > 50% have mediastinal disease
- Patients may have systemic "B-symptoms" such as unexplained fevers, drenching night sweats, weight loss
- Patients with HIV have an increased incidence of HL (usually while CD4 count is still relatively preserved)

DIAGNOSIS

- Excisional biopsy of lymph node or other involved tissue is essential for diagnosis. Fine needle aspiration is not adequate for the diagnosis of HL.
- Pathology should always been reviewed at LHSC if biopsy was done elsewhere

CLASSIFICATION

- Classical Hodgkin's Lymphoma (95%)
  - Lymphocyte rich
  - Nodular Sclerosis
  - Mixed cellularity
  - Lymphocyte deplete
- Nodular lymphocyte predominant HL (5%)

STAGING INVESTIGATIONS

- Full history and physical examination
- CBC, differential, ESR, LDH, renal function tests, liver function tests, calcium, albumin, uric acid
- Chest X-ray
- CT scans of thorax, abdomen & pelvis
- Gallium scan
- Bone marrow aspirate and biopsy in patients with B-symptoms, an abnormal CBC or stage III or IV disease
- Consider MUGA scan for assessment of baseline ejection fraction if clinically indicated (age > 60, hypertension, congestive heart failure, coronary artery disease, cardiac arrhythmia, cerebrovascular disease, peripheral vascular disease)
- Consider baseline PFT's if clinically indicated (known prior lung disease such as COPD, heavy smoker)
- Hepatitis B & C serology
- Assessment of HIV risk factors +/- HIV serology
- Additional imaging test(s), e.g. MRI, bone scan, ultrasound, as determined by symptoms or clinical situation
- At present, PET scans are not readily available at LHSC, which is why there are no recommendations regarding its use in this document; this will hopefully change once access to PET scans improves

STAGE

The staging system used for HL is the Ann Arbor Staging System:

Stage I: involvement of a single lymph node region (I) or single extralymphatic organ/site (IE)

Stage II: involving 2 or more lymph node regions on the same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions same side of the diaphragm (IIE)

Stage III: involving node regions on both sides of diaphragm +/- spleen

Stage IV: diffuse involvement of one or more extralymphatic organs

The suffix “A” or “B” is added as follows:

A: no B-symptoms

B: presence of at least one of the following B-symptoms
- unexplained weight loss ≥10% of baseline body weight during 6 preceding months
- recurrent unexplained fever > 38^{o}C
- drenching night sweats

E: extralymphatic site

Bulky disease:
- defined as a single mass of tumor tissue ≥ 10 cm in largest diameter

Bulky mediastinal disease:
- mediastinal mass ≥10 cm or > 1/3rd transverse thoracic diameter

PROGNOSTIC FACTORS

Early stage disease:

Adverse risk factors that predict for dissemination:
- MC or LD histology
- High ESR > 40
- Age >50
- B-symptoms
- Bulky disease >10cm in diameter
- Mediastinal mass > 1/3rd transverse thoracic diameter
- ≥ 4 (or 3) involved regions

Advanced stage disease:

International Prognostic Score (IPS) for advanced Hodgkin’s lymphoma
7 adverse prognostic factors have been identified:
- Albumin < 40 g/L
- Hemoglobin < 105 g/L
- Male gender
- Stage IV disease
- Age ≥ 45 yrs
- WBC > 15 x 109/L
- Lymphocyte count < 0.6 x 109/L or <8% of WBC

Prognostic score	% of patients	5 yr OS (%)	5 yr FFP (%)
0	7	89	84
1	22	90	77
2	29	81	67
3	23	78	60
4	12	61	51
≥5	7	56	42

A score should be generated for all patients with advanced stage HL.
IPS subgroups are based on the number of adverse prognostic factors at diagnosis:

- 0, 1
- 2, 3
- 4 -7

TREATMENT

- HL is very responsive to both radiation therapy (RT) and chemotherapy, with high cure rates, even in advanced stage disease
- The standard combination chemotherapy regimen for HL is ABVD

ABVD:

Adriamycin	25 mg/m2	IV d.1, 15
Bleomycin	10 U/m2	IV d.1, 15
Vinblastine	6 mg/m2	IV d.1, 15
Dacarbazine	375 mg/m2	IV d.1, 15

- Each cycle consist of a "Part A" (given d.1) and a "Part B" (given d.15). Cycles are repeated every 28 days.

- Although the risk of infertility with ABVD is low, male patients should be offered the option of sperm banking prior to initiating chemotherapy.

TREATMENT GUIDELINES

N.B. There are many recently completed and ongoing studies evaluating the optimal treatment of HL at all stages, so these recommendations are certainly subject to change.

"Limited Stage" = Stage IA, IB or IIA disease, non-bulky (no site ≥ 10 cm)

Combined modality therapy: ABVD x 4 followed by involved field radiation therapy (IFRT) 30 Gy in 20 fractions

*Special exception: Stage IA NLPHL ≤ 3cm in a peripheral nodal site (high neck or epitrochlear): recommended treatment is IFRT alone, 35 Gy/20 fractions

Stage IIB

Treat as "advanced stage" disease (see below)

"Advanced Stage" = Stage IIB, III or IV disease, Non-Bulky (no site ≥ 10 cm)

Treat with full course of ABVD chemotherapy (6-8 cycles).

- The decision of whether to stop after 6 cycles or to proceed to a total of 8 cycles is based on response assessment on CT scans after cycles 4 & 6.
- If CT scans done after cycle 6 show CR or evidence of residual disease that is unchanged compared to the scans done after cycle 4, one would stop at a total of 6 cycles.
- If CT scans done after cycle 6 show residual disease but improved compared to the scans done after cycle 4, one would proceed to 2 more cycles for a total of 8.

IFRT (35 Gy) may be added if a solitary residual mass persists following chemotherapy (PR)

Patient with initial Bulky disease - any stage
(ex. mediastinal or other site ≥ 10 cm))

ABVD x 6-8 followed by IFRT (35 Gy) to sites of initial bulk

RESPONSE ASSESSMENTS

- Patients are assessed for response to therapy as well as toxicity at each clinic visit, by history, physical examination, blood tests, including CBC/differential, renal & liver function, LDH.
- Limited stage: Patients undergo restaging CT scans of previously involved areas after 4 cycles of chemotherapy, and again after completion of IFRT
- Advanced stage: Patients undergo restaging CT scans of previously involved areas after 4 cycles of chemotherapy, and again after 6 cycles (+/-8 cycles, if applicable). Patients should also have repeat CT scans after any IFRT that may follow.
- After completion of all planned treatment, patients may also undergo repeat gallium scan (if gallium avid at diagnosis), and repeat bone marrow biopsy (if previously positive).

FOLLOW UP

Follow-up frequency in lymphoma clinic:

First 2 years	-	every 3-4 months
2 - 5 years	-	every 6 months
> 5 years	-	Annually (or transfer care to family physician)

At each follow-up visit:

- Monitor for relapse & for late effects of treatment
- History, physical examination, CBC, differential, ESR, LDH, renal function tests, liver function tests
- No routine surveillance CT scans (unless following a known residual lesion); restaging CT scans should be done for investigation of suspected relapse.
- Counselling regarding physical and psychological health issues, including impact of treatment on quality of life, reproduction, cardiovascular fitness, risk of recurrence, and risk of second malignancy. Counsel re. minimizing cardiovascular risk factors, smoking cessation, avoidance of sun exposure, breast screening, etc..
- Annual TSH and CXR (if patient received radiation involving thyroid/thorax)
- Annual screening mammography to begin 8-10 years following treatment or at age 40 (whichever comes first) in women who received chest or axillary radiation

MANAGEMENT OF REFRACTORY & RELAPSED DISEASE

Younger patients with no serious comorbidities are offered treatment with salvage chemotherapy (typically 2-3 cycles of “GDP”), followed by high-dose therapy and autologous stem-cell transplantation.

Older patients or patients who are transplant ineligible may be offered treatment with palliative chemotherapy (i.e. weekly vinblastine) or possibly with local radiation if disease is amenable to radiation.

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