Hodgkin’s Lymphoma

Introduction

Hodgkin’s lymphoma is a relatively uncommon malignancy with 150-200 new cases diagnosed annually in Ontario [1]. Cure rates are high following treatment, but late toxicities have emerged as a significant concern.

Diagnosis

The diagnosis of Hodgkin’s lymphoma is dependent on an adequate biopsy specimen (preferably an open surgical biopsy) with immunohistochemistry. Extra care should be taken to distinguish Hodgkin’s lymphoma from anaplastic large cell lymphoma and T-cell rich NHL [2]. The WHO classification system recognizes two major sub-classifications of Hodgkin’s lymphoma, Nodular Lymphocyte Predominant Hodgkin’s Lymphoma (NLPHL) and Classical Hodgkin’s lymphoma (CHL).

NLPHL is a monoclonal B-cell neoplasm characterized by a nodular or nodular and diffuse, polymorphous proliferation of scattered large neoplastic cells known as popcorn or L&H cells.

CHL is characterized by malignant Reed-Sternberg cells occurring in the context of a pleomorphic mixture of inflammatory cells including lymphocytes, histiocytes, eosinophils, and plasma cells. Four morphologic subtypes of CHL are recognized: nodular sclerosing HL, mixed cellularity HL, lymphocyte rich HL, and lymphocyte depleted HL.

Baseline Investigations

The following investigations are indicated for most patients with Hodgkin's lymphoma:

- CBC + differential
- Electrolytes (including calcium) and creatinine
- AST, ALT, ALP, bilirubin, albumin
- LDH, ESR
- Uric acid
- Chest x-ray
- CT chest, abdomen, pelvis
- Total body gallium scan
- HIV serology

Gallium Scan

A total body gallium scan should be performed in all patients being treated with curative intent, particularly those who would be considered for salvage therapy if not in complete remission after initial therapy. The need for gallium scanning at diagnosis may become less important if access to PET scanning for investigation of residual masses following treatment is increased.
HIV Serology

HIV positive patients have an increased incidence of Hodgkin's lymphoma. Hodgkin's in such patients has a worse prognosis with a greater predilection for advanced disease and extranodal involvement. Most patients with HL should undergo HIV serology testing at diagnosis. If serology testing is not planned, patients should be asked in detail regarding risk factors, including blood transfusion, intravenous drug use and sexual contact with persons who may have been at risk for HIV, and testing should be performed in patients with risk factors.

Bone Marrow Biopsy

A unilateral bone marrow biopsy should be performed on patients with advanced stage (III-IV), B-symptoms, anemia, or leukopenia. Patients > 35 years of age with inguinal or iliac involvement should also be considered for bone marrow biopsy [3].

Cardiac Assessment

A clinical cardiac assessment should be performed in all patients being considered for anthracycline-based chemotherapy (such as ABVD). MUGA scan or 2D-echocardiogram should be performed in patients with any of the following:

- Age > 60
- Hypertension
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Angina
- Cardiac arrhythmia
- Myocardial infarction

Anthracyclines should be used with caution in patients with an EF < 45%, recent MI (< 3 months) or severe arrhythmia.

Pulmonary Function Test

Pulmonary function testing should be considered for patients with:

- COPD
- Heavy smoking
- Radiation pneumonitis
- Prior extensive radiation to mediastinum or lungs

Bleomycin should be avoided in patients with severe reductions in diffusion capacity or hypoxia. All patients should be encouraged to quit smoking and to minimize their exposure to second hand smoke.

FDG-PET Scanning

The role of PET in lymphoma is the subject of CCO-PEBC EBS 6-20 (www.cancercare.on.ca). Positron emission tomography (PET) imaging with 2-fluoro-2-deoxy-D-glucose (FDG) is a new imaging modality that shows promise in the management of lymphoma. In the United States and much of Europe, PET scans and PET/CT fusion scans have been rapidly adopted into the routine staging and management of patients with HL. PET scans provide complementary information to CT scans and bone marrow biopsies during initial staging investigations leading to the upstaging of 10-40% and may change in management in some cases [4, 5]. PET appears to have a greater role in assessment of response to treatment. At the time of writing, there is limited access to PET scanning in Ontario and criteria for funding of PET are still being defined. Nonetheless, it is likely that in the near future these scans will be selectively incorporated into the care of patient with Hodgkin's lymphoma.

The role of PET in assessing treatment response is discussed on page 8.
Staging & Prognosis

All patients with Hodgkin’s should be staged according to the Ann Arbor staging system. Patients with advanced Hodgkin’s should also have their “International Prognostic Factor Score” determined [6].

Modified Ann Arbor Staging System

The Ann Arbor stage provides prognostic information and allows for tailoring of therapy [7]. It was modified in 1989 to incorporate CT-staging and to reflect an improved understanding of the natural history of HL [8].

Stage Definition

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Involvement of a single lymph node region (cervical, axillary, etc.), lymphoid structure (spleen, thymus, Waldeyer’s ring), or a single extranodal site.</td>
</tr>
<tr>
<td>Stage II</td>
<td>Involvement of two or more lymph node regions or lymphoid structures on the same side of the diaphragm.</td>
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<tr>
<td>Stage III</td>
<td>Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm.</td>
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<tr>
<td>Stage IV</td>
<td>Diffused or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.</td>
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The absence (A) or presence (B) of fever > 38.5 °C, drenching night sweats, and/or unexplained weight loss of 10 percent or more body weight in the six months preceding diagnosis are to be denoted in all cases by the suffix A or B respectively.

The presence of extranodal disease that is contiguous to an involved lymph node and can be captured in a single radiation field should be denoted with the suffix “E”. More extensive extranodal disease should be designated stage IV.

A subscript of “X” can be added to indicate patients with bulky disease. Bulky disease is defined as a mediastinal mass > 1/3 of the thoracic diameter at T5/6 or any nodal mass > 10 cm in maximal diameter [8].

Patients should not be upstaged to stage III solely on the basis of a positive gallium scan or a CT showing splenomegaly without focal defects [8].

The prognosis in patients with Hodgkin’s lymphoma has improved substantially over the past 2 decades [9]. The prognosis of NLP HL is particularly favorable. A majority of patients with HL will be alive 10 years following treatment (> 80%) and most will be in remission (> 75%). Younger patients with limited stage disease can be expected to do very well. For instance, 5 year overall survival for patients < 45 years old is > 90% [10]. Older patients, patients with advanced disease, and patients with concurrent HIV infection should be expected to do less well.

International Prognostic Factor Score for Advanced HL

A prognostic factor scoring system for advanced HL has recently been published by an international project [6]. Seven prognostic factors were identified:

- Albumin < 40 g/L
- Hemoglobin < 105 g/L
- Male sex
- Stage IV
- Age ≥ 45 yrs.
- WBC > 15 x 10⁹/L
- Lymphocyte count < 0.6 x 10⁹/L
### Prognostic Score

<table>
<thead>
<tr>
<th>Prognostic Score</th>
<th>% of Patients</th>
<th>5 year OS %</th>
<th>5 year FFP %</th>
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<tbody>
<tr>
<td>0</td>
<td>7</td>
<td>89</td>
<td>84</td>
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<tr>
<td>1</td>
<td>22</td>
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<tr>
<td>4</td>
<td>12</td>
<td>61</td>
<td>51</td>
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<tr>
<td>≥5</td>
<td>7</td>
<td>56</td>
<td>42</td>
</tr>
</tbody>
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A score should be generated for all patients with advanced stage disease.


SEER[10] Relative Survival Rates by Sex for Hodgkin's Lymphoma  
(All stages, all ages), 1988-2001
Management of Localized Disease

Modern risk-adapted treatment protocols yield high rates of cure for all subsets of patients with localized disease. While incremental gains in disease free survival are conceivable, the focus of ongoing clinical trials has shifted from improving disease control to limiting late toxicities of therapy. Late toxicities of chemotherapy including AML/MDS, cardiac failure and pulmonary fibrosis are rare with modern chemotherapy regimens. The use of lower doses and smaller volumes of radiotherapy has significantly reduced the incidence of late cardiovascular complications. However, the risk of radiation induced malignancy remains a concern.

Most centres now recommend combined modality therapy for almost all patients with localized disease [11-13] in an effort to limit late toxicity. A reduction in treatment intensity may be possible in selected patients as suggested by preliminary results of the GHSG HD.10 trial.

GHSG HD.10

The German Hodgkin’s Disease Study Group HD.10 trial randomized 1131 patients with CS I-II HD without risk factors between 4 cycles and 2 cycles of ABVD and 30 Gy IF-RT vs 20 Gy IF-RT in a 2 x 2 factorial design between 5/1998 and 5/2002 [14]. An interim analysis performed 9/2003 comprising 847 patients documented a complete response in 98.4%. FFTF and OS was 96.6% and 98.5% respectively with a median follow-up of 2 years. No statistical differences were noted between arms. A transition to 2 cycles of ABVD and IF-RT 20-30 Gy may be possible in the future if these encouraging results hold up with longer follow-up.

Recent clinical trials are exploring the possibility of omitting radiotherapy altogether in selected patients. The publication of NCI(C) HD6 provides preliminary information on the potential of chemotherapy alone in patients with non-bulky disease.

NCI(C) HD6

Meyer et al. reported results for 399 patients with non-bulky CS I-IIA disease followed for a median of 4.2 years [15]. Patients allocated to radiation-containing therapy received subtotal nodal radiation if favorable risk or combined modality therapy if unfavorable risk. Patients allocated to ABVD received four to six cycles. In comparison with ABVD alone, 5-year freedom from disease progression was superior in patients allocated to radiation therapy (93% vs. 87%, p = 0.06). No differences were documented in event-free survival (88% vs. 86%, p = 0.40) or overall survival (94% vs. 96%, p = 0.40). In a subset analysis comparing patients stratified into the unfavorable cohort, freedom from disease-progression was superior in patients allocated to combined modality treatment (95% vs. 88%, p = 0.004). There was no difference in overall survival (92% vs. 95%, p = 0.30). Patients achieving a CR or CRu after 2 cycles did better than those achieving only a PR (5YFFP 95% vs. 81%, p = 0.007). The superior progression-free survival of patients treated with combined modality therapy appears to have been offset by deaths due to causes other than progressive HD, or acute treatment-related toxicity. Second cancers were seen in 4 patients allocated to ABVD (2 fatal) and 8 patients allocated to RT (3 fatal). No breast cancers were reported. Longer follow-up will be required to see if any differences emerge in overall survival.

Preliminary results of recent European studies have raised some concern about the safety of omitting RT in the treatment of early stage disease. EORTC-GELA H9-F closed the chemotherapy only arm (EBVP x 6) because of an unacceptably high relapse rate (4y EFS 70%) [16]. In the German multinational GPOH-HD 95 trial, 211 of 1018 pediatric patients achieved CR with 2, 4 or 6 cycles and did not receive RT [17]. The DFS of CS I/IIA patients was 96%. The DFS of intermediate and high-risk groups treated with chemotherapy alone was only 69% and 77% respectively. When RT was used after a PR to chemotherapy in the intermediate and high-risk groups, the DFS improved to 92%.

Accepting a somewhat higher relapse rate in patients treated with chemotherapy alone may prove to be an acceptable long-term strategy if the long-term event free survival of patients undergoing salvage therapy can be shown to be comparable to results achieved with combined modality therapy at presentation. Until this is clarified by emergence of further long-term outcome data, combined modality therapy remains the standard of care for patients with limited stage classical HL.
The Risk of Radiation Induced Breast Cancer

Breast cancer represents the most common radiation-induced malignancy in women. Not all radiation-induced breast cancers will prove to be fatal. However, it is generally acknowledged that radiation-induced breast cancers contribute to the excess mortality from second cancers in long-term female survivors of Hodgkin’s disease.

Age at time of treatment is an important prognostic factor. Most published studies have identified an excess risk of breast cancer in women less than 30 years of age at time of treatment [18, 19]. Higher risks have been identified in peripubertal and adolescent women, an observation presumed to reflect the susceptibility of the developing breast to ionizing radiation. Aisenberg [20] reported an excess relative risk of 34 in women treated at < 19 years of age. Estimates of relative risk in published reports range from 6 to 112 highlighting the methodological difficulties in this population.

A recent report by Travis et al. [21] has overcome some of the methodological difficulties by using modified standardized incidence ratios to relate cohort breast cancer risks to those in the general population, and allowing for competing risks by using population-based mortality rates in female Hodgkin’s survivors. The analysis was based on a case control study of 5 population registries in Europe and North America documenting treatment outcomes for 3817 women between the age of 13 and 30 at time of treatment. Cumulative absolute risks of breast cancer increased with age at end of follow-up, time since Hodgkin’s diagnosis, and radiation dose. For a Hodgkin’s survivor who was treated at age 25 with a chest radiation dose between 20 Gy and < 40 Gy without alkylating agents, the estimated cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.1% (95% CI = 0.7% to 1.7%), 9.1% (95% CI = 5.9% to 13.7%), and 24.6% (95% CI = 16.6% to 34.8%), respectively. Cumulative absolute risks were lower in women treated with alkylating agents, an observation thought to reflect the protective effect of ovarian ablation. ABVD has been associated with minimal ovarian toxicity and is unlikely to exert a protective effect.

Travis cautions that these estimates should not be applied to patients treated with involved field radiotherapy. However, the authors have published a related article [22] documenting a 3.2 fold increase in risk with radiation doses of 4 Gy or more delivered to the breast. There appeared to be a linear relationship with dose. Of the 105 women who developed breast cancer, 49% developed a cancer infield, 24% under the block, 15% at the block edge, 8% at the field edge and 3% out of field. Given the apparent linear relationship between dose and cancer risk, the use of lower total doses (25 Gy) and smaller volumes (IFRT) of radiation, as per the Odette Cancer Centre treatment guidelines, could be expected to reduce, but not to eliminate the long-term risk of breast cancer.

Odette Cancer Centre Policy (Localized Disease)

In view of the ongoing changes in therapy for patients with localized disease, it is strongly recommended that a radiation oncologist and a medical oncologist assess all patients with localized disease jointly as soon as the staging workup is completed.

It is important that the assessment of response to chemotherapy be evaluated with CT scans and gallium scans as appropriate after the second cycle. To avoid a false negative gallium result, the scan should be performed immediately before the third cycle. To avoid a delay in consolidation radiation, patients should be referred for radiotherapy planning within one week of their last cycle of chemotherapy.

Stage I NLPHL, ≤3 cm, in peripheral nodal site (high neck, epitrochlear, inguinofemoral)

- Involved-field Irradiation (IF-RT) 3500 cGy in 20 fractions.

Bulky mediastinal disease (masses ≥ 10 cm or exceeding 1/3 of greatest transverse thoracic diameter)

- 6 cycles of ABVD followed by IF-RT to a dose of 2500 cGy in 15 fractions. Patients in CRU (gallium negative masses measuring <25% of pre-treatment volume) will be boosted with an additional 1000 cGy in 5 fractions.
Remaining patients:

- ABVD x 4 cycles: Patients who achieve a CR will receive involved field irradiation to a dose of **2500 cGy in 15 fractions**. Patients in CRU will be boosted with an additional **1000 cGy in 5 fractions**. Patients in PR as well as those with a positive Gallium scan will receive a further 2 cycles of ABVD (total 6 cycles) followed by involved field irradiation as above. Patients who fail to achieve at least a PR to chemotherapy have refractory disease (see Advanced Stage Disease).

- Consideration may be given to omitting radiotherapy in women less than the age of 30, provided they achieve a clinical and radiologic CR after 2 cycles of ABVD. The use of PET imaging is encouraged to confirm a radiologic CR. Women achieving a complete response will be treated with two additional cycles of ABVD for total of 4-6 cycles.

Stage IIB

- Patients with IIB disease have a worse prognosis and consideration should be given to treatment as advanced stage disease (see below).

Management of Advanced Stage Disease

The outlook for patients with advanced stage Hodgkin’s lymphoma was dramatically altered with the introduction of combination chemotherapy [23]. MOPP was the first regimen to be widely used, followed by hybrid and ABVD regimens. A series of randomized trials established that ABVD is superior to MOPP and at least equivalent to MOPP/ABVD combinations with respect to survival [24-26]. In addition, short and long-term toxicities of treatment are lower with ABVD than with MOPP or hybrid regimens [24-26], thus it has become the standard of care for HL throughout most of the Western world.

ABVD is the designated regimen for all patients in our centre. Patients are scheduled to receive 6 cycles of treatment at 28-day intervals (Appendix B). Response will be assessed clinically at each visit and by CT scan of involved areas after 3-4 cycles of treatment. Patients progressing on treatment or who fail to achieve a 50% reduction in disease bulk after the 3rd – 4th cycle of chemotherapy will be considered refractory to therapy and should be considered for salvage therapy. At the completion of the 6th cycle of treatment patients will be re-staged with assessment of all sites that were initially involved including bone marrow and gallium scan if appropriate.

A number of new regimens have been developed, two of which warrant further mention. The Stanford V regimen consisting of nitrogen mustard, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, and prednisone is an active regimen, which shows promise. Potential advantages include shorter duration of therapy and preservation of fertility [27]. The escalated BEACOPP regimen is also an active regimen and has been reported in one randomized trial to result in superior 5 yr. overall survival as compared to COPP-ABVD in high-risk, advanced HL patients [28]. This regimen appears to be associated with an increased risk of infertility and treatment-related AML. This regimen is being compared to ABVD in high-risk patients in the NCIC-CTG HD8 trial. Patients should be encouraged to consider participation in these studies.

Dose Modification of ABVD

The intent is to deliver full dose chemotherapy for all patients; however, dose modification may be required in selected cases. Doses will not be modified for advanced age alone. Patients with hematologic impairment due to marrow involvement with Hodgkin’s should also receive full dose therapy, potentially with growth factor support (see next page). Patients with cytopenias for other reasons should be treated with caution. Those with hepatic or renal dysfunction may require dose modification of vinblastine and Adriamycin. Those with bilirubin levels > 50 should not receive either agent, while patients with bilirubin levels of 20-50 should have a 50% dose reduction. Patients with significant peripheral neuropathy and those at risk due to diabetes, alcoholism, or other factors should receive vinblastine with caution, but will not routinely be dose-reduced.
Patients with severely restricted diffusion capacity or obstructive lung disease should not receive bleomycin. Patients with an ejection fraction < 45%, recent MI (within 3 mo.), or severe arrhythmia should not receive Adriamycin and should be considered for non-anthracycline-based therapy such as MOPP.

**Growth Factor Support (see Prophylaxis & Treatment of Febrile Neutropenia)**

Maintenance of dose and schedule is desirable for patients with HL undergoing chemotherapy [29]. G-CSF will not be started at the first cycle of treatment (primary prophylaxis). However, patients who develop febrile neutropenia with any cycle of therapy, as well as those who have a neutrophil count below 1.0 prior to cycle 2-6 of treatment should be started on G-CSF for all remaining cycles. Dose delays and reductions should be kept to a minimum (see CCO-PEBC EBS 12-2 at www.cancercare.on.ca).

**Antibiotic Prophylaxis**

Antibiotic prophylaxis is not routinely indicated for patients undergoing ABVD. It can be considered for highly selected patients, but must be weighed against the potential development of antibiotic resistance, as well as increased difficulty using outpatient therapy for febrile neutropenia.

**Bleomycin Pulmonary Toxicity**

Bleomycin pulmonary toxicity, manifested as respiratory symptoms and infiltrates on CXR in the absence of infectious etiology, occurs in approximately 10-15% of patients treated with ABVD. Risk factors include age > 40 years, and possibly the use of G-CSF [30, 31]. All patients with bleomycin pulmonary toxicity should have bleomycin omitted from future cycles of ABVD. Severe cases should be treated with steroids and referred for respirology assessment. Bleomycin pulmonary toxicity has been correlated with a significantly increased risk of death (from toxicity), however it’s omission from ABVD does not appear to significantly affect the risk of HL relapse at 5 or 10 years [30, 31].

**Assessment of Response**

Responses are classified according to the Cheson criteria (Appendix C). These criteria are currently in evolution, with new PET-based criteria being proposed. In the United States and much of Europe, PET scans and PET/CT fusion scans have been rapidly adopted into the routine management of patients with HL. This has occurred despite a paucity of evidence that PET scans lead to substantive changes in HL management or outcomes. At the time of writing, there is limited access to PET scanning in Ontario. Nonetheless, PET appears to be of value in selected clinical situations. The role of PET in lymphoma is addressed in CCO-PEBC EBS 6-20 (www.cancercare.on.ca).

Preliminary evidence suggests that PET scans are a powerful method of detecting residual HL. Patients with a negative PET scan at the end of HL therapy have an excellent prognosis (negative predictive value of PET 81-100%). The positive predictive value of PET however is reported to be more variable (25-100%) [32]. Clinical experience with PET, timing of the PET scan, presence of brown fat, and inflammatory lesions may all contribute to the incidence of PET false positives. Until greater experience has been accumulated PET scans will not be routinely performed at our centre, but if available should be considered in the following situations:

- In patients with residual masses after completion of therapy in whom further potentially curative treatment could be offered
- In patients with limited stage HL felt to be at excess risk of toxicity from radiation. The PET scan should be performed after 3-4 cycles of ABVD in such patients.

PET/CT scans may also have an increasing role in the planning of radiotherapy in patients completing short course chemotherapy. The use of radiotherapy in the treatment of Hodgkin’s disease has changed from extended fields developed for single modality treatment to more and more conformal fields designed for combined modality treatment. Today, in most situations, the target volume is limited to the pre-chemotherapy macroscopically involved tissues in early stage disease, and residual masses after chemotherapy in advanced disease [33]. This evolution in practice has made it even more important to accurately define the target with PET offering the potential to change target volumes [34].
According to the 1999 Cheson criteria (Appendix C), a complete response (CR) requires disappearance of all clinical and radiological evidence of disease and of all disease-related symptoms, and normalization of biochemical abnormalities. A CRU involves $\geq 75\%$ reduction in lymph node masses with a normal or indeterminate bone marrow.

Responses will be deemed to be incomplete if the above criteria are not met. Wherever possible, a biopsy or a PET scan (if available) should be performed to confirm incomplete response.

**Management of Incomplete Response (Primary Refractory Disease)**

Patients who fail to achieve a response to initial chemotherapy do poorly. Younger patients (< 65 yr.) progressing on ABVD chemotherapy should be considered for salvage therapy with mini-BEAM and stem cell transplantation. Patients who are not eligible for transplantation should be considered for palliation with radiation or lower dose chemotherapy (typically low-dose, weekly vinblastine).

**Role of Radiotherapy**

In advanced HL, radiotherapy improves local disease control, but does not improve long-term survival [35-37]. Thus, IFRT should not routinely be incorporated into the treatment of advanced HL patients. However, consolidative radiation may improve the 5 year event free survival of patients with advanced Hodgkin’s and initial bulky disease [35]. As a result, patients with advanced disease and initial bulk should be referred to a radiation oncologist for assessment and may be candidates for involved field radiation (2500 cGy/15 fractions).

A recent study has argued that advanced HL patients who achieve a PR after ABVD can be successfully converted to a CR with consolidative radiation therapy. However, the study was not designed to assess this question and was under-powered, thus the claim remains controversial [36].

**Odette Cancer Centre Policy (Advanced Stage Disease)**

- Standard therapy will be ABVD x 6 cycles at 28-day intervals (Appendix B)
- G-CSF will be used in patients who experience febrile neutropenia, or neutrophil count < 1.5 immediately prior to cycle 2-6
- Re-staging CT scans of involved areas will be completed after 3-4 cycles of treatment and at the end of 6 cycles
- Patients progressing on treatment or who fail to achieve a 50% reduction in disease bulk after the 3rd – 4th cycle of chemotherapy will be considered refractory to therapy and will be considered for salvage therapy
- Patients with bulky disease will be referred to radiation oncology for consideration of consolidative IFRT

**Management of Relapsed Disease**

While most patients with Hodgkin’s lymphoma have an excellent long-term prognosis, approximately 20-25% of patients will relapse. A majority of relapses occur in the first 3 years following HL treatment [10]. However, late relapses (beyond 10 years) are well described.

**Relapse Following Radiation Alone**

Patients who relapse following local radiation generally do well with chemotherapy. Such patients should be treated with ABVD (see Management of Advanced Stage Disease).
Relapse Following Chemotherapy Alone For CS I-II Disease

Patients who relapse following chemotherapy alone for localized disease may be candidates for radiotherapy. The criteria for patient selection have yet to be defined. Those judged unsuitable for radiotherapy salvage should be managed as described below.

Relapse Following Chemotherapy or CMT

HL patients who relapse following chemotherapy do less well than those initially treated with radiation alone [38]. Nonetheless, with aggressive treatment including high-dose therapy and stem cell transplant, a significant number will experience long-term survival. Two small randomized trials report superior outcome with a high-dose therapy and autologous stem cell transplant approach than with chemotherapy alone [39, 40]. Three-year event free survival is approximately 50% and 3 yr. overall survival is approximately 70% with this strategy [39-41]. The major prognostic factors in this setting are duration of first complete response and chemosensitivity at relapse. Patients who relapse within one year of initial treatment represent a high-risk group and should, if eligible, be referred for consideration of HDT + autologous stem cell transplant.

Patients who relapse > 1 year after initial treatment have a better prognosis. Whether such patients should routinely be referred for autologous stem cell transplantation or be treated with salvage chemotherapy (BEACOPP, mini-BEAM, GDP, etc.) is controversial. Some authors have argued that long-term response to autologous stem cell transplant is best when transplant is completed at first relapse, and thus advocate for autologous stem cell transplant for all young, relapsed HL patients irrespective of time to relapse [42]. A recent randomized controlled trial of autologous stem cell transplant in patients with chemosensitive HL at relapse has demonstrated an improved 3y FFTF in both patients with early (< 1 yr.) and late relapse. A trend to improved 3 yr. OS (p = 0.08) was reported in patients with late relapses only [40].

High-Dose Therapy

As discussed above, autologous stem cell transplant should be considered first line treatment for young (< 65 years old) HL patients with primary refractory disease or early relapse (< 1 yr. post-treatment). Newer evidence suggests that ASCT may also be appropriate for young patients with late relapse [40].

Traditionally, the ability to obtain at least a PR with salvage chemotherapy has been considered a prerequisite for consideration of ASCT. Recent non-randomized evidence however suggests that a small, but not insignificant number (approximately 15%), of relapsed HL patients who fail to achieve a PR with salvage chemotherapy can still experience long-term survival with ASCT [43]. Some, but not all, transplant centres in Canada will consider such patients for ASCT. Patients who progress on salvage chemotherapy are unlikely to benefit from ASCT and should be considered for palliative therapy.

Radiation Therapy

A small number of retrospective cohort studies address the role of radiotherapy in patients with relapsed HL after chemotherapy [44]. Acceptable outcomes (75% 5 yr. OS) have been reported in highly-selected, good risk, relapsed patients [44, 45]. Patients not fit for further curative chemotherapy should be considered for curative radiation treatment.

Allogenic Stem Cell Transplant

Allogenic stem cell transplant should be considered an experimental technique in patients with relapsed/refractory HL. Initial trials of this modality report high transplant related mortality and poor long-term survival [46]. Reduced-intensity allo-SCT’s may result in reduced transplant related mortality with improved long-term survival and are an area of active investigation. Young HL patients who relapse after autologous SCT could consider allo-SCT and should be referred for allo-transplant opinion if they have a matched sibling donor.

Palliative Therapy

Most patients with recurrent Hodgkin’s lymphoma will be treated with aggressive chemotherapy +/- transplantation with an aim for cure or long-term disease control. Selected patients with poor risk at first recurrence, as well as those who progress with salvage therapy will be managed palliatively. In this setting therapy should be minimized. Palliative symptom control can often be accomplished using weekly vinblastine (6 mg/m² weekly) [47].

Odette Cancer Centre Policy (Relapsed/Refractory Disease)

- GDP will be used as the standard first-line salvage regimen (2-4 cycles at 4 week intervals) given to maximal response
- Patients potentially eligible for transplantation should be referred for a transplant opinion early
- Patients < 65 years old with refractory disease or with relapse < 1 year after initial chemotherapy will be considered for high dose therapy and autologous stem cell transplant (ASCT)
- Patients who relapse late (> 1 year after) chemotherapy should be advised of the controversy over the role of ASCT in this setting
- Selected patients with good risk, limited, late relapse will be considered for treatment with radiation alone
- Patients who relapse following radiation alone (usually patients treated years ago with EFRT) will be treated with ABVD x 6 cycles
Preservation of Fertility

**Males**

Sperm banking should be offered to all men scheduled for pelvic radiation, chemotherapy or combined modality therapy who are keen to preserve fertility. Secondary scrotal shielding will be used to reduce gonadal dose to ≤ 2.5% of the tumor doses delivered to the abdomen and pelvis during infra-diaphragmatic radiation.

Oligospermia is relatively common in men at the time of HL diagnosis occurring in up to 50% [48]. In most cases, the abnormality is temporary, however a small number of men will have long-term infertility after therapy. ABVD is much less gonadotoxic than its predecessors (MOPP, MOPP/ABV, etc.). Permanent azoospermia is estimated to occur in ≤ 2% of men post-ABVD, however more subtle semen abnormalities may occur in up to 70%[49]. Aggressive regimens such as BEACOPP and ABMT have a much higher incidence of permanent azoospermia.

**Females**

Pelvic radiation causes infertility in women. The dose at which 50% of primordial follicles are lost has been estimated to be only 4 Gy. Thus, all women undergoing pelvic radiotherapy should be offered laparoscopic oophoropexy if they are keen to preserve ovarian function. Lateral transposition of the ovaries to the iliac fossa is preferred to medial transposition to the pelvic midline [50].

Less is known about the fertility risks of ABVD chemotherapy in women. Permanent amenorrhea is uncommon after ABVD, occurring in < 2% of women [49]. However, amenorrhea is a poor surrogate marker for infertility and/or sub-fertility, thus the true reproductive implications of ABVD are unknown. Nonetheless, there are multiple published and anecdotal reports of successful pregnancies following HL treatment. Thus it is likely that the risk of infertility is increased only slightly if at all following ABVD. Older women are likely at increased risk. Higher dose regimens such as BEACOPP or ABMT are much more likely to produce permanent amenorrhea and hence infertility (50% incidence after BEACOPP) [51].

In the absence of definitive data on the risks of infertility post-treatment, it is recommended that physicians err on the side of caution. All young, female HL patients interested in maintaining fertility should be referred to the Fertility Clinic at Women’s College Hospital. There they will typically be offered either oral contraception and/or a GnRH agonist [51-53]. In special cases, ovarian cryopreservation and/or embryo cryopreservation may be available.

**Pregnancy**

Male and female patients should be strongly advised to use contraception during therapy to avoid pregnancy. We advise deferring plans for pregnancy for at least two years following completion of chemotherapy or radiation because the adequate washout period is unknown, and the risk of HL relapse is highest in the first three years.

Patients who are diagnosed with HL during pregnancy should be managed on a case-by-case basis. Staging should be completed without the use of CT, gallium or PET scans. If possible treatment should be avoided in the first trimester. In many cases, because HL is a relatively slow growing cancer, it will be possible to defer treatment until the end of pregnancy. In some cases vinblastine may be given to temporarily control the HL pending definitive treatment after delivery.
Follow-up

Patients should be followed every 3-4 months for two years, every 6 months in the 3rd - 5th year and every one-year thereafter. Assessment should consist of:

- History and Physical
- CBC and differential
- Serum Creatinine, LDH

Routine imaging of patients who have had a complete response (CR or CRU) to therapy is expensive, an insensitive way to pick up relapse, and has a high false positive rate. In most cases imaging should be reserved for the investigation of suspected clinical relapse [54]. Patients with initial bulky disease (> 10 cm) and or significant residual adenopathy/fibrosis may have a repeat CT scan at 12 months to rule-out progression.

Patients who have received radiation to the neck or mediastinum should have a TSH done on completion of therapy and yearly thereafter. Women who have undergone upper mantle irradiation should be referred to the Breast Diagnostic Clinic with a plan for surveillance mammography to begin 10 years after radiation or at age 40 (whichever comes first).

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