HODGKIN LYMPHOMA (ADULT)

Executive Summary

Hodgkin lymphoma (HL) is a lymphoid malignancy of B-cell origin which is classified into either nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) or classical Hodgkin lymphoma (cHL) in accordance with 2008 WHO classification. This disease is more frequently a disease of young people between the ages of 20-35. Although they have characteristics in common, these two disease entities differ in their clinical features and behavior as well as their cellular properties. cHL accounts for 95% of all HLs and can be further subdivided into four histological subtypes: lymphocyte-rich (LR), nodular sclerosis (NS), mixed cellularity (MC) or lymphocyte-depleted (LD). HL is an uncommon neoplasm with estimated number of cases of 65,950 globally, an incidence that varies significantly by age, sex, ethnicity, geographic location and socioeconomic status.

Incidence rates are higher in more developed regions and among males and lower in Asia. However, HL accounts for 15% of all cancers in young adults globally with a high impact on quality of life. Up to the 1960s, the 5-year survival rate for HL was less than 10% worldwide. Since then, the outcome for patients diagnosed with HL has progressively improved, and the current 5-year OS rate increased up to 80% for patients with advanced and to more than 90% for those with limited stage disease. A success attributed to improved chemotherapy and radiation therapy (RT) approach used to treat these patients. Among the regimens developed to treat HL, the regimen including doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine, referred to as “ABVD” is recommended as the standard therapy, and BEACOPP regimen (drugs listed on page 3) as an acceptable alternative for high-risk patients. Hence, we recommend that the drugs in ABVD and BEACOPP be included on the Essential Medicines List.

Public Health Relevance

GLOBOCAN estimates that in 2012 there were 65,950 cases and 25,469 deaths of Hodgkin’s lymphoma worldwide. Of these cases, 28,852 occurred in more developed regions and 37,098 occurred in less developed regions. The age-standardized rate of Hodgkin’s lymphoma is 2.1 per 100,000 in more developed regions versus 0.6 in less developed regions. Regions most affected by Hodgkin’s lymphoma include the Americas (ASR of 1.5 per 100,000), East Mediterranean Region (ASR of 1.5 per 100,000), and Europe (ASR of 2.0 per 100,000). The East Mediterranean region has the highest age-standardized mortality rate of 1.0 per 100,000. Men (ASR of 1.1 per 100,000) are slightly more at risk than women (ASR of 0.7 per 100,000) of developing Hodgkin’s lymphoma. Hodgkin’s lymphoma is most often diagnosed between ages of 15 and 30 and in populations older than 55. Previous exposure to an Epstein-Barr viral infection is a possible risk factor for Hodgkin’s lymphoma. Additionally, those infected with immune-compromising conditions, such as HIV/AIDS, are more at risk for developing Hodgkin’s lymphoma.
Requirements for diagnosis, treatment, and monitoring

Diagnostics:
Pathology laboratory analysis of surgically excised lymph node, lymph node core or extranodal tissue is required. In classical Hodgkin lymphoma cHL, the presence of Hodgkin and Reed–Sternberg (HRS) cells is disease-defining while the detection of lymphocyte predominant (LP) cells is required for the diagnosis of NLPHL. The immunophenotype of the malignant cells in cHL and NLPHL differs significantly. In contrast to HRS cells that stain consistently positive for CD30 and CD15, occasionally positive for CD20 and negative for CD45, LP cells are characterized by the expression of CD20 and CD45 but they lack CD15 and CD30.1

Testing:
It has been recommended that pre-treatment tests include staging utilizing contrast enhanced computed tomography (CT) scan, and blood counts and chemistries to assess critical organ function, including renal and hepatic function, and determine prognosis. Several groups have developed scoring systems to predict survival of patients and guide decision of therapy. Most consider the presence of constitutional symptoms, and bulky mediastinal disease, as unfavorable features in limited stage disease (stage I/II), whereas stage III/IV disease is considered advanced stage disease.1 In addition, a baseline positron emission tomography (PET) should be carried out according to the recommendations for staging and response assessment in lymphoma whenever this diagnostic tool is available. 6,7 The PET/CT scan can be performed after two cycles of ABVD and complete response is associated with better prognosis and can result in a patient receiving overall fewer cycles of ABVD. If a PET-CT is performed; bone marrow biopsy is no longer indicated for HL. 6To identify patients at increased risk for acute and/or long-term complications, pulmonary function tests should be performed in older patients. Since chemotherapy and RT can potentially cause permanent fertility damage, reproductive counseling must be offered to young patients of both genders before treatment.8

Administration and Care of Patients:
Administration requires intravenous infusion capacity, and requires that the patient have regular access to clinical care. A central venous catheter such as a Hickman or PICC aids in minimizing pain that is associated with peripheral administration of ABVD. In developed countries administration is usually performed in outpatient facilities, though in other setting, patients may be treated in in-patient facilities. IV hydration and anti-emetics should accompany administration of ABVD. Careful monitoring is mandatory to prevent soft tissue extravasation, which can cause severe local reactions and necrosis, especially with dacarbazine.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential adverse events caused by the treatment itself, including bone marrow suppression, infection, mucositis, nausea and vomiting.9 Special attention is needed to acute reactions to bleomycin, including fever, and anaphylactoid reactions. 9 Bleomycin induced pulmonary toxicity (BPT), may occur in 20-30% of patients; while on therapy or up to 6 months after treatment. Patients receiving bleomycin should be assessed carefully for signs and
symptoms of pulmonary toxicity before each dose. A history of new or worsening dyspnoea or pulmonary crackles should lead to stopping of bleomycin until an alternative cause is identified. Among patients, who develop BPT, omission of bleomycin does not compromise efficacy of therapy, but BPT diagnosis by itself could potentially compromise outcome. Clinicians should be sensitive to aspects of fatigue and related (emotional) symptoms in patients and encourage their patients to seek further support if needed.

Overview of Regimens

The treatment of HL (both cHL & NLPHL) relies on multimodality treatment with standard chemotherapy, radiation therapy, and autologous or allogeneic stem cell transplantation in cases of relapsed disease (20-30% of advanced cases).

ABVD is considered the standard of care for HL in many countries. However, over the past decade, other regimens were developed for patients with advanced HL (stage III/IV) to improve efficacy or reduce toxicity. Dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone (escalated BEACOPP or BEACOPP), was developed by the German Hodgkin Study Group (GHSG) to improve efficacy, and has emerged as a very effective regimen. Another combined modality therapy (CMT) approach is Stanford V. The premise of this protocol was to substantially lower the cumulative doses of agents known to contribute to late effects and modify RT for the same reason. The following tables include administration and dosing for ABVD, BEACOPP, and Stanford V, but exclude ancillary medications pertaining to the management of side effects.

Standard Regimen (ABVD)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABVD</strong>: 2-4 cycles for limited disease and 6-8 for advanced disease, (repeated every 28 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Intravenous infusion</td>
<td>25 mg/m²</td>
<td>day 1&amp;15</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Intravenous infusion</td>
<td>10 units/m²</td>
<td>day 1&amp;15</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Intravenous infusion</td>
<td>6 mg/m²</td>
<td>day 1&amp;15</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Intravenous infusion</td>
<td>375 mg/m²</td>
<td>day 1&amp;15</td>
</tr>
</tbody>
</table>

Alternative Regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BEACOPP</strong>: 6-8 cycles (repeated every 21 days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Intravenous infusion</td>
<td>10 mg/m²</td>
<td>day 8</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Intravenous infusion</td>
<td>200 mg/m²</td>
<td>days 1-3</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Intravenous infusion</td>
<td>35 mg/m²</td>
<td>day 1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Intravenous infusion</td>
<td>1250 mg/m²</td>
<td>day 1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Intravenous infusion</td>
<td>1.4 mg/m² (maximum 2mg)</td>
<td>day 8</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Oral</td>
<td>100mg/m²</td>
<td>days 1-7</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Oral</td>
<td>40 mg/m²</td>
<td>days 1-14</td>
</tr>
<tr>
<td>GCSF*</td>
<td>SQ</td>
<td></td>
<td>starting day 8</td>
</tr>
</tbody>
</table>
**Review of Benefits and Harms**

**Benefits**

CMT has transformed HL from a disease uniformly fatal few decades earlier to mostly a curable disease nowadays. The study by Canellos and colleagues established ABVD as more efficient and less toxic regimen as compared to other combinations. In 1992, the Cancer and Leukemia Group B (CALGB) reported the results of a prospective three-group randomized trial involving 359 patients with Hodgkin's lymphoma. This trial compared the following regimens: ABVD for 6 to 8 months, Mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) for 6 to 8 months, and MOPP alternating with ABVD for 12 months. The trial was limited to patients with advanced disease (clinical stages III and IV). No radiotherapy was administered. The results indicated an event-free survival advantage of ABVD over MOPP but no differences in OS between the ABVD and MOPP groups. However, the toxicity profile was remarkably better with ABVD. These findings were confirmed in a follow-up study of the data published in 2002, and later at a median follow up of 20 years. Most patients (more than 90-95%) with limited-stage disease, usually defined as nonbulky (largest tumor diameter < 10 cm) stage IA or IIA disease can be cured with 2-4 cycles of ABVD followed by involved field radiation therapy.

An alternative to ABVD as the standard of care for patients with advanced Hodgkin's lymphoma is the intensive regimen BEACOPP. This regimen has shown superior activity to ABVD in terms of improving event free survival in many randomized studies, but limited impact on OS. However, it is associated with significant short-term and long-term toxic effects. As for Stanford V, randomized trials have failed to demonstrate superior outcome as compared to ABVD.

**Harms and Toxicity Considerations**

**Common**

Patients receiving chemotherapy for HL will suffer from temporary alopecia, and myelosuppression, including suppression of the neutrophil count increasing the risk of infection, although infection incidence remains low at 2%. However, the escalated BEACOPP regimens, when compared to ABVD, caused more haematological toxicities and infections, with subsequently higher risk for transplant related mortality especially among those with poor performance status and patients older than 50 years.

**Serious**

Patients should be monitored for symptoms indicating the existence of long-term toxicity, particularly of heart and lung. Treatment with bleomycin may result in late bleomycin-related pulmonary toxicity, particularly when used in combination with mediastinal irradiation. Toxicity may occur in up to 20-30% of patients and fatal pulmonary complications have occurred. There may be a significant decline in median forced vital capacity and diffusing capacity.
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(DLCO)\(^{24}\). Therefore, a high index of suspicion is warranted to allow omission of the bleomycin as early as possible when toxicity occurs.

Doxorubicin can lead to long term cardiomyopathy when cumulative doses exceed 450mg/m\(^2\). However, ABVD provides cumulative doxorubicin doses of 300-400mg/m\(^2\) and therefore is uncommonly associated with cardiomyopathy.

Escalated BEACOPP regimens are associated with higher risk for gonadal toxicity especially among women.\(^{26,27}\) Additionally, the BEACOPP regimen can lead to secondary malignancy in 2-7% of patients, cancer screening should be conducted regularly due to the increased risk.\(^{22}\)

Systematic Reviews

The majority of patients with Hodgkin lymphoma are cured with ABVD. However, almost 20% of patients with advanced disease fail to achieve complete remission. While several randomized trials have confirmed prolongation of progression-free survival with BEACOPP compared to ABVD, a survival advantage has been difficult to demonstrate. Given the comparable survival between BEACOPP and ABVD, as well as the greater toxicities of the former, including infertility, myelosuppression, and secondary malignancies – the latter increased at least in one trial\(^{28}\), we recommend ABVD to be added to the Essential Medicines List.

- A review of the 12 consecutive series of prospective, randomized therapeutic trials involving a total of 6200 patients with advanced Hodgkin's lymphoma, revealed only one trial in which a small statistically significant difference in overall survival was noted.\(^{18}\)

- A meta-analysis of 5 randomized trials examining the efficacy of BEACOPP compared to ABVD for first line treatment of HL demonstrated the positive impact of BEACOPP on EFS but not OS.\(^{22}\)

- A network meta-analysis of randomized trials comparing BEACOPP regimens to ABVD based regimens, demonstrated 10% OS advantage at 5 years, but emphasized the importance of availability of appropriate supportive care.\(^{21}\) However, that difference was corrected by effective salvage therapy.\(^{18}\)

- ESMO clinical practice guidelines endorse ABVD as standard regimen for patients with all stages, especially so for fit patients older than 60 years. For advanced stages, if BEACOPP is used, they emphasize the need for appropriate supportive care and close surveillance to control short and long term toxicities.\(^1\)

- A similar recommendation was made by the British Committee for Standards in Haematology, the Italian Society of Haematology and the Italian Society of Experimental Haematology, and the Spanish Society of Haematology.\(^{8,29,30}\)
Recommendations

The reviewers recommend the incorporation of Hodgkin Lymphoma treatment options into the WHO Model List of Essential Medicines, and recommend specifically that G-CSF be added to the core Essential Medicines List.

Additions proposed for Section 8.2 of the EML

G-CSF*

*Please refer to the supplemental document on granulocyte colony-stimulating factors that is appended to the overall proposal for details on the use of G-CSF
References

2. GLOBOCAN. Estimated cancer incidence, mortality, and prevalence worldwide in 2012.
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31 Horwitz S, Yahalom J. Initial treatment of advanced (stage III-IV) classical Hodgkin lymphoma. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA, 2014.
