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Saudi Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up of Hodgkin's Lymphoma

National Cancer Center

(NCC)

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Hodgkin's Lymphoma: Saudi Clinical Practice Guidelines for

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Overview

Hodgkin lymphoma (HL) is an uncommon malignancy involving lymph nodes and the lymphatic system. The age of diagnosis of most of the patients is in between the age of 15 and 30 years old and a peak age of ≥55 years among adults. The WHO classification divides HL into 2 main types: classical HL (CHL) and nodular lymphocyte-predominant HL (NLPHL).[1] CHL is characterized by the presence of Reed-Sternberg cells in an inflammatory background, whereas NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocyte-predominant cells and sometimes termed popcorn cells.

Histologically, classical HL (cHL) accounting for ~95% of all HL cases is distinguished from nodular lymphocyte predominant HL (NLPHL) representing ~5% of all HL cases. Hodgkin's lymphoma ranked the seventh among the most common cancers in Saudi males and eighth among Saudi females. There were 411 cases of Hodgkin's lymphoma accounted to 3.5% of all cancer cases diagnosed among Saudi nationals in 2014. There was a slight predominance of males diagnosed with HL. The ASR was 2.3/100,000 for males and 1.8/100,000 for females. However, the median age of diagnosis was 25 years (ranged between 3 and 88 years) in males and 25 years (ranged between 3 and 112) in females.[2] Over the past few decades, there has been a significant progress in the management of patients with HL and rate of treatment success increases to 80% of patients. With the advent of more effective treatment options, the 5-year survival rates has improved significantly as compared to any other cancer over the past 4 decades.

1. Diagnosis and Work-up

1.1. The diagnostic works up for HL patients have evolved over the past few years with the introduction of PET scanning. Given the high sensitivity of PET/CT for bone marrow

involvement, a bone marrow biopsy is no longer indicated in patients undergoing PET/CT evaluation. However, bone marrow biopsy must be carried out if PET/CT is not available. [3-5]

1.2. Cardiac and pulmonary function test must be carried out before the initiation of treatment to identify patients who are at increased risk for acute and/or long-term complications. Since chemotherapy and radiotherapy (RT) can potentially cause permanent fertility damage, reproductive counseling must be offered to young patients of both genders before starting the treatment.

1.3. Summary of the diagnostic work-up: [3-7]

1.3.1. History and physical exam;

1.3.2. Diagnosis by excisional biopsy;

1.3.3. CBC, renal and liver profile, albumin, LDH, ESR; [6]

1.3.4. Bone marrow biopsy (III and IV) if PET not available;

1.3.5. Pregnancy test in childbearing woman;

1.3.6. Screening for Hepatitis B, Hepatitis C and HIV;

1.3.7. TSH if radiation is planned;

1.3.8. PET/CT is the preferred imaging modality;

1.3.9. CT neck/chest/abdomen/pelvis;

1.3.10 Cardiac wall motion study (MUGA) or Echo-2D;

1.3.11. Pulmonary function test.

1.4. Multiple prognostication models have been developed over the past few decades. The International Prognostic Score (IPS) is defined by the number of adverse prognostic factors present at diagnosis and helps determine the clinical management and predict prognosis for patients with stage III–IV disease.[8] Score ranges from 0 to 7 with Median survival at the end of 5 years ranges from 89% (0 score) to 56% (5 or more score).

1.4.1. International Prognostic Score for Hodgkin Lymphoma (stage III and IV): -

1.4.1.1 Serum albumin <40 g/L;

1.4.1.2 Hemoglobin <105 g/L;

1.4.1.3. Male gender;

1.4.1.4. Stage IV disease;

1.4.1.5. Age >45 years;

1.4.1.6 White blood cell count ≥15,000/mm3;

1.4.1.7 Lymphocyte count <600/mm3 or <8 % of white cell count.

2. Pathological Diagnosis

2.1. It should be made according to the World Health Organization (WHO) classification from an excisional lymph node biopsy "preferred" to provide enough material for fresh frozen and formalin-fixed samples.

2.2. A diagnostic assessment based solely on FNA biopsy is insufficient except in unusual circumstances when, in combination with immunohistochemistry, it is judged to be diagnostic of HL by an expert hematopathologist or cytopathologist. [9-11]

2.3. Immunostaining for CD3, CD15, CD20, CD30, CD45, CD79a, and PAX5 is recommended for cHL.

2.4. In 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.

2.5. The immunophenotype of the malignant cells in cHL and NLPHL differs significantly.

2.6. 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.[12]

3. Treatment of Classical Hodgkin's Lymphoma

The management to HL generally follows two widely acceptable North American or European (German) approaches. The Saudi lymphoma expert panel have reviewed the current guidelines and literatures and proposed the following management strategies to help in standardizing the local practices, optimizing patient's outcomes and support future research initiatives. Treatment of Hodgkin's lymphoma is dependent on the stage of the disease and the presence of any adverse prognostic feature which would stratify the patient as unfavorable prognosis. [6,-8]

3.1. Limited Stage I-II (Non-bulky and No B-symptoms)

3.1.1. Combined modality therapy (2 cycles of ABVD plus 30 Gy IFRT) is the preferred treatment. [13-15,22-24]

3.1.2. ABVD alone could be a reasonable choice of treatment, especially for younger patients who are in CR after 2 cycles as documented interim PET NEG (Deauville score of 1 to 3 on PET scan) followed by ABVD 1-2 cycles (total of 4 cycles of ABVD), in order to avoid the long-term risks of RT.[15-21, 25-27]

3.1.3. However, if interim PET Positive (Deauville score of 4-5), consider completing the planed 2 cycles of ABVD + IFRT and evaluate end of therapy PET and if still positive re-biopsy and proceed for salvage therapy if biopsy proven residual disease.[15,16,25-27]

3.2. Advanced stage (Bulky, B symptoms, III and IV)

Chemotherapy is always used for patients with advanced-stage disease, combined modality therapy is the management approach for some treatment regimens, especially for patients with bulky disease, and is used for poor responders to chemotherapy in other treatment regimens.[28]

3.2.1. Based on the review of the literature, we recommend:[26-36]

3.2.1.1. 2 cycles of ABVD followed by interim PET/CT.

3.2.1.2. Patients with a negative interim PET/CT (Deauville score of 1 to 3) are treated with:

3.2.1.2.1. 4 cycles of AVD (total of 6 cycles) followed by observation or IFRT to initially bulky.

3.2.1.2.2. 4 cycles of ABVD (total of 6 cycles) based followed by observation or IFRT to initially bulky.

3.2.1.3. In patients with an interim positive PET scan (Deauville score of 4 to 5):

3.2.1.3.1. 4 additional cycles of ABVD (total of 6) with or without ISRT and this approach is recommended by the panel.

3.2.1.3.2. An alternative option is 4 cycles of escalated BEACOPP with or without IFRT.

3.2.1.4. End of therapy PET/CT:

3.2.1.4.1. If PET/CT NEG, observe or +/- IFRT.

3.2.1.4.2. If PET/CT Positive, A biopsy is recommended.

3.2.1.4.3. If the biopsy is negative, observe or +/- IFRT.

3.2.1.4.4. Patients with a positive biopsy should be managed as described for refractory disease.

3.2.1.5. Note: If PET/CT is not available then it is appropriate to utilize CT scan to assess response after 3-4 cycles and complete 6 cycles of ABVD in clinically responding patients. If there are evidence of disease progression then consider as a refractory disease and proceed with salvage chemotherapy and ASCT.

3.3. Refractory/Relapsed disease

Most patients with Hodgkin lymphoma will achieve complete remission and achieve long-term disease control with standard management approach (ie, cure). However, relapse may occur in 10 % of patients with limited HL and in 15 to 30 % of patients with advanced HL. Approximately 10 to 15 % of patients may have refractory disease that either does not respond to standard therapy or progresses after an initial partial response. [13,17,20,24,35]

3.3.1. Any suspected relapse must be confirmed with a new biopsy and obtaining new biopsy should be considered in refractory disease.

3.3.2. In some patients with localized late relapse, salvage RT alone appears to be sufficient.[37]

3.3.3. For most patients with refractory or relapsed HL, the treatment of choice should consist of platinum-based or brentuximab vedotin containing regimen followed by high dose chemotherapy and autologous stem cell transplantation (ASCT).[38-49]

3.3.3.1 Salvage regimens such as GDP, DICEP, ESHAP, DHAP, IGEV, ICE, B-ICE, B-ESHAP, BeGEV or BvB have been shown to reduce the disease burden and mobilize stem cells before high-dose chemotherapy and ASCT, however, no comparative trails have been done to establish the best salvage approach.

3.3.3.2. Multiple conditioning regimes have been used such as BEAM or single agent High dose melphalan.

3.3.3.3. Brentuximab vedotin as maintenance for one year is highly recommended post ASCT for high risk patient (primary refractory or patients who relapsed within 12 months or relapse with extra-nodal disease).

3.3.3.4. Post-ASCT, responding patients with residual localized PET positive consolidative radiotherapy to the active site is recommended.

3.3.3.5. Patient who experience a relapse post-ASCT have been shown to respond to the following treatment options:

3.3.3.5.1. Brentuximab vedotin [50,51]

3.3.3.5.2. Nivolumab [52,53]

3.3.3.5.3. Pembrolizumab [54]

3.3.3.5.4 Reduced-intensity conditioning allogeneic stem cell transplantation (RIC-Allo) can be considered in young, chemo-sensitive patients in good general condition.[55] However, RIC-Allo is not a standard approach in HL and should be conducted within clinical trials whenever possible or in highly selected case.

3.4. Treatment of Lymphocyte Predominant Hodgkin's Lymphoma (NLPHL)

NLPHL has similar natural history to indolent lymphomas. As the malignant cells of NLPHL consistently express CD20, addition of an anti-CD20 antibody improve treatment efficacy and the current data support the use of rituximab. [56]

3.4.1. Limited stage:

3.4.1.1. Observation is a reasonable option for completely excised lymph node.

3.4.1.2. 30 Gy ISRT alone.[57]

3.4.1.3. Combination chemotherapy (R-ABVD, R-CHOP, ABVD) 2-4 cycles + ISRT. [57]

3.4.2. Advance stage:

3.4.2.1. The preferred option is combination chemotherapy (R-ABVD, R-CHOP, ABVD) 6 cycles +/- ISRT. [57]

3.4.2.2. Single agent Rituximab. [58]

3.4.2.3. Observation is a reasonable option for selected asymptomatic patients

3.4.3. Relapsed:[58-60]

3.4.3.1. Relapsed NLPHL patients must confirmed by a new biopsy before salvage therapy is initiated, since transformation into aggressive non-Hodgkin's lymphoma must be excluded.

3.4.3.2. Individualized treatment should be considered since the disease natural history is variable.

3.4.3.3. Localized NLPHL relapses can be effectively treated with rituximab alone +/- ISRT.

3.4.3.4. Advanced disease at relapse often require a more aggressive salvage therapy including high dose chemotherapy and ASCT.

3.4.3.5. Observation is a reasonable option for selected asymptomatic patients.

3.5. Evaluate for treatment response and long term follow up

3.5.1. The preferred imaging modality for assessing response to therapy is PET/CT which is typically done after the initial 2 cycles of chemotherapy "interim", 4-6 weeks after completing the planed chemotherapy protocol, 6-8 weeks after ASCT or 9-12 weeks after completion of radiation treatment. After Completion of Treatment, patient's follow-up mainly focuses on monitoring for recurrence and late side effects in patients with HL. Patients should be encouraged to undergo counseling on issues regarding survivorship, long-term treatment effects, health habits, and psychosocial issues. Secondary cancers, cardiovascular disease, hypothyroidism, and fertility issues are the most serious late effects among long-term survivors of HL. The incidence of these late effects increases with longer follow-up time. The risk may be less with current treatment protocols compared with those used >10 years ago.

3.5.1.1. The followed scheduled post remission;

3.5.1.1.1. Every 3 months for 2 years, then every 6 months for 3 years, then annual: -

3.5.1.1.1.1. History and physical examination;

3.5.1.1.1.2. CBC, differential, ESR and LFT;

3.5.1.1.1.3. Thyroid-stimulating hormone (TSH) at least annually if patient received radiotherapy to the neck;

3.5.1.1.1.4 Annual influenza immunization.

3.5.1.1.2. Chest x-ray each visit during first 2 years, then every other visit especially for patients who previously had intrathoracic disease.

3.5.1.1.3. Mammogram for women beginning 10 years after diagnosis of HL or at age 40 years, whichever comes first.

3.5.1.1.4 Pap smear.

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