Editorial

Advances in the Management of Hodgkin's Lymphoma

Hodgkin's lymphoma (HL) is a malignant lymphoma of B cell origin. It is commonly seen in young adults, more so in males. The survival of patients with HL has improved dramatically over the past two decades as a result of treatment with combination chemotherapy (CT) and / or radiotherapy (RT).[1-2] Though the disease has been widely reported and carefully studied in the West, limited data are available from developing countries. Earlier studies from India have shown a spectrum of HL different from that reported in western studies; the important differences include - an earlier median age of onset, increased frequency of the mixed cellular (MC) histological subtype (55%-70%), presence of 'B'symptoms and advanced disease (stage III and IV) in more than 50% of patients at diagnosis.[3]

Work up for a newly diagnosed case of HL includes: complete haemogram including differential counts and ESR, urine examination, chest x-ray P/A view, liver, & renal function tests, electrolytes, serum calcium/phosphate, uric acid, serum LDH, CAT scan of chest, abdomen & pelvis and bilateral bone marrow biopsy from iliac crest. Bone involvement in HL is rare therefore, a routine bone scan is not indicated in asymptomatic patients. For patients $\geq$ 40 years of age, echo-cardiography or MUGA scan must be done to assess cardiac functions before starting on anthracycline based chemotherapy. Bone marrow involvement is infrequent in patients with early stage HL. Therefore, routine bone marrow examination is not indicated in such patients. However, in all patients with advanced stage HD, bilateral trephine BM biopsy must be done.

Recently, fluorodeoxyglucose (FDG) – positron emission tomography (PET) has become available and is being used for staging and follow up of HL patients. Compared to CT scan which requires enlargement of anatomical structures for imaging, PET relies on detection of metabolic alterations observed in cancer cells. PET has been found to be more sensitive for detection of both nodal (eg. small sized nodes) and extra-nodal (especially spleen and bone) involvement . High FDG uptake in brown fat tissue or muscle can hamper the interpretation of the head and neck and mediastinal regions. More over physiological uptake in gut and the renal collecting system can obscure the evaluation of lymphoma in adjacent nodal sites. Therefore, combination of PET with CT scan is more useful and can improve accuracy by increasing the certainty of diagnosis in difficult regions. Incorporating PET in initial staging in lymphomas results in upstaging or downstaging in 10% to 20% of patients.[4] Ann Arbor staging was routinely used in past but recently, Cotswald staging is used more commonly.

Treatment

The prognosis of patients with early stage HL is excellent with cure rates being > 90%. Extended field (EF) radiation used in the past, is no longer used now due to high relapse rate and long term toxicity. Presently, it is advisable to tailor the therapy for patients with early stage HL based on risk factors . The EORTC and the German Hodgkin's Lymphoma Study Group (GHSG) have divided the early stage into favourable and unfavourable subgroup.[5]

Treatment Groups according to the EORTC and GHSG (adapted from ref. 5)

Risk factors	EORTC	GHSG
	A large mediastinal mass	A large mediastinal mass
	B age ≥ 50 years C elevated ESR* D ≥4 involved regions	B extranodal disease C elevated ESR* D ≥3 involved regions
Early-stage favourable	CS I-II without risk factors (Supradiaphragmatic)	CS I-II without risk risk factors
Early-stage unfavourable (intermediate)	CS I-II with ≥ 1 risk factors (Supradiaphragmatic)	CS I, CS IIA with ≥ 1 risk factors CS IIB with C/D but without A/B
Advanced Stage	CS III-IV	CS IIB with A/B CS III-IV

GHSG, German Hodgkin's Lymphoma Study Group; EORTC, European Organization for Research and Treatment of Cancer. *Erythrocyte sedimentation rate (≥50 without B symptoms or ≥30 with B symptoms).

Currently, for early stage, favourable HL. most centres prefer combined modality treatment. This generally includes- 2 to 4 cycles of ABVD (adriamycin, bleomycin, vinblastine and dacarbazine) followed by involved field (IF) radiation (30 to 35 Gys). The only exception is nodular lymphocytic predominant Hodgkin's lymphoma (NLPHD), stage IA without risk factors which can be treated by lymph node excision followed by wait and watch policy or IF radiation , 20 to 30 Gys. Patients with advanced NLPHD stage IIB-IV have poor outcome and are best treated with 6-8 cycles of chemotherapy followed by IF radiation for bulky disease. For patients with early stage unfavorable (IA-IIA, intermediate category) our policy is to give 4 cycles of ABVD followed by involved field radiation. For patients with advanced HL (stage IIB, III-IV) we recommend the use of 6 cycles of ABVD or 2 more cycles after achievement of complete remission (CR). IF radiation is added for bulky disease (>10 cm or large mediastinal mass -≥ of 1/3rd of cardiothoracic ratio).

Hasenclever (1998) for the International Prognostic Factors Project on Advanced HL have identified 7 adverse prognostic factors for patients with advanced HL. These include- Serum albumin <=4g%, Hb <10.5g%, male sex, age≥45 years, stage IV disease, WBC counts >15,000/cmm and absolute lymphocyte count of <600/cmm. The presence of each factor decreases the 5 -year progression-free survival (PFS) by 7% to 8%. Patients with none of above factors had PFS of 84% compared to 42% in those with 5 or higher adverse factors.[6]

For advanced disease, use of hybrid regimens e.g. MOPP/ABVD or MOPP/ABV have been compared with ABVD in randomized trials[78]; ABVD alone is equally effective but less toxic. Recently, new multidrug chemotherapy regimens have been studied to improve response rates and to reduce late toxicity and second malignancy with no or minimal radiation. Stanford V- a seven drug combination given over 12 weeks, BEACOPP (bleomycin, etoposide, adriamycine, cyclophosphamide, vincristine, procarbazine, and prednisone) or MOPPEBVCAD (mechlorethamine, vincristine, procarbazine, prednisone, epidoxirubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine) etc.[9-14] are examples. Some of these have been compared with standard ABVD or COPP/ABVD hybrid.[11-12] Long term follow up data is now available for some of these studies; results indicate that multidrug regimens are

associated with higher complete and partial response rates but with higher toxicity. The lymphoma-free survival was improved but overall survival was not significantly different compared to ABVD or COPP/ABV hybrid. Thus, at present ABVD with limited radiation remains treatment of choice for advanced Hodgkin's lymphoma.[15]

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