Hodgkin's Disease: Kuwait Experience

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Key Words

Hodgkin's disease, treatment · Kuwait

Abstract

Objective: To describe histologic subtypes, clinical presentation and treatment outcome of Hodgkin's lymphoma in Kuwait. **Subjects and Method:** Patients older than 15 years, diagnosed with Hodgkin's lymphoma between 1980 and 1998, were included in this retrospective analysis. Data were collected using a standardized form that included demographics, histologic subtypes, clinical presentation, stage, extranodal involvement, treatment modality and follow-up. Histology reports were obtained from hospital records. **Results:** There were 83 (59%) males and 57 (41%) females. Dominant histologic subtypes were nodular sclerosis 65 (46.4%) and mixed cellularity 42 (30%). Constitutional symptoms were reported by 54 (38.6%) of the cases. Two thirds (64%) of the cases were advanced. Primary extranodal involvement included liver (8%), gastrointestinal tract (7%), lung and bone marrow (4% each). Disease-free survival according to treatment groups were: radiotherapy alone 100%, chemotherapy alone 88%, and combined modality 65%. The 5-year Kaplan-Meier estimates of overall disease-free survival was 84%. **Conclusion:** In the cohort of 137 patients with Hodgkin's disease the treatment with com-

bined radiotherapy and chemotherapy had a remarkable outcome. However, evaluation of long-term treatment complications is needed.

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Introduction

Hodgkin's disease (HD) is a relatively uncommon lymphoid malignancy but responsive to therapy with very high remission and event-free survival rates. Although Thomas Hodgkin described the disease over 160 years ago, the etiology and pathogenesis of HD remain unknown, however, an infective cause has been indirectly implicated [1]. In contrast to non-Hodgkin's lymphoma, in which all or most of the cells of the involved lymph nodes are neoplastic, the vast majority of cells forming the bulk of enlarged lymph nodes in HD are benign. In fact, the neoplastic cells of HD (Reed-Sternberg cells, RS cells), their variants, or the mononuclear cells with cytologic features of RS cells may be difficult to find. The paucity of RS cells in most cases of HD has hindered attempts to identify their cellular origin and lineage. From case to case, there are differences in the morphology of the RS cells and the composition of the cellular background that are associated with differences in patient demographics, clinical sites of disease, and natural history [2, 3].

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Table 1. Patient characteristics (n = 140 cases)

Median age (range), years	29 (15–65)
Males	83 (59%)
Females	57 (41%)
Nationality	
Kuwaitis	65 (46.4%)
Arabs	60 (42.9%)
Others	15 (10.7%)
Histologic subtypes	
Nodular sclerosis	65 (46.4%)
Mixed cellularity	42 (30%)
Lymphocyte predominance	24 (17.1%)
Lymphocyte deplete	3 (2.1%)
Unclassifiable	6 (4.3%)
Stage	
Early	51 (36%)
Advanced	89 (64%)
Bulky	
Yes	34.3%
No	65.7%
Constitutional symptoms	
Yes	54 (38.6%)
No	86 (61%)
Extranodal involvement	
Liver	8%
Gastrointestinal tract	7%
Lung	4%
Bone marrow	4%
Thyroid	0.7%
Skin	0.7%

In Kuwait lymphoma is the second and the fifth leading cancer for males and females, respectively [4]. Kuwait is a country with a population of 2.2 million, according to the 2000 year census and it has one cancer referral center. This retrospective study was designed to describe Kuwait experience in terms of pathological subtypes, presentation, treatment modalities and outcome among adult cases of HD.

Subjects and Methods

From 1980 to 1998, 140 patients with HD, aged over 15 years, were treated at Kuwait Cancer Control Center, Kuwait. In all the cases the diagnosis was proved by histology and HD was classified according to the WHO classification of lymphoid malignancies [5]. The histologic data were obtained from clinical records. Pathology slide review was carried out upon referral to our center. Three patients without slides were excluded. Immunohistochemical study was part of the routine diagnostic procedure. A standardized data extraction form that included demographic data, clinical presentation, histologic types, stage, treatment and follow-up data was used to collect

information. The follow-up for all cases ranged from 2 to 15 years. All cases had initial workup, which consisted of a detailed history, full clinical examination, biochemical and hematological profiles, chest X-ray, CT scan of the chest and abdomen, and bone marrow examination. Cases were staged clinically according to the Ann Arbor staging system [6].

Three treatment modalities were used: radiotherapy for stages IA and IIA, chemotherapy and combined therapy for advanced stages. For radiotherapy, a dose of 4,000 cGy in 20–25 fractions (range 180–200 cGy/day) in 4–5 weeks using megavoltage beam, shielding of vital structures, was given with a boost of 400–600 cGy to any nodal mass more than 5 cm in diameter. For chemotherapy the most commonly used combinations were cyclophosphamide-nitrogen mustard, oncovin, prednisone, procarbazine alternating with Adriamycin, bleomycin and vinblastin (MOPP/ABV hybrid) and Adriamycin, bleomycin, vinblastin and decarbazine (ABVD). When chemotherapy alone was unsuccessful additional radiotherapy was given at the site of residual disease. Similarly, additional radiotherapy was given to sites of initial bulky disease.

Data Analysis

Survival curves were estimated using Kaplan-Meier method. Disease-free survival and overall survival were calculated from the date of original diagnostic biopsy. The analyses were performed using SPSS software version 10.5.

Results

Patient characteristics are summarized in table 1. There were 83 (59%) males and 57 (41%) females; median age 29 years (range 15–65); 65 (46.4%) were Kuwaitis, 60 (42.9%) other Arabs and 15 (10.7%) of East Asian or European descent. Histologic subtypes were nodular sclerosis: 65 (46.4%); mixed cellularity: 42 (30%); lymphocyte predominance: 24 (17.1%); lymphocytic depletion: 3 (2.1%), and unclassifiable: 6 (4.3%). Most of the cases were advanced (IIB, III, IV, 64%) and bulky 48 (34.3%). Adenopathy was the dominant presentation and the constitutional symptoms were documented in 54 (38.6%) of the cases. Extranodal manifestations were seen in 25 (14.3%) of cases, mainly in patients with nodular sclerosis. The most common extranodal sites of involvement were as follows: liver 8%, gastrointestinal tract 7%, bone marrow 4%, lung 4%, thyroid and skin 0.7% each.

Three cases were excluded from the analysis because their treatment details were missing. Radiotherapy was used as a primary treatment method in 28 patients. This group has previously been described [7], in which Kaplan-Meier estimate of overall survival at 10 years was 100%. The relapse-free survival at 5 years was 100% and at 10 years 83%.

Chemotherapy was carried out as a primary treatment in 45 patients; combined therapy was used in patients with advanced stages. Different combinations were given:

Fig. 1. The Kaplan-Meier probability of DFS for the whole group is 64% at 5 years.

ABVD 22, MOPP/ABV hybrid 7, MOPP alternating with ABVD 3, MOPP 5, and others 8. Thirty-eight patients achieved durable remission and 7 patients relapsed upon subsequent follow-up (3 in the ABVD group, 2 in the MOPP/ABV hybrid group and 2 in the MOPP group).

In 64 cases combined modality treatment (CMT) with radiotherapy and chemotherapy was used, particularly for cases with initial bulky tumor or residual masses. However, some patients with early stage disease were treated with limited cycles of chemotherapy followed by involved field radiotherapy. Sixty-three achieved complete remission, 1 patient progressed on therapy and 9 patients relapsed upon subsequent follow-up.

Kaplan-Meier estimates of disease-free survival (DFS) are shown in figure 1. Out of 137 cases, 17 (12.4%) patients relapsed. DFS for the whole group was 84% at 5 years. DFS according to stage category is shown in figure 2. No relapses were seen in stage I. In the stage II–III category, 11 out of 82 (13%) patients relapsed with a median follow-up of 113 months. In stage IV category, 6 out of 24 (25%) patients relapsed at a median follow-up of 92 months. The DFS per treatment regimen is shown in figure 3. The 5-year DFS for those who received CMT and chemotherapy alone was 65 and 60%, respectively.

Fig. 2. DFS according to stage category. Thirty percent of the stage-IV group has relapsed at a median follow-up of 38 months.

Fig. 3. DFS according to treatment group. Patients who received CMT had advanced stages with adverse prognostic factors that resulted in lower DFS.

Discussion

HD has a characteristic bimodal age curve with one peak in early adult life (15–35 years) and a second increase in incidence at 50 years of age or older [8]. A similar pattern was noted among our population, the first peak was at 15.9 years and the second peak at 55 years, and median age was 29 years. There was a slight male predominance over females, and also predominance of nodular sclerosis subtype. More than half of the cases (64%) were at advanced stage at presentation.

In the last three decades, HD has turned from a fatal disease into one of the most curable ones. The results obtained in this study are similar to those of other studies [9, 10].

Three decades ago, MOPP was introduced in the management of advanced HD [11]. Of the original 188 patients, 84% achieved complete remission, 54% had DFS and 48% were alive at 15 years [12]. More recently, it has become clear that MOPP alone is inferior to MOPP/ABV hybrid [12–14] or ABVD [15, 16] in the control of advanced HD. Currently ABVD alone is the treatment of choice in those with advanced disease at our institution.

Recently, patients with localized presentation (CS I, II) but with unfavorable prognostic factors (systemic manifestations, high ESR, age >50, ≥ 3 sites of involvement)

have received CMT with reduced chemotherapy and radiotherapy [16, 17]. Promising results were reported by an Italian study; patients were given 4 cycles of ABVD followed by 3,600 cGy to involved sites and 3,000 cGy to uninvolved sites [17]. Similarly, the Stanford V program consisting of 12 weeks of intensive chemotherapy followed by 3,600 cGy to sites of initial bulky disease was introduced to treat advanced stage HD [18]. All of these patients were alive and disease-free. At our institution, we have recently adopted this strategy.

Adjuvant radiation therapy for advanced disease was advocated as the majority of chemotherapy relapses occur at sites of bulky disease [19, 20]. Moreover, adjuvant radiotherapy in doses less than 3,000 cGy were well tolerated and reduced local recurrences [21–23]. However, an improvement in overall survival was not demonstrated [24]. In this study, adjuvant radiotherapy was given to the majority of patients with bulky disease. A similar observation was noted in this study.

Conclusion

In the cohort of 137 patients with HD, CMT had a remarkable outcome. However, evaluation of long-term treatment complications is needed.

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