
RESEARCH COMMUNICATION

Hodgkin's Disease: Assessment of Treatment and Survival Rates in Iran

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Abstract

Background and Objective: Each year an estimated of 7,500 new cases of Hodgkin's disease are reported in the United States. It is a type of malignancy, where 75% of patients can recover and be cured with modern therapeutic approaches if presentation is in an early stage. While primary prevention is not a focus of attention, prevention of mortality is thus possible. The main objective of this investigation was to assess the current situation with the disease in Iran, with determination of 5- and 10-year-survival rates.

Materials and Methods: This retrospective, descriptive, analytical and cross-sectional study was performed on patients identified in Tabriz Shahid Ghazi hospital. The information obtained through medical files was organized and the rate of response to treatment and overall survival (OS) were computed. Resulting data were analyzed using SPSS10 and Chi-square software.

Results: Overall, there were 121 male patients (67%) and 59 females (33%). The patient age (with a median of 31.8±17.1 years) did not show any effect on survival rate. Neck masses were the most common (40%) complaint among new patients, mostly classified as stage III. Mixed cellularity (47.2%) accounted for the most common histological subtype. Complete remission was achieved with the ABVD chemotherapy regimen, included in 37.6% of overall chemotherapy regimens. The five- and 10-year-survival rates were determined to be 65 and 61.3 percent respectively.

Conclusion: Chemotherapy was a significantly more effective treatment compared to other modalities, and provided complete remission in 52.7% of patients. Overall, 5- and 10-year-survivals were shown to be highest in patients treated with ABVD and a variant of the MOPP regimen, respectively. As general conclusions, early diagnosis, on time management of the patients, and use of appropriate treatment modalities provide significant prevention of mortality in Hodgkin's disease patients.

Key Words: Hodgkin's disease - chemotherapy regimen - survival

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Introduction

Hodgkin's disease is a clonal neoplastic disease of lymphatic system with variable clinical manifestation. It is one of the first malignancies which can be cured in its early and advanced stages. This statement points out to the importance of its medical and radiation therapy evaluation in HD patients (Kaufman and Longo, 2000). Its anatomical extension and in lesser extent histological subtypes are the preliminary factors on defining the signs during presentation, prognosis and treatment of Hodgkin's lymphoma (Horning, 2001).

Significant improvement on survival of the patients has been reported by previous studies so that as many as 80% of patients affected by Hodgkin's may demonstrate complete

recovery (Kaufman and Longo, 2000). Nearly 7500 new cases of the disease, with male predominance, are diagnosed each year in the United States alone. The disease incidence is more common among whites, and its age related occurrence in developed countries provides a double peak. The first peak in incidence occurs in the third decade of the life (20-24 years) and the second one after 50 (80-84 years).

The mortality rate of the disease has decreased in the recent years so that five-year survival was increased from 40% during 1960-1963 to 78% during 1983-1988 (Kaufman and Longo, 2000). The etiology of the disease remains unknown, so that primary prevention is not feasible. The emphasis must therefore be on early diagnosis and finding the most beneficial treatment modality. Some studies have shown a genetic predisposition, with some relation between

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Hodgkin's disease and specific HLAs. Overall it presents a peripheral lymphadenopathy. The most common clinical symptom is enlarged lymph nodes in young adults, located mostly in the cervical and supraclavicular (60-80%) regions, and to a lesser extent in the upper cervical and axilla. Liver involvement in newly diagnosed cases is uncommon, but splenic involvement is frequent (Kaufman and Longo, 2000).

The aim of medical treatment is to cure the majority of the patients with minimal side effects. Although chemotherapy and radiation treatment are effective choices, their combination has been reported to present the most successful results (Horning, 2001). The radiation fields in Hodgkin's patients includes Mantle field, Para aortic field and pelvic. Routine radiotherapy of extended field type is used in a few patients, but care should be taken with this approach.

The first modern combination chemotherapy presented by Devita et al, was MOPP (Nitrogen mustard, Vincristin, Procarbazine and Prednisone) (Horning, 2001). Unfortunately, toxicity of this regimen, including infertility and second myeloid malignancies like acute myeloid leukemia and myelodysplastic syndrome, was notable. With MOPP-like regimens, such as the MVPP regimen, Vincristin is substituted by Vinblastin, and for the Chl-VPP regimen, in which Chlorambucil and Vinblastin are used instead of Nitrogen Mustard and Vincristin respectively.

An important alternative regimen is ABVD (Adriamycin, Bleomycin, Dacarbazine,) which is effective, both as a primary treatment in advanced stages, and in cases which have failed on MOPP. The only important and life-threatening adverse effect of ABVD is its lung toxicity, while treating with ABVD/MOPP or hybrid MOPP-ABVD provides lesser toxicity than that of ABVD alone, because the cumulative dose related toxicity of Bleomycin becomes smaller. Stanford research group has created (Vinblastin, Bleomycin, Metotrexate) regimens as an adjuvant treatment with radiotherapy. New treatment regimen with Doxorubicin, Vinblastin, Bleomycin, Nitrogen mustard, Etoposide and Prednisone are under intense studies (Horning, 2001).

Materials and Methods

The objective of this investigation was to assess the results of treatment and survival rate of the Hodgkin's Lymphoma in Shahid Ghazi hospital and study the relation of variables such as age, gender, location of lymph nodes, stage of the disease, blood group, etc. All of the cases of Hodgkin's lymphoma (n=180) who were referred to Shahid Ghazi hospital were reviewed. In this retrospective, descriptive, analytic and cross sectional study, special forms were designed for collecting patient's personal data, demographic information of the cases, pathological results, signs of presentation and the type of treatment used. Response to treatment, 5 and 10-year DFS (Disease Free Survival) and OS (Overall Survival) were estimated and data were analyzed using SPSS10 software and the Chi-square test.

Results

A total of 180 cases of HD, 59 female (33%) and 121 male (67%), with a median age of 31.8±17.1 years, were assessed in this study. The age range varied from 4 to 71 years. Considering the age distribution, patients were divided into six groups. The majority (26.1%) were in the third decade of life followed by those who in their second decade (24.4%). Each of A+ and O+ blood groups with an incidence of 31% were most common among 71 cases with known blood groups. Neck masses (40%), night sweating (23.3%) and fever (20%) were the most common complaints as presentation signs.

Cervical lymphadenopathy demonstrated frequent involvement (54.4%) followed by axillary lymphadenopathy (27.7%). Most of the cases were in stage III (42.7%) and the MC (mixed cellularity) histological subtype (47.2%) was most common. NC (Nodular Sclerosing) type constituted 25% of cases. Most of the cases had been treated with combination chemotherapy, and ABVD was the regimen predominantly used (Fig. 1).

Most of the patients obtained complete remission following treatment (Fig. 2). The average survival rate was estimated to be 65 months. Assessment of survival revealed 5- and 10-year survival rates to be 65 and 61.3% respectively.

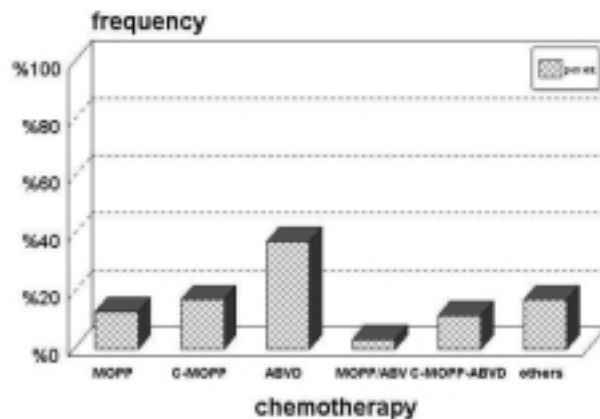


Figure 1. Frequency of the Type of Chemotherapy Used in HD Patients in the Last 10 Years

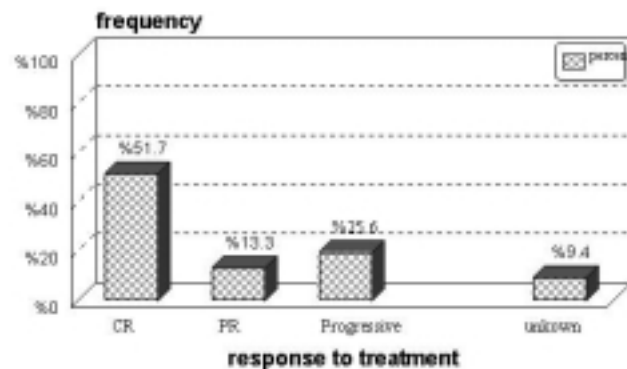
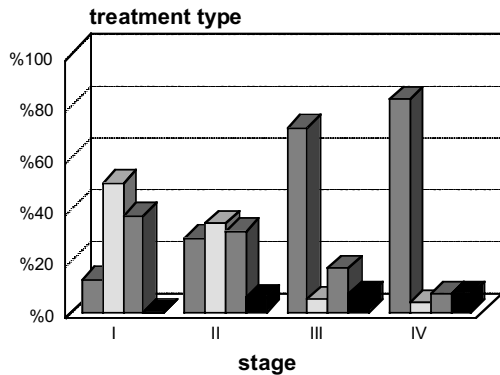


Figure 2. The Percent of Response to Treatment in the Last 10 Year

Table 1. Following data was revealed through assessment of Disease Free Survival (DFS) in patients

Period	Total No	Disease Free Survivors (%)	
5-year	103	41	(39.8)
10-year	31	9	(29.0)

**Figure 3. Assessment of Correlation between the Stage of Disease and the Type of Treatment in HD Patients in the Last 10 Years.** (Columns each from left to right: chemotherapy, radiotherapy, combined, unknown)

A total of 27 cases (15%) experienced relapse and 52.7% of the patients who were treated with combination chemotherapy entered remission. Most of the cases with stage I and II disease underwent radiotherapy while cases in advanced stages III and IV were treated with combination chemotherapy (Fig. 3). The statistical assessment showed no difference between 5 and 10-year survival rates.

Discussion

The male/female ratio (121/59) observed among our 180 Hodgkin's cases demonstrated a male predominance, with roughly twice the risk in males as in females. These findings are in line with the results of earlier studies and should encourage establishment of research programs to study genetic predispositions of males or other hormonal factors which could have causal effects on disease development. The median age of the patients was shown to be early 30's with extremes of 4 and 71 years, again similar to most studies performed in western countries. Unlike the literature, however, where the nodular sclerosing (NS) histological subtype general accounts for 60-80% and the mixed cellularity (MC) only 15-30% of cases, in this study the MC type included 47.2% and NS consisted 25% of cases, and almost half of the patients had stage III disease.

Nearly as much as 75% of patients are cured by treatment with modern chemo- and radiotherapy. The treatment strategy is selected according to the stage of the disease and prognostic factors (Fung and Nademanee, 2002). In our study, on the basis of frequency of treatmental programs, patients evaluated in four distinct groups consisting those treated with chemotherapy (51.15%), radiotherapy (14.4%), combined chemo/ radiotherapy (17.4%) and a group with

unknown mode of treatment (16.7%). Considering the type of regimen used for chemotherapy, patients were divided into five groups, most of them being treated with the ABVD regimen. Applying such chemotherapy we obtained complete remission in about 56.3% of the cases. The results of a long-term follow up in 188 patients studied in NCI (National Cancer Institution) treated with MOPP regimen, demonstrated a complete remission rate of 84%, toxic side effects being the major restriction on its application (Kaufman and Longo, 2000).

Previous studies have shown that age (i.e. older or younger than 65) and combination chemotherapy (with or without Adriamycin) could be used as prognostic factors. In other words, chemotherapy with Adriamycin-based regimen results in better survival. In our institute in Iran, Adriamycin-based combination chemotherapy is frequently used, and those patients treated with ABVD had a better 5-year survival. Ten-year OS of the patients who received different chemotherapy was estimated as 42.1%, whereas those treated with ABVD demonstrated a lower value. Even though ABVD is the preferred regimen for chemotherapy in Hodgkin's patients, on long-term follow up C-MOPP proved to be better.

According to the literature, approximately 60 percent of the patients with HD are in stage I disease at presentation, and 80-90 % of them can be cured using appropriate treatment (Ng and Mauch, 2002). Our patients had higher stages at diagnosis and the proportion of patients in stage I and II disease was low, pointing to the need for better awareness. It has been shown that for disease free survival (DFS) at stage I and II, the combined modality treatment is preferred to radiotherapy alone (Press et al., 2001). According to a Japanese study on malignant lymphoma, HD has a good prognosis, but survival of older patients is less than for younger ones. We here evaluated the patients 5-year survival in two age groups of lower and higher than 50-years. The outcome was 85.1 and 14.9 percent respectfully for young and old, showing a significant difference ($p > 0.05$). Factors such as inadequate treatment, lack of ability to tolerate chemotherapy, and co-association with other disease affected survival rate and resulted in a poor outcome.

Evaluation of the response to treatment is important for determining the treatment strategy. While high dosage chemotherapy is required for refractory HD, discontinuing the aggressive treatment is suggested for patients gaining complete remission. Gallium 67 scintigraphy has been utilized to evaluate the clinical results at the end of chemotherapy, especially mediastinal responsiveness. It has been shown that the patients with positive values on gallium scans relapse more than those who had negative scans, the DFS and OS both differing significantly ($p < 0.05$) (Landgren et al., 2002).

The importance of PET (Positron Emission Tomography) scanning has been demonstrated for assessing the residual disease after treatment, where patients with positive PET scan had relapse rate of 62.5%, while it was only 4% in

those with negative PET scan. Thus it appears that PET scanning is an excellent non-invasive procedure for evaluating residual disease after treatment and for predicting relapse in patients with complete remission and resolved residual masses (Brenot-Rossi et al., 2001).

Conclusion

This project was conducted at Shahid Ghazi hospital of Tabriz to provide an overall assessment of treatment results and survival status of patients affected by Hodgkin's disease. Those in stage I and II were treated with radiation, but chemotherapy was the main modality for stage III and IV disease.

Most of the cases were in stage III at presentation and received ABVD regimen chemotherapy. Median survival was 65 months. Five and ten-year overall survival rates were 65%, 61.3% and five and ten-year disease free survival rates were estimated to be 39.8% and 29% respectively. The obtained results showed that the cases who received chemotherapy alone demonstrated a higher complete remission rate compared with those treated with other modalities. Complete response with the ABVD regimen was significantly better than with the other chemo regimens although ten-year OS in cases who had been treated with C-MOPP was shown to be the best. This would imply recommendation of this regimen for longer duration after completion of initial therapy, but this needs further attention and follow-up programs.

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