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Hodgkin lymphoma novel management; A 20-year retrospective study

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Abstract

Introduction: Hodgkin lymphoma (HL) is one of the pediatric and adult cancers, with the treatment of chemotherapy alone or combined with radiotherapy.
Objectives: We aimed to evaluate the consequences and outcomes of the treatment with or without radiotherapy in a retrospective study.
Patients and Methods: We carried out a cross-sectional retrospective study by referring and reviewing records for all patients admitted to Motahari hospital with HL diagnosis from 1995 to 2016. The Ann Arbor staging system classified the staging of disease.
Results: Totally, 35 patients enrolled in our study that 54.3% were female, and 45.7% were male patients. The mean age of patients was 10.08±6.38 years. 10 (28.6%) cases classified in stage 1, 13 (37.1%) case in stage 2, 9 (25.7%) cases in stage 3, and 3 (8.6%) cases in stage 4. 30 patients (85.7%) were treated by chemotherapy and 5 (14.3%) patients with chemotherapy and radiation combination. In our study, the overall survival was 97.1% of patients treated with chemotherapy alone, and one patient died due to drug side effects. That is comparable with other studies that treated patients with chemotherapy and radiotherapy.
Conclusion: According to our findings, chemotherapy without radiotherapy as initial treatment in HL would have similar results to concomitant radiotherapy and chemotherapy, so considering the cost and harms of radiotherapy, we suggest a limitation of radiotherapy to patients with resistant diseases that do not respond to chemotherapy solo-protocols.

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Introduction

Hodgkin lymphoma (HL) is a type of lymphocyte cancer, previously known as Hodgkin's disease, described by Thomas Hodgkin and contains 6% of childhood cancers. In the United States, the incidence of HL is age-related and highest among adolescents aged 15 to 19 years; then, children aged 10 to 14 years, 5 to 9 years, and neonates to 4 years have approximately lower rates, respectively. For adolescents, the incidence rates are similar in developing countries, with a much higher incidence rate in childhood (1,2). There are theories about the association of the HL with Epstein Barr virus infection and/or activation of the virus in the body (3,4). Also, the risk of HL in close relatives of patients with HL is approximately three- to fivefold greater than the average population (5,6). Patients with primary immune deficiencies or individuals with HIV/AIDS and solid organ transplantation have an increased risk of HL (7-9). Due to the 2018 age-standardized statistics of WHO, HL's incidence and mortality rates are 0.97 and 0.3 per 100 000, respectively, with an approximately 5-year prevalence of 276 000 patients worldwide. In Iran, the age-standardized incidence and mortality rates are 1.3 and 0.71, respectively (10,11).

Key point

Chemotherapy without radiotherapy as initial treatment in Hodgkin lymphoma would have similar results to concomitant radiotherapy and chemotherapy.

Lymphadenopathy, mediastinal mass, and systemic complaints are common signs and symptoms of the HL in children, but 80%-85% of the patients may present with only lymph node and/or splenic enlargement. Painless lymphadenopathy that feels rubbery and more firm than inflammatory adenopathy, a mediastinal mass on chest radiograph, digital clubbing and painful hyperostosis of tubular bones (rarely in intrathoracic HL), nonspecific systemic symptoms including

fatigue, anorexia, and weight loss, fever >38°C, night sweats, hepatic and/or splenic enlargement may be present in patients with advanced-stage HL (12,13).

Generally, the treatment starts based on subtype, staging, response to the therapy, pathological diagnosis, and grading. Traditionally, management contains a combination of chemotherapy and radiotherapy. Due to high cure rates for HL and substantial secondary side effects of MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) - ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) therapies, new guidelines aim to reduce therapy (eliminate radiotherapy) in patients with lower-stage disease or disease rapidly responsive to chemotherapy (14-16). Therefore, most of the new studies prioritize the safety of the patients. Previously, radiotherapy was used extensively in the treatment of HL Due to progress in chemotherapy programs, and this use has been reduced over time. Radiotherapy-related complications such as hypothyroidism, secondary malignancies, growth retardation, and hypogonadism are more common in HL (17-20).

Objectives

This study aims to assess pediatric HL treatment's clinical and pathological manifestations in children with HL referred to Motahari pediatric center of Urmia in a 20-year retrospective study.

Patients and Methods

Study design

In this descriptive-analytical study, all patients with Hodgkin's lymphoma treated in the pediatric oncology department of Urmia University of Medical Sciences from 1996 to 2016 (20 years) were examined. Pathological subtypes of patients were classified according to who classification, according to the Ann Arbor staging system (29,30). Radiography, computed tomography (CT) or proton diffusion tomography (PET-CT), and bone marrow aspiration were used to determine the stage of the disease chest. The type of treatment (chemotherapy with or without radiotherapy) was recorded. Survival response rates have been reported for patients at different stages. In our study, the patients treated with the COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)-ABVD chemotherapy regimen and patients with other protocols were excluded from the study. The response rate and 5-overall survival in this study were investigated. Complete remission is defined as the elimination of all manifestations of the disease. Partial remission is defined as a tumor regression of more than 50%. The overall survival was calculated based on lymphoma diagnosis until death, failure to respond, or the last follow-up date.

Statistical analysis

The mean and standard deviation were used for descriptive statistics, qualitative variables, the percentage of frequency, and quantitative variables. Survival was estimated using the Kaplan-Meier method, the log-rank test was used to determine the prognostic factors, and COX regression analysis was performed to identify independent predictor factors. The significance level for all tests was <0.05, and all data analysis was performed using SPSS version 26 software.

Results

In our study, 37 patients entered the study based on the study's criteria. One of the patients was excluded from receiving the study due to unusual chemotherapy courses, and the other one due to the incompleteness of the file. A total of 35 patients were examined. The duration of treatment, the duration of follow-up, and some paraclinical characteristics of patients were evaluated in Table 1.

Age and genders

There were 19 (54.3%) males and 16 (45.7%) females between 3 and 16 years and a mean age of 10.58 ± 3.08 years. Three cases (8.6%) of the children were under five. The mean age of the boys in our study was 9.07 ± 3.86 years, and the mean age of the girls was 11.34 ± 2.83 years, but no statistically significant difference was observed between the sexes in terms of age ($P = 0.07$).

Pathology subtype

To our study results, 14 cases (40%) of lymphocyte predominant HL, 10 cases (28.6%) of nodular sclerosing

Table 1. Clinical and paraclinical characteristics of the patients

Variable	Unit	Mean (SD)	Range
Treatment duration	Day	430.69 (356.53)	25-2005
Follow-up duration	Day	1026.25 (740.06)	20-2720
LDH	U/L	512.13 (192.45)	122-1000
Ferritin	ng/mL	96.95 (98.66)	16.8-435
ESR	mm/h	35.41 (33.84)	1-146
Hemoglobin	g/dL	11.01 (2.38)	3-14.9
Platelet	$\times 10^3/\mu L$	363.805 (173.219)	76-825
WBC	$\times 10^3/\mu L$	12.130 (9.792)	0.82-76.99

LDH; Lactate dehydrogenase, ESR; Erythrocyte sedimentation rate, WBD; White blood cell.

HL, and 11 cases (31.4%) with mixed cellularity HL were reported.

Primary manifestation

Our study investigated the initial manifestation patients were referred to Motahari pediatric center. The most common complaints referred to the center were cervical lymphadenopathy in 22 cases (62.9%), 4 cases (11.5%) with abdominal lymph node involvement, 3 cases (8.7%) with abdominal and cervical involvement simultaneously, 2 cases (5.6%) mediastinal and neck involvement simultaneously, one case mediastinal involvement (2.8%), one case of inguinal lymphadenopathy (2.8%), one case of abdominal and axillary involvement (2.8%), and one case of simultaneous involvement of abdomen, mediastinum, and neck (2.8%).

Metastasis

No metastasis was reported in 27 patients (75%). In 3 cases (8.3%), liver involvement, 2 cases (5.6%), splenic involvement, one case (2.8%), both liver and spleen involvement, two cases (5.6%), lung involvement, and in one case (2.8%), bone involvement was observed.

Treatment type

In our study, 30 patients (85.7%) received only chemotherapy, and 5 (14.3%) patients were simultaneously treated with radiotherapy and chemotherapy. Our study showed that one case (2.9%) of patients had only two chemotherapy courses, one patient had three chemotherapy courses (2.9%), and the rest had four chemotherapy courses. In our study, patients were evaluated based on the type of treatment (single chemotherapy, chemotherapy, and radiotherapy) separately, which showed no significant difference in the type of treatment and the stage of the disease (P=0.339).

Stage, survival and response to treatment

The study results indicated that the 5-year overall survival of patients was 97.1% in patients treated with chemotherapy alone, and one patient (2.9%) died of chemotherapy side effects. Thirty-four patients (97.1%) were also alive. In the Ann Arbor staging system, 10 cases (28.6%) of patients in stage 1, 13 cases (37.1%) in stage 2, 9 cases (25.7%) in stage 3, and 3 cases (6.8%) of patients were in stage 4 of the lymphoma. The overall survival of patients in the low-risk stages (1 and 2) was 95.7% and in the high-risk stages (3 and 4) was 100%, which did not show a statistically significant difference (P=0.65). The overall response to treatment was 94.2%, and in one case, the patient did not respond to initial chemotherapy and underwent radiotherapy and chemotherapy. The overall response to treatment based on the stage of the disease did not differ significantly in the study (P=0.36). The event-free survival rate was not significantly different in our study based on the stage of the disease (P=0.36). In low-risk stages (1 and 2), this rate was 85.7%, and in high-risk stages, it was 91.7%. Our study did not significantly differ from the event-free survival based on the pathology subgroup (P=0.957). Also, the event-free survival did not differ based on the presence or absence of metastasis (P=0.620). However, event-free survival was assessed based on the initial manifestation of the disease, and patients whose initial manifestation was cervical mass had significantly higher event-free survival rates (P=0.011).

Relapse

Among the patients studied, 4 cases (12.1%) relapsed after the initial chemotherapy response, thereby radiotherapy was added to chemotherapy. The event-free survival rate during follow-up was 87.9%. The duration of the disease-free period in patients who had relapsed was 6.11±4.3 months.

Discussion

Hodgkin's lymphoma (HL) is a relatively rare malignancy in the pediatric population but accounts for almost 40% of all childhood lymphomas and is the most common malignancy in children and adolescents. HL is sensitive to chemotherapy and radiotherapy; in fact, HL was the first cancer to be treated with radiation therapy alone or combined with several chemotherapeutic agents (21, 22). In the present study, the mean age of the patients was about ten years. Epidemiological studies show that HL is less common in children under five, so it is about 5% in developing countries, which is consistent with our study (23-25). In our study, 19 of the patients (54.3%) were male patients, and in general, the prevalence of HL was higher among boys and at an early age, it was reported as high as 3:1, but with increasing age and in adolescents its rate gets equal in both sexes. Previous findings in developing Asian and African countries show that the initial peak of the disease in boys occurs at a younger age due to early infections in these areas. Previous studies have shown a link between HL and low family income, low socio-economical class socioeconomic status, and high family members, all risk factors for infection (26). In our study, most patients were diagnosed in the early stages of the disease (65% were in stages 1 and 2 of lymphoma). In developed countries, about 75% of patients are diagnosed with lymphoma in the early stages (1 and 2), however in developing countries, about half of patients develop advanced stages of the disease. This can be rooted in the late diagnosis, or there may be a delay in referring patients to oncology centers (26,27). In our study, a study of HL subtype in patients showed that 14 cases (40%) of lymphocyte predominant HL and, 10 cases (28.6%) of nodular sclerosing HL, 11 cases (31.4%) were mix cellularity. In a study in which Sherief et al (26), reported Mix cellularity accounted for more than 50% of cases, the

lymphocyte predominant and nodular sclerosing subtypes had subsequent degrees of prevalence among subtypes, respectively. However, several studies in Europe have shown that nodular sclerosing is the most common type, regardless of age (26, 27). The most common type of HL in developing countries is mix cellularity, which is more common in younger children and boys and often presents as a more advanced disease. These features may be related partly to the etiological role of Epstein-Barr virus in HL pathogenesis (27). In our study, the overall survival of patients was 97.1%, and one died due to drug side effects. The overall survival of patients in the low-risk stages (1 and 2) was 95.7% and in the high-risk stages (3 and 4) was 100%. The overall response to treatment was 94.2%, and in one case, the patient did not respond fully to treatment and underwent radiotherapy and chemotherapy. The survival rate of the event during the follow-up period was 87.9%. In the study of Sherief et al (26), 59 children were 3-8 years old, with a total overall survival rate and event-free survival was 96.6% and 84.7%, respectively. Overall, event-free survival in their study was slightly lower than ours. However, in Sherief et al study, the children with the early stages of disease (1 and 2) underwent 2100 cGy, and the higher stages underwent 3500 cGy radiotherapy, while in our study, only five cases (16.7%) of patients treated with radiotherapy and chemotherapy simultaneously so it may affect the rate of patient's survival. Based on our results, chemotherapy without radiotherapy as initial treatment in HL would have similar concomitant radiotherapy and chemotherapy results, except that the patient is protected from known side effects of radiotherapy, such as secondary radiotherapy malignancy and organ failure (28). In another study conducted in Turkey by Uysal et al, the overall survival of patients was 89%, and event-free survival was 72% (29), which was lower than our study. In the study of Uysal et al, patients in the early stages of the disease (stages I and II-A) were treated with four courses of ABVD regimen. Patients with stage II-B and III diseases were treated with six ABVD courses. Patients with stage IV disease were treated with eight ABVD courses. Patients with recurrence were treated with four COPP-ABV courses. The main difference between the study by Uysal et al and our study were how patients were treated. In our study, the chemotherapy regimen that treated the patients was COPP-ABVD, the most common treatment regimen (30). Our study also showed that treatment with this chemotherapy regimen is satisfactory. In other studies in other countries, this treatment has been more effective than other regimens, and its toxicity has been assessed as optimal (30). In our study, only one patient died from drug complications. According to our department guidelines, children were treated with four courses of COPP-ABVD. At the end of the third stage, chemotherapy was evaluated in response to treatment; in case of recurrence or failure to respond, children will be treated with radiotherapy. It seems better for patients to undergo combination therapy if recurrence occurs. Our study demonstrated that patients with cervical mass had higher overall survival. It may be due to early diagnosis in patients with cervical mass due to early diagnosis by parents, which can prevent the progression of the disease and delay treatment. Finally, according to our findings, chemotherapy without radiotherapy as initial treatment in HL would have similar results of concomitant radiotherapy and chemotherapy, so with consideration of cost and harms of radiation therapy, we suggest a limitation of radiation therapy to patients with resistant disease that do not respond to chemotherapy solo-protocols.

Conclusion

According to our findings, chemotherapy without radiotherapy as initial treatment in HL would have similar results to concomitant radiotherapy and chemotherapy, so considering the cost and harms of radiotherapy, we suggest a limitation of radiotherapy to patients with resistant diseases who do not respond to chemotherapy solo-protocols.

Limitations of the study

This study is restricted due to the limited number of patients enrolled for final analysis, despite 20 years of retrospective assessment.

Authors' contribution

Conceptualization: Farid Ghazizadeh, Mehran Noroozi, Amin Sedokani.
Data curation: Javad Rasouli, Amir Ebadpour, Amin Sedokani.
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Investigation: Farid Ghazizadeh, Amin Sedokani.
Methodology: All authors.
Resources: All authors.
Supervision: Farid Ghazizadeh, Amin Sedokani.
Validation: Farid Ghazizadeh.
Visualization: All authors.
Writing–original draft: Farid Ghazizadeh, Mehran Noroozi, Amin Sedokani.
Writing–review & editing: All authors.

Conflicts of interest

There is no kind of conflict of interest in this study to declare.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki. This study was observational, and there was no cost or intervention for the patients, and the data were collected from medical records. The patients' information remained confidential. All of the stages of study (proposal, design, and performance) were under observation and approval of the ethical committee of Urmia University of Medical Sciences (IR.UMSU.REC.1396.215). The authors have observed ethical issues (including plagiarism, data fabrication, and double publication). The patients' legal guardian gave the consent to publish.

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