Hodgkin Lymphoma Management; A 20-year Retrospective Study

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Abstract

Object: Hodgkin lymphoma (HL) is one of the pediatric and adult cancers, with a cure rate of over 90% and high long-term survival rates by treatment with chemotherapy alone or combined with radiotherapy (RT). However, survivors of pediatric HL are at high risk of secondary cancers and cardiovascular disease due to treatment. Considering the complications of RT, we aimed to evaluate the consequences and outcomes of the treatment with and without RT in a retrospective study in the pediatric oncology department of Urmia medical sciences university.

Method: We carried a cross-sectional retrospective study by referring and review of records for all patients admitted in Motahari hospital with HL diagnosis from 1995 to 2016. The incomplete records and taking chemotherapy out of protocol were our exclusion criteria. The staging of disease was classified by the Ann Arbor staging system.

Results: 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 who treated with chemotherapy alone and one patient died due to drug side effects. That is comparable with the result of other studies that treated patients with chemotherapy and radiotherapy.

Conclusion: According to our findings chemotherapy without radiotherapy as initial treatment in Hodgkin lymphoma 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.

Introduction

Hodgkin lymphoma (HL) is a type of lymphocyte cancers, previously known as Hodgkin disease, described by Thomas Hodgkin and contains 6% of childhood cancers. In the United States, the incidence of HL is age-related and is the 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 (1-3). There are theories about the association of the HL with Epstein Barr virus infection and/or activation of the virus in the body (4, 5). Also, the risk of HL in close relatives of patients with HL is approximately three- to fivefold greater than the normal population (6-9). Patients with primary immune deficiencies or individuals with HIV/AIDS and solid organ transplantation have an increased risk of HL (10-14). Due to the 2018 age-standardized statistics of WHO the incidence and mortality rates of HL, are 0.97 and 0.3 per 100,000, respectively, with the approximately 5- year prevalence of 276,000 patients all

around the world. In Iran, the age-standardized incidence and mortality rates are 1.3 and 0.71 respectively (15, 16).

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 periostosis 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 (17-19).

generally, the treatment based on subtype, staging, response for the therapy, pathological diagnosis, and grading. Traditionally, management consists of a combination of chemotherapy and radiotherapy. Due to high cure rates for HL and substantial secondary side effects of therapies of MOPP[1]-ABVD[2], new guidelines aim to reduce therapy (eliminate radiotherapy) in patients with lower-stage disease or disease rapidly responsive to chemotherapy (20-22). So, most of the new studies, prioritize the safety of the patients. Previously, radiotherapy was used extensively in the treatment of the HL. Due to progress in chemotherapy programs, this use has been reduced by time. Radiotherapy related complications such as hypothyroidism, secondary malignancies, growth retardation, and hypogonadism are more common in Hodgkin lymphoma (23-28).

In this study, we have aimed to assess the clinical and pathological manifestations of pediatric Hodgkin lymphoma treatment in children with Hodgkin lymphoma, referred to Motahari pediatric center of Urmia in a 20-year period retrospective study.

Material And Methods

In this descriptive-analytical study, all patients with Hodgkin's lymphoma who have been 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. The patient's staging was according to the Ann Arbor staging system (29, 30). To determine the stage of the disease chest radiography, computed tomography (CT) or proton diffusion tomography (PET-CT), and bone marrow aspiration were used. The type of treatment (chemotherapy with and without radiotherapy) was recorded. Survival response rates have been reported for patients at different stages. In our study, the patients treated with the COPP[1]-ABVD chemotherapy regimen, and patients with other protocols were excluded from our 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 the date of diagnosis of lymphoma until death or failure to respond or the last follow-up date.

Data Analysis

For descriptive statistics, qualitative variables, the percentage of frequency, and quantitative variables the mean and standard deviation were used. Their parametric was used. Survival was estimated using the Kaplan-Meier method. the Log-rank test was used to determine the prognostic factors. COX regression analysis was performed to identify independent predictor factors. To judge the level of significance for all tests was <0.05. All data analysis was performed using SPSS

V.26 software.

Ethical Statement

This study was an observational study and there was no cost or intervention for the patients, and the data was collected from medical records. Patients information remained confidential. All of the stages of study (proposal, design and performance) was under observation and approvement of the ethical committee of Urmia University of Medical Sciences (IR.UMSU.REC).

Results

In our study, 37 patients entered the study based on the criteria for entering the study. 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 Sex

There were 19 (54.3%) male and 16 (45.7%) female with an age range between 3 and 16 years and a mean age of 10.58±3.08 years. Three cases (8.6%) of the children were under 5 years of age. 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

As our study results; 14 cases (40%) of Lymphocyte predominant HL, 10 cases (28.6%) of Nodular sclerosing HL, and 11 cases (31.4%) with Mixed cellularity HL reported.

Primary Manifestation

In our study, the initial manifestation with which patients were referred to Motahari pediatric center was investigated. 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%) 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 treated with radiotherapy and chemotherapy simultaneously. The results of our study showed that 1 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 that there was no significant difference in the type of treatment and the stage of the disease (P=0.339).

Stage, Survival, and Response to Treatment

The results of the study indicated that the 5-year overall survival of patients was 97.1% in patients who treated with chemotherapy alone and one patient (2.9%) died for chemotherapy side effect. 34 patients (97.1%) were also alive. As … 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) were 95.7% and in the high-risk stages (3 and 4) were 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 then chemotherapy. The overall response to treatment based on the stage of the disease did not differ significantly in the study (P=0.36). The rate of event-free survival 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%. the event-free survival based on the pathology subgroup was not significantly different in our study (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%) had a relapsed after initial response to chemotherapy so radiotherapy was added to chemotherapy. The event-free survival rate during follow-up was 87.9%. 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. In all age groups, HL is sensitive to chemotherapy and radiotherapy; in fact, HL was first cancer to be treated with radiation therapy alone or in combination with several chemotherapeutic agents (31, 32). In the present study, the mean age of the patients was about 10 years. Epidemiological studies show that HL is less common in children under 5 years of age so that in developing countries it is about 5%, which is consistent with our study (33-35). 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. Overall, previous findings in developing Asian and African countries show that the initial peak of the disease in boys occurs at a younger age, which can be due to early infections in these areas. Previous studies have shown a link between HL and low family income, low socioeconomical class socioeconomic status, and high family members, all of which are risk factors for infection (36). 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), but in developing countries, about half of patients develop advanced stages of the disease. The reason for this can be rooted in the late diagnosis or there may be a delay in referring patients to oncology centers (35, 36). 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, (36) 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 (36, 37). 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 form of the disease. These features may be related in part to the etiological role of Epstein-Barr virus (EBV) in HL pathogenesis (37). In our study, the overall survival of patients was 97.1% and one patient died due to drug side effects. The overall survival of patients in the low-risk stages (1 and 2) of patients was 95.7% and in the high-risk stages (3 and 4) were 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 then chemotherapy. The survival rate of the event during the follow-up period was 87.9%. In the study of Sherief et al. (36), 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 our study, but 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 patients survival. Based on our results, chemotherapy without radiotherapy as initial treatment in Hodgkin lymphoma would have similar results of concomitant radiotherapy and chemotherapy, except that the patient is protected from known side effects of radiotherapy, such as secondary malignancy and organ failure (38). In another study conducted in Turkey by Uysal et al, the overall survival of patients was 89% and event-free survival was 72% (39), which was lower than our study. In the study of Uysal et al, patients on 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 Uysal et al study and our study was how patients were treated. In our study, the chemotherapy regimen with which the patients were treated was COPP-ABVD, the most common treatment regimen in patients (40). 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 (40). In our study, only one patient died from the effects of drug complications. As our department guidelines, children were treated with 4 courses of COPP-ABVD. At the end of the third stage, chemotherapy was evaluated in terms of response to treatment in case of recurrence or failure to response children will be treated with radiotherapy. In general, it seems better for patients to undergo combination therapy if recurrence occurs. our study demonstrated that patients with cervical mass had a 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.

Conclusion

According to our findings chemotherapy without radiotherapy as initial treatment in Hodgkin lymphoma 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.

Declarations

Conflict of Interest

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

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Clinical and paraclinical characteristics of the patients

Variable	Unit	Mean	Standard Deviation	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	gr/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