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CLINICAL PROFILE AND TREATMENT OUTCOMES OF CLASSICAL HODGKINS LYMPHOMA - SINGLE CENTRE EXPERIENCE

Oncology

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ABSTRACT

Background: Classical Hodgkins lymphoma is one of the common hematological malignancies . With the advent of multiagent chemotherapy , radiotherapy in the frontline therapy and autologous stem cell transplantation in the relapsed setting , the overall survival of classical hodgkins lymphoma patients have improved . We performed this study to analyse the clinical profile , treatment outcomes and survival data for patients treated for cHL in our centre. **Methodology:** A study sample from a database of patients treated at a tertiary care centre in South India between January 2016 and december 2018 was analysed retrospectively. A total of 42 cHL patients were included in the study. Information regarding the patient , tumor characteristics , details of upfront treatment , salvage chemotherapy and follow up details were collected retrospectively. The collected data were analysed with IBM SPSS Statistics for Windows, Version 29.0.To describe about the data descriptive statistics , frequency analysis, percentage analysis were used for categorical variables and the mean and S.D were used for continuous variables. To find the overall Survival and progression free survival Kaplan-Meier curve with Log-rank method was used. **Results:** The median age is 21 years (range : 13 - 69 years) .Male to female ratio is 1.2:1 . The most common histology is nodular sclerosis (50%).28.6% of patients had early disease(stage 1 and 2) and 71.4% of patients had advanced disease .The most common presentation is lymphadenopathy (83%) , followed by fever(28.5%), loss of weight(14.2%) and loss of apetite(7.1%) .73.8% of the patients received ABVD ,11.9% received ABVD/BEACOPP , 4.6% received EBVD , COPP/ABV and 2.3% received CEPP as frontline chemotherapy.21% of patients received radiation as a form of combined modality therapy and 11.9% of patients received radiation at the end of frontline chemotherapy for residual disease .The median follow up is 67 months .The 5 year overall survival is 88.1% and 5 year progression free survival is 52.4% . The covariates that were found to be prognostic for survival is age(P=0.003) and stage of the disease(P= 0.04) . The covariates that were prognostic for PFS were age of the patient (P=0.003) , stage of the disease (P=0.002) and bone marrow involvement (P = 0.002) .47% (20) of patients relapsed following frontline chemotherapy. The most common salvage chemotherapy used was ICE(70%) followed by GDP(60%) and DHAP(35%).The median salvage chemotherapy received in relapsed setting is 2 (range 1 - 4) . 8 patients (40%) underwent ASCT as consolidation post salvage chemotherapy and 5 patients received RT to residual disease post salvage therapy .One patient relapsed post autologous stem cell transplant .2 patients received only palliative chemotherapy in view of lack of fitness to salvage therapy. **Conclusion:** The 5 year overall survival and 5 year PFS are only 85% and 52% respectively in our centre. Survival is very low in elderly HL patients .So better frontline chemotherapy is required especially in the elderly population. Delayed presentation to oncologists and lack of accessibility and affordability to standard of care drugs may be reasons for poorer survival in our population.

KEYWORDS

stem cell transplantation, salvage chemotherapy, relapse, radiation, chemotherapy

INTRODUCTION

Hodgkins lymphoma is a common hematological malignancy with more than 82,000 cases reported globally in 2022 as per globocan data [1] .It is the most common cancer among adolescents aged 15 to 19 years [2] . It has a bimodal distribution with a second peak after 55 years of age. It constitutes 11% of all lymphomas . HL is classified into two major types: classical HL (cHL) and nodular lymphocyte-predominant HL(NLPHL), accounting for 95% and 5% of all HL cases, respectively .Classical HL is further subdivided into four major histological subtypes: nodular sclerosis, lymphocyte-rich, lymphocyte-depleted, and mixed-cellularity [3]

Hodgkins lymphoma has an excellent prognosis with cure rate of more than 80 percent in patients less than 60 years of age [4] .However in LMIC countries the mortality is higher than western population [5] due to delayed presentation of patient ,financial crises and lack of access to modern therapeutics .We performed this retrospective study the clinical profile and treatment profile of Classical HL patients treated in our centre.

MATERIALS AND METHODS

A study sample from a database of patients treated at Department of medical oncology , Madras Medical College , a tertiary care centre in South India between January 2016 and december 2018 was analysed retrospectively. A total of 42 cHL patients were included in the study . Information regarding the patient , tumor characteristics , details of upfront treatment , salvage chemotherapy and follow up detail were collected retrospectively.

Inclusion Criteria :

All patients above the age of 12 treated in our centre for CHL were included in the study .

Patients treated in other instituition and referred to our centre for salvage chemotherapy or stem cell transplantation were also included.

Exclusion Criteria:

Patients who didnt complete the treatment and defaulted during evaluation or treatment Patient profiles with missing data .

Patients with NLPHL histology was also excluded .

Treatment Protocol :

The diagnosis of cHL was confirmed by either excision biopsy or core needle biopsy specimen.

Staging was done as per the Lugano modification of Ann Arbor staging system [6] .Either PET CT or CT neck , chest ,abdomen and pelvis was used for staging.Bone marrow examination was not done as a routine staging procedure if petct was done for the patient [7].

Stage 1 and stage 2 cHL patients (early CHL) were classified into favourable and unfavourable as per NCCN criteria [8] . Presence of B symptoms , elevated ESR , bulky disease and involvement of three or more lymph node areas are risk factors for unfavourable disease .

Early favourable disease was treated by combined modality treatment with 2 cycles of ABVD and 20gy of RT as per HD10 trial [9] .Early stage unfavourable disease was treated with 4 cycles of ABVD and 30gyRT as per EORTC - GELA H8 trial [10]. Stage 3 and stage 4 patients were labelled as advanced disease . Advanced disease was treated with 2 cycles of ABVD followed by interim PETCT. Patients who were PETCT negative on interim PET were treated with 4 more cycles of ABVD . Patients with positive interim PETCT was treated with 4 cycles of escalated BEACOPP as per Rathl trial [11] but de escalation was avoided in the pet negative arm as per instituition protocol . At the end of treatment , PETCT was taken and if end of treatment PETCT has focal residual disease more than 2.5 cm was treated with consolidation RT. Response assessment with PET CT at interim and end of treatment were done as per lugano criteria 2014 [6]. Patients with known cardiac diaease was treated with EBVD and

patients more than 60 years or with pre existing lung disease were treated with AVD as per instituition protocol . Elderly patients with poor PS were treated with CEPP as oral metronomic chemotherapy in a palliative intent [12]. At the end of treatment if PET CT is negative , patient was followed up regularly with history , clinical examination and imaging as per NCCN guidelines [8]

If end of treatment PETCT was positive , biopsy was taken from suspicious lesion and if positive for residual disease was treated as primary refractory cHL. Patients who relapsed during follow up period were labelled as early or late relapse based on a cut off period of 12 months after end of initial treatment. Relapsed patients were again staged as per lugano modification of Ann Arbor classification . Early stage at relapse especially if they relapsed late were treated with salvage chemotherapy alone plus consolidation RT for residual disease if not received received initially [13] . Advanced disease at relapse , early stage with early relapse and primary refractory disease was treated with salvage chemotherapy and autologous stem cell transplantation [14] . Patients who were not eligible for autologous transplantation due to lack of fitness or lack of insurance were treated with consolidation RT for residual disease if RT not received at that site initially .

Statistical Methods:

The collected data analysed with IBM SPSS Statistics for Windows, Version 29.0.(Armonk, NY: IBM Corp).To describe about the data descriptive statistics , frequency analysis, percentage analysis were used for categorical variables and the mean and S.D were used for continuous variables. To find overall survival and PFS Kaplan-Meier curve with Log-rank method was used.

OUTCOMES Definition:

Complete response (CR) , Partial response (PR) , Stable disease (SD) and progressive disease (PD) were defined as per lugano criteria [6].

Overall survival (OS) was calculated from the date of diagnosis to the date of death or last contact. Progression free survival (PFS) was defined as time from start of treatment till relapse or PD, no CR at the end of first-line treatment, or death due to any cause, loss to follow-up with disease.

RESULTS

Sociodemographic Characteristics :

The median age is 21 years (range : 13 -69 years) .There was an early peak in young adults aged 13 to 20 years with a second peak at a later age group above 50 . 23 patients were male and the male to female ratio is 1.2:1.The most common histology is nodular sclerosis (50%), followed by cHL - non specified (30.9%) and mixed cellularity (16.6%) .Only one patient had lymphocyte depleted histology and none of the patients had lymphocyte rich histology . 28.6% of patients had early disease(stage 1 and 2) and 71.4% of patients had advanced disease . 45.2% of patients had stage 4 disease.The most common presentation is lymphadenopathy (83%) , followed by fever(28.5%) , loss of weight(14.2%) ,loss of apetite(7.1%) and dyspnoea(7.1%).

Table 1: Baseline Characteristics Of The Patients.

Parameter	Value
Age at diagnosis, year(median; range)	21 years (range: 13-69 years)
Sex	N(%), N=42
Males	54% (23)
Females	46% (19)
Histology	
- Nodular Sclerosis	50% (21)
- cHL - Non Specified	30.9% (13)
- Mixed Cellularity	16.6% (7)
- Lymphocyte Depleted	2.4% (1)
- Lymphocyte Rich	None
Disease Stage	
Stage 1	9.5% (4)
Stage 2	19.1% (8)
Stage 3	26.2% (11)
Stage 4	45.2% (19)
Clinical Presentation	
- Lymphadenopathy	83% (35)
- Fever	28.5% (12)
- Weight Loss	14.2% (6)
- Loss of Appetite	7.1% (3)
- Dyspnoea	7.1% (3)
-PUO	2.3% (1)
-Abdominal pain	2.3% (1)
-Breast lump	2.3% (1)
-Pruritis	4.6% (2)
Other Characteristics	
- Bulky Disease	30.9%, (13)
- Extranodal Involvement	21.4% ,(9)
-Bone Marrow infiltration	35.7% ,(15)
-B symptoms	26.2% ,(11)

TREATMENT CHARACTERISTICS:

All patients received standard frontline chemotherapy except one patient who received oral metronomic chemotherapy (CEPP). 31 patients (73.8%) received ABVD ,5 patients (11.9%) received ABVD/BEACOPP ,2 patients (4.6%)received EBVD and 2 patients (4.6%) AVD as frontline chemotherapy. 9 patients (21%) received radiation as a form of combined modality therapy and 6 patients (11.9%) received radiation at the end of frontline chemotherapy for residual disease.

None of the patients died during frontline chemotherapy. Following frontline chemotherapy 32 patients had complete remission (CR) , 5 patients had a partial response (PR) and one patient had stable disease (SD) . 4 patients had progressive disease (PD) .

20 patients (47%) relapsed following frontline chemotherapy. The most common salvage chemotherapy used was ICE(70%) followed by GDP(60%) and DHAP(35%).The median salvage chemotherapy received in relapsed setting is 2 . 8 patients (40%) underwent ASCT as consolidation post salvage chemotherapy and 5 patients received RT to residual disease post salvage therapy .One patient relapsed post autologous stem cell transplant .2 patients received only palliative chemotherapy in view of lack of fitness to salvage therapy.

Table 2: Treatment Characteristics And Response Assessment.

Parameter	Value
Frontline treatment	N(%), N=42
- ABVD	73.8% (31)
- ABVD/BEACOPP	11.9% (5)
- EBVD	4.6% (2)
- AVD	4.6% (2)
-CEPP	2.3% (1)
Radiation Therapy	
- Radiation as combined modality	21% (9)
- Radiation for residual disease	11.9% (6)
Mortality During Frontline Chemotherapy	None
Response to Frontline Chemotherapy	
- Complete Remission (CR)	76.2%, (32)
- Partial Response (PR)	11.9%, (5)
- Stable Disease (SD)	2.3%, (1)
- Progressive Disease (PD)	9.5%, (4)
Relapse Post Frontline Chemotherapy	47% (20)
Treatment characteristics of relapsed HL	N%, N=20
Salvage Chemotherapy	
- ICE	70%, (14)
- GDP	60%, (12)
- DHAP	35%, (7)
-COPP	5%, (1)
-GVD	5%, (1)
Median Salvage Chemotherapy received by a patient	2
Consolidation Post Salvage Chemotherapy	
- Autologous Stem Cell Transplant (ASCT)	40%, (8)
- Radiation Therapy to Residual Disease	25%, (5)
Relapse Post ASCT	5%, (1)
Palliative Chemotherapy	10%, (2)

Survival Analysis:

The median follow up is 67 months .The median overall survival and median progression free survival of the overall population was not reached . The 5 year overall survival is 88.1% and 5 year progression free survival is 52.4%. Using univariate analysis , only age of the patient and stage of the disease was found to be prognostic for overall survival .5 year overall survival for patients less than 40 is 96.7% compared to an OS of 66.7% in patients more than 40 years of age (P=

0.003).The covariates that were prognostic for progression free survival were age(P=0.03) , stage of the disease (P = 0.02)and bone marrow involvement(P=0.02) . 20 patients relapsed after frontline chemotherapy following disease progression , PR or relapse after complete response . 5 patients died during follow up . 2 patient died due to progressive disease , 1 patient due to neutropenic sepsis post salvage chemotherapy , 1 patient died due to comorbid end stage renal disease(ESRD) and 1 old patient died due to cerebrovascular accident (CVA).

Table 3: Association Between 5-Year OS And PFS With Risk Features

Risk features	N of patients (N=42) N%	5 year OS RATE %	P value	5year PFS RATE %	P value
AGE					
1.less than 40	71.4% (30)	96.7%	0.003	60.1%	0.003
2.More than 40	28.5% (12)	66.7%		38.5%	
Bulky disease					
1.Yes	30.9% (13)	76.9%	0.154	38.5%	0.253
2.No	69.1% (29)	93.1%		58.6%	
Stage					
1.Early	28.5% (12)	100%	0.04	73.9%	0.002
2.Advanced	71.5% (30)	79%		26.3%	
Extra Nodal Disease					
1.Yes	21.4% (9)	88.9%	0.980	44.4%	0.563
2.No	78.6% (33)	87.%		54.4%	
Bone marrow involvement					
1.Yes	35.7% (15)	86.7%	0.659	20%	0.002
2.No	64.3% (27)	88.9%		70.4%	

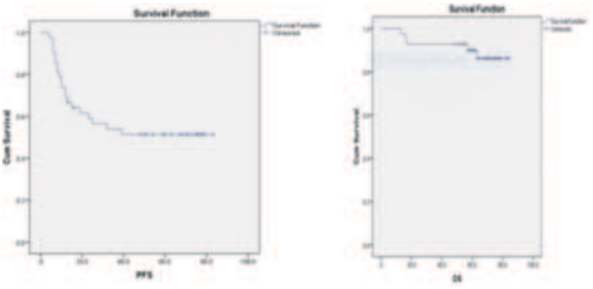

Figure 1: Keplan Meier Curve For OS And PFS For The Entire Cohort Of Patients.

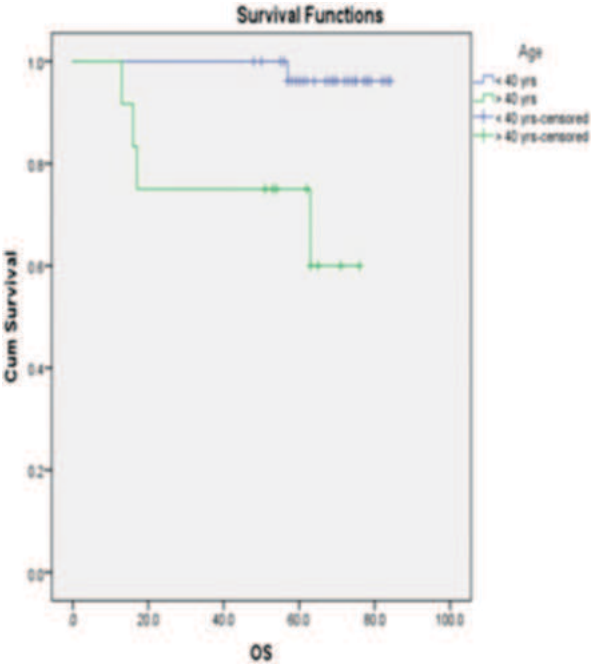

Figure 2: Kaplan Meier Survival Curve For OS Of Patients Less Than Age 40 And More Than Age 40. P value=0.003

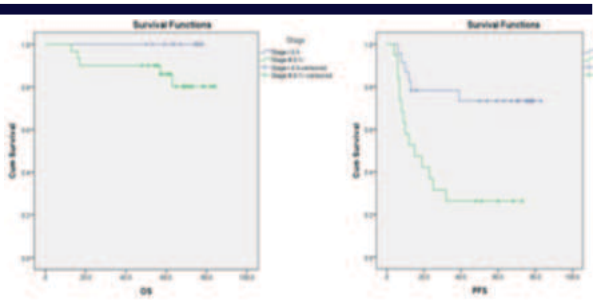

Figure 3: Kaplan Meier Survival Curve For OS And PFS For Early Stage And Advanced Stage Disease

Toxicities:

4 patients developed neutropenic sepsis during treatment, 1 developed pulmonary fibrosis secondary to bleomycin, and 1 developed cardiac failure secondary to anthracycline during the follow up period . No secondary malignancies post therapy were documented in any of the patients.

DISCUSSION

In this study we aim to present the clinical profile and treatment outcomes of classical Hodgkins lymphoma treated in our institute.

The median age of diagnosis in our cohort is 21 years compared to 39 years in US SEER data [15] and 36 years from an Indian study [16] .Low number of patients in our study and variation in age cutoff for inclusion criteria in the above studies maybe the reason for variation in age of presentation.

71.4% of patients had advanced disease which is very high compared to the seer data which is 43% only [15] . Lack of education among patients , financial burden , native medications and delay in diagnosis may be reasons for advanced disease at presentation. As incidence of tuberculosis is higher in India , physicians tend to do FNAC from the enlarged node and ATT is initiated for the granulomatous lesion. Excision biopsy is delayed in such patients (after poor response to ATT) which leads to delay in diagnosis [17].

Nodular sclerosis is the most common histological subtype(50%). Few patients were not assigned subtype according to WHO classification 2019 and labelled as classical HL - non specified . This is because only core needle biopsies were done in some patients from the referral centre and patients deferred further excision biopsy . These patients were also included in the study because lack of subtype will not modify the treatment protocol of the patients.

73.8 percent of patients received ABVD as frontline chemotherapy . This is in contrast to western data where other regimens like AAVD , BEACOPP and BrECADD are also being increasingly used in the frontline setting. Ease of administration as a day care chemotherapy , low toxicities , no requirement of GCSF support , lower price and easy availability are the reasons for ABVD being commonly used frontline chemotherapy in our study.

20 patients (47%) relapsed after frontline chemotherapy . 2 had early disease and 18 had advanced disease. The PFS of frontline chemotherapy in early disease is 73.9% and for advanced disease is only 26.3% in our study . Most of the elderly patients above 60 years of age progressed following frontline chemotherapy. Regimens like BEACOPP [18] , AAVD [19] , BrECADD [20] and Nivolumab -AVD [21] have superior PFS rates compared to ABVD .But administration of these regimens require affordability to these drugs , G CSF support and frequent inpatient admission for toxicity management which is difficult in our centre. The very low cure percentage is also due to inclusion of relapsed cHL patients referred to our centre from other oncology centres for salvage therapy in this study.

The median lines of salvage chemothery was 2 (range : 1-4) . 2 patients received three lines and one patient received four lines of salvage chemotherapy before transplantation. ICE and GDP were the common salvage regimens that were used.Low toxicities , cheaper price and ease of administration were the reason these regimens were preferred . GDP is given as a day care chemotherapy in our institute due to lack of bed availability in inpatient wards due to higher patient load.

Better salvage regimens with higher response rates like Nivolumab -

ICE [22] and pembro - GVD [23] couldnt be given as they were cost limiting .

We investigated the relationship of several disease risk features and patients' clinical characteristics, including age, disease stage, bulky disease, and extranodal disease with OS and PFS. The age of the patient and stage of disease was found to be prognostic for overall survival .5 year overall survival for patients less than 40 is 96.7% compared to an OS of 66.7% in patients more than 40 years of age (P= 0.003). 5 year overall survival for early stage disease was 100 percent and the 5 year OS for advanced disease was 79 percent (p = 0.04) . The covariates that were prognostic for progression free survival were age(P=0.03) , stage of the disease (P = 0.02)and bone marrow involvement(P=0.02) .

This study is limited by its retrospective nature and small sample size . Our documentation of long term follow up for second malignancies or cardiovascular and respiratory complications from therapy was not comprehensive. This is important as part of the treatment outcome. Although this is a single center study, it provides insight into the clinical presentation and treatment outcomes among patients with HL in south India. A longer follow-up and a larger cohort size would be important to discover differences in outcomes with various chemotherapeutic regimens.

CONCLUSIONS

This study provides insight into the clinical presentation and treatment outcomes among patients with cHL in a South Indian tertiary care centre. Though the survival of hodgkins lymphoma in the western population is very high , the 5 year overall survival and 5 year PFS are only 85% and 52% respectively in our centre.

Survival is very low in elderly HL patients with a 5 year overall survival of 66% .So better frontline chemotherapy is required especially in the elderly population . Delayed presentation to oncologists , advanced stage of disease , lack of affordability to modern standard of care drugs may be reasons for poor survival.

Abbreviations:

cHL - Classical Hodgkins lymphoma10 of 10
HL - Hodgkins lymphoma
ABVD - Adriamycin , Bleomycin , Vinblastine , Dacarbazine
BEACOPP - Bleomycin , Etoposide , Adriamycin , Cyclophosphamide , Vincristine , Procarbazine , Prednisolone
EBVD - Etoposide , Bleomycin , Vinblastine , Dacarbazine
CEPP - Cyclophosphamide , Etoposide , Procarazine , Prednisolone
COPP/ABV - Cyclophosphamide , Vincristine , Procarbazine , Prednisolone , Adriamycin , Bleomycin , Vinblastine
RT - Radiotherapy OS - Overall Survival
PFS - Progression Free Survival
ICE - Ifosfamide , Carboplatin , Etoposide
GDP - Gemcitabine , Dexamethasone , Cisplatin
DHAP - Dexamethasone , High dose cytarabine , Cisplatin ASCT - Autologous Stem Cell Transplantation
NCCN - National Comprehensive Cancer Network SEER - Surveillance Epidemiology and End Results
AAVD - Brentuximab vedotin , Adriamycin , Vinblastine , Dacarbazine
BrECADD - Brentuximab vedotin , Etoposide , Cyclophosphamide , Adriamcin , Dexamethasone and Dacarbazine
GVD - Gemcitabine , Vinorelbine , Liposomal doxorubicin

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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