

DOI: 10.21767/2254-6081.100168

# Evaluation of the Response to Chemotherapy in the Treatment of Hodgkin's Disease at the Mother and Child Center of the Chantal Biya's Foundation in Yaounde, Cameroon

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## Abstract

**Background:** Hodgkin's disease (HD) is a malignant disorder of the lymphatic tissue which mainly affects the lymph nodes and is characterized by a particular cell called Reed Sternberg cell. It represents 5% to 10% of malignancies in children with two peaks one around 6 years and the other around 14 years.

**Objective:** The aim of the study was to evaluate the response of HD to a chemotherapy regimen without radiotherapy.

**Methods:** We conducted a prospective study from 2007 to 2016. Were included, all records of patients admitted for Hodgkin's disease and having a histological evidence of HD. Children were treated with the protocol COPP/ABV at the Mother and Child Center of the Chantal Biya's Foundation in Yaoundé using only chemotherapy.

**Results:** During that period, we collected 26 cases of HD. Which represented 1.96% of all cancers in children. The mean age at diagnosis was 11.6 years (7-16 years). The most represented age group was that of 10 to 14 with 57.7% of the cases. The sex ratio was 1.88. Forty-two per cent of patients had consulted more than 12 months after the beginning of symptoms. The circumstances of discovery were dominated by the appearance of peripheral adenopathies, particularly cervical (76.9%). Signs of clinical evolution were found at diagnosis in 61.5% of patients. The scleronodular, mixed cellular and the lymphocyte-rich forms were found in the following respective proportions: 38.4%, 34.6% and 27% and 82.60% of our patients were classified as unfavourable prognosis at the time of diagnosis. Overall survival at 5 years was estimated to be 82%.

**Conclusion:** Hodgkin's disease is a chemo sensitive and radiosensitive disease, for which most international protocols combine the two modalities of treatment. This study has demonstrated the feasibility of this modified treatment in our context where radiotherapy is unavailable.

**Keywords:** Hodgkin's disease; Child; Treatment; Evaluation; Chemotherapy

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**Citation:** Hermine PA, Rodrigue DM, Bernadette NN, Paul KN (2018) Evaluation of the Response to Chemotherapy in the Treatment of Hodgkin's Disease at the Mother and Child Center of the Chantal Biya's Foundation in Yaounde, Cameroon. Arch Cancer Res. Vol.6 No.1:2

**Received:** December 01, 2017; **Accepted:** January 22, 2018; **Published:** January 29, 2018

## Introduction

Hodgkin's disease (HD) is a malignant disease of the lymphatic tissue mainly affecting the lymph nodes and characterized by a very particular cell, called the Reed Sternberg cell (RSC) [1-3]. It is a pathology of the adolescent and the young adult. The annual

incidence is estimated to be between 3 to 6 new cases per million children aged 0 to 15 years [4-6]. In developing countries, clinical, epidemiological and therapeutic data are poorly known, and many studies have shown a predominance of the mixed cellular form most often associated with a worse prognosis [5,7]. In Cameroon, Hodgkin's disease is not uncommon, so the authors have reported

70 cases of HD over a period of 11 years (1979-1989), or almost 6 cases/year [8]. Modern therapies, including those combining radiotherapy and chemotherapy, have significantly improved the prognosis of the condition in developed countries. In Cameroon, the lack of a suitable protocol in children and the difficulties or even the impossibility to access radiotherapy are the cause of the death of many children for lack of appropriate treatment. To treat children with HD, we have used the COPP/ABV hybrid protocol without radiotherapy. Thus, the purpose of our study was to evaluate the response to treatment of children with HD by this protocol.

## Materials and Methods

This is the analysis of data from a child cohort monitored at the CME/FCB for HD. The study was carried out from 1<sup>st</sup> January 2007 to 31<sup>st</sup> December 2016. In all children, the diagnosis was confirmed by lymph node biopsy and the histological type was determined according to the WHO classification [9,10]. A pre-therapeutic assessment included a physical examination, laboratory tests (complete blood count, erythrocyte sedimentation rate and lactate dehydrogenase assay) and radiological examinations (chest x-ray and abdominopelvic ultrasound). The disease was classified according to the classification of Ann Arbor.

### Initial staging and medications

The Ann Arbor was used for staging patients based on the absence (A) or presence (B) of: Fever >38°C for at least one week, weight loss (>10% body weight during the last 6 months) Night sweats (requiring the patient to change or waking him/her at night). Thus, the patients were stratified into 2 prognostic groups according to the Ann Arbor classification: The favourable group=G1 (stage I and IIA, and mediastino-thoracic index <0.45 and lymph node's tumor volume <6 cm and no contiguous lesion). Unfavourable group=G2: all patients not included in the favourable group: (IIB, III, IV with large mediastinum with mediastino-thoracic index superior or equal to 0.45 or adenopathy's volume superior or equal to 6 cm or visceral involvements).

At the end of this stratification the patients were treated according to the following regimen: Vincristine 1.5 mg/m<sup>2</sup> (max 2 mg) on the first day, Cyclophosphamide 650 mg/m<sup>2</sup> on the first day, Procarbazine 100 mg/m<sup>2</sup> from 1<sup>st</sup> to 7<sup>th</sup> day, Adriamycin 35 mg/m<sup>2</sup>; The 8<sup>th</sup> day, Vinblastine 6 mg/m<sup>2</sup> on the 8<sup>th</sup> day, Bleomycin 10 mg/m<sup>2</sup> on the 8<sup>th</sup> day, Prednisone 40 mg/m<sup>2</sup> from the 1<sup>st</sup> to the 14<sup>th</sup> day.

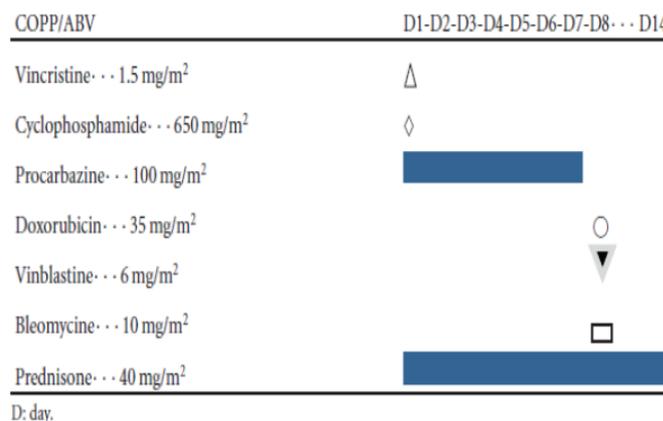
Premedication (25-50 mg of hydrocortisone hemisuccinate) was administered slowly intravenously before bleomycin cures. The cures were done every 28 days shown in **Figure 1**.

### Evaluation of the response

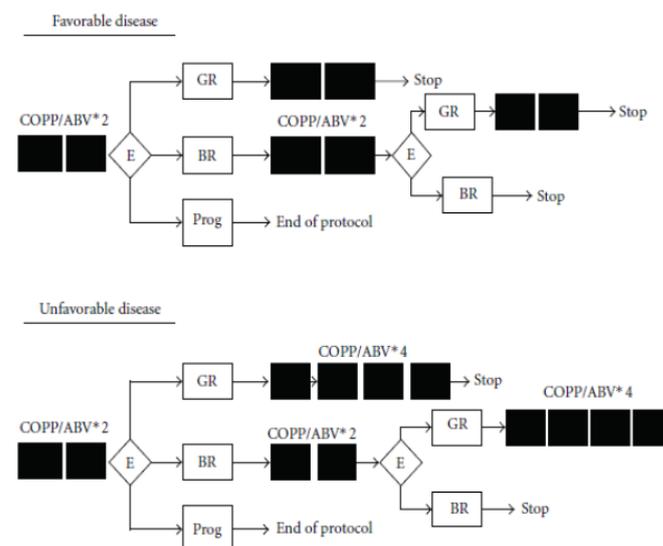
It was done according to the following criteria: A good response was defined as a clinical, biological and radiological response ranging from 70% to 100% (complete remission), a partial response was defined as a response between 50% and 70%. Failure was defined as either a lack of response or a response of less than 50%, or a clinical, biological or radiological progression of the disease. Survival was assessed using the Kaplan-Meier

method from the date of initiation of treatment to the date of last consultation (**Figure 2**).

The study was approved by the institutional committee on ethics and research of the University of Douala, the National Ethics committee of Cameroon and the administrative authorities of the Center for the Mother and Child Center of the Chantal Biya Foundation.



**Figure 1** GFAOP Hodgkin lymphoma treatment protocol.



**Figure 2** General treatment diagram. GR: Good Responder, BR: Bad Responder, E: Evaluation, Prog: Progressive disease. (Patients in the favorable group received 4 courses and those in the unfavorable group 6 courses. However, an evaluation was made after the first 2 courses defining the continuation of the treatment for the patients of the favorable group: Good responders patients after 2 courses: If in Complete remission and If in the favorable group they received 2 cures, and then stop giving 4 treatments in total. If in the unfavorable group, they were given 4 courses and then stop giving 6 treatments in total. Insufficiently responders' patients: If RP, new evaluation after 2 courses, if progressive disease, exit from the protocol).

## Results

### Population characteristics

Out of a total of 1325 cases of childhood cancers at CME-FCB during the study period, 26 children had Hodgkin's disease, giving a hospital's prevalence of 1.96%. The mean age of patients at diagnosis was 11.5 years with extremes of 7 and 16 years. The most represented age group was 10 to 14 years (57.7%, 15/26). The sex ratio 1.88 (17 boys and 9 girls). The mean consultation time was 11.05 months with extremes of 1 and 48 months. Eleven patients (42.3%) consulted after more than 12 months after the beginning of symptoms. The most common presenting clinical sign was the presence of peripheral adenopathies of the cervical region in 20 patients (76.9%). At pathology, the scleronodular, mixed cellular and the lymphocyte-rich forms were found in the respective proportions of 38.4%, 34.6% and 27%. Biologically, the erythrocyte sedimentation rate was done in 12 patients and revealed a rise of more than 30 mm at the first hour in 11 of them and anemia (hemoglobin less than 12 g/dl) was observed in 11 children. Bone marrow biopsy was performed in 3 patients. The chest radiograph showed enlargement of the mediastinum in 8 patients out of 17 who did the exam (47.05%). Abdominal Ultrasound (of the abdomen was done in 20 patients; it revealed retroperitoneal adenopathies in 13 patients, splenomegaly in 10 patients and hepatomegaly in 12 of them. After the physical, biological and radiological work-up, 7/26 (26.9%) patients had localized Hodgkin's disease (two stage I and five stage II) and 19/26 (73.67%) patients had advanced stage III and stage IV disease at the time of diagnosis. Of these, 16 patients had clinical signs of progression shown in **Table 1**.

### Response to treatment

Of the 7 patients with localized Hodgkin's disease (stages I-II), 6 cases were in complete remission and 1 case was in partial remission. While in those with advanced stages 73.1% (19/26) (stages III-IV) 12 cases were in complete remission, 2 cases relapsed, 3 cases died, and 2 cases were lost to follow-up.

### Distribution of patients by causes of death

Analysis of the causes of death revealed greater imputability to the natural course of the disease in 2 patients out of 3 (66.70%), while the other causes of death were unrelated to the disease or its treatment in one case (33.3%). The later died secondary to renal failure prior to diagnosis of the 3 patients who died, one had relapse meanwhile, the other two never had remission. Social factors: Common reasons for delayed time from diagnosis to treatment

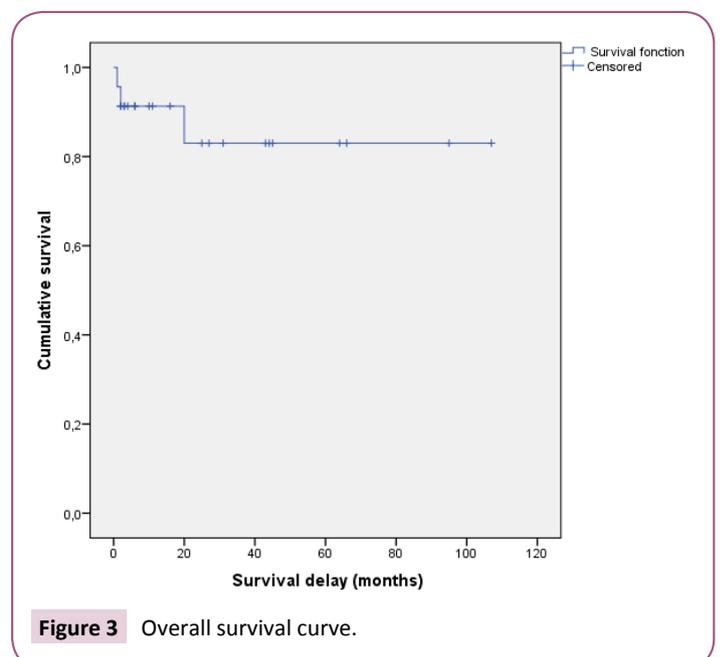
### Study of survival and prognostic factors

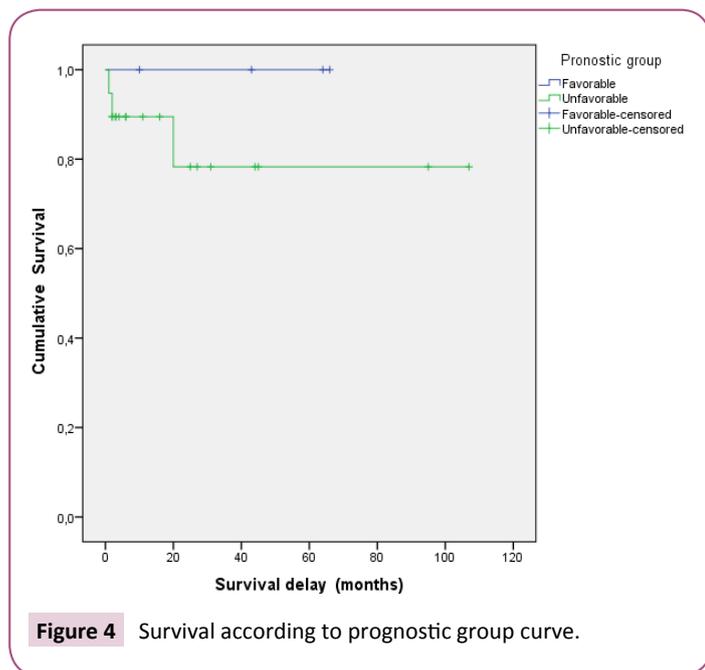
The five-year overall survival rate was estimated to be 82% (**Figure 3**). This five-year overall survival rate was 100% in patients ranked prognosis favourable to initiation of treatment and 78% in patients ranked prognosis Unfavourable (**Figure 4**). The analysis of survival according to age, sex, histological type, stage, clinical and biological signs of evolution did not find any significant impact on these parameters on overall survival. However, advanced stages were associated with greater mortality.

**Table 1** Characteristics of the population.

Variables	Number	(%)
<b>Age</b>		
5-9 years	7	26.90%
10-14 years	15	57.70%
>14 years	4	15.40%
<b>Gender</b>		
Male	17	65.40%
Female	9	34.60%
<b>Adenopathy Localisation</b>		
Cervical	20	76.90%
Inguinal	11	42.30%
Axillar	9	34.60%
Maxillar	5	19.20%
<b>Extra-ganglionic signs</b>		
Splenomegaly	14	53.80%
Hepatomegaly	13	50.00%
General state alteration	16	61.53%
<b>Stage and sign of disease progression</b>		
I A	2	7.69%
II A	3	11.53%
II B	2	7.69%
III A	4	19.23%
III B	13	50%
IV B	1	3.86%
Fever (n=16)	16	100.00%
Weight loss (n=16)	12	75.00%
Sweats (n=16)	8	50.00%
<b>Histological type ganglionic signs</b>		
Lymphocyte rich	10	38.40%
Scleronodular	9	34.60%
Mix cellularity	7	27%

A : Absence of signs of improvement ; B: Presence of signs of improvement





**Figure 4** Survival according to prognostic group curve.

## Discussion

The incidence of HD in Cameroon and especially in its pediatric form is not well known due to the scarcity of available data. Thus, during our study period at the MCC/CBF, we collected 26 cases of HD from 1325 cases of all pediatric cancers, giving a prevalence of 1.96%. Similar prevalence has been found in other developing countries [11,12]. However, this may be under-estimated, because of the unfavourable socio-economic context, which limits access to the public health system in general and to the country's only pediatric oncology unit.

The average age of our patients at the time of diagnosis was 11.5 years with extremes of 7 and 16 years, the age group of 10-14 years was the most represented 57.70%. These data are broadly similar in the series of developing countries [12-14] and lower than those reported by the western series, most often over 13 years. In 2002, Donaldson et al found an average age of 13 years in the USA [15-17]. We noted a male predominance with a sex ratio of 1.87 less than those reported by Togo et al in Mali in 2011, Khanfir et al. in Tunisia in 2007, who found a sex ratio of 6 and 3.6 respectively [12,18]. The advanced stages were predominant (73.67%). Patients in stages III and IV are more common in developing countries; their frequency may exceed 70%. Conversely, in Western countries, predominance of localized forms (stages I-II) is more common, the frequency of which often exceeds 60% [14,19]. This predominance of the advanced stages in our series is due to missed diagnosis: The patients being most often treated for another pathology, usually

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tuberculosis. The high frequency of advanced stages may as well be due to the wandering of these patients in hospitals and the delay of diagnosis due to financial constraints.

Histologically, the scleronodular, mixed cellular and lymphocyte-rich forms were found in the respective proportions of 38.4%, 34.6% and 27%. With a non-significant difference. However, it should be noted that the predominant histological type varies from country to country. Indeed, in western countries the scleronodular type is predominant with a frequency exceeding 60%. But in developing countries, the mixed cellular type is the most frequent (50% to 75% of the cases) [12,20-22]. However, due to the small size of our sample, we cannot draw any conclusions about the distribution of the histological types.

Chemotherapy was the only therapeutic modality. Thus, at the end of treatment, the complete remission rate was 61%, with 4% partial remission and 9% relapse 13% death and abandonment.

In our series, the overall 5-year survival rate for all stages was 82% with an average survival time of 90.6 months. This rate is close to those found in the literature, which ranged between 80 and 90% [18,19,23-25]. However, the survival rate varied according to the prognostic group. Thus, the 5-year survival of patients in the favourable group was 100%. Whereas the unfavourable group was 78%. Results like those of Baez et al. in Nicaragua in 1997, which found a three-year survival rate of 100% for stages (I, II and IIIa) and 74.9% for stages (IIIb and IV).

We deplored 3 cases of death due in two cases to the tumor progression and in one case to renal insufficiency. Deaths were associated with discontinuation of treatment due to multiple factors, including those impeding access to the treatment center.

## Conclusion

Hodgkin's disease is a chemo-sensitive and radiosensitive disease whose management according to international recommendations is based on the combination of radio and poly chemotherapy. However, the virtually non-existent functional radiotherapy unit in our context limits the therapeutic options to chemotherapy alone. Thus, at the end of this work, we found a good feasibility of the COPP-ABV protocol in the treatment of children with HD with less toxicity. However, relapse analysis is difficult to evaluate due to multiple impediments, such as poor attendance during and after treatment, low availability of paraclinical data, and small number of patients. Availability of radiotherapy would increase the therapeutic outcomes.

## Conflict of Interest

The authors declare that they have no conflict of interest that competes with any of the contents of the manuscript.

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