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The therapy of Hodgkin's disease in Nigeria: a five year study

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Summary

Between 1970 and 1974 seventy patients suffering from Hodgkin's disease were admitted and treated in University College Hospital (UCH), Ibadan, out of which fifty (71·4%) had well documented chemotherapy. Standard combination chemotherapy of COPP/MOPP i.e. cyclophosphamide or mustine hydrochloride, oncovin, procarbazine and prednisolone was used on nineteen cases. Of these, twelve (63·2%) achieved complete remission. The longest survival to date is 4 years. Two patients (4%) had surgical excision of the affected lymph node and are alive and disease-free after 4 years of this treatment. They have had no maintenance therapy. The two patients (4%) in whom surgical removal of glands was followed by combination chemotherapy are also alive, well and disease free. Four patients had single agent therapy (Endozan) and died soon after starting treatment. One patient died shortly after diagnosis before therapy was instituted. Of the group treated with MOPP or COPP, all the patients were clinically stage IV and sixteen of the nineteen (84·5%) had histological mixed cellularity type of Hodgkin's disease.

We confirm that combination chemotherapy gives very good tumour response and longest survival to patients with Stage IV disease. The main problems encountered during the period were the difficulty and the irregularities of supply of the chemotherapeutic agents. Better results can be obtained if these problems and that of high default rate can be solved.

Résumé

De 1970 à 1974, ont été hospitalisés et sognés à UCH, Ibadan, 70 malades souffrant de la malade de Hodgkin dont quelques 50 (soit 71·4%) ont eu une chimiothérapie bien documentée. On a employé dans 19 cas une chimiothérapie combinée normale de COPP/MOPP—c'est à dire—de cyclophosphamide ou de chlorhydrate de mustine, oncovin, procarbazine et prednisolone sur les 19, 12 (soit 63·2%) ont eu une rémission complète et le plus long survivant est sans maladie depuis 4 ans. 2 malades (4%) ont subi une excision chirurgicale du nodus lympatique atteint, et ils vivent encore sans maladie 4 ans après ce traitement. Ils n'ont eu aucune thérapie d'entretien. Les deux malades (4%) chez lesquels une excision chirurgicale des glandes a été suine de chimiothérapie combinée sont également vivants et en bonne santé. 4 malades ont été soignés par thérapie à un seul agent (endoxan) et ils sont morts peu après le commencement de la thérapie. Une malade est mort peu de temps après le diagnostic et avant que ne soit commencée aucune thérapie. Tous les malades du groupe traités avec 'MOPP' ou 'COPP' étaient cliniquement das la 4ème phase et 16 des 19 malades concernés avaiént la maladie de Hodgkin du type cellularisme histologiquement mixte.

Nous confirmons que la chimiothérapie combinée donne la meilleure réaction tumeurale et assure la plus lonque survivance aux malades de la 4ème phase.

Les problemes pricipaus recontrés pendant la période ont été la difficulté et les irregularités de la fourniture des agents chimiothérapeutiques.

On obtiendrait de meilleurs résultats si on arrivait à éliminer cas problemes aussi bien que le taux élevé de l'absenteisme de la part de malades.

Introduction

Hodgkin's disease is a malignant tumour of the lymphoreticular system characterised by a pleomorphic histological picture. Although it occurs through-

out the world, the epidemiological patterns vary (Correa & O'Conor, 1971, 1973). The histological patterns of cases described in Africans appear to have distinguishing features as compared with other areas. In contrast to the United States, where there is generally an excess of the mixed cellularity and lymphocyte depletion and a clear paucity of the lymphocyte predominant and nodular sclerosing types (Bum *et al.*, 1971; Olweny *et al.*, 1971; Onyewotu, Francis & Montefiore 1972; Edington, Osunkoya & Hendrickse 1973). It has also been suggested (Olweny *et al.*, 1971) that adult Hodgkin's disease may be more aggressive in its biological behaviour in Africans than in Caucasians.

Reports in Nigeria of Hodgkin's disease include those of its incidence by Edington & Maclean (1965) who found forty-three cases among a total of 1,920 malignancies diagnosed in the 4-year period 1960–1963 and by Mulligan (1970) who reported eight cases in a 14-year retrospective survey of malignant diseases in a peripheral hospital. An analysis of the histological patterns has been presented by Edington *et al.* (1973). None of these reports concerned itself with therapy and its effects on the outcome of the disease. However, Duncan (1968) mentioned the use of alkylating agents, particularly nitrogen mustard for the great number of neoplastic diseases and concluded that 'reasonable palliation was obtained with these agents in our lymphomas including Hodgkin's disease'. Onyewotu *et al.* (1972) concluded that no prolongation of survival from onset of symptoms was achieved with the use of single agent or combination of two or more drugs. The reports of the treatment appear to be at variance with the experience elsewhere of considerable success in the treatment of advanced Hodgkin's disease with combination chemotherapy e.g. De Vita *et al.*, (1970), in the United States; Nicholson *et al.*, (1970) in Britain; and Ziegler *et al.*, (1972) and Olweny *et al.*, (1971) in Uganda. It is in consideration of the above that we report here our experience of the therapy of Hodgkin's disease in the University College Hospital (U.C.H.), Ibadan, in the 5-year period 1970–74.

Patients and methods

One hundred and two cases of Hodgkin's disease were diagnosed in UCH Ibadan in the period January 1970 to December 1974. Of these, seventy were registered as in-patients whilst thirty-two were histological specimens sent from outside sources. Of the seventy in-patients, fifty had sufficient documentation (history, physical findings, laboratory work-up, histological classification and clinical staging to be included in the analysis: one of these unfortunately had no documented therapy.

The clinical staging of the disease was done in the standard way of a clinical evaluation including full blood count, electrolytes and urea and uric acid estimation, liver function tests including total and conjugated bilirubin, SGOT, SGPT, alkaline phosphatase; bone marrow aspiration, and X-ray of the chest and abdomen. Lymphangiograms were done in four of the patients and one patient had the benefit of bone scan with strontium 85, tomogram of chest, and biopsy of the lung tissue. Diagnostic laparotomy was not performed on any of the patients The histological classification was done according to the Rye Conference (Lukes *et al.*, 1966).

Clinical features

The youngest patient in the series was aged 5 years whilst the oldest was 68 years old. The peak age incidence was in the third decade. Of the thirty-eight patients who were less than 40 years old, eleven were under 15 years whilst only two were less than 10 years at the time of diagnosis. There were forty-five males and five females, giving an overall male to female (M/F) ratio of 9:1. However, the M/F ratio of the 102 cases diagnosed in the same period is 3:1. This last figure is in agreement with other workers viz Edington & Maclean (1965) M/F ratio of 3·8:1; Duncan (1968) M/F ratio 2:8·1. There were no female patients below 20 years in the group analysed in this report.

The commonest symptom was that of a mass in the neck which occurred in forty-four patients (88%). Thirty-three patients had inguinal lymphadenopathy and thirty patients had axillary lymphadenopathy. Only 4% were clinically jaundiced. One patient had paraplegia. See Table 1.

The four-drug combination chemotherapy of De Vita *et al.* (1970) formed the main treatment and was administered to forty patients whilst single drug chemotherapy was given to four patients early in the period of study. Five patients had radical surgical excision of the affected nodes; in two of these single agent chemotherapy was additionally used, whilst one had irradiation to the site of the excision (Table 2).

TABLE 1. Physical signs on admission IV

Physical sign	No. of Patients	Positive (%)
Anaemia	25	50
Fever	24	48
Cervical Lymphadenopathy	44	88
Axillary Lymphadenopathy	30	60
Inguinal Lymphadenopathy	33	66
Splenomegaly	24	48
Hepatomegaly	26	52
Jaundice	2	4
Ascites	1	2
Spinal Cord Compression with paraplegia	1	2

TABLE 2. Therapeutic regimen used in fifty cases of Hodgkin's disease

Therapy	Dead	Alive	Lost to follow up	Total no. of cases
Nil	1	0	—	1
Single Drug (endoxan)	1	0	3	4
Surgery and radiotherapy	1	0	—	1
Radical surgical excision	—	2	—	2
Radical surgical excision chemotherapy single drug	0	2	—	2
Combination chemo-therapy MOPP/COPP	7	12	21	40

The drug combination was given in cyclic form each lasting 28 days, and six courses were aimed for (see Table 3). The dosage was regulated by twice weekly full blood counts whilst serum electrolytes, urea, uric acid and liver function rests were estimated usually fortnightly but not less than monthly. X-ray of the chest and abdomen were also taken monthly. When there was evidence of myelotoxocity or neurotoxicy as recorded by hypoplasia with paucytopenia and peripheral neuritis respectively, the time of treatment was advanced forwards by a week or two and never more than 2 weeks during which time, the toxicity was noticed to have abated. This was the only departure from the series of De Vita *et al.* (1970) where the sliding scale reduction of drugs was used in cases that had evidence of myelotoxocity which failed to improve in 1 week.

Patients were classified as having partial or total response depending on their status at the end of the 6 months of six cycles of therapy. For total response, the abatement of the patient's complaints, the improvement of haematological parameters, the complete regression of enlarged lymph nodes and organomegaly, total normalcy of bone marrow and, where done, a return to normalcy of previously abnormal lymphangiogram. If any evidence of disease was present, the patient was considered as a partial or no response.

TABLE 3. Single cycle of combination chemotherapy in Hodgkin's disease (after De Vita *et al.* (1970))

Drug	Dose (mg/m²)	Route and period of administration
VCR	1·4	IV days 1 and 8
HN_2 or Cyclophosphamide	6·0	IV days 1 and 8
Procarbazine	100·0	Orally days 1–14
Predenisolone*	40	Orally days 1–14

* Cycles 1 and 4 only
VCR = Vincristine sulphate, HN_2 = Nitrogen mustard

Results

Histological classification and clinical staging

Table 4 shows that the mixed cellularity (MC) and lymphocyte depleted (LD) types were most commonly diagnosed, and constituted 66% and 20% respectively. The lymphocyte predominant and nodular sclerosing types occurred in much lower proportions of 10% and 4% respectively. The high occurrence of mixed cellularity and lymphocyte depleted varieties constituting 86% of the total is in agreement with the finding of other workers in Nigeria (Edington *et al.*, 1973 and Onyewotu *et al.*, 1972).

Thirty-two cases (64%) were clinical stage IV of whom twenty-four (75%) had systemic involvement as shown by weight loss, nausea, vomiting and fever. Eight patients (16%) were in Stage III of whom four (50%) had systemic involvement. Of the five (10%) in stage II only one had systemic involvement. It is clear the more widespread the disease the greater the chances of systemic involvement. The mixed cellularity type beside being the most commonly diagnosed presented in the most advanced stage.

TABLE 4. Relationship of histological types to clinical stages

Histological types	Stage I	Stage II	Stage III	Stage IV	Total no of cases
Lymphocyte predominant	0	1	4	0	5 (10%)
Lymphocyte depleted	0	0	3	7	10 (20%)
Mixed cellularity	5	2	1	25	33 (66%)
Nodular sclerosing	0	2	0	0	2 (4%)
Total	5 (10%)	5 (20%)	8 (16%)	32 (64%)	50 (100%)

TABLE 5. Summary of clinical features, therapy and fate of patients

Patient	Age of onset	Sex	Stage	Systemic symptoms	Nodes affected	Organs affected	Histology	At diagnosis P.C.V.	At diagnosis W.B.C.	At diagnosis Platelets	Type and Length of Therapy	Period of Follow up (Months)	Subsequent Fate
1	63	M	IIIA	O	CI	O	MCT	37	4200	146,000	EN 6^4	1	D
2	49	M	IIIB	P, WL	AI	LS	LD	34	7400	++	COP_4	2	D
3	22	M	IIIB	P, WL	CAI	O	LP	36	10,000	++	NT	Defaulted before diagnosis made	D
4	10	M	IIA	P	CA	O	NS	36	6150	100,000	$COPP_6$	12	D
5	50	M	IVA	P	CAI	O	MCT	31	5100	90,000	COPP	2	A
6	38	M	IVB	P, WL	CAI	S	MCT	34	6600	101,000	$COPP_6$	6	E
7	30	F	IVB	P, WL	CAI	LS	MCT	36	4500	95,000	COP_1	2	E
8	50	M	IVB	P, WL	CAI	LS	MCT	32	3400	74,000	$COPP_4$	6	A
9	34	M	IVB	P, WL	I	L	MCT	36	8000	++	COPP BCV	12	A
10	12	M	IIIA	—	C	L_T	LP	36	3500	121,000	$COPP_6$	12	A
11	55	M	IVA	P, WL	CA	LS	MCT	35	4500	141,000	$COPP_4$	6	A
12	49	M	IVB	P, WL	CAI	LS	MCT	30	8150	31,000	Chloramb $COPP_4$	2	D
13	22	F	IVB	P, WL	CAI	LS	MCT	27	3900	++	$COPP_6$	30	A
14	40	M	IVB		AI	LS	MCT	34	5700	496,000	COPP	10	E
15	27	M	IVA	O	CA	L	MCT	44	6400	159,000	$COPP_4$		D
16	40	M	IVB	O	CA	S	LD	31	44,700	142,000	COPP	3	E
17	40	M	IB	P, WL	CAI	O	MCT	25	7600	115,000	$COPP_3$	2	E
18	20	M	IIIB	P	AI	O	LD	34	6250	209,000	COP	7	D
19	27	M	IVB	P, WL	CA	L	MCT	37	3550	++	$COPP_4$	4	D
20	35	M	IVB	P	CAI	O	MCT	50	9550	++	$COPP_5$	26	E
21	60	M	IIB	P, WL	C	O	NS	39	6450	++	$COPP_5$	4	D
22	40	M	IA	O	O	O	MCT	40	ND	ND	Hemico-lectomy	36	A
23	15	M	IV	P, WL V	CAI	LS	LD	19	1750	ND	Surgical Excision + Endoxan	24	E
24	27	M	IIB	P, WL	CI	H	LD	40	5000	115,000	COPP	24	A
25	12	M	IA	NIL	C	O	MCT	33	4500	99,000	Radical surg. Excision with Radiotherapy	34	D
26	13	M	IIB	P, WL	C	O	LD	37	5500	100,000	Surgical Excision + Endoxan	20	D

Table 5 (continued)

Patient	Age of onset	Sex	Stage	Systemic symptoms	Nodes affected	Organs affected	Histology	At diagnosis P.C.V.	At diagnosis W.B.C.	At diagnosis Platelets	Type and Length of Therapy	Period of Follow up (Months)	Subsequent Fate
27	24	M	IIIB	P, WL	CI	O	LD	35	6100	244,000	COP	4	D
28	45	F	IVB	WT, L	CAI	LS	MCT	17	6650	91,000	$COPP_6$	4	A
29	10	M	IA	P	C	O	MCT	37	12,000	296,000	Radical Excision + Radio-therapy	42	A
30	25	M	IVA	P	C	Com-pression D8	MCT	39	4300	Normal	Laminec-tomy $COPP_6$	30	A
31	6	M	IVA	WL, P	CAI	LS	MCT	21	4200	17,000	$COPP_6$	12	A
32	35	M	IVB	P, WL	CAI	LS	MCT	32	3300	152,000	$COPP_3$	3	D
33	12	M	IB	P, WL	O	O	MCT	27	8500	148,000	$COPP_6$	5	E
34	5	M	IIA	P	C	L	MCT	36	8150	148,000	$COPP_6$	18	A
35	14	M	IVB	P	CI	L	MCT	22	1850	++	$COPP_1$	1	D
36	49	M	IIA	O	CI	O	MCT	35	11,100	++	EN_8	3	E
37	15	M	IVB	P, WL	CIA	LS	MCT	22	1450	ND	COP	2	D
38	27	M	IVB	P, WL	AI	L	MCT	35	13,400	120,000	$MOPP_3$	5	D
39	35	M	IVB	P, WL	I	O	LD	28	2400	++	$COPP_2$	3	D
40	55	M	IIIA	O	CAI		LP	26	9100		Chloramb $COPP_4$	8	D
41	32	M	IVB	P	CI	LS	MCT	42	5250	++	COP_1	1	D
42	67	M	IIIB	P	CAI	S	LP	40	15,800	135,000	EN_8	3	D
43	40	F	IVA	O	C	L	MCT	33	4600	165,000	COP	1	D
44	14	M	IVB	P, WL	C	L	LD	35	4100	104,000	$COPP_6$	6	A
45	20	M	IVA	O	CAI	LOS	MCT	37	11,350	++	$COPP_6$	12	A
46	27	F	IVB	P, WL V	CAI	LS	LD	35	3850	++	COP_6	15	E
47	68	M	IVB	WL, P	CAI	LS	MCT	29	6200	67,000	$COPP_6$	24	A
48	26	M	IA	O	A	O	MCT	49	6350	++	Radical excision only	36	A
49	27	M	IVA	O	C	5 Pal pab le. ABD Masses	MCT	38	3150	++	COPP	10	
50	13	M	IVB	WL, P	CAI	LS	MCT	—	—	—	None Recorded	—	D

Symptoms: Pu = pruritus; O = no symptoms; WL = weight loss; V = vomiting; P = pyrexia. Histology: MCT = mixed cellularity; LD = lymphocyte depleted; LP = lymphocyte predominant; NS = nodular sclerosis. Nodes affected: C = cervical; A = axillary; I = inguinal; O = no nodes affected. Organs affected: L = liver; S = spleen; O = no organs affected. Subsequent fate: D = defaulted; A = alive; E = dead.

Response to therapy

Twenty six (52%) of our patients were lost to follow up. Of these nine patients were started on the three drugs namely cyclophosphamide, oncovin and prednisolone, twelve were on the complete regimen and four were on endoxan only. One patient had no documented therapy. He defaulted and is known to have died of his extensive disease. Up to the time of default clinical signs of remission were noticed in all except three of those who were on Endoxan who had persistence of their lymphadenopathy, organomegaly and pyrexia.

Of the remaining twenty-four patients, three did not have drug therapy. Two of these had radical surgical excission of the glands in the axilla and neck respectively. Both are alive and well and symptom free after 36 months and 34 months respectively. One had radical surgical excision of cervical glands followed by radiotherapy to site of excision, he remains disease free after 3½ years. Two patients had surgical excision followed by single agent chemotherapy (Endoxan) and are alive and well at the time of writing. The remaining nineteen patients had full course of combined chemotherapy. Seven of these (36·7%) had died after a partial remission and the median survival was 40 weeks. The other twelve (63·3%) are in complete remission. One of them, a 5 year old boy with MC type and in clinical stage IVB has been disease free for 24 months. The median survival time of the twelve patients so far is 82 weeks. The details of all the cases are shown in Table 5.

Discussion

The clinical features of the cases reviewed here are similar to previous reports from this country. We confirm that the patients present rather late in their disease (majority in Stages III and IV). Only four of our patients had the benefit of a satisfactory lymphangiographic study, thus it is possible that some were placed in a lower stage than would have been the case if this had been available. We also confirm that the mixed cellularity and lymphocyte depleted histological types predominate in this locality.

The response of the patients to therapy can be classified as fair, and certainly not as good as achieved in other centres quoted above, but is far more encouraging than previous reports from this country. One of the reasons for our failure to achieve as good a result as we would have liked is the very high default rate. Perhaps a systematic search for the patients could have prevented this, but several of the patients came from areas far removed from the hospital and were not easily traced. Further, a large number came to us as a last resort after trying many hospitals and native therapy and already had very extensive disease which is known to be less responsive to treatment.

One other factor contributing to the relatively unsatisfactory response rate is the difficulty in obtaining regular supplies of the drugs; caused partly by their expense (which in turn contributed to the high default rate) and partly by losses during transportation from the manufacturers. We did not find any evidence in this study for the suggestion that Hodgkin's disease in Africans is more fulminant or more resistant to therapy. A more objective assessment of this claim must await the time when the other problems of a high default rate, irregularity of supply of drugs and very late presentation can be eliminated.

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