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A Reappraisal of the Management of Common Childhood Abdominal Malignancies in Ibadan

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Johnson AOK and Williams CKO. A Reappraisal of the Management of Common Childhood Abdominal Malignancies in Ibadan. *Nigerian Journal of Paediatrics* **1984; 11: 29.** The relative frequency of neoplastic diseases causing gross abdominal tumours in childhood at the University College Hospital, Ibadan, between 1969 and 1978, was studied. Among 424 cases of malignant conditions identified, 297 occurred in the abdomen and these included 190 cases of Burkitt's lymphoma (BL), 61 of Wilm's Tumour (WT) and 36 of neuroblastoma (NBA). Less common abdominal malignancies in the series included rhabdomyosarcoma (4), reticulosis (3), hepatoblastoma (2) and hepatoma (1). The mortality rates for BL, WT and NBA were 96%, 93% and 100% respectively. Survival was longer than 6 months in only 16%, 9% and 14.6% respectively, among BL, WT and NBA patients. These mortality and survival rates were not better than those previously reported from the same institution; they were, indeed, inferior to those reported from other parts of the world. A mortality rate of 42% and survival of over 6 months was observed in 42% of 19 BL patients who were treated prospectively with combination chemotherapy. Improvement in the management of childhood abdominal malignancies is advocated since, with appropriate management, two of the three most common of these diseases are curable in a high percentage of the patients.

Introduction

THE high morbidity and mortality among children in less technically developed countries of the world is due mostly to preventable diseases, but Sinnette[1] has shown that neoplastic diseases also account for a large number of deaths among children in Ibadan. Previous studies on childhood malignancies from the University College Hospital (UCH), Ibadan, concerned specific types of tumours.[1-7] However, only the histopathological studies by Williams[5] from the same institution involved a determination of the relative incidence of all childhood tumours. Because of our observation that abdominal tumours appear to be relatively common and often present problems of diagnosis and management, the present study was undertaken (*a*) to determine the relative frequency as well as to review the management and outcome of the common abdominal tumours

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in childhood seen at the UCH between 1969 and 1978, a period of ten years and (*b*) to compare the management and outcome in cases of Burkitt's lymphoma (BL) studied prospectively and treated with multiple chemotherapeutic agents between 1978 and 1979 with those treated during the previous ten years.

Materials and Methods

The admission records of all paediatric wards and the necropsy records in the department of Pathology, UCH, Ibadan, during the 10-year period, 1969-78, were scrutinized and the records of all proven cases of malignant diseases reviewed. Information abstracted from the records included age, sex, duration of symptoms before presentation, clinical stages at presentation and outcome of management with emphasis on the commonest abdominal tumours. The treatment regimens used for a majority of the patients with all types of malignancies seen during the 10-year period as well as that used for BL in particular, during the period October, 1978 and December, 1979 are given below:

Burkitt's Lymphoma (1969-78)

During the 10-year period under review, a majority of patients with BL were treated initially with cyclophosphamide (10-15mg/kg body weight/day) administered intravenously for 5-10 days depending on the response. This course was repeated if the tumour regressed and no severe bone marrow depression occurred. A maintenance dose of 3-5mg/kg body weight/day orally, for 4-8 weeks was used in some of the patients, including those with good initial response and others with partial response. In patients with little or no response and in those in relapse, other drugs which were used included nitrogen mustard, vincristine, melphalan, cytosine arabinoside and methotrexate, which was usually given intrathecally, often when there was already evidence of central nervous system (CNS) involvement. Surgical treatment was irregular and very occasional. Nine of the 101 cases studied had limited tumour resection, while seven others had exploratory laparotomy and biopsy of the tumour only.

Burkitt's Lymphoma (October, 1978-December, 1979)

Between October, 1978 and December, 1979, nineteen consecutive patients with BL were studied prospectively. All but four of these were previously untreated. Following discharge from the hospital, several of these patients were seen and followed up at the Haematology Day-Care Unit. It was originally intended to manage all the patients with a regimen of drug combination (Table I) as described by Ziegler.[8] However, because of erratic drug supply, modifications had to be made from time to time. Table II shows the percentages of the projected drug-dose that were actually given at each of the 15-day treatment cycle. After 6-7 cycles of 15-day cycles of combination chemotherapy, a maintenance therapy,

TABLE I

Schedule of Drug Combination in the Treatment of Burkitt's Lymphoma according to Ziegler [8]

Drug	*Dose* (mg/m^2)	*Route*	*Schedule*
Cyclophosphamide	1000	IV*	Day 1*
Vincristine	1.4	IV	Day 1
Methotrexate	12.5	IT	Day 1 and 3
Methotrexate	12.5	IV*	Day 1, 3 & 4
Prednisolone**	1000	IV	Day 1

IV = Intravenous IT = Intrathecal

The following modifications were effected because of erratic drug supply:

*Oral route of equivalent dose spread over 5 days was used when injectable cyclophosphamide, or over three days when injectable methotrexate was not available.

**Equivalent dose of dexamethasone was given on two consecutive days when methylprednisolone was not available.

TABLE II

Doses of drugs actually given at each treatment cycle expressed as percentages of originally scheduled doses

Drugs	*No. of cycles*								
	1	2	3	4	5	6	7	8	9
Cyclophosphamide (iv or oral)	100 (17)	100 (15)	96.1 (13)	93.6 (11)	88.9 (9)	100 (9)	100 (8)	97.8 (3)	100 (1)
Vincristine	98.2 (17)	78.4 (15)	70.0 (13)	42.7 (11)	60.0 (9)	54.4 (9)	33.8 (8)	46.7 (3)	0 (1)
Methotrexate (iv or oral)	79.4 (17)	83.3 (15)	95.4 (13)	81.8 (11)	77.8 (9)	82.5 (9)	100 (8)	100 (3)	100 (1)
Methotrexate (IT)	40.0 (17)	40.0 (15)	38.5 (13)	40.9 (11)	33.3 (9)	22.2 (9)	12.5 (8)	0 (3)	0 (1)
High dose steroids	33.8 (17)	35.0 (15)	42.5 (14)	29.1 (11)	44.4 (9)	27.8 (9)	12.5 (8)	0 (3)	0 (1)

Figures in parenthesis represent the number of patients treated at each cycle
IV = Intravenous
IT = Intrathecal

consisting of the same drugs and doses, was given at monthly intervals for a total of one year. As at the time of this review, only one of the 19 patients had completed this programme. One patient underwent splenectomy, partial pancreatectomy as well as enucleation of a destroyed eye following 3 courses of chemotherapy. The patient subsequently received 4 more cycles of chemotherapy post-operatively.

Wilm's Tumour (1969–78)

Surgery played a prominent part in the management of Wilm's tumour (WT). Twenty-four (55%) of 44 cases underwent laparotomy. Surgery was undertaken as soon as possible after essential investigations had been performed and diagnosis made. However, when technical problems were anticipated owing to the bulkiness of the tumour, a course of chemotherapy consisting of actinomycin D (15 micrograms/kg body weight/day) was given intravenously for 3–5 days with or without nitrogen mustard (0.1–0.2mg/kg/day) for 5–7 days. This was followed by nephrectomy and more courses of chemotherapy. Three patients, who were *in extremis*, died before treatment could be initiated. Seventeen other patients who were considered unfit for surgery received chemotherapy only.

Neuroblastoma (1969–78)

Chemotherapy with or without surgery was the main method of treatment in the 39 cases included in this series of both abdominal and extra-abdominal neuroblastoma (NBA). Methotrexate, nitrogen mustard, cyclophosphamide, and vincristine were the drugs used in the majority of cases, usually in combination and in standard doses for 5–7 days. All the children received drug treatment, whereas 28 had exploratory laparotomy. Complete tumour resection was carried out in six cases, while 22 had partial tumour resection.

Results

Total admissions and mortality

During the 10-year period (1969 to 1978), the total admissions into the paediatric wards (excluding the Special Care Baby Unit) were 11,368 of which 424 (3·7%) were due to malignant diseases. Over the same period, there was a total of 2,306 cases of death, of which 321 (13·9%) were due to malignant diseases.

Frequency of tumours

Table III shows that 297 (70%) of the 424 cases of tumours occurred within the abdomen.

TABLE III

Frequency of 424 Childhood malignant Tumours in Ibadan between 1969 and 1978

Tumour	*No. of cases*	*% of Total*
Abdominal		
Burkitt's lymphoma	190	44.8
Wilm's tumour	61	14.4
Neuroblastoma	36	8.5
Rhabdomyosarcoma	4	0.9
Reticulosis	3	0.7
Hepatoblastoma	2	0.5
Hepatoma	1	0.2
Non-abdominal		
Extra-abdominal Burkitt's lymphoma	47	11.1
Leukaemia	30	7.1
Extra-abdominal neuroblastoma	21	5.0
Retinoblastoma	15	3.5
CNS Tumours	14	3.3
Total	424	100.0

Abdominal Burkitt's lymphoma was the commonest, comprising 190 (44.8%) of the total number of cases followed by Wilm's tumour 61 cases (14.4%) and neuroblastoma 36 cases (8.5%). Less common abdominal tumours included urogenital rhabdomyosarcoma (4 cases), three of whom presented with bladder involvement and one as a vaginal tumour (sarcoma botyroides) with pelvic extension; hepatoblastoma (2 cases); Hodgkin's disease (2 cases), hepatoma and lymphosarcoma (one case each). Of the extra-abdominal tumours, Burkitt's lymphoma was again the commonest, constituting 11.0% of the total followed by the leukaemias (7.0%), extra-abdominal neuroblastoma (4.9%), retinoblastoma (3.5%) and tumours of the central nervous system (3.0%).

Age and Sex distribution

The age distribution of the 297 children with abdominal tumours are summarized in Table IV. The peak age incidence in BL was 7 years and 129 (67.9%) of the 190 cases occurred between 5 and 10 years of age. The peak age incidence for WT was three years, 32 (52%) of the 61 cases occurring between 1 and 3 years of age. Although there was a wide scatter in the ages of children with abdominal NBA, 12 (30%) of the 36 cases were under 1 year (2 were less than one month old) at presentation. The three cases of reticuloses ("non-Burkitt's" malignant lymphoma) occurred between the ages of 10 and 14 years.

There were 246 male and 177 female children (M:F ratio, 1.4:1). The male:female ratio of patients with BL and WT was approximately the same, while the ratio for those with abdominal NBA was 3.5:1. However, in the combined abdominal and extra-abdominal cases with NBA the male:female ratio was 1.4:1. Thus, it would appear that the male sex is more prone to developing abdominal NBA. Three of the four cases of rhabdomyosarcoma occurred in females.

TABLE IV

Age at Presentation among 297 Children with Abdominal Tumours

Age (years)	*Number of cases*							*Total*
	BL	*WT*	*NBA*	*RHMA*	*RETIC*	*HBA*	*HPA*	
< 1	—	—	12	—	—	—	—	12
1	—	8	1	2	—	—	—	11
2	—	8	5	—	—	1	—	14
3	7	16	5	—	—	—	—	28
4	13	5	2	1	—	—	—	21
5	15	4	1	—	—	—	—	20
6	20	8	2	1	—	—	—	31
7	37	4	2	—	—	—	—	43
8	24	—	—	—	—	—	—	24
9	15	—	—	—	—	—	—	15
10	18	4	2	—	1	1	1	27
11	11	4	1	—	—	—	—	16
12	24	—	2	—	1	—	—	27
13	4	—	—	—	—	—	—	4
14	2	—	1	—	1	—	—	4
Total	190	61	36	4	3	2	1	297

BL = Burkitt's lymphoma NBA = Neuroblastoma HBA = Hepatoblastoma
RETIC = Reticulosis

Duration of symptoms and diseases stage at presentation

In all the three commonest types of tumour, more than 50% of the patients presented within the first three months of onset of symptoms although 8 (4%) of 190 children with abdominal BL and as many as 9 (15%) of 61 children with WT presented more than 6 months after onset of symptoms. Using the staging criteria for BL as proposed by Ziegler and Magrath,[9] 5% of the cohort of children studied prospectively (1978–79) presented in stage A, 5% in stage B, 16% in stage C and 74% in stage D. According to the staging criteria of D'Angio *et al*,[10] 28 (64%) of 44 cases of WT had either intra-abdominal or distant metastasis i.e. Stage III or IV, at presentation. Similarly, only 8 (14%) of 57 cases of neuroblastoma had local disease (Stages I and II), while others had disseminated disease (Stages III and IV) at presentation.

Outcome of Management

Burkitt's Lymphoma

Of the 101 patients with BL who were studied retrospectively, 47 (47%) showed initial total tumour regression after chemotherapy. Of these 47 patients, 31 (66%) relapsed within 2–9 months of the initial treatment and died. Thirteen defaulted from the clinic after the initial good response to chemotherapy and only 3 were known to be alive 3–11 months after initial treatment. Thirty-one children showed no significant tumor regression and 29 died, while two defaulted. There was partial regression in the remaining 23 patients, nine of whom died during subsequent follow-up, while 14 defaulted from clinic attendance. Only 16% of the patients survived longer than 6 months. A complete response rate of 47% in the present study is unimpressive compared with a rate of 94% reported by Ziegler,[11] 83% by Olweny *et al*[12] and 81% by Nkrumah *et al*, [13] using cyclophosphamide alone. The 47% response rate is the same as that previously reported earlier from the same institution. Similarly, a mortality rate of 96% occurred in the present series as compared to 77% previously reported from the same institution.[14]

The outcome of treatment of 19 patients who received a combination of chemotherapy is shown in Table V. The results were analysed to demonstrate the degree of control of BL of the CNS and of the non-CNS organs (i.e. systemic regions). This is because the CNS, which is frequently involved in BL, is exposed differently to the parenterally administered drugs as a result of the "protective" functions of the blood-brain barrier. This and the additional fact of unavailability of drugs that could be injected intrathecally made it necessary to evaluate the

TABLE V

Outcome of Treatment in 19 Patients with Burkitt's Lymphoma Using Combination Chemotherapy

Stage of disease	*No of Patients*	*Remission pattern*				*6 months remission duration*				*Relapse/complete response*	
		Systemic	%	*CNS*	%	*Systemic*	%	*CNS*	%	*Systemic plus CNS*	%
A	1	1/1	100	—		1/1	100	—	—	0/1	0.0
B	1	1/1	100	—	—	0/1	0	—	—	1/1	100.0
C	3	1/2 (1)	50	—	—	1/1	1000	—	—	0/1	0.0
D	14	11/11 (3)	100	8/10	80	6/7×*+	86	3/6X	50	4/11	36.0
Total	19	14/15 (4)	93.3	8/10	80	8/10	80	3/6	50	5/14	36.00

Figures in Parenthesis = No of patients that died of various causes other than systemic tumour progression (see Text)

* = 2 patients not yet followed-up long enough at time of analysis

X = 2 patients died in systemic remission before 6 months of follow-up

\+ = One patient had splenectomy and partial pancreatectomy in addition to intensive chemotherapy

CNS separately from the rest of the body in respect of outcome of treatment. Of the 19 patients, four died within the first week of management from various causes other than failure of response to treatment. They could therefore, not be evaluated in terms of response to chemotherapy. One of the patients died of *Pseudomonas aeruginosa* meningitis which was believed to have been acquired through a lumbar puncture. One patient died within 24 hours of initiation of chemotherapy, presumably of metabolic disorders. Two patients died suddenly on day 6 of observation, one apparently from uncontrolled raised intracranial pressure and the other from an unknown cause. Fourteen (93%) of the remaining 15 patients achieved complete remission. Eight of 10 patients presenting with CNS involvement achieved satisfactory control of neurological impairments, including reversal of coma in 1, of paraparesis in 1, of paraplegia in 3, of faecal and urinary incontinence in 1, and of cranial neuropathies in 2 patients. Of the 14 patients who achieved complete remission, 3 of 6 (50%) and 6 of 7 (86%) evaluable patients were in remission of BL of the CNS and of the "systemic" regions respectively, longer than 6 months after attainment of remission. Thus, at the time of reporting, 8 (42%) of the 19 patients in this series had survived more than 6 months and eight had died, giving a mortality of 42%.

As shown in Table II, between 89% and 100% mean values of the proposed total dose of cyclophosphamide was actually given at each treatment cycle. Comparatively, much lower percentages of the planned doses of vincristine, oral or injectable methotrexate or steroids were actually given. Less than 45% of the amount of methotrexate planned for intrathecal injection was actually given. The reason for this suboptimal drug administration was the unavailability of supply from the hospital pharmacy. However, we found no evidence to suggest a link between the quantity of treatment given and failure to achieve remission or occurrence of early relapse of BL in the "systemic" areas of the body. On the other hand, it appeared that there was a close correlation between the intensity of chemotherapy of BL of the CNS with intrathecal methotrexate and the degree of control of the disease achieved.

Wilm's Tumour

Of the 44 cases of Wilm's tumour, three died without treatment, while 17 others (39%) received only chemotherapy because the disease was advanced and widespread. Fifteen of these 17 (88%) died within 2 weeks of admission and two were apparently discharged at the parents' request. Twenty-four of the 44 (55%) patients underwent laparotomy, 9 of these after an inital course of chemotherapy. Nephrectomy was followed by chemotherapy in all cases. At the time of this review, three (75%) of 4 among the 24 operated patients in whom the disease was localized to one kidney, were alive and free of demonstrable disease between 9 and 17 months after surgery. Two others with more extensive disease, were also alive 12 and 15 months later respectively, although they have both developed radiologically demonstrable metastatic pulmonary disease. Twelve patients died between a few hours and 2 weeks after surgery, while seven others defaulted from the clinic after discharge from the ward. Thus, of the 34 patients who were treated and adequately followed-up, only 3 (9%) were alive and free of disease at about 12 months after treatment. As shown in Table VI, a mortality rate of 93% was recorded in this series, compared to 83% from an earlier report from the same institution[2] and to 38% from a recent report from Zaria and Kaduna.[15]

TABLE VI

Outcome of Treatment and Mortality[a] *in three Commonest Childhood Malignancies in three Nigerian Teaching Hospitals*

	Johnson and Williams, Ibadan, 1969–79	*Bankole et al,*[2] *Ibadan 1959–68*	*Familusi et al,*[7] *Ibadan 1962–74*	*Aderele and Antia,*[14] *Ibadan 1964–73*	*Yakubu et al*[15] *Zaria/Kaduna 1973–83*
Burkitt's Lymphoma					
Single-agent Chemotherapy					
No of cases	190	None	None	133	None
% CR	47	—	—	48	—
% Surviving 6 months	16	—	—	17–20	—
% Mortality	96	—	—	77	—
Combination Chemotherapy					
No of cases	19	None	None	None	None
% CR	93	—	—	—	—
% Surviving 6 months	42[b]	—	—	—	—
% Mortality	42	—	—	—	—
Wilm's tumour					
No of cases	61	35	None	None	44
% CR	?15	?	—	—	?
% Surviving 6 months	9	14.2	—	—	13.6
% Mortality	93	83[c]	—	—	38[d]
Neuroblastoma					
No of cases	36	None	31	None	None
% CR	0	—	?19.3	—	—
% Surviving 6 months	14.6	—	12.7[e]	—	—
% Mortality	?100	—	87	—	—

a = As derived from data presented by the various publications

b = Maximum observation period of 14 months

c = Maximum observation period of 15 months

CR = Complete Remission

d = Maximum observation period of 5 years

e = Maximum observation period of 3 years

f = Present report

Neuroblastoma

Of the 36 patients with this tumour, significant tumour regression occurred in six patients who were treated with surgery and chemotherapy. However, relapse occurred in 4 of the 6 patients within 7 months of surgery and all 4 children died, while the remaining 2 patients defaulted from the clinic. Twenty-four other children died between a day and 11 weeks of their initial admission without any significant response to treatment. Nine patients who had only a biopsy taken at laparotomy and who were subsequently discharged, were lost to follow-up. Thus, in this series, 14.6% of the patients survived longer than 6 months. In view of the aggressive nature of neuroblastoma, and in view of the fact that, at least, 9 of the 11 defaulting patients were discharged in an extremely poor condition, they were all presumed dead, thus giving an estimated overall mortality of about 100%. This does not rule out the possibility of occurrence among these patients of the rare, but well-known spontaneous remission in neuroblastoma.

Discussion

In Nigeria, as in most other developing countries, the importance of childhood cancer is likely to increase with improvement in the socio-economic status of the society and effective control and eradication of infectious diseases which presently constitute the main health problems. There is, therefore, a need to improve our understanding and management of these diseases in order to improve on associated morbidity and survival rates.

Although Ngu[16] reported in the mid-1960s from the UCH, Ibadan, BL patients surviving 2 years and longer, following treatment with cyclophosphamide, we observed only a survival of less than 12 months among our retrospectively studied patients. Furthermore, the remission rate of 47% observed among these patients was inferior to 94%, 85% and 81% following a similar treatment modality reported by Ziegler,[11] Olweny *et al*[19] and Nkrumah *et al*[13] respectively. Our present experience with a combination chemotherapy used in the 19 patients studied prospectively, in this series was encouraging. Not only was higher complete remission rate of 93% achieved, but also, the percentage of the patients surviving longer than 6 months was improved from 16% to 42%. Similarly, the overall mortality decreased from 96% to 42%. Although the maximum observation period was only 14 months, at the time of assessment of the results, one patient had been free of disease for more than 12 months. In view of the unique cell kinetic properties of Burkitt's lymphoma, whereby it is the fastest growing human neoplasm[17] with a short doubling time,[18] Burkitt's lymphoma cells surviving chemotherapeutic assault would be expected to manifest as overt clinical disease latest, 6 months after discontinuation of anticancer chemotherapy. Hence, it is probably safe to predict that the prospectively studied patients would experience prolonged remission and would probably be cured of the disease. This is supported by the observation of Ziegler, Magrath and Olweny who reported that 50% of their patients treated at the Uganda Cancer Institute were in remission 5–10 years after discontinuation of chemotherapy.

The last two decades have witnessed a phenomenal improvement in the long-term survival of patients with nephroblastoma. This has been achieved through the current awareness that the treatment of choice for this disease is a combination chemotherapy with actinomycin D and vincristine. The role of adjuvant chemotherapy is to effect an eradication of systemic occult micrometastasis.[20] The successful outcome of treatment may also be explained by the slow-growing nature of nephroblastoma. Jenkins[20] has reported that between 1963 and 1968, there was a 5-year survival in 70% of a group of Canadian children and that this improved to 81% in the 1969–1974 period. By contrast, Bankole, Familusi and Ngu[2] reporting from Ibadan, observed in 35 patients treated between 1959 and 1968 (10 years) that

14% survived for 6 months or longer and only 2% for 4–5 years. The six-month survival rate of about 9% observed in the present series for another 10-year period (1969–78) is a further deterioration from the earlier experience which was discouraging. However, the recent results by Yakubu *et al*[15] appear to be more encouraging. The reasons for their lower mortality rate of 38% (compared to 93% in this series) for Wilm's tumour are not clear.

The results of the treatment of neuroblastoma has been unimpressive throughout the world.[21-22] This is especially striking in view of the remarkable improvement that has been achieved in the results of chemotherapy of other types of cancer through the multi-modality approach to management.[23] The two-year survival rate in neuroblastoma has remained about 30% over a span of several years.[22 24] A previous study of neuroblastoma in Ibadan by Familusi, Aderele and Williams[7] showed that 12.7% of patients were apparently tumour-free 8–15 months following treatment. In the present review, no significant improvement over the results of the earlier series was evident since 14.6% of the patients who did not default, survived up to 7 months after treatment.

The main reasons for the poor results in the management of the three commonest childhood neoplasia seen in Ibadan and analysed in this report include (1) late presentation at an advanced stage of disease at which, even with the best available resources, only a partial degree of disease control can be expected (2) unavailability of necessary treatment facilities, including drugs and radiotherapy. Unfortunately, the poor results obtained in childhood cancers tend to dampen the enthusiasm of physicians, especially the younger ones. It is, however, important to emphasise that the prognosis of two of the 3 most common abdominal malignancies of childhood, namely: Burkitt's lymphoma and nephroblastoma, needs not be gloomy, because there is evidence that both of them may be highly curable.[19 20] There is a need to promote the attitude of approaching the management of childhood malignancies with a curative rather than palliative intention. This approach would necessarily include an improvement of our primary health services for children, more regular drug supply and establishment of adequately equipped treatment centres, including radiotherapy units, for the management of these childhood malignancies.

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