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High-Dose Cytosine Arabinoside Chemotherapy of Burkitt Lymphoma: Advocating Sustainable Strategies for Capacity Building in Systemic Cancer Care in Nigeria

Christopher KO Williams*

Hematology/Oncology Consultancy, Port Angeles, WA 98362, USA, FHCRC/UW Center For AIDS Research (CFAR), Seattle, WA 98104, USA

***Corresponding author:** Christopher KO Williams, Hematology/Oncology Consultancy, Port Angeles, WA 98362, USA, FHCRC/UW Center For AIDS Research (CFAR), Seattle, WA 98104, USA, Tel: +1 360 797-4472; E-mail: cwilliam@nisa.net

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Abstract

Background: Major factors of treatment failure in Burkitt lymphoma (BL) in Nigerian children include drug resistance and the central nervous system (CNS) "sanctuary effect". A phase II randomized trial of high-dose cytosine arabinoside was designed to address both problems.

Materials and methods: Children with advanced BL, with or without CNS involvement, seen at the University College Hospital, Ibadan, Nigeria from 1984 to1985, and with life expectancy of at least one month, were randomized to an investigational (R-I) treatment regimen of cyclophosphamide (CTX) 1000 mg/m^2 IV day 1, Vincristine (VCR) 2·0 mg/m^2 IV day 1, cytosine arabinoside (AC) 50 mg/m^2 q12hr × 6 doses in cycles 1 and 4, and 1000 mg/m^2 q12hr × 4 doses and 50 mg/m^2 q12hr × 2 doses for cycles 2 and 3 cycles q14days × 4cycles; or a standard regimen (R II) of CTX 1000 mg/m^2 IV day 1, VCR 2·0 mg/m^2 IV day 1, AC 50 mg/m^2 q12hr × 6 doses q14days × 4 cycles. AC 50 mg/m^2 was given intrathecally on days 1 and 5 of each cycle.

Results: Complete remission rate (CR) in R-I vs R-II was 9/9 (100%) vs 6/11 (54.5%), partial response 0/9 vs 4/11 (36·4%), non-response 0/9 vs 1/11 (9·1%) and probability of overall survival (OS) 64% vs 19%. Challenges encountered then, including manpower inadequacies and unreliable drug supply continue to impact management of BL three decades later as reported from 10 Nigerian institutions between 1984 and 2014, with cost related, public health support, and manpower deficiencies resulting in poor outcomes (CR<35%, and OS< 5%).

Conclusion: HDAC overcomes drug resistance and CNS sanctuary effect in BL and could serve as basis for cancer chemotherapy research in sub-Sahara Africa, provided cultural deficiencies are addressed.

Key words:

Burkitt lymphoma; Pediatric cancer; High-dose chemotherapy; Capacity building

Introduction

Burkitt lymphoma (BL), the most common childhood cancer in Sub Sahara Africa, has long been a model disease in the studies of etiology and systemic therapy of cancer [1,2]. Single agent chemotherapy of the disease with cyclophosphamide was reported as yielding long-term survivorship of 15% in Ibadan, Nigeria, while investigators in Uganda reported about 50% 10-15 year disease free survival, an apparent cure, following combination chemotherapy with cyclophosphamide, methotrexate and vincristine, including intrathecal administration of methotrexate [3]. In earlier reports from Ibadan, Nigeria, factors responsible for BL treatment failure were identified as including primary drug resistance as well as pharmacologic sanctuary effect of the central nervous system [4,5] with some indication of possible high rate of cure of BL if these factors of treatment failure could be overcome.

The concept that when given at very high doses (greater than 10 times the conventional dose), methotrexate (MTX) and cytosine arabinoside (AC) cross the blood-brain barrier to produce pharmacological concentrations of the drugs in the cerebrospinal fluid (CSF) was recognized as promising to change the prevention and management of CNS in BL [6-8]. Following the observation in three Burkitt lymphoma children of a dramatic reversal of cerebrospinal fluid pleocytosis with effective control of central nervous system lymphomatous involvement AC 1000 mg/m^2 12 hourly × four doses (each dose being 20 times the conventional dose), with acceptable side-effects (C.K.O. Williams, unpublished), an experimental trial of a high-dose AC based regimen was conceived. The expectation was that of overcoming resistance of systemic disease, improving remission rate and better control of CNS disease, and eventually increasing the cure rate of BL with acceptable risk of side effects in the conventional setting of a resource-limited healthcare environment.

The challenges experienced in the course of the administration of the innovative cancer management are presented to illustrate the barriers that need to be surmounted in the building of sustainable capacity in systemic cancer management in modern-day Africa, if the region is to acquire proficiency in addressing the challenges of systemic cancer management specific for the region rather than adopting programs developed elsewhere.

Materials and Methods

Diagnosis

From January 1984 to December 1985, a study of efficacy, tolerability and practicability of high dose cytosine arabinoside in Nigerian children with a diagnosis of BL was initiated at the University College Hospital, Ibadan, Nigeria. Children were considered eligible if they were accessible for follow-up, had at least a cytological diagnosis of BL, presented at Ziegler's Stage C or D with or without CNS involvement, based primarily on physical examinations: stage C-intra-abdominal masses, with or without facial bone involvement; stage D-intra-abdominal masses with one or more extra-abdominal masses [9].Fine needle aspiration biopsy of conveniently localized abdominal mass was undertaken with a view to establish a rapid cytological diagnosis. Smears were prepared from the aspirate and processed with Giemsa and methyl-green pyronine stains. Other studies performed on initial patient evaluation included complete blood count (CBC), routine blood chemistry, including uric acid and lactic acid dehydrogenase (LDH), bone marrow biopsy and aspirations at two sites, lumbar puncture for examination of cerebrospinal fluid for cells, glucose, protein, LDH and microorganisms. In addition, plain radiography of the chest and abdomen were obtained. Other medical imaging facilities, including ultrasonography or computerized axial tomographic (CAT) scans were unavailable. Life expectancy of at least one month and parents' or guardians' ability to give oral consent to study were ascertained prior to inclusion in the study. At the time of the study, HIV seroprevalence was negligible in the area, thus making it most unlikely that any the cases of endemic were epidemic variant of BL [10].

Treatment protocols

Sixty children were to be assigned equally randomly by blind selection of pre-labeled cards to either the standard (Regimen II – R-II) or the investigational treatment (Regimen I – R-I) protocol. Regimen I consisted in cyclophosphamide (CTX) 1000 mg/m^2 IV day 1, vincristine (VCR) 2·0 mg/m^2 IV day 1, cytosine arabinoside (AC) 50 mg/m^2 q12hr × 6 doses in cycles 1 and 4, and 1000 mg/m^2 q12hr × 4 doses followed by 50 mg/m^2 q12hr × 2 doses for cycles 2 and 3 q14 days. Regimen II consisted in CTX 1000 mg/m^2 IV day 1, VCR 2·0 mg/m^2 IV day 1, AC 50 mg/m^2 q12hr × 6 doses q14 days × 4 cycles. AC 50 mg/m^2 was given intrathecally on days 1 and 5 of each cycle. Figure 1 illustrates the treatment regimens. There was adequate supply of AC (from a foreign drug company donation), and CTX (from hospital pharmacy). However, the supply of VCR from the hospital pharmacy was irregular, and the drug had either to be purchased by family members from outside sources if hospital supply was unavailable. Otherwise, it was omitted from the patient's treatment. Treatment protocol stipulated delay of commencement of a treatment cycle for up to a week for wbc of <3·0 × 10^3/mm^3 or platelet count of <90 × 10^3/mm^3 (i.e <3·0 × 10^9/L and <90 × 10^9/L respectively). Thereafter, a dose-adjustment of the CTX and/or AC was made by sliding scale. Dose modification of AC was similarly done based on the liver function test results. VCR was omitted for overt neurological complications, including ileus, constipation or weakness or numbness of the extremities. Given the various factors that had the potential of influencing the quality of treatment delivered, chemotherapy dose-intensity was used as a treatment quality measurement. It was calculated for each of the chemotherapeutic agents using the methods of Hryniuk et al. [11].

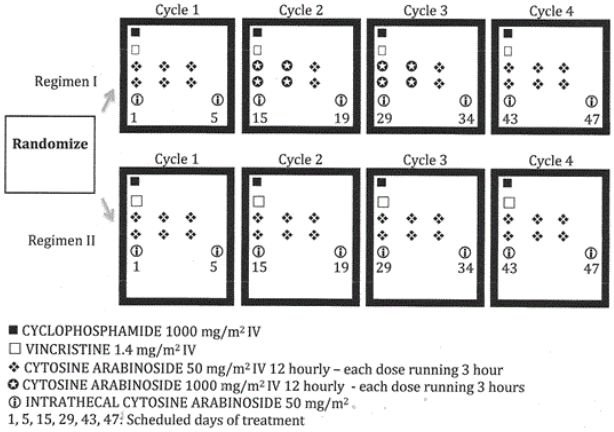

Figure 1: Diagram of treatment regimens.

All patients also received proguanil 100 mg daily as prophylactic antimalarial therapy for the duration of treatment and observation. Allopurinol 100 mg three daily was given during each treatment course. Adequate hydration by oral or intravenous routes was emphasized.

Response rates and survival analysis

Analysis of the data was carried out with Excel 2013 spread sheets. Survival analysis and comparison of the treatment regimens were performed by the Kaplan-Meier method, using Graph Pad Prism version 6·0f for Mac OS X, GraphPad Software, La Jolla, California USA.

Results

Fourteen and 16 children respectively were randomly assigned to Regimen I and Regimen II, a short-fall of 14 and 16 of the planned assignment of 30 to each treatment arm. This was due to the departure from the institution of the principal investigator, and lack of suitable replacement. The demographic features of the patients and their disease patterns are provided in (Table 1). Five of the 14 Regimen I patients were excluded from evaluation for the following reasons: 1 because of undetermined disease stage; 1 due to change of diagnosis; 2 due to early withdrawal from study; 1 due to death within 24 hours of commencement of treatment. Five of the 16 children assigned to Regimen II were excluded from evaluation because of lack of adequate documentation in 2, while 3 died within 24 hours of commencement on treatment. Table 2 shows the number of days of treatment delays between cycles. The mean days of treatment delays were significantly longer for Regimen I than Regimen II in each of the cycle intervals: 9·1 vs 2·1 ($p<0·001$) in the cycle 1/cycle 2 interval; 13·4 vs 4·8 ($p<0.01$) in cycle 2/cycle 3 interval; and 15·7 vs 3·2 ($p<0·01$) in the cycle 3/cycle 4 interval. (Table 1) shows the mean dose-intensities of the 3 agents used systemically as well as intrathecally. The mean dose-intensities (MDI) of VCR, CTX and intrathecal AC were not significantly different between the two regimens. MDI of intravenous AC was, however, significantly higher in Regimen I than in Regimen I. Similarly, the

relative mean dose intensity of Regimen I was significantly superior to that of Regimen II.

Complete remission was observed in 9 of 9 (100%) and 6 of 11 (54·5%) fully evaluable patients assigned to R-I and R-II regimen respectively. Correspondingly, partial response and non-response were observed in 0 of 9 versus 5 of 11 (45·5% and 0 of 9 versus 1of 11 (9·1%) patients (Table 1). Figure 2 illustrates the survival proportions observed for the patients in Regimen I and Regimen II with the surviving proportion of 64% and 19·7% respectively but the difference is not statistically significant.

			R-I	R-II	P-VALUE
DEMOGRAPHY	#RANDOMIZED		14 (20 to 30)*	16 (20 to 30)*	
	MALE/FEMALE		4/10	6/10	
	AGE		9.5 ± 3.5	8.5 ± 2.5	>0.5
		C	5	6	
	STAGE	D-CNS+	4	6	
		D-CNS-	4	3	
		Undetermined	1	1	
	VCR		0.34	0.45	0.2
RDI OF AGENTS					
	CTX		304.4	353.9	0.54
	IV-AC		592.2.0	102.6	<0.0001
	IT-AC		26.6	33.7	0.39
OUTCOMES	#EVALUATED		9	11	
	CR		9/9 (100%)	6/11 (54.5%)	
	PR		0/9	4/11 (36.4%)	
	NR		0/9	1/11 (9.1)	
	Survival proportion (%)		64.2	19.7	0.68

Tablet 1: Characteristics of patients, treatment agent dose-intensities, and outcomes by treatment regimens. *Maximum planned; D-CNS+: Stage D with central nervous system involvement; D-CNS-: Stage D without central nervous system involvement; MDI: Mean Dose Intensity; VCR: Vincristine; CTX: Cyclophosphamide; IV-AC: Intravenous Cytosine Arabinoside; IT-AC: Intrathecal Cytosine Arabinoside; CR: Complete Remission; PR: Partial Remission; NR: Non Responder; OS: Overall Survival.

Discussion

The study presented in this report explores the efficacy of a high-dose cytosine arabinoside (AC) based regimen as compared to a standard dose regimen. It was carried out in a standard treatment environment of an African academic medical center. While the weakness of the study is its small size, its strength lies in its design as a randomized phase II research protocol. In an era that predated the use of granulopoiesis stimulating agents, the only side effect attributable to the use of high-dose AC is the prolongation of treatment interval durations in the high-dose arm of the study (Table 2). However, neither are the leukocyte nadirs between the treatment cycles, nor the occurrence of treatment complications, including infections, significantly different between the two regimens. The treatment outcomes, including the remission rates and proportional survival patterns (Table 1), suggest the superiority of the high-dose chemotherapy strategy. The study was, however, not designed to show a statistically significant survival difference. The survival curves (Figure 2) suggest that factors causing early rapid demise are similar in both arms, as the curves start to separate only after three months. In this respect, it would seem that the augmented AC dose of R-I did not play a role in the survival events.

Cycle Interval		Regimen I	Regimen II	P-VALUE
#	Events			
1-2	Duration (days)	9.1	2.1	<0.001
	WBC* nadir (× 10^9/L)	1.36	1.36	>0.5
2-3	Duration (days)	13.4	4.8	<0.01
	WBC nadir (× 10^9/L)	1.70	1.70	>0.5
3-4	Duration (days)	15.70	3.2	<0.01
	WBC nadir (× 10^9/L)	1.74	2.43	>0.5

Table 2: Chemotherapy induced myelosuppression analyzed by inter-cycle interval duration and leukocyte nadir; *WBC: White Blood Cell Count.

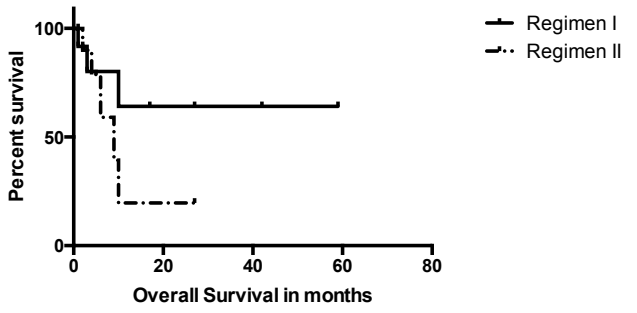

Figure 2: Survival proportions: Regimen I vs Regimen II.

The study suffered from several limitations including inadequate drug supply, especially VCR, which the family of the children had to procure on their own. This probably impacted on the quality of the treatment that could be provided and its outcomes, especially given the importance of this agent in the management of BL [12]. Other problems included manpower training and recruitment deficiencies. These contributed in the premature ending of the study upon the departure of the principal investigator of the study due to lack of institutional support, when only about half as many of the proposed number of patients had been recruited to either arm of the study. Thus, sustainability of the research effort was severely compromised by manpower deficiencies. Follow-up of patients after discharge was a major problem, in spite of the effort of dedicated social workers laboring to locate families in a multi-million city, which was largely unplanned, with many unnamed streets and unnumbered houses, and extreme rarity of a landline telephone. While the need of progress through scientific methodology was recognized, there was also concern about the ethics of medical research in the midst of socio-economic deprivation, rampant illiteracy and urgency of care.

Essentially, the manuscript illustrates the challenges of the development of clinical scientific research in sub-Sahara Africa. An attempt to invent a solution to prevalent clinical problems received the recognition and support of a foreign entrepreneurial organization, but not that of the local institution, thus setting back the initiative.

Thirty years following the publication of the preliminary findings of this study, no work has been done in the locale to confirm or refute the work described [13]. A review of publications on the chemotherapy of BL in Nigeria in the 30 years since the initiation of the study shows that none of them is a product of a scientific endeavor designed to address a specific problem of the management of BL [14-24]. The publication of Ngoma et al,[23], which is an international study of the treatment of BL, piloted by the International Network for Cancer Treatment and Research (INCTR), based in Brussels, Belgium, and in which two Nigerian centers were included, would seem to be an exception. Similarly, the Groupe Franco-Africain d'Oncologie Pédiatrique (GFAOP), which is based in France, coordinates clinical research in Francophone Africa [25]. While the reports from the Nigerian institutions uniformly show poor management outcomes, as indicated by CR of less than 35% [16,19,22] compared to 67% that was reported earlier from the region(4), and one-year OS of less than 5% [16,22] compared to the earlier report of 44% (4), the INCTR, using treatment regimens other than the high-dose AC-based, reported CR of up to 81%, and OS of 61%. GFAOP reported similarly favorable results [25]. Improved results are therefore, possible in Nigerian medical institutions. There is, however, a need to promote clinical scientific research activities within medical institutions in the country and other parts of sub-Sahara Africa.

Conditions outlined in (Figure 3) underline the prevailing constraints in the provision of cancer care, including cost and manpower related deficiencies resulting from a lack of public health support. Particularly concerning is the observation in some of these publications [17], which appears to link the prevailing unsatisfactory childhood cancer care in the country to the economic hardship imposed on the healthcare system by the so-called Structural Adjustment Program, which was introduced into the national socio-economic milieu around 1986 in response to some international economic dictates [26].

Treatment strategies with augmented doses of AC, as described in this report, can probably be safely delivered in prevailing environment in today's academic centers in Nigeria, which is unlikely to be worse than the situation in which the study was done 30 years ago. The treatment outcomes also suggest that such regimens could serve as alternatives to other regimens developed elsewhere. However, the regimen described in this manuscript needs to be confirmed for safety and efficacy. Thereafter, it can be developed further, especially given the improved safety measures of modern cancer therapy, including the availability of granulopoiesis stimulating factors. Furthermore, acquisition of management capability for BL is likely to influence the systemic cancer care for more difficult cancer types of both adults and children, such as the leukemias and non-Burkitt lymphomas. An example is the childhood acute lymphoblastic leukemia, which is highly curable in developed countries, but is associated with poor treatment outcomes in Nigeria when it is managed with standard systemic therapy approaches, thus, indicating a need for an innovation in the management of its African variants [27,28]. The acquired capacity could also be useful in the management of other malignancies, such as breast and colon cancer.

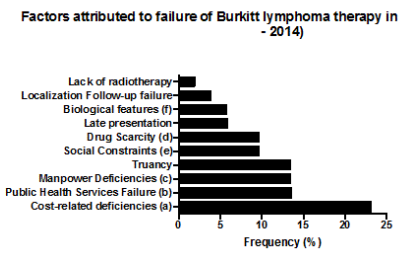

Figure 3: Factors attributed to Failure of Burkitt lymphoma therapy in Nigerian studies; Financial contraints to adequate chemotherapy, diagnostic procedures, follow-up visit leading to truancy; Care contraints resulting from laboratory and drug-user fees following the introduction of "Structural Adjustment Program" (SAP) in the Nigerian national medical service provision; lack of specialized care centers; lack of governmental oversight to prevent fake drug circulation; Qualitative and quantitative deficiencies; Lack of genuine pharmaceuticals and absent control of circulating fake drugs; Literacy, depency on unorthodox and associated premature abandonment of conventional therapy; Atypical anatomical and biological disease characteristics.

The data provided in this paper support a justification to encourage active promotion of clinical practice and research in systemic cancer therapy in African countries. Systemic therapy of BL is highly instructive in the African setting for several reasons. The disease frequently afflicts a critical population segment that not only predominates nationally, but also has significant economic potentials, thus signifying it as a priority health target. Furthermore, it is not only a potentially curable cancer, it is a relatively cheap cancer to treat [17]. It is a model disease for learning the principles of cancer chemotherapy, as reported earlier [12] as well as the findings in this paper. Developing capacity in the management of BL in sub-Sahara Africa is likely to yield dividends in the management of more complex cancers of adults in much the same way as the management of childhood acute lymphoblastic leukemia in developed countries led to the evolution of universal approaches in the management of complex malignancies of children and adults.

The reported experiences of Nigerian workers suggest a need for cultural changes that will involve a broad spectrum of stakeholders at several layers of the community, including the adoption of team approach in cancer care, encompassing physicians, nurses, pharmacists, social workers, hospital administrators and public health ministries, as opposed to the prevailing "lone wolf" attitude of "leading experts" in clinical and academic practice. Appropriately trained individuals, such as hematologists/oncologists, should lead such teams, unlike what obtains currently in much of the cancer treating centers in Nigeria, and in much of sub-Sahara Africa. Members of the team, including providers from disciplines such as general surgery, internal medicine, pathology, pharmacy, general nursing, social services and others, would learn to interact among themselves with a view to producing the best patient centered outcomes, while modeling their role after their counterparts in countries where systemic cancer therapy is well established. In addition to promoting good clinical practice of systemic cancer care, it should promote the development of clinical trials. Regular interactions of the team with the hospital administration and policy makers at the regional or national health ministries would go a long way in ensuring stability and sustainability of the efforts of the team. The team would also develop ways and means of interacting with lawmakers in the national parliaments with a view to educating them about cancer and its systemic management.

Conclusion

A high-dose cytosine arabinoside-based treatment regimen administered in a randomized phase-II study setting thirty years ago to Nigerian children with advanced Burkitt lymphoma was well tolerated in spite of the of healthcare limitations of the era. It resulted in improved treatment outcomes. However, social and cultural challenges encountered then persist today, resulting in setback of management outcomes and signaling a need for cultural changes at various community levels, including public healthcare system and various categories of care providers so as to promote capacity for creative endeavor in addressing local systemic cancer care challenges.

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