THE BENEFITS OF A COMBINATION OF SURGERY AND CHEMOTHERAPY IN THE MANAGEMENT OF BURULI ULCER PATIENTS

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ABSTRACT

Buruli ulcer, a tropical, swampy climate disease, is one of the commonest diseases associated with most typical villages such as those in the Bomfa sub-district of Ejisu-Juaben District in the Ashanti Region of Ghana. In response to the World Health Organization's guidelines on the use of Buruli ulcer chemotherapy a study was conducted to investigate the role of surgery combined with chemotherapy in the control of Buruli ulcer in this endemic area.. In all 62 patients within the period January 1st till December 31st 2005 ranging from 4 to 79 years were treated through the combination of surgery and chemotherapy,72.6% of which had their lesions on their lower limbs. The sizes of edematous forms reduced by 80% as a result of chemotherapy thereby enabling lesser area of excision as compared to the pre-chemotherapeutic era. There was a 50% reduction in the number of multiple surgeries per patient as compared to the pre-chemotherapeutic era. The "dual" mode of treatment (chemotherapy + surgery) reduced hospitalization period to 44.2% which should directly reduce the cost of treatment. Follow-up on these patients recorded no signs of recurrence. The recommended dosage of Rifampicin and Streptomycin - the Buruli chemotherapeutic drugs - was strictly adhered to in the treatment protocol.

Keywords: *Buruli ulcer, chemotherapy, surgery*

INTRODUCTION

Buruli ulcer (BU), a chronic, dermal and sometimes bony infection caused by *Mycobacterium ulcerans,* since 1980, has emerged in tropical swampy regions especially in West Africa (Agbenorku, 2000; Asiedu *et al.,* 2000). BU has low mortality but causes long-term disability in about 25% of its victims (Lehman *et al.,* 2005). In 2004, the World Health Organization adopted a resolution to improve the surveillance and control of BU, to accelerate its research and control (Grosset and Portaels, 2004). Hitherto, BU was considered only a surgical disease with sporadic antibiotic administration (Hayman, 1993; Agbenorku and Akpaloo, 2001; Buntine *et all.,* 2001; Agbenorku *et all.,* 2005).

BU had become one of the commonest diseases associated with typical villages such as those in

the Bomfa sub-district of Ejisu-Juaben District in the Ashanti Region of Ghana. The population of Bomfa and its immediate environs (altogether known as Bomfa sub-district) was 21,924. Children form about 16.5 percent of the population (Demographic records of Ejisu-Juaben District, 2000).Bomfa is 30km from Ejisu, its district capital and 10km from Konongo, the district capital of the nearby Asante Akim North District (Fig. 1).

For proximity, most Bomfa sub-district patients patronized Konongo Government Hospital rather than Ejisu Government Hospital at Ejisu, their district capital. There were four health facilities in the Bomfa sub-district, namely, *Bomfa Health Centre* at Bomfa, *Agyenkwa Clinic* at Hwereso, *SDA Clinic* at Nobewam and *Huttel Health Centre* at Buamadumase.

A study was conducted using *Patients' In–take and Engagement Form* as data base to find out factors that would enhance the treatment of the patients and subsequent eradication of the disease from the Bomfa area.

MATERIALS AND METHODS

By the permission and advice from the Ejisu-Juaben District Health Administration thirty-two community based volunteers (two from each of the 16 communities in the Bomfa sub-district), ten teachers from selected basic schools and two staffs each from the four health centres/clinics in the sub-district were trained to identify cases. Two clinical nurses from each of the four health centres/clinics were also trained on the administering of Buruli chemotherapeutic drugs and wound dressings. These trainings were conducted in a series of four sessions in the health centres/clinics. Additionally five clinical nurses from the Bomfa Health Centre were given further trainings in wound care and prevention of disability techniques in a week long session at the Global Evangelical Mission (GEM) Hospital at Apromase in the Ejisu-Juaben District.

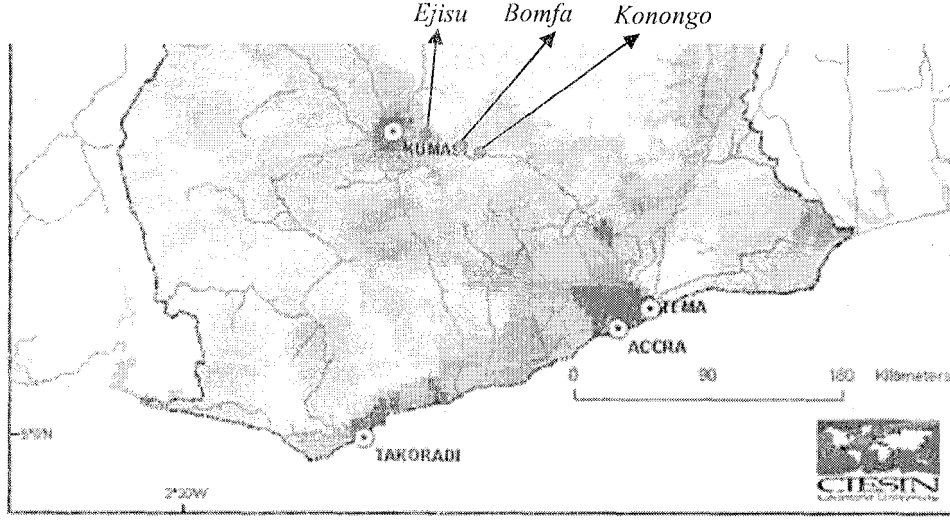


Fig. 1: Map Showing Kumasi, Bomfa, Ejisu and Konongo

Source: *Center for International Earth Science Information Network (CIESIN) - The Earth Institute at Columbia University Website*

"Patients' In-take and Engagement Form" was filled for the identified patients at the beginning of the medical intervention. These filled forms were randomly sampled as the main source of information for this write up. That is, a purposive sampling technique was used in selecting the population target after which one out of every *"Patients' In-take and Engagement Form"* filled was taken based on random sampling for analysis.

Protocol for Treatment

Antibiotics: In the antibiotic treatment of Buruli ulcer patients the WHO guidelines were strictly adhered to. The antibiotics used were Rifampicin tablets given 10mg/kg of body mass and Streptomycin injection given deep intramuscularly daily in the dosage of 15mg/kg body mass. Rifampicin, an antimycobacterial agent, is a semisynthetic derivative of rifamycin which is obtained from *Streptomyces mediterranei.* Rifampicin is a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. Streptomycin is also an antimycobacterial agent. It is an aminoglycoside antibiotic derived from *Streptomyces griseus* (Grosset and Portaels, 2004). The two drugs were generally given four weeks before surgery. After surgery the medications continued for the next four weeks. Some continued for four more weeks making a total of twelve weeks. Most often the medications were given on out-patient basis with monitoring from the local health staff.

Surgery: Surgery was started usually after the first course of the antibiotics (four weeks). Excision was done first and a week later grafting - split-thickness skin graft - was done. Generally those cases that needed contracture release were done after the wounds had been treated. Normally patients stayed further on admission for two to three weeks after the final surgery. Further dressings and drug therapy were continued on out-patient basis. Patients were then reviewed fortnightly initially and later on monthly either in the GEM Hospital, in the community clinic/health centre or at home by the local health staff or GEM Hospital team.

Prevention of Disability (POD): POD has become an integral part of BU treatment process just as antibiotics and surgery. Several exercises have been developed for patients depending on the location of their lesion to regain the proper functioning of the affected part (Lehman *et al.,* 2005). All the patients went through a process of disability prevention which started from the very first day of treatment. This continued in the operating theatre during splinting and proper positioning and bandaging through the wound care process and after discharge until the patient totally regained the use of the affected part. This drastically reduced the number of contractures that had to be released and thereby reducing the period of hospitalization.

Problems encountered

The problems associated with this study were many. Important among them were:

- ***Choice of project area***
  The choosing of a specific area for this pilot project took some time because there were so many sub–districts in the various districts in the Ashanti Region that equally needed help just as the Bomfa sub–district.

- ***Lack of resources***
  In the process of case detection, it took a great effort financially to get dedicated people for the task as it was time consuming. In transporting the patients to the hospital, the health education team had no choice but often had to squeeze in the same vehicle with the patients. The maintenance of these patients at the hospital was also financially burdening as many were subsistence farmers.

- ***Lack of access roads***
  Most of the patients from the Bomfa subdistrict as already stated were settlers on

farmlands in thick evergreen tropical forests that had no link roads. It was therefore very difficult in some instances for the health team to get to the dwelling places of the patients. In such situations the vehicle would be packed and the team had to walk some kilometers to the destinations of the patients. Local bed stretchers were designed with the help of patients' family members to carry the patients to the vehicle.

- ***Lack of care-takers***
  A number of the patients could not be brought to the hospital because they had no care-takers to look after them during their period of hospitalization. A care-taker is a person who stays with the patient till recovery, to cook, wash and provide any assistance needed by the patient. The lack of care-takers coupled with the hospital's inability to provide catering and laundry services for the patients had resulted in some untreated.

RESULTS

The pilot project for the Bomfa sub-district within its first one year of operation – January to December 2005 - brought a total of sixty- five patients out of the identified ninety to the GEM Hospital. Out of these sixty-five for whom the *"Patients' In-take and Engagement Form"* was filled, sixty-two of the forms were used for the purpose of this work. The following findings from the sixty-two forms were therefore a representation of all patients:

- The ages of the analyzed 62 patients ranged from 4 to 79 years (Table 1; Fig. 2).
- Males were affected more than females to the ratio 18: 13 as evident from Table 1 and Fig. 2 below:

Table 1: Age and Gender Distribution of Patients

Age Range	No. of Female Patients	No. of Male Patients	Total Number of Patients
0 – 4	3	1	4
5 – 9	7	8	15
10 – 14	2	5	7
15 – 19	1	5	6
20 – 24	3	3	6
25 – 29	5	0	5
30 – 34	1	1	2
35 – 39	0	1	1
40 – 44	1	1	2
45 – 49	0	0	0
50 – 54	0	1	1
55 – 59	0	0	0
60 – 64	0	2	2
65 – 69	0	2	2
70 – 74	1	2	3
75 – 79+	2	4	6
TOTAL	26	36	62

Source: Study Material – *Patients' In–take and Engagement Form*

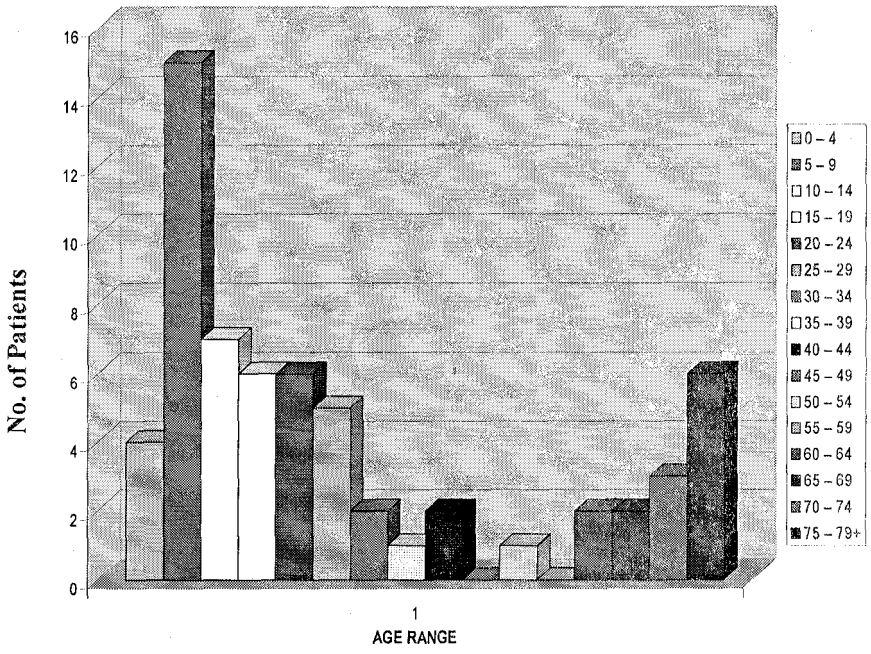


Fig. 2: Age Distribution of BU Patients

Source: Study Material – *Patients' In–take and Engagement Form*

- Sizes of edematous forms reduced by 80% as a result of chemotherapy thereby enabling lesser area of excision as compared to the pre-chemotherapy era.
- There was a 50% reduction in the number of multiple surgeries per patient as compared to the pre-chemotherapeutic era.
- No complication was observed in the use of Buruli chemotherapeutic drugs (Streptomycin & Rifampicin).
- No signs of recurrence were observed with the follow-up on the patients.

The patients were further grouped into three categories:

I - *children* majority of who are school pupils;
II -*working force* and
III - *the aged.*

These are shown in Table 2 and Figure 3 below:

This categorization represented 26:23:13 ratio of the disease among *children*, the *working force* and *the aged* respectively. That is, *children* constituted 41.9% while the *working force* was

Table 2: Deductive Age Limits of Patients from Table 1 In Relation to their Economic Strengths

Age Limits	No. of Patients	
0 – 14	26	*Children*
15 – 29	17	
30 – 44	5	*Working Force*
45 – 59	1	
60 – 75+	13	*The Aged*
Total	62	

Source: Study Material - Patients' In-take and Engagement Form

37.1% with the remaining 21.0% being *the aged*. Thus among the inhabitants of the Bomfa sub-district children were more vulnerable as far as Buruli ulcer infection was concerned (Table 2; Fig. 2).

Analyzing the marital status of the patients, nine of them (14.5%) were married, twenty-six (42.0%) were single, seventeen (27.4%) were divorced and ten (16.1%) of them widowed as shown in Table 3.

Diagnoses

The various diagnoses of the 62 patients were analyzed. Fifty-five, that is, 88.7% of the Buruli ulcer patients had their cases being late ulcers. There were six patients (i.e. 9.7%) with nodules and one with plaque (1.6%) as shown in Table 4. The cases were confirmed by histopathology.

Table 3: Marital Status/Occupation of Patients

Marital Status	Number of Patients	Occupation
Single	26	Students/Pupils/Children
Married	9	Farming/Petty trading
Divorced	17	Farming/Petty trading
Widower/ Widow	10	Farming/Petty trading
TOTAL	62	

Source: Study Material – *Patients' In–take and Engagement Form*

Fig. 3: Economic Status of Patients

Source: Study Material – *Patients' In–take and Engagement Form*

Table 4: BU Patients' Medical History

Serial No.	SOBU	DOHT(W/M/Y)	SOL(Cm/L)	TOT	DOH(Days)
1.	Late ulcer	3 – 6m	10 -20	AB + (EX + SG)	25
2.	"	6 – 10w	6 – 10	AB + (EX + SG)	11
3.	Nodule	3 – 5w	1 – 2	AB + (EX)	2
4.	Late ulcer	1y+	10 – 20	AB + (EX + SG)	55
5.	"	7 – 12m	10 – 20	"	89
6.	"	3 – 6m	10 – 20	"	45
7.	"	7 – 12m	10 – 20	"	17
8.	"	7 – 12m	>20	"	49
9.	Nodule	0 -2w	1 – 2	AB + (EX)	2
10.	Plaque	3 – 5w	3 – 5	AB + (EX + SG)	14
11.	Late ulcer	1y+	>20	AB + (EX + SG + RC)	41
12.	Late ulcer	1y+	10 – 20	AB + (EX + SG)	33
13.	Late ulcer	3 -5m	10 – 20	"	28
14.	Nodule	0 – 2w	1 – 2	AB + (EX)	2
15.	Nodule	6 – 10w	1 – 2	"	2
16.	Late ulcer	7 – 12m	6 -10	AB + (EX + SG)	42
17.	"	3 – 6m	10 -20	"	36
18.	"	1y+	>20	"	48
19.	"	1y+	10 -20	"	72
20.	Late ulcer	6 – 10w	6 – 10	AB + (EX + SG)	34
21.	Nodule	0 – 2w	1 – 2	AB + (EX)	2
22.	Late ulcer	7 – 12m	10 – 20	AB + (EX + SG)	48
23.	"	3 – 6m	>20	"	36
24.	"	3 – 6m	6 – 10	AB + (EX + SG)	41
25.	"	7 – 12m	10 – 20	AB + (EX + SG + RC)	60
26.	"	1y+	10 – 20	AB + (EX + SG)	29
27.	"	1y+	6 – 10	"	44
28.	"	3 – 6m	10 – 20	"	30
29.	"	6 – 10w	>20	AB + (EX + SG + RC)	90
30.	"	7 – 12m	6 – 10	AB + (EX + SG)	90
31.	Nodule	3 – 5w	1 – 2	AB + (EX)	2
32.	Late ulcer	3 – 6m	10 -20	AB + (EX + SG)	44
33.	"	6 – 10w	6 – 10	AB + (EX + SG)	39

Serial No.	SOBU	DOHT(W/M/Y)	SOL(Cm/L)	TOT	DOH(Days)
34.	Late ulcer	1y+	10 – 20	AB + (EX + SG)	60
35.	"	7 – 12m	10 – 20	"	70
36.	"	3 – 6m	10 – 20	"	40
37.	"	7 – 12m	10 – 20	"	30
38.	"	7 – 12m	>20	"	42
39.	Late ulcer	1y+	>20	AB + (EX + SG + RC)	39
40.	Late ulcer	1y+	10 – 20	AB + (EX + SG)	31
41.	Late ulcer	3 -5m	10 – 20	"	38
42.	"	1y+	10 -20	"	52
43.	Late ulcer	6 – 10w	6 – 10	AB + (EX + SG)	34
44.	Late ulcer	6 – 10w	6 – 10	AB + (EX + SG)	36
45.	Late ulcer	3 – 6m	10 – 20	AB + (EX + SG)	30
46.	"	7 – 12m	10 – 20	"	20
47.	"	7 – 12m	>20	"	42
48.	Late ulcer	1y+	>20	AB + (EX + SG + RC)	49
49.	"	3 – 6m	10 – 20	"	20
50.	Late ulcer	3 -5m	10 – 20	"	38
51.	"	1y+	10 -20	"	62
52.	Late ulcer	6 – 10w	6 – 10	AB + (EX + SG)	44
53.	Late ulcer	6 – 10w	6 – 10	AB + (EX + SG)	36
54.	Late ulcer	3 -5m	10 – 20	"	28
55.	"	1y+	10 -20	"	39
56.	Late ulcer	6 – 10w	6 – 10	AB + (EX + SG)	34
57.	"	1y+	6 – 10	"	44
58.	"	3 – 6m	10 – 20	"	30
59.	"	6 – 10w	>20	AB + (EX + SG + RC)	90
60.	"	7 – 12m	6 – 10	AB + (EX + SG)	79
61.	Late ulcer	1y+	>20	AB + (EX + SG + RC)	57
62.	Late ulcer	1y+	10 – 20	AB + (EX + SG)	51

Source: Study Material – *Patients' In–take and Engagement Form*

Legend:
DOHT – Duration Of Home Treatment
SOL (CM/L) - Size Of Lesion in Centimeter by Length
TOT - Type Of Treatment
DOH - Duration Of Hospitalization
(W/M/Y) – *Week/Month/Year*
SOBU – *Stage Of the Buruli Ulcer*
AB + (EX) – *Antibiotics and Excision*
AB + (EX + SG) – *Antibiotics, Excision and Skin Grafting*
AB + (EX + SG + RC) – *Antibiotics, Excision, Skin Grafting and Release of Contracture*

Location of BU lesions

Forty-five out of the sixty-two patients had their lesions on their lower limbs representing 72.6% of the total number of patients treated. Fifty-six patients had their lesions on the lower and upper limbs combined representing 90.3% of the total number of patients treated. One patient had his lesion on the head and neck region representing 1.6% and also one (1,6%) had his lesion at the perineum while four (6.5%) had them on their trunk. These are shown in Figure 4 below:

Type of Treatment

All the patients had antibiotics – Streptomycin and Rifampicin - (AB)

- The 6 nodules were excised–Nodulectomies - and also had antibiotics-AB+(EX)
- There was only one plaque which also had antibiotics and excision –AB+(EX)
- The 55 ulcers had antibiotics; were excised and were skin-grafted-AB+(EX+SG)
- Seven ulcers had in addition their contractures released-AB+(EX+SG+RC)

Multiple surgeries:
were done on the entire 62 patients except for the six nodules
i.e. six patients had single surgeries – EX;
56 patients had multiple surgical interventions (the plaque also had excision and grafting):

- 62 Excisions - EX
- 56 Split-thickness skin grafts - SG
- 7 Contracture Release – RC
- giving a total of one hundred and twenty-five surgical interventions performed on the sixty-two patients.
- None of the 62 patients needed an amputation.

These are evident from Table 4 above.

An example of four treated patients is presented below (Figs. 5-8).

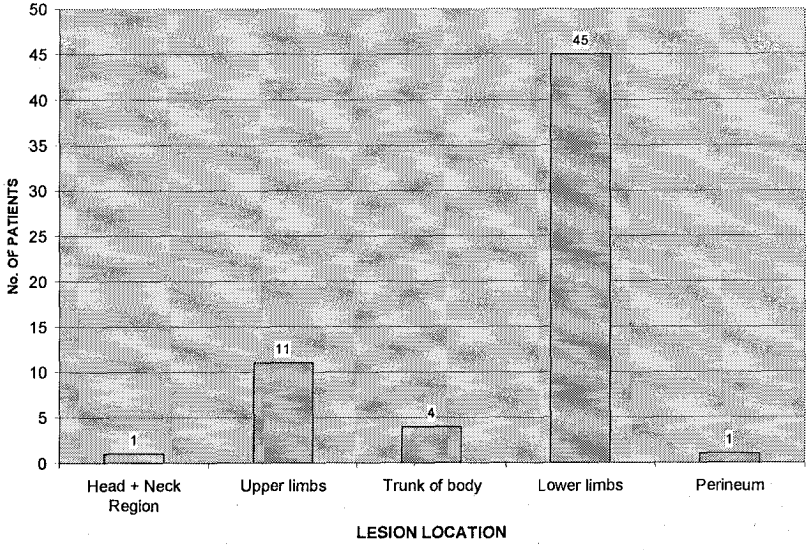
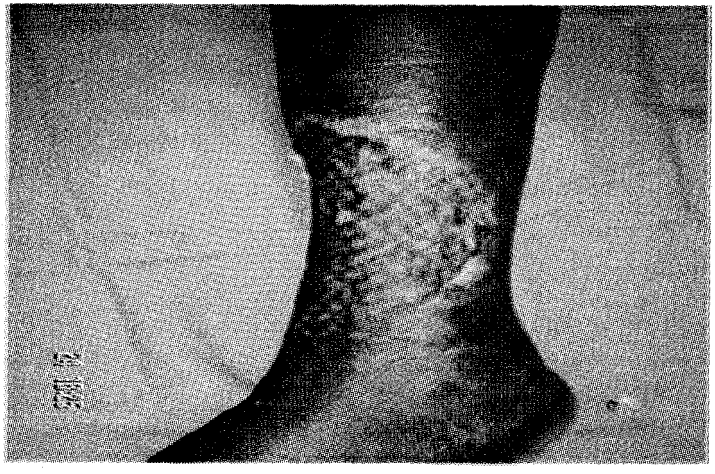


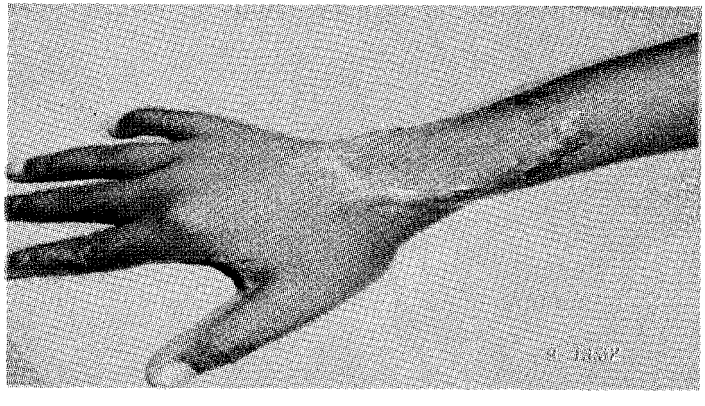
Fig. 4: Location of BU Lesion on Patients

Source: Study Material – *Patients' In–take and Engagement Form*

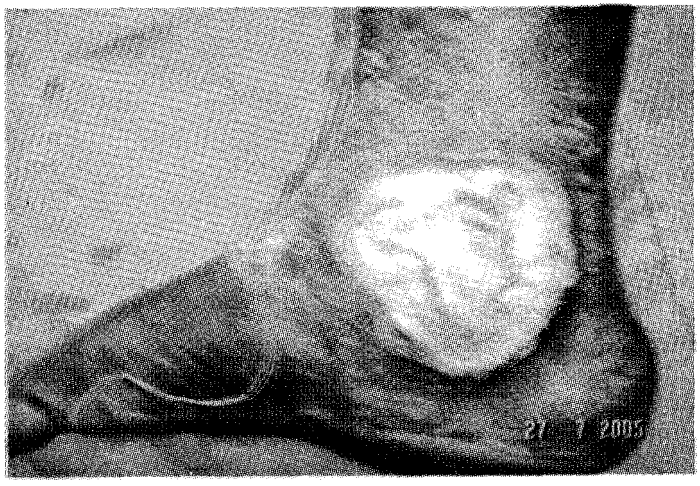
Case Presentations



Patient A - Fig. 5
Two weeks post meshed graft. He had four weeks pre-excision chemotherapy and four weeks post-excision chemotherapy. Grafting was done one week post excision. Total admission period was 28 days.

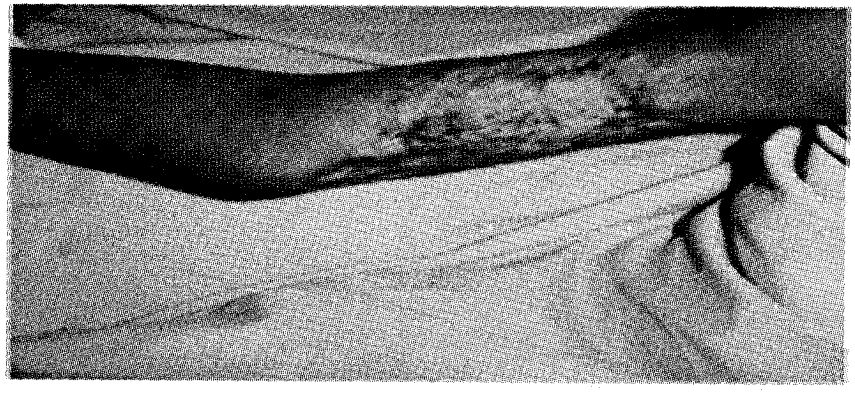


Patient B - Fig. 6: *Four weeks post graft; patient had four weeks pre-surgery OPD chemotherapy and four weeks post-surgery chemotherapy. Total admission period was 20 days.*



Patient C - Fig. 7a *Late ulcer; started pre-excision chemotherapy and wound dressings on OPD basis at the local health centre.*

Patient C - Fig.7b *Same patient as in Fig. 7a. Patient on OPD review three weeks post discharge; development of hypertrophic scarring. He had excision after four weeks of OPD chemotherapy and continued chemotherapy for four more weeks Grafting was done one week after excision. Total hospital stay was 25 days.*



Patient D - Fig.8: *On OPD review after five weeks discharge home after 17 days hospitalization. Patient earlier had four weeks OPD pre-excision chemotherapy; had skin graft one week after excision and got discharged home 10 days post-graft to continue further dressings at the local health centre and exercises of the elbow at home under the control of the local health centre staff.*

Duration of Hospital Admission

The number of days spent at the hospital depended on the stage and size of the ulceration which was greatly affected by the duration of home treatment as well. The following could be deduced from Table 4 as well:

Median = 23 days

Mode = 90 days

Mean = Summation fx/62

Mean = Summation of the DOH/62 = 2467/62 = 39.8 days

Therefore Mean of hospital admission = 39.8 days

DISCUSSIONS

From the evidence presented above, the central focus of this paper is on the impact of the combination of surgery and chemotherapy. This will be discussed with reference to the prechemotherapy era (before the year 2005) and chemotherapy era (from the year 2005).

Prechemotherapy era

This was an era prior to the introduction of specific antibiotics Streptomycin and Rifampicin - in the treatment of BU. In this era, the BU lesions had wide and extensive excisions and patients depended basically on good nutrition to enhance the treatments given at the hospital. It should however be noted that, not all patients had the economic capacity to feed well. Most patients were therefore malnourished making it impossible for immediate surgery when hospitalized. Many weeks or even months were spent taking care of the patient's condition before surgery. This added to the increasing number of the months and years spent at the hospital (Agbenorku and Akpaloo, 2001).

Figs. 9 and 10 are examples of such wide excisions that were often done serially sometimes up to about 3 or 4 excisions and often resulting in acute severe anemia which had to be corrected by haemotransfusions. During this era also the ulcers

Fig. 9: Pre-chemotherapeutic period wide excision

Fig. 10: Pre-chemotherapeutic period wide excision

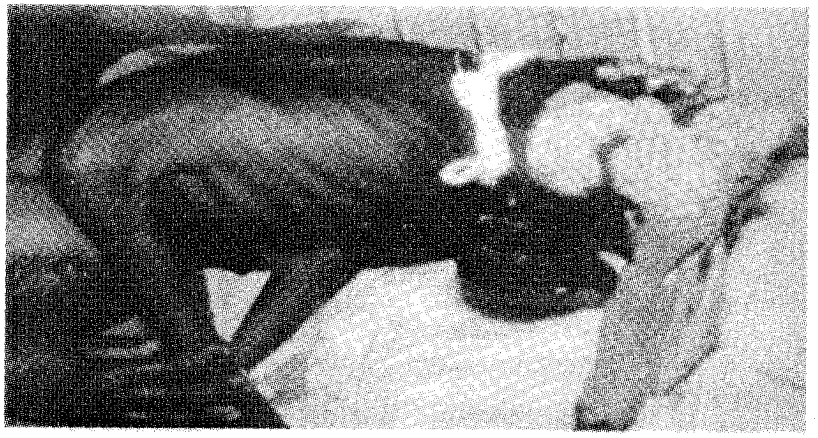


Fig. 11: Pre-chemotherapeutic period patient

***Fig. 11** shows a ten year-old boy who was treated about 8 years prior the emergence of Buruli chemotherapy. A small nodule that started on the left gluteal region eventually got ulcerated and virtually "ate-up" both lower limbs and the perineum necessitating a colostomy. No reconstructive surgery could help him. Today Buruli chemotherapy in combination with surgery could have helped him!*

never got clean early enough to allow skin grafting. Various broad-spectrum antibiotics had to be administered. Sometimes the antibiotics were given according to the antibiotic-grams which were often checked fortnightly.

Prechemotherapy era also witnessed BU patients with large lesions of which nothing could be done prior to surgery. The size of the lesions related to the number of days spent home while the patient contemplated whether to go to hospital or not. It is an appreciable fact that, before the chemotherapy era health education on the disease was also minimal. Patients were therefore seen for the first time at a health facility with big lesions dressed with herbs. This took the medical staffs a number of days to get the wounds clean for the first excision. Depending on the size of the lesion and its cleanliness, a number of excisions were done before grafting. The duration between excisions also took a number of weeks or even months thus prolonging the duration of hospitalization (Buntine et al., 2001). Some cases were malnourished patients whose lesions had to be debrided but could not have any part of their skins donated for the grafting. This group of patients usually had the longest period of hospitalization of well over six months and sometimes years. However, the average period of hospitalization for all categories of BU patients was estimated to be about three months, that is, ninety days.

Chemotherapy era

It is an era in which antibiotics have been introduced resulting in an improvement in the treatment of Buruli ulcer. The problems in the prechemotherapy era which resulted in the long hospitalization period were well taken care of by

the use of the specific antibiotics (Streptomycin and Rifampicin) lessening the hospitalization period. In our series, patients were given Streptomycin and Rifampicin usually at their local health facilities for four weeks before the surgical intervention. The administration of the antibiotics often did not need hospitalization of the patient. This meant that though the treatment had commenced the patient still had the opportunity to continue with his/her normal life. Once these antibiotics were well administered, the size of the lesions reduced considerably before the first excision. Numerous excisions were therefore not needed before grafting. The period between excision and grafting was also less. Meanwhile the extensive use of the antibiotics before and after surgery had brought about speedy recovery of patients.

This period is also accompanied with intensive education on the disease. It is therefore not common to have patients with lesions dressed with herbs as it used to be in the former times. Such cases are few now with the help of community based volunteers. An average of 39.8 days is therefore the mean average according to this research that a patient has spent at the hospital for treatment. In comparison therefore in the chemotherapy era the average hospitalization period has reduced to 44.2% (from 90 to 39.8 days).

CONCLUSION

In investigating the benefits of a combination of chemotherapy and surgery in the management of Buruli ulcer the paper has been able to establish that the application of Buruli chemotherapy resulted in "minimal" surgery as against the traditional extensive tissue debridement in the pre-chemotherapeutic era. The "dual" mode of treatment (surgery + chemotherapy) reduced hospital admission period from 90 to 39.8 days, that is, to 44.2%. This would directly reduce the cost of treatment for the BU patients.

RECOMMENDATIONS

- All the 62 patients in the series needed regular and long term follow-ups so as to look for any signs of recurrences.
- The combination of chemotherapy and surgery is recommended to Buruli ulcer management centres.
- The "current" treatment costs as a result of the reduction in hospitalization period need be studied.

ACKNOWLEDGEMENT

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