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Patterns of Treatment Failure in Burkitt's Lymphoma

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Abstract—*We have studied patterns of treatment failure in 49 evaluable children with Burkitt's lymphoma (BL) who received chemotherapy at different levels of intensity of cyclophosphamide, vincristine, methotrexate (MTX) or cytosine arabinoside, with or without high-dose dexamethasone, combined with intrathecal MTX. We observed 8 (16%) non-responders (NR), 8 (16%) partial (PR) and 33 (67%) complete responders (CR). PR + NR were all dead by the 10th observation month, while the survival graph plateaued at 70% around the 10th month for CR. We projected that 44% of all evaluable patients would experience prolonged survival beyond the 12th observation month. Three and 5 CR relapsed systemically and in the CNS respectively. Thus 11, 10 and 3 of 26 treatment failures were directly attributable to resistance to chemotherapy, sanctuary effect of the CNS or both respectively. Late complications of paraplegia were responsible for the other two failures. We conclude that drug resistance of BL cells and pharmacological sanctuary effect of the CNS are the major problems in the chemotherapeutic eradication of BL.*

INTRODUCTION

IN A disease like Burkitt's lymphoma (BL), which is the most common childhood tumour in some parts of Africa [1–3], treatment strategies should aim at cure rather than palliation of the disease in a high percentage of the patients. A number of characteristics of BL, e.g. its exquisite sensitivity to some chemotherapeutic agents and its cell-kinetic behaviour [4], would tend to suggest that BL should be a highly curable disease. However, experience from some studies are to the contrary [5, 6], although others have recently reported more encouraging results [7–9].

We have analysed the data gathered from the experience of management of 64 BL patients seen at the University College Hospital (U.C.H.), Ibadan, Nigeria over a period of about 3 yr with the aim of identifying constraints in the attainment of better treatment results. Our findings suggest that there is a need to reduce our initial failure rate and improve the control of central nervous system involvement by Burkitt's lymphoma (CNS-BL).

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MATERIALS AND METHODS

BL was diagnosed by appraisal of clinical findings and by needle aspiration of easily accessible lesions for cytological examination. When the diagnosis was in doubt and the clinical state of the patient permitted, a surgical biopsy was obtained for histological diagnosis. A lumbar puncture as well as bone marrow aspiration was also routinely done as part of the staging procedure.

The first patients managed in this series were treated with a modified type of a regimen described by Ziegler [10], consisting of i.v. cyclophosphamide 1000 mg/m^2 on day 1, i.v. vincristine 1.5 mg/m^2 on day 1, i.v. methotrexate 12.5 mg/m^2 on days 1, 3 and 4, i.v. dexamethasone 1000 mg/m^2 on day 1 and intrathecal methotrexate 12.5 mg/m^2 on days 2 and 5 of a 14-day cycle for a total of 4 cycles as an induction course. Thereafter 3–6 more cycles were given at monthly intervals as a maintenance course. Patients receiving at least 6 cycles of this treatment plan were considered 'sufficiently adequately' (SA) treated.

Subsequent to frequent occurrence of shortage of drugs the treatment regimen was modified as follows: i.v. cyclophosphamide 1000 mg/m^2 on day 1, i.v. vincristine 1.5 mg/m^2 on day 1,

methotrexate 37.5 mg/m² on day 1 given i.v. as one dose or orally in 3 divided daily doses or i.v. cytosine arabinoside 50 mg/m² in 6 × 12-hourly doses (each dose being given as a 3-hr infusion), and intrathecal methotrexate 12.5 mg/m² or cytosine arabinoside 50 mg/m² on days 1 and 5 of a 14-day cycle. Four cycles were given as a remission induction regimen and no maintenance course was given. Patients receiving at least 75% of the total projected dose of each of the 3 i.v. medications were considered 'adequately' (A) treated, while those receiving a lower percentage were considered 'less adequately' (B) treated. Similarly, intrathecal medication with at least 75% of the total projected drug dose was termed 'type 1', while lower percentages delivered constituted 'type 2' intrathecal chemotherapy. Thus 6 types of treatment combination emerged, depending on whether SA, A or B systemic chemotherapy was given in association with 'type 1' or 'type 2' intrathecal chemotherapy.

The result of treatment was considered as complete remission if it led to total disappearance of all physical and laboratory evidence of disease and progressive improvement of impaired organ function, e.g. neurological impairment. Persistence of residual neurological impairment, for instance, did not exclude a patient from being classified as a complete responder. Partial responders were patients who showed only partial reversal of physical and laboratory evidence of disease. Patients showing transient but almost complete regression of their tumor but whose disease eventually progressed during the induction period were considered partial responders. Non-responders were patients whose tumour failed to show significant reduction in size or whose tumours continued to grow after the first 2 cycles of chemotherapy. Patients were considered unevaluable if they were very sick at the onset of chemotherapy and died within 5 days of initiation.

Most of the patients received all cycles of the induction phase of chemotherapy in the hospital. In a few cases part of the treatment was given in a day-care unit on an outpatient basis. The patients were followed up as outpatients at the Medical and Children's Outpatients Departments. Social workers helped in tracing defaulting patients or in obtaining information on them. Two patients who could not be traced following discharge were regarded as 'primary defaulters' and were excluded from subsequent evaluation. Three other patients, one partial and two complete responders, who defaulted after variable periods of follow-up and who subsequently became untraceable were considered as having been withdrawn from study as from the time of the last observation. The probability of survival or freedom from relapse was computed using statistical methods as outlined by Colton [11].

RESULTS

Between November 1978 and February 1982 64 previously untreated children with BL were treated according to one of the six treatment combinations that have been described earlier (see Materials and Methods). The stages of their disease as determined by the criteria of Ziegler *et al.* [12] are shown in Table 1. Forty-three (86%) of the evaluable patients presented with advanced disease (stages C and D). Thirty (61%) were neurologically impaired, of whom 23 (77%) had evidence of infiltrative CNS disease with or without malignant CSF pleocytosis, while 3 (23%) had paraplegia alone. Stage D disease was established in 4 patients without CNS disease but with evidence of involvement of the liver, testis, bone marrow or lung in one of each case.

Table 2 shows the type of response obtained in evaluable patients: 8 (16%) failed to respond to treatment, while 8 (16%) achieved only a partial response. Thirty-three (67%) achieved complete response. A comparison between the remission rate of 10 out of 17 (59%) SA-1 and A-1 patients with 6 out of 8 (75%) B-1 patients suggests that 'inadequate' chemotherapy alone cannot be

Table 1. Disease state of previously untreated BL patients correlated with response type and site of residual disease

	NR + PR				
	CNS*	SYS	CNS + SYS	CR	Total
Stage A	—	—	—	3	3
Stage B	—	1	—	3	4
Stage C	—	4	—	9(1)†	13
Stage D (with CNS-BL)	5	1	3	15	24(3)‡
Stage D (without CNS-BL)	2	—	3	4§	

*Site of residual disease: CNS = central nervous system disease; SYS = systemic disease.
†(): Patient died on day 7 of infection: no recognized residual disease.
‡(): CNS-involved on the basis of presence paraplegia only.
§Liver, testis, lung and bone marrow: 1 case each.

Table 2. Chemotherapy of Burkitt's lymphoma patients at the U.C.H., Ibadan (1978–1982)

Treatment type	No. of patients	NR	PR	CR
SA-1	3	0	0	3
SA-2	6	1	0	5
A-1	14	4	3	7
A-2	10(1)*	3	3	4(1)*
B-1	8	0	2	6
B-2	8(1)*	0	0	8(1)*
Unevaluable	15†	—	—	—
Total	64(2)	8(16%)	8(16%)	33(2)* (67%)

NR = non-responder; PR = partial responder; CR = complete responder.
SA-1, SA-2, A-1, A-2, B-1, B-2: see Materials and Methods.
*() Primary defaulters.
†Unevaluable patients: 6 due to early death, 9 due to insufficient records.

responsible for the relatively low overall remission rate.

The quality of control of systemic disease as measured by the duration of systemic remission following the three types of systemic chemotherapy is shown in Fig. 1. One patient relapsed in each of the treatment categories, thus suggesting that the quality of control of systemic disease by the type of treatment that we described as 'sufficiently adequate' was not different from that that was obtained with 'inadequate' chemotherapy. The last patient to relapse in the 3 treatment categories did so between the 4th and 5th months of remission. On the basis of the observation lasting between 6 and 42 months, it was projected that 28 of the 31 (90%) patients attaining systemic remission (i.e. excluding two primary defaulters) would remain free of systemic disease. Eighteen of these have now been followed up for more than 6, 13 beyond 12, 11 for longer than 24 and 3 for longer than 36 months. Five have died of progressive CNS disease, while 3 have defaulted after 3½, 4 and 5 months of observation respectively; the latter two are believed to be alive and well more than 24 months after remission induction. Two patients have died in remission of complications related to paraplegia.

The duration of CNS remission is illustrated in Fig. 2. Five patients relapsed in the CNS: 2 at 2–3 months, 2 at 4–5 months and 1 at 5–6 months. Sixty-two percent and 78% of patients who received 'type 1' and 'type 2' intrathecal medication respectively continued to be in prolonged remission beyond 8 months. The significance of this difference is not clear and may be attributable to factors unrelated to the treatment itself, especially since this is not a randomized study and the number of patients is small.

CNS relapses occurred in 2 of 9 and none of 11 patients who were given 'type 1' and 'type 2' intrathecal chemotherapy prophylactically respectively. The probability of freedom from CNS relapse following prophylactic i.t. medication (Fig. 3) was observed to vary from just below 70 to 100% respectively for patients receiving 'type 1' and 'type 2' modes of i.t. chemotherapy. The relevance of this margin of difference in such a small sample of patients is not clear.

The survival duration of evaluable patients is

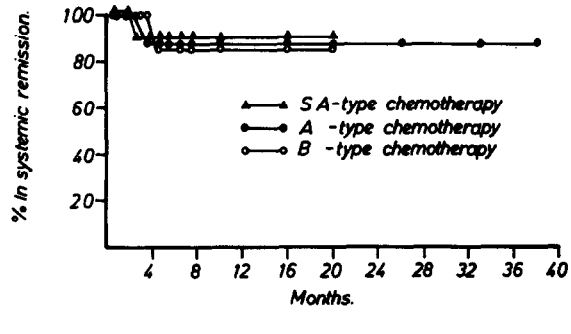

Fig. 1. Duration of systemic remission in Burkitt's lymphoma patients following chemotherapy at U.C.H., Ibadan, 1978–1982. For description of types of chemotherapy see Materials and Methods. Number of patients evaluable in each treatment category: SA = 9; A = 23; B = 15.

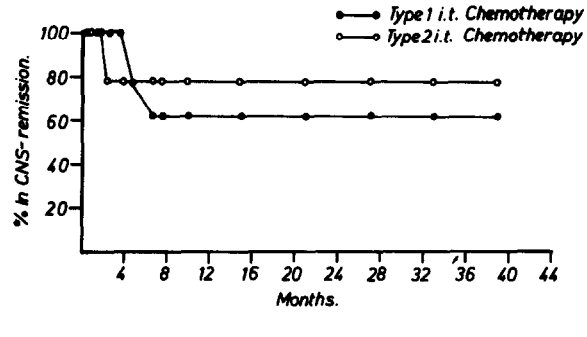

Fig. 2. Duration of CNS remission in Burkitt's lymphoma patients following intrathecal chemotherapy at U.C.H., Ibadan, 1978–1982. For description of types of chemotherapy see Materials and Methods. Number of patients evaluable in each treatment category: type 1 = 11, type 2 = 9.

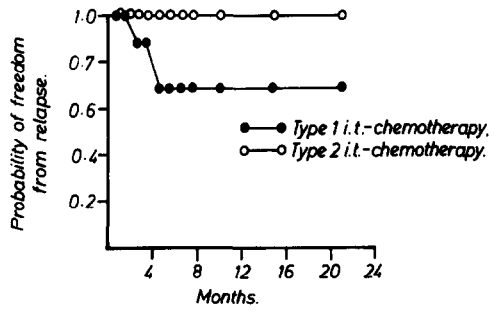

Fig. 3. Probability of freedom from CNS relapse following prophylactic intrathecal chemotherapy in Burkitt's lymphoma patients at U.C.H., Ibadan, 1978–1982. For description of types of chemotherapy see Materials and Methods. Number of patients evaluable in each treatment category: type 1 = 9, type 2 = 11.

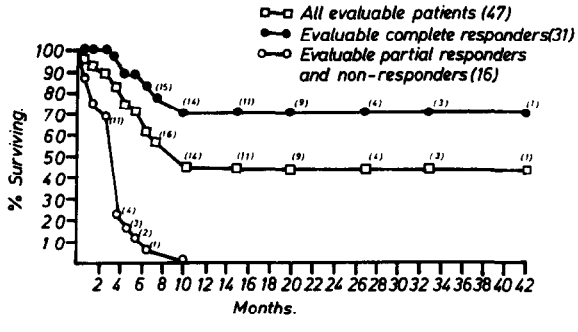

Fig. 4. Survival of Burkitt's lymphoma patients treated at the U.C.H., Ibadan, 1978–1982. Since the time of preparation of this diagram 12 patients have been followed up for more than 6, 13 for more than 12, 11 for more than 24 and 3 for more than 36 months respectively (see Results).

shown in Fig. 4. The initial response status is clearly the most important factor in terms of prolonged remission duration. While the longest surviving non-complete responder was dead at 10 months, 70% of the complete responders were expected to be in remission beyond 12 months. Forty-four percent of all 49 evaluable patients are expected to be alive and disease-free beyond 12 months.

DISCUSSION

The two major determinants of survival in this study of BL patients are the ability to attain complete remission (Fig. 4) and the degree of control of CNS involvement. Thirty-two percent of evaluable patients were either partial or non-responders and were all dead before 12 months. A similar observation has been reported earlier by Olweny *et al.* [8]. Thus of 26 treatment failures, 10, 11 and 3 were directly attributable to inadequate control of CNS disease, systemic disease or both respectively. The remaining two treatment failures were caused by death attributable to complication of paraplegia. Our experience appears to confirm Skipper's hypothesis on treatment failure in cancer chemotherapy, namely that this results from drug resistance, existence of pharmacological sanctuary and the size of the growth fraction of the tumour [13–15]. Since the growth fraction is almost 100% in BL [4], that factor is unlikely to be a major cause of treatment failure in this disease. Drug resistance *ab initio* of the tumour as well as selection and overgrowth of specifically drug-resistant BL cells probably represent an important mechanism of treatment failure in BL. This pattern of failure manifested itself in our series of BL patients in the form of non-response or partial response of the systemic disease in 11 cases (Table 1) and in early systemic relapse in 3 cases (Fig. 1), i.e. in 14 of 26 (54%) treatment failures. We believe that the most dramatic manifestation of selection and overgrowth of drug-resistant BL cells was seen in those patients in whom rapid destruction of massive tumours was quickly followed by regrowth and rapid progression of the tumours, despite the continuation of the previously effective chemotherapeutic regimen. We have categorized such patients as partial responders (see Materials and Methods). The possible role in this process of a drug-induced somatic mutation leading to a change in drug sensitivity as has earlier been suggested [16] is a matter for consideration. However, if this mechanism were to be ascribed a role in treatment failure in BL, it would seem that the somatic mutation occurs relatively rapidly since our programme of chemotherapy was relatively brief.

A strategy aimed at improvement of survival in BL patients must, therefore, reduce the high rate of primary treatment failure while at the same time breaking down the pharmacological sanctuary of the CNS. Efforts to control CNS-BL with various agents, including the 'blood–brain barrier'-crossing agents like the nitrosoureas [17], have failed. However, the recently reported success with the use of intravenous methotrexate at the dose of 500 mg/m^2 (combined with leukovorin) in the prevention of CNS spread in acute lymphoblastic leukaemia [18] appears to be a workable proposition in the management of CNS-BL. A recently reported regimen of combination chemotherapy including high-dose methotrexate is said to have led to over 70% prolonged survival in all evaluable BL patients [9]. This result is probably partly attributable to effective control of CNS-BL. It is, therefore, indicative of the direction in which clinical research in the chemotherapy of BL should advance in the near future, especially in view of the ineffectiveness of radiotherapy in CNS-BL

[19] and its inavailability in many African treatment centres.

The fact that a third of all evaluable patients failed to achieve complete response shows that there is no room for complacency in BL chemotherapy, despite the proverbial dramatic response observed in some BL patients. In half of these failing patients there was absolute resistance to the primary agents, while in the other half the problem was that of the rapid evolution of drug resistance. There is, therefore, a great need to identify new agents which are effective in BL and which are not cross-resistant with the agents being presently used. The availability of such agents may allow the design of a treatment programme that will further improve the initial response rate as advocated theoretically by Skipper *et al.* [13] and demonstrated in practice for Hodgkin's disease by Santoro *et al.* [20].

The observation made in this study that 4 × 2-weekly cycles of 3 seemingly 'inadequately' administered chemotherapeutic agents produced a similar long-term result as more cycles of a 4-drug combination (Fig. 1) is in agreement with an earlier observation by Durodola [21], who showed that there was no difference in the quality of response obtained with high-, medium- and low-dose cyclophosphamide in BL patients. Thus the doses of the drugs that are now being routinely used, e.g. cyclophosphamide, can be reduced in order to allow for addition of non-cross-resistant effective agents without necessarily increasing overall treatment morbidity in these patients.

With 44% of our patients expected to survive longer than 12 months, our experience is comparable to those of others [3]. In view of the kinetic behaviour of BL, which is such that significant residual disease existing after discontinuation of chemotherapy would be expected to lead to overt clinical disease within a few months, it is understandable why relapses in BL rarely occur after 6 months of complete remission [22]. We therefore believe that, in spite of our relatively brief observation period, most, if not all, of our patients who are now alive and disease-free beyond 1 yr are probably cured of their disease. We therefore anticipate a similar end-result to that of Ziegler *et al.* [7], who recently reported 50% of 10- to 15-yr disease-free survival in their patients. In order to further improve this cure rate new approaches in the control of systemic and CNS disease will need to be evolved.

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