The Central African Journal of Medicine

Supplementary Issue to 1992 Volume 38,
1991 University of Zimbabwe Annual Research Day

CENTRAL AFRICAN
JOURNAL OF MEDICINE

Vol. 38, No. 11, 1992

THE CENTRAL AFRICAN JOURNAL OF MEDICINE

ORIGINAL ARTICLES

Multicentre study of the treatment of primary liver cancer in Africa with two anthracycline drugs

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INTRODUCTION

Hepatocellular carcinoma (HCC) is among the twelve commonest cancers affecting mankind.[1] In tropical Africa HCC is the most common malignant tumour, particularly among men. In Kyadondo County of Uganda the incidence rate is 5,1 cases per 100 000 men. In Nigeria the figure quoted for both sexes is 5,9 per 100 000 population. In Zimbabwe the incidence among the Black population is 20,8 per 100 000, while in Mozambique the figure is 103,8 per 100 000 males. These figures are in contradiction to what is observed in Europe and North America. In England HCC occurs in 2,5 per 100 000, while in North America it is seen in 1,8 per 100 000.

In Africa HCC attacks young men with a peak incidence at 35 years (i.e. two to three decades younger than in Europe and North America. The disease runs a fulminant downhill course with over 90 pc of untreated patients being dead within one month of diagnosis.[2]

In Africa, HCC is superimposed upon pre-existing post-hepatic macronodular cirrhosis in about 80 to 90 pc of cases. Surgical resection is seldom possible because of extensive disease with multifocal lesions and concomitant cirrhosis.

The use of systemic chemotherapy has generally been disappointing. The very high response rate in a preliminary phase II trial of Doxorubicin in Uganda in 1975 was welcome.[3] Subsequent overall response of 44 pc was observed in a group of 50 patients with 10 pc achieving complete response.[4] Studies in other centres confirmed the Uganda experience.[5,6,7,8] In Zambia objective response was observed only in patients given over 60 mg/m^2 of Doxorubicin although cardiotoxicity was the limiting factor.[8] Tsega in Ethiopia failed to show beneficial effects of Doxorubicin in HCC patients.[9]

More recently a Doxorubicin analogue 4-epidoxorubicin (Epirubicin) has been shown to be active in HCC.[10,11] The studies suggested that it has a similar anti-tumour activity but with less toxicity than its parent compound Doxorubicin.

The aim of this study was to assess the usefulness of Epirubicin in African HCC and compare its effectiveness with that of its parent compound Doxorubicin as well as determining the optimal doses for both compounds in the treatment of African HCC.

MATERIALS AND METHODS

Eligibility criteria: Patients aged up to 70 years with histologically proven hepatocellular carcinoma were eligible for inclusion in this study. A Karnofsky performance status of at least 30 pc was required. Criteria for exclusion included previous or current cardiac pathology, previous treatment with cytotoxic agents, the

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presence of brain metastases or a second malignancy. Prior to entry patients were required to have adequate hepatic excretory function (serum bilirubin <50 umol/litre) and bone marrow reserve (WBC <3,000/mm^3, platelet count >75,000/m^3).

Therapeutic regimes: Patients were stratified by institution and randomized to receive either Doxorubicin or Epirubicin at three different dose levels. The doses for Doxorubicin were Doxo I (60 mg/m^2) Doxo 2 (75 mg/m^2), Doxo 3 (90 mg/m^2) and for Epirubicin, Epi I (75 mg/m^2), Epi 2 (90 mg/m^2) and Epi 3 (105 mg/m^2). Both drugs were given as an IV bolus injection. Treatments were repeated every three weeks. Dose reduction was applied according to standard criteria

Patients showing disease progression after two courses of chemotherapy were regarded as treatment failures and were observed until death without further chemotherapy. If remission or stable disease occurred, treatment was continued until disease progression, or unless prohibitive toxicity occurred, or until the maximum possible dose of Doxorubicin (550 mg/m^2) and Epirubicin (1 000 mg/m^2).

Pre-treatment and follow-up: Baseline studies included a full history with special emphasis on weight loss, jaundice, abdominal discomfort and upper gastrointestinal bleeding. A complete physical examination was performed paying particular attention to weight loss, jaundice, ascites, hepatic as well as splenic size, tumour measurements and Karnofsky score. Complete blood counts, biochemical profile chest X-ray, and ECG were done in all cases. Echocardiography and radionuclide cardiac scans were performed in some centres. Nadir blood counts between one and two weeks after treatment were optional. All baseline investigations were repeated before each course of treatment and at the time of discontinuation.

Definition of response: Patients were considered evaluable for response if they had receivd at least two courses of chemotherapy. The end point of study was death from HCC. Survival was calculated from the time treatment was begun. Responses were defined according to WHO criteria.[12]

RESULTS

From February 1987 to February 1989, 284 patients were randomised into the study. A total of 50 patients were considered ineligible due to inadequate histology (15 patients) and performance status <30 pc (35 patients). Among the 234 eligible patients who were entered (Table I), 35 patients were too early to evaluate. Forty three patients were not evaluable because of early death (40 cases) and treatment refusal (three cases).

*Table I: Case series.**

	Doxorubicin	Epirubicin	Total
Entered	120	114	234
Too early	15	20	35
Not evaluable	25	18	43
Evaluable	80	76	156

*Excluding 50 ineligible patients

One hundred and fifty six patients were fully evaluable with 80 receiving Doxorubicin and 76 receiving Epirubicin. These two groups were comparable with regard to age, sex, performance status disease stage, hepatitis B status, histological typing and biochemical test. Doxorubicin produced one complete response and 31 partial responses for an overall response rate of 40 pc (Table II).

Table II: Comparative response.

	Doxorubicin		Epirubicin	
Type of response	n	pc	n	pc
Complete response (CR)	1	1	0	0
Partial response (PR)	31	39	30	39
Complete + partial response (CR + PR)	32	40	30	39
No change (NC)	30	37	26	34
Progressive disease (PD)	18	23	20	27

X2 (CR + PR), p = 0,21

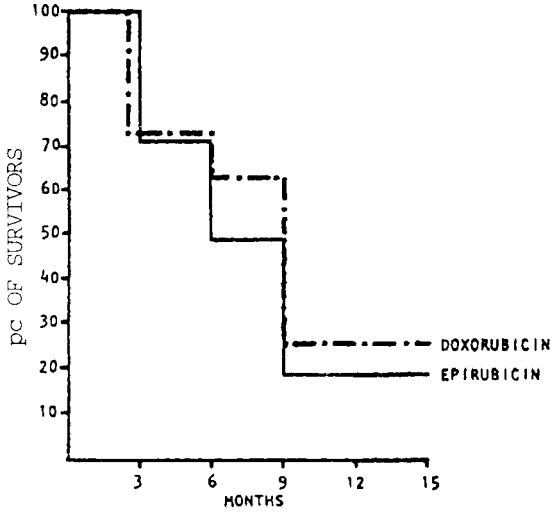
No change was observed in 37 pc and progressive disease occurred in 23 pc in this arm. Epirubicin produced no complete response in any patient and 30 partial responses for an overall response rate of 39 pc. The difference in response rate is not significant (p=0,21). Duration of survival was identical in the two groups (Figure I).

Table III gives details of survival according to the different dose levels of Doxorubicin and Epirubicin and was identical in the six treatment groups. The median survival among responders was nine months compared with two months among non-responders (p = 0,05).

Table III: Survival according to the different dose schedules.

Product	3 Mths	3–6 Mths	7–10 Mths	11–12 Mths	More than	Total
EPI-1	2	6	13	3	1	25
EPI-2	3	5	11	4	0	23
EPI-3	6	4	12	5	1	28
DOXO-1	4	2	13	7	0	26
DOXO-2	4	6	10	6	2	28
DOXO-3	5	5	11	4	1	26
Total	24	28	70	29	5	156

Figure I: Survivors following treatment



Haematological toxicity encountered during the first two cycles of therapy is shown in Table IV.

Nadir blood counts (days 7–14 after chemotherapy) were available for a total of 95 patients; 47 treated with Doxorubicin and 48 with Epirubicin. Doxorubicin significantly produced more haematological toxicity than Epirubicin. The difference between the two groups was highly significant (p = 0,007, chi square test for linear trend).

Non-haematological toxicities during the first two courses are shown in Table V.

Nausea and vomiting and alopecia were significantly more frequent and pronounced in patients treated with Doxorubicin than in those with Epirubicin.

Table IV: Haematological toxicity. Leucocytes during first two cycles.

Grade	Leucocytes/mm3	Doxorubicin	Epirubicin
0	4 000	14	24
1	33 000–3 900	9	13
2	2 000–2 900	11	8
3–4	2 000	11	3

X2 test for linear trend, p = 0,007

Table V: Non-haematological toxicities recorded during the first two courses

Type of toxicity	Doxorubicin (pc)	Epirubicin (pc)	X2 for trend p value
Nausea and vomiting	95	76	0,05
Diarrhoea	10	7	0,5
Anorexia	47	36	0,10
Mucositis	16	10	0,20
Alopecia	38	27	0,0008

Five cases of cardia symptoms occurred in the Doxorubicin arm with one patient on the 60 mg/m², two patients on the 75 mg/m² and two patients on the 90 mg/m² regimes respectively. One patient developed a grade two cardiac dysfunction after receiving a cumulative dose of 474 mg/m². Three patients had arrthymias and grade four dysfunction at a dose of 550 mg/m². One patient had a significant decrease of the ejection frac-

tion at a cumulative dose of 271 mg/m². In the Epirubicin group, only one patient developed grade two dysfunction after receiving 1 000 mg/².

DISCUSSION

The results in this study show that Epirubicin is an active agent in African HCC. The overall response rate of Epirubicin (39 pc) was comparable to that of Doxorubicin (40 pc). There were no differences in duration of response or survival among the two drugs or the six dosage levels (three for each drug) tested.

Although nadir blood counts were only available in 95 patients (61 pc) it was apparent that Doxorubicin was significantly more toxic than Epirubicin and that this was also the case for occurrence of nausea and vomiting as well as alopecia. Cardiac toxicity was also more commonly seen with Doxorubicin.

It is concluded that Epirubicin is active in African HCC and that its activity is equal to that of Doxorubicin but with less toxicity. Higher cumulative doses of the drug can be employed with a wider safety margin. Thus more cycles of chemotherapy can be administered either for response maintenance or palliative purposes.

With regard to Doxorubicin we have firmly established that the optimal dose is 60 mg/m² as there is no increased benefit with higher doses of the drug and yet one runs the risk of increased toxicity with higher doses. The results open up the possibility of a more aggressive treatment with higher doses of Epirubicin which might yield a higher durable incidence of clinical remission or prolonged survival.

ACKNOWLEDGEMENTS

This study was financially supported by Farmitalia Carlo Erba and the African Organisation for Research and Training in Cancer (AORTIC).

REFERENCES

1. Parkin DM, Stjernsward J, Muir C S. Estimates of the world-wide frequency of twelve major cancers. *Bull WHO* 1984; 62(2):163–184.
2. Olweny CLM. Hepatocellular carcinoma in Uganda. M.D. Thesis, Makerere University, Kampala, Uganda, 1976.
3. Olweny CLM, Toya T, Katongole-Mbidde E *et al.* Treatment of hepatocellular carcinoma with Adriamycin. Preliminary communication. *Cancer* 1975; 36:1250–7.
4. Olweny CLM, Katongole-Mbidde E, Bahendeka S, Otim D, Mugerwa J, Kyalwazi SK. Further experience in treating patients with hepatocellular carcinoma in Uganda. *Cancer* 1980; 46:2717-22.
5. Bern NM, McDermott W, Cady B *et al.* Intra-arterial hepatic infusion with Adriamycin for treatment of hepatocellular carcinoma: clinical and pharmacological report. *Cancer* 1973; 42:399–405.
6. Falkson G, Moertel CG, Lavin P, Pretorious FJ, Carbone PP. Chemotherapy studies in primary liver cancer: a prospective randomised clinical trial. *Cancer* 1978; 42:2149–56.
7. Johnson PJ, Williams R, Thomas H, Sherlock S, Murray-Lyon IM. Induction of remission in hepatocellular carcinoma with Doxorubicin. *Lancet* 1978; i:1006.
8. Vogel CL, Bayley AC, Brooke RJ, Antony PP, Ziegler JL. A phase II study of Adriamycin (NSC 123127) in patients with hepatocellular carcinoma from Zambia and United States. *Cancer* 1977; 39:1923–29.
9. Tsega E. Trial of Adriamycin on primary hepatocellular carcinoma. *Ethiop Med J* 1984; 22:55–59.
10. Muggia FM, Hochster H, Green M. Favourable experience with Epirubicin in hepatoma. International symposium: advances in anthracycline chemotherapy: Epirubicin Abstract 1984.
11. Nagasue N, Yukaya H. Intra-arterial administration of 4'Epi-Adriamycin in the treatment of non-resectable hepatocellular carcinoma. International symposium: advances in anthracycline chemotherapy: Epirubicin Abstract 1984.
12. WHO Handbook for reporting of cancer treatment. Geneva, Switzerland: WHO offset publication, no. 48; 1979.