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Short Communication

Phase II Study of High-dose 4′-Epidoxorubicin in the Treatment of Advanced Gastrointestinal Cancer

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4′-EPIDOXORUBICIN is well tolerated at the recommended dose of 60–90 mg/m^2 3 weekly. The maximal tolerated dose (MTD) of 4′-epidoxorubicin in untreated patients is, however, 150–165 mg/m^2 i.v. every 3 weeks [1–8].

4′-Epidoxorubicin, at doses ranging from 10 to 105 mg/m^2 every 3 weeks, gives an overall response rate of 8% in patients with colon cancer and of 25% in previously untreated patients with rectosigmoid carcinoma [9]. 4′-Epidoxorubicin, at doses ranging from 75 to 90 mg/m^2 i.v. every 3 weeks, gives a response rate of 18–26% in patients with advanced stomach cancer [10].

This present study was undertaken to evaluate the efficacy and toxicity of 4′-epidoxorubin 150 mg/m^2, 3 weekly in patients with advanced stomach and colorectal cancer.

Sixteen patients with advanced colorectal cancer and six patients with advanced stomach cancer were entered on study. There were eight males and 14 females with a median age of 54.5 years (range, 20–70). Performance status (PS) [11] was 0 in three, 1 in 11, 2 in seven and 3 in one patient. Five had one metastatic site, and 17 patients had two or more metastatic sites. Sites of metastases were the liver [15], peritoneum [13] and lung [5] (see Table 1).

Eligibility criteria included no prior chemotherapy, PS < 3, measurable and/or evaluable disease, adequate hematologic reserve (WBC $\geq$ 4000/mm^3, platelets $\geq$ 100,000/mm^3), hepatic functions (normal bilirubin, SGOT and alkaline phosphatase ≤ 2 times the upper limit of normal) and renal functions. Patients with cardiac disease were not eligible.

4′-Epidoxorubicin 150 mg/m^2 in 200 ml of normal saline was administered as an intravenous infusion in 30 min 3 weekly. The dose was modified for toxicity. ECOG toxicity and response criteria were used [11].

Three patients were unevaluable for either toxicity or response: one patient with rectum cancer

Table 1. Patient characteristics

Number of patients	22
With stomach Ca	6
With colon Ca	10
With rectal Ca	6
Sex	
Male	8
Female	14
Median age	54.5 (20–70)
PS	
0	3
1	11
2	7
3	1
Number of metastatic sites	
1	5
≥ 2	17
Site of metastases	
Liver	15
Abdominal cavity	13
Lung	5
Pelvic cavity	3
Bone	1

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with a PS of 3 and very advanced disease died 2 weeks after receiving one dose of treatment. Two patients with colon cancer refused further treatment after the first dose of 4'-epidoxorubicin. Four patients received one dose, 6 two doses, 5 three doses, 3 four doses and 1 patient received 5 doses. The median total dose administered to the 19 evaluable patients was 300 mg/m^2 (range, 150–682 mg/m^2).

Two patients developed Grade 4 leukopenia (see Table 2). Ten of the 18 patients who received more than two doses of 4'-epidoxorubicin and/or who were on study more than 3 months had baseline and follow-up gated radionuclide scanning for the assessment of the left ventricular ejection function (LVEF). Four of these 10 patients had an absolute LVEF decrease of 11, 12, 30 and 39% at 4'-epidoxorubicin doses of 300, 454, 545 and 600 mg/m^2 respectively.

No objective response was documented (see Table 3). Eleven patients (eight colorectal and three stomach cancer) had disease stabilization with a median duration of 6 weeks (range, 4–24 weeks). The median survival time of patients with colorectal cancer was 19 weeks and of patients with stomach cancer 10 weeks.

As this dose is close to the MTD further dose escalation is not practical and it is improbable that this anthracycline analog will be of significant value for patients with advanced stomach and colorectal cancers.

Table 2. Toxicity: 150 mg/m^2 4'-epidoxorubicin

	ECOG grade*			
	1	2	3	4
Hematologic toxicity				
Anemia	7	4	2	0
Leukopenia	5	8	5	2
Thombocytopenia	0	1	0	0
Non-hematologic toxicity				
Nausea and vomiting	7	10	1	0
Diarrhea	2	1	0	0
Stomatitis	6	3	2	0
Anorexia	5	1	0	0
Infection	0	2	0	0
Alopecia	5	13	0	0

*See Ref. [11]

Table 3. Therapeutic response to 150 mg/m^2 4'-epidoxorubicin

	Disease stabilization	Progressive disease	Unevaluable	Total
Colon Ca	5	3	2	10
Rectum Ca	3	2	1	6
Stomach Ca	3	3	—	6
Total	11	8	3	22

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