Letters

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Weekly Low Dosage Epirubicin in Advanced Breast Cancer

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WITH CURRENT cytotoxic agents no patient is cured of advanced breast cancer. Treatment is therefore palliative. In the hope of achieving higher response rates most clinicians use combination chemotherapy rather than single agents, but at the expense of higher toxicity. Doxorubicin is the most effective single agent. Objective response rates of 43–57% in untreated and 28% in previously treated patients have been recorded. Low-dose weekly schedules have been advocated to reduce toxicity while maintaining efficacy [1–3]. Epirubicin is reported to have similar response rates to its parent drug but with reduced toxicity [4]. For palliation with lower toxicity, weekly epirubicin (20 mg) has been proposed; 35–45% of patients showed no toxicity and responses of 43–46% were claimed [5, 6]. We report our experience with such a regimen.

Between December 1986 and January 1988, 49 patients with advanced breast cancer received a weekly regimen of low dose epirubicin. 48 had received previous hormonal therapies and 29 radiotherapy, 9 following conservative surgery. 7 patients had received mitozantrone (14 mg/m^2). The median age was 63 years (33–80). Major sites of disease are shown in Table 1. Metastases included: bone (9), lung (5), bone and lung (5), visceral (11), and skin (6). Informed consent was obtained.

Before starting therapy, all patients were examined and palpable disease was measured. The WHO performance score was documented. Limited skeletal radiology and electrocardiograms were done, and isotopic bone scans and liver sonography done when indicated. Full blood count was repeated before each dose of epirubicin. Chemotherapy continued unless the white cell count was less than 2.5 × 10^9/l or platelets less than 100 × 10^9/l, or haemoglobin fell below 10 g/dl. Patients received nine weekly 25 mg injections total. Treatment was stopped if in the patient's best interest, or at the patient's request. Adverse effects were recorded weekly by questionnaire and clinical examination; antiemetics were prescribed if symptoms persisted. Response was assessed at 12 weeks with UICC criteria. Patients with responsive or static disease were offered a further course.

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Table 1. Major sites of disease in patients treated with epirubicin

Site of disease	Previous Cytotoxic Chemotherapy	
	No	Yes
Locally advanced primary cancer	8	1
Locally advanced primary and metastases	14	1
Local recurrence	3	1
Local recurrence and metastases	10	3
Metastatic disease	7	1

41 patients were evaluable for response and toxicity after completing the 9 week course; 8 patients died before course completion, 7 of which were evaluated for toxicity. There were no complete responders. Partial responses, accompanied by an improved performance status, occurred in 4 (10%) patients. All progressed after a second 9 week course. 15 patients (36%) had static disease and 21 (51%) had disease progression. 11 patients with stable disease received a further course (4 refused). When reassessed at 6 months, 7 had progressed and 4 remained static. 4 patients received a third course; 3 progressed at 36 months, the remaining patient died at 31 months.

31 patients (65%) had nausea and vomiting (grade 2 in 7, grade 3 in 4). 26 (54%) patients had alopecia (9 and 6 in grades 2 and 3, respectively). 10 patients had stomatitis (4 at grade 2). 11 patients had mild pulmonary symptoms (7 grade 1, 4 grade 2) in the absence of pulmonary disease. 2 patients had diarrhoea and 1 phlebitis (both at grade 1). 8 patients (17%) reported no toxicity.

One review reported a 31% response rate with epirubicin in 338 patients, the rate rising to 62% in patients who had not received previous chemotherapy [7]. Epirubicin at 75 mg/m^2 was associated with lower levels of toxicity than doxorubicin. To reduce toxicity whilst maintaining efficacy, weekly regimens of low dosage doxorubicin have been advocated. Remission rates have varied widely: 16–59% [8, 9]. 20 mg per week in 43 patients gave a 51% response rate; toxicity was claimed to be negligible [5]. Less favourable were the results of Tucci *et al.* [10], who reported a 34% remission rate in 29 patients with epirubicin at 15 mg/m^2; toxicity remained negligible.

Jones [6] later reported results in 56 patients treated with 20 mg per week for 16 weeks. 42 were evaluable and of these 43% showed a partial response (no complete responders); 20 patients (48%) had static disease. Using a similar regimen we recorded a response rate of 10%. Symptomatic toxicity was more severe in our series. We therefore cannot recommend this regimen in patients with hormone-resistant advanced breast cancer. Toxicity was similar to other regimens which appear more efficacious. Weekly attendances are also inconvenient to patients and clinic staff.

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Methylglyoxal bis-Guanylhydrazone in Advanced Bladder Cancer

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ALTHOUGH there has been progress in the development of combination chemotherapy regimens for patients with advanced bladder cancer there is a need for new active agents [1–3]. Methylglyoxal bis-guanylhydrazone (MGBG) is a polyamine biosynthesis inhibitor which induced complete remission in patients with transitional cell carcinoma of the bladder in phase I trials with the agent [4].

46 patients with advanced metastatic transitional cell carcinoma of the bladder were entered into a phase II trial. Eligibility criteria included: histologically confirmed, bidimensionally measurable metastatic transitional cell carcinoma of the bladder; only one previous systemic chemotherapy or immunotherapy regimen (up to two previous intravesical chemotherapy or immunotherapy regimens were acceptable); patients could have had radiotherapy if the disease had progressed (if measurable disease existed outside the previous radiation field); patients had to have a SWOG performance status of 3 or less; white cells 3500/μl or more and platelets 100,000/μl or more; serum creatinine 177 μmol/l or less and serum bilirubin 34 μmol/l or less; and patients' informed consent.

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Table 1. Patients' characteristics

Entered	46
Total eligible (1 patient had no measurable disease)	45
M/F	34/11
Median age in years (range)	61 (40–80)
Performance status (SWOG)	
0	11
1	16
2	13
3	5
Previous therapy	
None	1
Radiation therapy + chemotherapy	15
Chemotherapy* or immunotherapy	29
No. of weeks of therapy	
<4	23
4	12
5–8	6
>8	2
Unknown (too early)	2
Best response achieved	
Complete	0
Partial	0
Stable disease	5
Progression	17
Assumed no response	19
No follow-up measurements	7
Early death	4
Refused further therapy secondary to toxicity	8
Too early	4

*Methotrexate + vinblastine + doxorubicin + cisplatin.

MGBG was administered weekly at 600 mg/m^2 as an intravenous infusion in 150 ml D5W or normal saline over 30 min or more. Dose escalations of 100 mg/m^2 were given if no toxicity was noted. Weekly doses were reduced by 100 mg/m^2 for severe (SWOG grade 3) toxicities. One course of therapy was defined as 4 weeks of MGBG. SWOG criteria were used to assess tumour response.

45 of the 46 patients entered were eligible (Table 1). 1 patient had no measurable disease. 20 of the eligible patients (44%) had at least one or more courses. There were no complete or partial responses. The exact 95% confidence interval of 0 out of 45 is 0–8%.

Toxicities in the study consisted of grade 3 (severe) or greater nausea and vomiting in 16% of patients, with 2 patients requiring admission. Grade 3 diarrhoea occurred in 9% of patients (1 admitted). 1 patient had grade 4 mucositis and 1 had a perforated diverticulum leading to death. Other grade 2 or greater toxicities included fatigue and weakness in 3 patients, hypoglycaemia in 2, hypotension (under 90 mmHg systolic) in 2, weight loss in 4 patients (1 lost 4.5 kg and 1 lost 7.7 kg), and anaemia in 8. Toxicities were so troublesome that 8 patients refused additional treatments (usually after only 1–3 doses).

Despite the protocol calling for failure on only one previous chemotherapeutic regimen it is clear the patient population was