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A Phase II Study of Doxifluridine in Patients with Advanced Breast Cancer

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INTRODUCTION

DOXIFLURIDINE (5′-deoxy-5-fluorouridine) is a new fluoropyrimidine analog, releasing 5-fluorouracil under the action of an intracellular pyrimidine phosphorylase [1]. Higher concentrations of 5-fluorouracil are released in tumors compared to normal tissues [2]. Previous studies by our group have shown that doxifluridine has a higher hematologic tolerance than 5-fluorouracil. Tumor responses have been observed in head and neck, colorectal and ovarian cancers [3–6]. A similar treatment schedule consisting of 5 daily i.v. injections every 3 weeks was investigated in patients with advanced breast cancer.

PATIENTS, TREATMENTS

Twenty-five female patients (age 41–75) with histologically proven advanced breast cancer had measurable lesions, normal blood counts, normal serum creatinine and serum bilirubin concentrations. Twenty had received prior chemotherapy, including fluorouracil in 17 cases. Doxifluridine was administered i.v. for 5 consecutive days, 4000 mg/m^2/day in patients without prior history of toxic myelosuppression and 3000 mg/m^2/day in other patients. Treatments were repeated every 3 weeks, or 4 weeks if toxicity persisted on day 22. The daily dose was reduced where there was residual toxicity on day 28. Tumor responses were assessed along with WHO guidelines [7]. The following data were recorded weekly: leucocyte count and differential, platelet count, hemoglobin, nausea, vomiting, signs and symptoms of mucositis, neuropathy, cardiac toxicity, alopecia, skin toxicity, local veno-cutaneous irritation, sepsis, renal, hepatic and lung toxicity. The percentage of due dose and the frequency and intensity of toxic effects were calculated separately for each treatment cycle.

RESULTS

One complete and four partial responses were observed (Table 1). There were 12 stable diseases, seven tumor progressions and one early non-toxic death. Four out of five patients without prior chemotherapy responded. One patient with rapid response of skin nodules experienced a severe myelosuppression and mucositis and died with cerebral hemorrhage on day 18. In this patient, serum creatinine was raised transiently from 59 to 143 μmol/l from day 1 to day 4 of treatment. One to six cycles were administered with a total of 66 cycles evaluable for toxicity. Toxic effects (number of patients with WHO toxicity grade 2 + 3/4) were leucopenia (12/2), thrombocytopenia (4/2), mucositis (2/2), cardiac toxicity (1/1), neurotoxicity (4/0) including ataxia-dizziness (3/0), peripheral paresthesia (2/0), mental depression (1/0), dysgeusia (1/0), nausea and vomiting (3/0), skin rash or skin edema (2/0) and alopecia (1/0). A ventricular fibrillation during the third day of the second cycle was rapidly reversed in one patient. Another patient complained of precordial pain without ECG or serum enzyme changes shortly after the first cycle that did not occur in further cycles.

CONCLUSIONS

One complete and four partial responses were observed in 25 patients with advanced breast cancer. Responding lesions were liver metastases in

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Table 1. *Characteristics of patients with tumor response*

	Age	Prior treatments	Indicator lesions	Responses	Daily dose (mg/m^2)	Time (days) to relapse
1	61	Surgery	Liver	Complete	4000	190
2	56	Surgery Radiotherapy	Liver	Partial	4000	127
3	74	Surgery Radiotherapy Hormonotherapy	Liver	Partial	4000	120
4	44	Surgery Radiotherapy	Liver	Partial	4000	51
5	40	Surgery Radiotherapy Hormotherapy Chemotherapy	Skin	Partial	3000	18 (Toxic death)

four cases and skin nodules in one case. Four responses were obtained in five patients without prior chemotherapy. These results suggest that doxifluridine as administered in this study is at least as active in breast cancer as 5-fluorouracil. As opposed to 5-fluorouracil, doxifluridine is mainly excreted by the kidney. A toxic death was observed shortly after the appearance of a moderate elevation of serum creatinine. Various symptoms of neurotoxicity were recorded in four patients, or 16%, thus confirming previous observations. The main limitation in the use of intravenous doxifluridine is illustrated in this series, as in others, by the infrequent but potentially lethal cardiac toxicity. Other modes of application are under investigation in order to reduce or suppress the risk of cardiac toxicity.

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