Correspondence and Short Communications

Comments on published articles, short communications of a preliminary nature, case reports, technical notes and the like are accepted under this heading. The articles should be short and concise and contain a minimum of figures, tables and references.

DOXORUBICIN AND 5-FLUOROURACIL VERSUS DOXORUBICIN AND ORAL FTORAFUR IN THE TREATMENT OF ADVANCED GASTRIC CANCER—A PHASE II AND III TRIAL

The major drugs in medical treatment of gastric cancer are 5-fluorouracil (5-FU), doxorubicin, and some additional drugs, as mitomycin C. Chemotherapy seems to have a beneficial effect as adjuvant to surgery (1) and as treatment of advanced or recurrent gastric cancer with response rates of 15–30% (2–7).

Ftorafur (FT) is the N1-tetrahydrofuran-2yl derivative of 5-FU. FT yields 5-FU in vivo (8) and can be administered orally. FT and 5-FU have shown similar antineoplastic effect towards gastric cancer in Japanese studies. The major side-effects of ftorafur are GI toxicity, and to a minor degree haematological toxicity (9). In the present study the result of treatment of gastric cancer with doxorubicin in combination with orally administered ftorafur versus doxorubicin in combination with intravenously administered 5-FU is presented.

Materials and Methods. The patients who were randomized to regimen I were treated with doxorubicin 50 mg/m^2 i.v. day 1 and 21 and 5-FU 500 mg/m^2 i.v. day 1, 7, 14 and 21. Next cycle started on day 42. The patients randomized to regimen II were treated with doxorubicin 50 mg/m^2 i.v. day 1 and 21 and ftorafur 1 g/m^2/day p.o. from day 1 to day 21 included. Next cycle started on day 42. Maximum cumulative doxorubicin dose was 500 mg/m^2. When this maximum dose was reached, the patient continued treatment with 5-FU or FT respectively in unaltered doses. The treatment was terminated if the patient was reluctant to continue, in case of intractable toxicity, if new metastases or other signs of progressive disease developed assessed as increase by more than 25%, measured by the two largest perpendicular diameters, of tumour, if there was a weight loss of more than 10%, and if there was a decrease of performance status at two consecutive series of treatment. The treatment doses were reduced if the white blood count was below 3×10^9/l, platelet count was below 100×10^9/l, creatinine above 200 mmol/l, bilirubin above 17 mmol/l and SGOT above 60 mmol/l at the time of treatment. Each treatment series lasted 6 weeks. Haemoglobin, WBC and platelet count was measured every week, bilirubin, SGOT and creatinine every 6 weeks.

The eligibility criteria included histologically verified inoperable, palliatively operated or recurrent gastric cancer in patients in performance status 0–3, no prior chemotherapy, no other malignancies, normal haematology, normal kidney and liver function assessed by serum creatinine <120 mmol/l, serum bilirubin <25 mmol/l and serum SGOT <40 mmol/l.

Fisher's exact test and the χ^2 test were used to determine differences in toxicities and patient characteristics. Wilcoxon's rank-sum test was used to evaluate survival.

Results. Sixty-eight consecutive patients entered the study in the period June 1, 1980 to January 31, 1985. The patient characteristics are listed in Table 1. Eight patients were excluded from study; two were lost to follow-up, 5 had major protocol violation and one was unable to swallow ftorafur capsules. Of the remaining patients, 29 were treated with doxorubicin/ftorafur and 31 with doxorubicin/5-FU. All patients were followed to death. The number of courses given is listed in Table 2.

Table 1

Patient characteristics

	Regimen I	Regimen II
Patients randomized	35	34
Protocol violations	3	4
Lost to follow-up	1	1
Evaluable patients	31	29
Measurable disease	9	7
Non-measurable disease	22	22
Intraabdominal disease	28	24
Extraabdominal disease	3	5
Primary disease	31	25
Secondary disease	0	4
Histology		
adenocarcinoma	26	20
sigillocellular	3	2
anaplastic	2	5
linitis plastica	0	2
solid	0	2
Performance status		
0–1	21	16
2–3	10	13
Age		
median (years)	62	57
range	28–76	23–75
Sex		
male	22	16
female	9	13

There was no difference in the overall haematological toxicity of the two treatments. The platelet nadir was above 150×10^9/l for both treatments. Twenty-two of 31 patients receiving treatment I and 15 of 29 patients receiving treatment II had an overall leukocyte nadir of $<3 \times 10^9$/l. Two patients treated with regimen II died early with no nadir registered. The acute haematological toxicity assessed by WBC nadir $<3 \times 10^9$/l during the first cycle of treatment was significantly greater for doxorubicin and 5-FU (19 of 31) than for doxorubicin and ftorafur (8 of 27) ($p < 0.05$; χ^2).

The patients treated with regimen I suffered significantly ($p < 0.05$) less from diarrhea (3 of 31) than patients treated with regimen II (12 of 29). There was no difference in the incidence of vomiting (17/31 vs. 19/29), stomatitis (0/31 vs. 2/29), infection (4/31 vs. 2/29) or haematemesis (2/31 vs. 1/29). Seven patients in group I and 8 in group II received second-line chemotherapy.

Table 2

Treatment characteristics

	Regimen I	Regimen II
No of courses given	97	91
Mean + SEM	3.1 ± 0.6	3.1 ± 0.6
Median	3	3
Range	1–8	1–7
Intended No. of doxorubicin doses	174	179
Full doses given	126	138
Reduced doses	48	41

One course of treatment included two doses of doxorubicin.

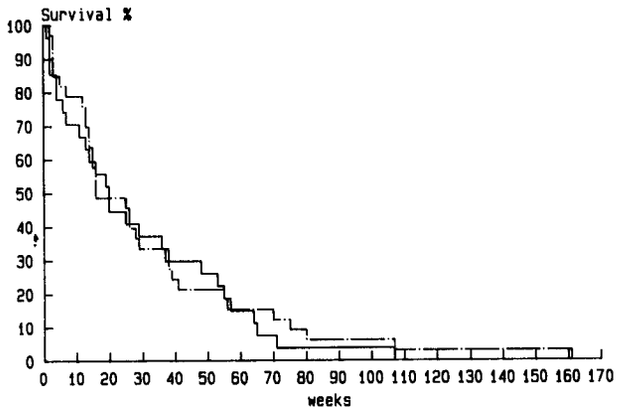

Figure. Survival plots for the two treatment regimens. Regimen I (——); regimen II (— · —).

The median time to progression was 16 weeks for patients receiving doxorubicin and 5-FU and 24 weeks for patients receiving doxorubicin and ftorafur. This difference was not statistically significant. There was no significant difference in survival between groups I and II. The median survival was 16 weeks for patients receiving doxorubicin and 5-FU and 25 weeks for patients receiving doxorubicin and ftorafur (Figure).

Discussion. The non-haematological toxicity was very similar in the two treatment regimens. However, the incidence of diarrhea was significantly higher in the ftorafur/doxorubicin-treated group. Aside from diarrhea and nausea/vomiting there was no major non-haematological side-effects. We found increase of liver enzymes (SGOT) in 5 patients from each treatment arm; this could not be attributed to drug toxicity, rather it indicated progressive disease. Kidney dysfunction has previously been reported (1) but was not observed in our series.

Haematological toxicity was more severe in the 5-FU/doxorubicin-treated group, with 61% of the patients having a WBC nadir below 3×10^9/l during the first cycle compared to only 28% in the ftorafur/doxorubicin-treated group. There was no significant depression of platelet count and all patients' platelet nadir during the first treatment course was above 150×10^9/l.

Despite the difference in toxicity there was no difference in the number of treatment cycles in which it was necessary to reduce the dose (28% vs 23%). We therefore conclude that the overall toxicity is about the same for the two drugs when given in the doses used in this trial and in combination with doxorubicin.

There was no difference in response to the two regimens, neither when assessed by time to progression nor as overall survival (Figure). The observed median survival in this trial was 16 weeks, which is in accordance with other reported results. In 33 trials including 1 100 patients the median survival was 22 weeks with a range of 7–38 weeks (10, 11).

In conclusion, we found no survival or toxicity benefit of ftorafur over 5-FU in the treatment of gastric cancer.

Key words: Gastric cancer, doxorubicin, 5-fluorouracil, oral ftorafur.

P. M. VESTLEV
H. PEDERSEN

Department of Oncology (ONK)
Rigshospitalet
Copenhagen
Denmark

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Request for reprints: Dr Peter Michael Vestlev, Department of Oncology (ONK), Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark.

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METASTASIZING SERTOLI CELL TUMOURS OF THE HUMAN TESTIS—A REPORT OF TWO CASES AND A REVIEW OF THE LITERATURE

More than 90% of human testicular tumours are derived from the germ cells in the seminiferous tubules (1, 2). Tumours derived from the sustentacular cells of Sertoli, the interstitial cells of Leydig and mixtures of these, constitute 4–6% of the testicular tumours.

The Sertoli cell tumours, named androbalstoma by Teilum, constitute 1–1.5% of the testicular tumours (3). The Sertoli cell tumours are generally benign tumours, but on reviewing the literature 19 cases were found with a malignant course and details of clinical data (4–20). A further 4 cases were reported to have had a malignant course, but clinical data are not available (21). The histologic criteria of malignancy in testicular Sertoli cell tumours have still not been clearly defined.

From January 1, 1970 to December 31, 1986, 555 patients with testicular tumours were treated in the Department of Oncology and Radiotherapy, Odense University Hospital, which serves as an oncologic centre of an area with about 900 000 inhabitants. Two of these patients had Sertoli-Leydig cell tumours and 4