Pergamon

European Journal of Cancer Vol. 33, No. 8, pp. 1230–1233, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00097-X

Original Paper

A Phase II Study of Continuous Infusion 5-Fluorouracil (5-FU) with Epirubicin and Cisplatin in Metastatic, Hormone-resistant Prostate Cancer: an Active New Regimen

D. Chao, M. von Schlippe and S.J. Harland

Department of Oncology, U.C.L. Medical School, The Middlesex Hospital, Mortimer Street, London W1N 8AA, U.K.

The aim of this phase II study was to examine the efficacy of combination chemotherapy comprising epirubicin, cisplatin and protracted infusion 5-fluorouracil in patients with metastatic prostate cancer. 21 patients were treated, of whom 9 (43%) responded for a minimum of 7 months. Continuation of previously effective second-line hormone therapies appeared to be a determinant of response; only 1 of 6 patients responded after its discontinuation. In a further 3 patients, response was only seen after re-introduction of previously effective hormone treatments. In patients of 70 years and under with prostate cancer resistant to androgen-deprivation therapy and who still have good performance status, ECF chemotherapy can achieve useful remissions. © **1997 Published by Elsevier Science Ltd.**

Eur J Cancer, Vol. 33, No. 8, pp. 1230–1233, 1997

INTRODUCTION

No cytotoxic chemotherapy regimen has been shown to improve survival in metastatic, hormone-resistant prostate cancer and response rates lie between 10 and 15%. The problem is compounded by the fact that prostate cancer affects the elderly who have reduced tolerance to the side-effects of chemotherapy. High response rates have been reported for adenocarcinoma of the stomach and breast treated with protracted venous infusion 5-fluorouracil (PVI 5-FU), epirubicin and cisplatin (known as ECF) [1, 2]. Epirubicin, cisplatin and PVI 5-FU all have single-agent activity against prostate cancer [3–5], and there may be synergistic interaction between cisplatin and 5-FU [6]. We therefore tested this regimen in prostatic cancer, a disease where benefit from chemotherapy is uncommon. The question of whether prior endocrine therapy should be continued during chemotherapy was retrospectively examined.

PATIENTS AND METHODS

Patients

Patients with biopsy-proven adenocarcinoma of the prostate and recurrent or metastatic disease with either bidimensionally measurable disease or elevated prostate-specific antigen (PSA) were eligible for this study. All patients had to have hormone-resistant disease as defined by progressive measurable disease or rising PSA after orchidectomy or medical castration. As a general rule, only patients ≤ 70 years old with ECOG Performance Status ≤ 2 were considered for chemotherapy. All patients had white blood cell (WBC) count $>4 \times 10^9$/l, platelets $>100 \times 10^9$/l and serum creatinine <120 μmol/l. An elevated bilirubin due to metastatic liver disease was allowed up to $5 \times$ the upper limit of normal (N) with a corresponding reduction in the dose of epirubicin of 50% with bilirubin $2.5–5.0 \times N$. Previous radiotherapy was permitted, but no patient had received chemotherapy before.

Treatment

Patients received PVI 5-FU 200 mg/m^2 via a Hickman line using an ambulatory pump for a maximum of 18 weeks with intravenous (i.v.) epirubicin 40 mg/m^2 and cisplatin 60 mg/m^2 i.v. every 3 weeks for a maximum of six courses. All patients received warfarin 1 mg/day orally to reduce the risk of line thrombosis. There was no fixed policy regarding continuation or discontinuation of previous endocrine treatment, except for patients on flutamide or bicalutamide when hormone treatment was either continued or stopped at least 4 weeks before starting chemotherapy to exclude the

Correspondence to S.J. Harland.
Received 20 Sep. 1996; revised 9 Jan. 1997; accepted 13 Feb. 1997.

flutamide withdrawal syndrome. If Hickman line-related problems occurred, patients were converted to bolus i.v. 5-FU 500 mg/m^2 plus folinic acid 100 mg/m^2 weekly. Treatment was only given if WBC $>3.0 \times 10^9$/l, platelets $>100 \times 10^9$/l and serum creatinine <120 μmol/l. If there was haematological toxicity causing treatment delay, or >WHO grade 2 at nadir, there was an initial 20% dose reduction of epirubicin, followed by 50% dose reduction if there was no improvement. Diarrhoea or stomatitis >WHO grade 2 and intractable shoulder or chest pain were treated by 20% reduction in 5-FU dose initially, followed by 50% dose reduction if there was no improvement. Persisting shoulder or chest pain resulted in a change to bolus i.v. 5-FU. Cisplatin was not given if the serum creatinine was >120 μmol/l.

Response criteria

Response was defined as a PSA level falling to less than 50% of pretreatment levels which was sustained for ≥1 month after completion of six courses (that is, 22 weeks) or, for measurable disease, standard WHO definitions applied: complete response was defined as complete resolution of disease sites and partial response as ≥50% reduction in the total tumour size of the measurable lesions without progressive disease elsewhere and sustained for 1 month, progressive disease as ≥25% increase in the size of the measurable lesions or the appearance of any new lesions, and stable disease as <50% decrease in total tumour size and <25% increase in the size of the measurable lesions.

RESULTS

Patients' characteristics

Between January 1992 and February 1995, 24 patients were entered, of whom 21 were evaluable; 3 patients were excluded as they did not receive a single full course of ECF. Only 1 patient did not have an elevated PSA and had measurable disease in the liver. 1 patient had only locally recurrent disease and all others had metastatic disease; of those with metastatic disease, all had bone disease which was not considered measurable, 4 had lymphadenopathy and 5 had liver metastases. One particularly fit patient who was just over the age limit was entered. The median age was 63 years (range 51–71 years). Prognostic groups were determined by duration of hormone response, performance status, creatinine and alkaline phosphatase [7]; group 1 has the best prognosis with median survival 10 months, group 2 with 6 months and group 3 with 3 months. As can be seen, patients selected for this study could be grouped into relatively good prognostic categories. The patients' characteristics are summarised in Table 1.

Table 1. Patients' characteristics

No. of patients	21
Age (years)	
Median	63
Range	51–71
ECOG performance status	
0	7
1	12
2	2
Initial hormonal treatment	
Orchidectomy	10
Gonadotrophin-releasing hormone analogues	8
Others	3
Second-line hormone treatment	18
Previous chemotherapy	0
Previous radiotherapy	13
Site of disease	
Bone only	13
Bone + soft tissue	7
Local recurrence only	1
Prostate-specific antigen on entry (μg/l)	
Median	148
Range	9.6–1681
Prognostic groups*	
Group 1	6
Group 2	15
Group 3	0

*According to Fossa and associates [7].

Tumour response

Nine out of the 21 (43%) evaluable patients responded (95% confidence interval (CI) 22–64%), with a median time to response of 6 weeks (range 3–15 weeks) and a median duration of response of 9 months (range 7–11 months). One patient had a complete response of his liver metastases by ultrasound scan, and had normalisation of the PSA. Two further responders had partial responses in their liver metastases. The median survival of the entire group was 8 months (range 1–19 months with 4 patients alive at 10 months). These results are summarised in Table 2.

It is interesting to note that of the 3 patients excluded from the trial, 1 patient who received only PVI 5-FU and cisplatin did respond. This gives a response rate of 10 out of 24 patients (42%) on an intention-to-treat basis.

Effect of stopping previous endocrine therapy

Two patients who were responding to chemotherapy interrupted their regular gonadotrophin-releasing hormone analogue therapy, resulting in a dramatic increase in their PSA levels. Restarting the endocrine therapy brought the patients back into remission. A further patient whose disease had formerly responded to stilboestrol given as a second-line agent only, showed PSA evidence of response to ECF when the stilboestrol, to which he was supposedly 'resistant', was restarted. These patients have been described fully elsewhere [8].

The inference from this experience was that at relapse only a proportion of the tumour cells had escaped endocrine control and that continuation of the endocrine treatment was required to prevent relapse of disease which, in these patients, was resistant to chemotherapy. If this was a common occurrence it would be expected that discontinuation of a previously effective hormone treatment (PEHT) would be associated with a lack of chemotherapy response. Table 3 suggests that this might be true as only 1 out 6 (17%) of those who stopped a PEHT responded to chemotherapy compared to 8 out of 15 (53%) of those who did not. The

Table 2. Response to ECF (21 patients evaluable)

Response by PSA	6
Response by PSA and measurable disease (1 PR and 1 CR)	2
Response by measurable disease only (1 PR)	1
Total	9
	43% (95% CI 22–64%)

Table 3. Effect of stopping a previously effective hormone treatment (PEHT) on chemotherapy response

Stopped a PEHT	Yes	No
Chemotherapy response	1	8*
No chemotherapy response	5	7
Total	6	15

*Includes 3 patients where response was only seen after a previous treatment was restarted.

sample size is clearly too small for statistical inference. The discontinued PEHTs have been itemised in Table 4. The proportion of patients receiving second-line endocrine therapy prior to starting chemotherapy was roughly the same for the chemotherapy responders (62%) as the non-responders (71%).

Toxicity

All 21 patients were evaluable for toxicity as shown in Table 5. Except for alopecia, other WHO grade 3 or 4 toxicities were rare (anaemia (3), leukopenia (3), emesis (3) and diarrhoea (1)). Two patients experienced more than a 1 week delay in treatment due to myelosuppression. 4 patients required dose reductions in epirubicin due to abnormal liver function from metastases (2) or myelosuppression (2). 5 patients were converted to 5-FU i.v. bolus after Hickman line thrombosis (4), line falling out (1) or shoulder pain (1). 2 further patients had PVI 5-FU dose reductions due to shoulder pain.

DISCUSSION

Assessment of response to treatment in prostate cancer remains controversial. Sclerotic bone metastases are not assessable by classic response criteria, and only 10% of patients have measurable soft tissue lesions. There is evidence that post-therapy PSA levels can be used as a surrogate end point to evaluate treatment in hormone-refractory prostate cancer. Kelly and associates [9] have suggested that a decline of ≥50% of baseline sustained over 2 months is indicative of response, but in our criteria for response the PSA fall must be sustained for 1 month after six courses of treatment, that is, at least 5.5 months.

Table 4. Discontinued previously effective endocrine treatments; all were second-line agents following relapse on prior endocrine treatments

Patient	Treatment	Maximum suppression of PSA	Duration of endocrine response
1	Hydrocortisone and stilboestrol*	87%	7 months
2	Stilboestrol	93%	8 months
3	(a) Hydrocortisone	59%	6 months
	(b) Stilboestrol	47%	7 months
4	Hydrocortisone†	99%	4 months
5	Goserelin‡	90%	9 months
6	Hydrocortisone and stilboestrol§	91%	8 months

*The standard doses given were hydrocortisone 40 mg/day + stilboestrol 1 mg/day.

†In this patient the hydrocortisone dose was reduced to 10 mg/day prior to chemotherapy, which is probably insufficient to suppress adrenal function.

‡In this patient bicalutamide was used before, during and after treatment with goserelin.

§This patient responded to ECF chemotherapy.

Table 5. Haematological and non-haematological toxicities: worst score for any course of treatment (21 patients evaluable)

Parameter	WHO grade 1–2	WHO grade 3–4 (%)
Haemoglobin	9	3 (14%)
Leucocytes	7	3 (14%)
Platelets	2	1 (5%)
Emesis	8	3 (14%)
Stomatitis	5	0 (0%)
Diarrhoea	6	1 (5%)
Alopecia	2	19 (90%)
Renal	2	0 (0%)
Neuropathy	1	0 (0%)
Plantar-palmar syndrome	2	0 (0%)
Hickman line infection	–	2 (10%)
Hickman line thrombosis	–	4 (19%)
Hickman line falling out	–	2 (10%)
Shoulder pain	–	3 (14%)

The majority of patients with metastatic prostate cancer cannot be considered suitable for combination chemotherapy on account of their age and frailty. However, there is an important minority of patients in which this approach could be considered provided durable responses can be obtained. The response rate in this study (43%) and median duration of response (9 months) compare favourably with results from other chemotherapy trials [3]. The toxicities were well tolerated and generally as expected. Hickman line thrombosis and shoulder pain, related to the PVI 5-FU, were the main causes of changes in the chemotherapy regimen.

By the selection criteria of good performance status and normal creatinine, we have clearly biased this study towards good prognosis patients. However, the results cannot be explained by prognostic factors alone as there is an even division of group 1, the best prognosis patients, in the responder and non-responder groups (results not shown). The small cell variant of prostate cancer might be expected to be more chemosensitive and, although none of the original biopsies showed this histology, it is possible that the small cell variant might have arisen later in the disease process. This possibility should be borne in mind, particularly in the case of the patient who had a complete response as judged by ultrasound scans of the liver metastases, but unfortunately died in his local hospital from suspected cerebral involvement at 10 months without a postmortem.

We have argued elsewhere that the observation that 3 of our patients who responded to chemotherapy required continuation of their previously ineffective endocrine treatment is evidence for there being two populations of tumour cells in certain patients—one sensitive to cytotoxic agents and resistant to endocrine treatment, the other vice versa [8]. The additional observation in this study that more of the non-responders to chemotherapy had discontinued endocrine treatment than the responders also fits with such a concept. The corollary is that the response rate to ECF chemotherapy would have been higher had the previous endocrine treatment always been continued. The issue of whether or

not to continue endocrine treatment in chemotherapy trials in prostate cancer is still undetermined, and our lack of a fixed policy at the time of the study was in line with many chemotherapy trials in prostate cancer. Two large-scale retrospective analyses of chemotherapy trials comparing the response and survival advantage of patients who continued androgen deprivation versus those who did not gave conflicting results [10, 11]. The question has not been simplified by the low response rate to chemotherapy in these studies.

Further evaluation is planned. A major problem was Hickman line thrombosis and for future studies formal anticoagulation with warfarin to an international normalised ratio of 1.5–2.0 will be adopted to try to reduce the risk. One approach to simplify the regimen would be to substitute carboplatin for cisplatin which would improve the tolerability of this regimen and make the treatment truly outpatient-based. There is preliminary evidence that this modified ECF regimen, called ECarboF, is active in breast cancer [12]. Quality of life is clearly an important issue for what remains palliative chemotherapy, and this will be incorporated into future studies. For the ECarboF study in prostate cancer, all patients will continue their previously effective endocrine treatment, but the question is unlikely to be settled until a randomised study of continuation of endocrine treatment versus discontinuation in patients receiving chemotherapy is carried out. Any advantage of continuing endocrine treatment is clearly dependent upon effective chemotherapy for prostate cancer. If the response rate to ECF or its derivatives is confirmed, then we may also be able to answer this important question.

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