Epirubicin carboplatin and 5-fluorouracil (ECarboF) chemotherapy in metastatic hormone refractory prostate cancer

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The aim of this study was to examine the efficacy and toxicity of the epirubicin, carboplatin and 5-fluorouracil (ECarboF) regime in patients aged 70 or less with metastatic prostate cancer resistant to LHRH analogues. The majority of patients had previously received steroids as part of their systemic management and had progressive disease on steroids. In total, 80 patients were treated over a 6-year period, with objective response rates (PSA or radiological) of 45% and median time to relapse of 9.5 months. Median survival of the group was 9.2 months. In all, 32% of patients were alive at 12 months. Grade 3/4 neutropenia occurred in 34% of patients. For a substantial minority of patients with hormone refractory prostate cancer, combination chemotherapy can induce remission of significant duration. While similar responses have been documented for systemic cytotoxic–steroid combinations, the responses in this study are likely to reflect the activity of cytotoxic drugs alone.

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The value of cytotoxic chemotherapy in patients with metastatic prostate cancer in progression following androgen suppression is uncertain. In recent times, mitozantrone has been shown to produce pain relief in a proportion of patients. In addition, using a fall in plasma prostate-specific antigen (PSA) as an end point, an additional 16–25% of patients (Berry et al, 2001; Kantoff et al, 2001) are seen to respond to the addition of mitozantrone to steroid in randomised studies, compared to the use of steroids alone (Tannock et al, 1996). A larger proportion of patients have been shown to respond to combined drug treatments in phase 2 studies. However, these combinations often comprise cytotoxic agents together with an oestrogen or a corticosteroid – the latter often given as prophylaxis against nausea or against the allergic manifestations of taxanes. Both oestrogens and corticosteroids have antitumour effects in prostate cancer (Fossa et al, 2001), and thus it is difficult to gauge the specific contribution of the cytotoxic drugs. Combination chemotherapy with 5-fluorouracil, epirubicin and cisplatin (ECF) in metastatic prostate cancer (Chao et al, 1997) showed an encouraging response rate – over 40% – in a limited number of patients. Carboplatin substitution for cisplatin (ECarboF) has been successfully implemented in the treatment of breast cancer (Bonnerof et al, 1996), and reduces auditory and renal toxicity at the cost of additional myelotoxicity. We wished to establish the efficacy and tolerability of this therapy in a large group of patients with hormone-refractory metastatic prostate cancer, while ensuring that any benefit related to the cytotoxic agents rather than co-administered steroids.

MATERIALS AND METHODS

Eligibility

Patients with biopsy-proven adenocarcinoma of the prostate with recurrent or metastatic disease, which had failed first-line hormone therapy, were included in the study. Both symptomatic and asymptomatic patients were eligible. Those without symptoms had three successive rises in serum PSA, in keeping with the American Society of Therapeutic Radiation Oncology guidelines (Horwitz et al, 1998). Previous hormone therapy was continued, with the exception of nonsteroidal antiandrogens (see below) and a change of hormonal therapy was not permitted. All patients had a PSA greater than 20 ng ml–1, or bi-dimensionally measurable disease. In general, only patients <70 years, with WHO performance status 0–2, with no history of previous chemotherapy were eligible. No previous hemi body radiotherapy or intravenous strontium treatment was allowed. All patients were required to have white blood cell (WBC) count >3.0 × 109 l–1 and platelets >100 × 109 l–1. EDTA clearance was performed prior to commencing chemotherapy. Serum alkaline phosphatase and renal function was recorded prior to treatment and patients classified into prognostic subgroups (Fossa et al, 1992).

Treatment

Patients received epirubicin 50 mg m–2 intravenously and carboplatin [calculated area under curve of 5] as an intravenous infusion, both 4 weekly. Initially, protracted venous infusion (PVI) 5-Fluorouracil (5FU) at a dose of 200 mg m–2 day–1 was given via a Hickman line, but due to Hickman line difficulties, this was changed mid-way through the study to 450 mg m–2 as a 1 h infusion on days 1 and 15 with folic acid 20 mg m–2. All patients with Hickman lines received low-dose anticoagulation, initially...
with 2 mg daily of warfarin. If the patient was taking endocrine therapy prior to chemotherapy, this was continued. If nonsteroidal antiandrogen therapy had been recently discontinued, 8 weeks were allowed to elapse before commencing chemotherapy to exclude any response due to androgen withdrawal. Patients who had responded to first-line hormonal therapy for < 9 months were usually given chemotherapy on relapse, whereas those patients with longer response times were routinely given a trial of second-line hormonal therapy, including oral hydrocortisone, before chemotherapy was considered. Thus, the majority of patients had disease which was also progressive on hydrocortisone therapy. In these patients, dexamethasone as antiemetic prophylaxis was given. Otherwise, steroids were omitted from the antiemetic regime in view of their potential antitumour action. However, if nausea persisted despite 5-HT3 antagonists, oral and/or intravenous steroid therapy was considered. If there was a nadir platelet count of $< 50 \times 10^9 l^{-1}$ or pretreatment platelet count $< 100 \times 10^9 l^{-1}$, the carboplatin dose was reduced by 25%. If the nadir WBC was WHO grade 3 (neutrophils $< 0.5 \times 10^9 l^{-1}$), or pretreatment WBC was WHO grade 2 ($2.0 – 2.9 \times 10^9 l^{-1}$), the epirubicin dose was reduced by 25%.

Diarrhoea and stomatitis of WHO grade 2 or above resulted in a 20% reduction of 5FU, or temporary cessation of treatment for at least 1 month after completion of six cycles of chemotherapy. Levels to less than 50% of pretreatment values, maintained for at least 1 month after completion of six cycles of chemotherapy were given before concluding that no response had been achieved. The decision to continue or stop chemotherapy was invariably made on the basis of patients’ clinical response, assisted by PSA values and occasionally radiological assessment. A rising PSA was based on a minimum of two successive increases. If chemotherapy appeared to be preventing progression, chemotherapy could be continued despite a stable PSA. Treatment was also stopped if there was patient intolerance or if six to eight cycles had been reached. If any steroid-naive patient had been commenced on steroids because of vomiting or suspected spinal cord or nerve root compression, the response documented at the cycle immediately prior to starting steroids was used. This allowed an assessment of the response due to cytotoxic therapy alone to be recorded. Duration of response and survival were defined from the time chemotherapy was initiated.

**Sample size**
The above regime is in regular use in our hospital. This report is generated at a time when the number of patients treated gives a lower confidence limit for response of greater than 25%.

**RESULTS**

**Patient demographics (Table 1)**

Between December 1995 and March 2002, 80 patients were entered, 75 of whom had elevated PSA levels (greater than 20 ng ml$^{-1}$) prior to treatment. In all seven patients with nonelevated PSA, disease was measurable on liver ultrasound and/or chest CT. The median age was 64 years (range 48–72 years) with four patients above the upper age limit, all of whom were of performance status 0–1 and hence entered at the physician’s discretion. Patients were classified into prognostic groups according to the Fossa classification (Fossa et al., 1992), wherein duration of hormone response, performance status, serum creatinine and alkaline phosphatase are predictive of survival. Subgroups 1 and 2 were defined, with predicted prognoses of 10, 6 and 3 months respectively. The majority of patients selected for this study were thus in relatively good prognostic categories. In total, 63 out of 80 patients (78%) had symptoms of progressive disease as previously described. Patients received a median of five cycles (range 1–8 cycles) and dose reductions or delays were seen in 46 patients (57%). A total of 59 out of 80 patients (73%) had disease that was progressive on hydrocortisone therapy, with a further 21 patients who had not

| Table 1 | Patient demographics |
|--------|----------------------|
| **Number of patients** | 80 |
| **Age (years)** | Median 64, Range 48–72 |
| **ECOG performance status** | 0: 43, 1: 39, 2: 8, Symptomatic: 63 (78%), Asymptomatic: 17 |
| **Site of disease** | Bone only: 56, Bone+soft tissue: 20, Local recurrence only: 4, Prostate-specific antigen on entry (ng ml$^{-1}$): 196, Range: 4.7–1832 |
| **Prognostic subgroups at entry** | Group 1: 24, Group 2: 49, Group 3: 7 |

*Prognostic subgroups according to Fossa et al (1992).*
received steroids as antitumour systemic therapy. Seven of these 21 steroid-naive patients received dexamethasone during the study due to persistent vomiting (five patients) or neurological deterioration (two patients).

Toxicity

A total of 75 patients (93%) were evaluable for toxicity (Table 2). The rate of neutropenic sepsis was low (8.7%) with nonhaematological WHO Grade 3 or 4 toxicity occurring in 22 patients (27.5%). One patient developed left ventricular failure (New York Heart Classification Grade 4) shortly after completing the sixth cycle of chemotherapy, but his cardiac function subsequently improved. There was one deep vein thrombosis despite prophylactic low-dose warfarin anticoagulation, and one patient suffered a subdural haematoma, the aetiology of which may have been related to his anticoagulation or to an unrelated intracranial haemorrhage. One patient also experienced rectal bleeding which required discontinuation of chemotherapy.

Tumour response (Table 3)

In all, 36 out of the 80 (45%) patients responded by PSA (study criteria) and/or radiological criteria (95% confidence interval (CI) 29–60%) with a median time to first suppression of PSA of 7 weeks (range 3–14 weeks) from commencing chemotherapy. When the specific study criteria of PSA response, defined as the fall in PSA maintained for 1-month postcompletion of chemotherapy was used, responses were seen in 30 out of 73 (41%) patients. When PSA response as defined by International Criteria was used, PSA responses were seen in 42 of the 73 (57%) patients with an elevated PSA prior to treatment. In all, 12 patients did not maintain the fall in PSA after completion of treatment. A slowing of the rate of rise of serum PSA accompanied by a symptomatic response as previously described was seen in a further five patients. Symptomatic response was seen in 41 out of 63 (65%) of patients who had been symptomatic prior to starting treatment. Of the seven patients with a pretreatment PSA of < 20 ng ml⁻¹, radiological responses, two of which were complete responses, were seen in six patients. The median duration of response was 9.5 months (range 7–17 months). Median survival was 9.2 months (range 1–29 months). In total, 40% of patients were alive at 12 months and 11% at 24 months.

**DISCUSSION**

Chemotherapy in prostate cancer has been traditionally discounted, after disappointing results in the 1980s. Indeed, the combination of mitoxantrone and prednisolone (Berry et al, 2002) although showing improvement in symptoms showed no survival benefit. This finding was reflected in previous trials of chemotherapy in prostate cancer comparing chemotherapy with best supportive care alone. Poor response rates of 10–15% to single agents with a median duration of response of 6–9 months have been quoted (Brausi et al, 1995). However, early studies in the pre-PSA era often relied on acid phosphatase levels and patient symptoms as markers of response, as only 20% of patients with metastatic prostate cancer, have measurable soft tissue disease (Figg et al, 1996). Post-therapy PSA levels have become widely accepted as a surrogate end point in the evaluation of treatment.

**Table 2** Grade 3/4 Haematological and nonhaematological toxicities in 75 evaluable patients

| Toxicity                  | Grade 3/4 (%) |
|---------------------------|---------------|
| Haemoglobin               | 13 (16%)      |
| Neutrophils               | 27 (33.8%)    |
| Platelets                 | 13 (16%)      |
| Neutropenic sepsis        | 7 (8.7%)      |
| Hickman line thrombus/re-insertion/shoulder pain | 7/45 (15%) |
| Renal                     | 1             |
| Skin                      | 2             |
| Emesis                    | 8 (of which five were in steroid-naive group) |
| Diarrhoea                 | 2             |
| Stomatitis                | 4             |
| Infection                 | 2             |
| Cardiac                   | 1             |
| Haematuria                | 2             |

**Table 3** Response to EcarboF chemotherapy (80 patients evaluable)

| PSA response                | 42/73 (57%) |
|----------------------------|-------------|
| Defined per International criteria | 30/73 (41%) |
| Radiological response       | 6/7         |
| Total objective responses   | 6/7         |
| Using International PSA response criteria | 48/80 (60%) |
| Using study PSA response criteria | 36/80 (45%) |
| Symptomatic response (doctor’s assessment) | 41/63 |

*Defined as >50% fall in initial level maintained for at least 4 weeks. **Defined as >50% fall in initial level maintained for at least 4 weeks from completion of chemotherapy. **PSA not elevated prior to treatment. In the 63 patients who were symptomatic at the initiation of treatment.

**Figure 1** (A) PSA trend in response to chemotherapy and addition of steroids in Patient 1. 1–7: chemotherapy cycles; Dex: dexamethasone commenced for a period of 6 weeks; ST: stilboestrol; HC: hydrocortisone. (B) PSA trend in response to chemotherapy and subsequent radiotherapy and steroids in Patient 2. 1–5: chemotherapy cycles; Dex + RT: dexamethasone and radiotherapy commenced; *dexamethasone given as antiemetic.
responses in hormone-refractory prostate cancer (Smith et al., 1998). One suggestion is that a decline of 50% or greater from baseline sustained over 2 months reflects a response (Kelly et al., 1993). We have used the Prostate Specific Antigen Working Group (Bubley et al., 1999a) criteria of a greater than 50% fall in serum PSA from pretreatment levels, sustained for at least 4 weeks but also our own specific definition of the PSA fall being maintained for a month or greater after completion of six cycles of chemotherapy. Previous work from this institution has shown response rates of 40% using epirubicin, cisplatin and 5-fluorouracil (Chao et al., 1997). However, significant toxicity is encountered with ECF, particularly nausea, renal toxicity, peripheral neuropathy and ototoxicity (Ross et al., 2002). Carboplatin substitution for cisplatin minimises renal, auditory and neurological toxicity and simplifies the outpatient regime but may prove more myelotoxic. It has not been used previously in metastatic prostatic tumours. In other Phase II studies, the combination of estramustine and docetaxel (Petrylak, 2002) has PSA response rates of up to 74 with a 77% 1-year survival. However, neutropenia rates were significant (43%) and prednisolone was also given at high dose as part of the premedication regime with each cycle.

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It is not clear, therefore, the extent to which docetaxel contributes to the high response rate in the steroid-cytotoxic combination.

We have previously presented data on the first 34 patients treated with the ECARBoF regime (Newby et al., 1999). The response rate of ECARBoF is similar (45 vs 43%) to that seen in a study from this institution with ECF (Chao et al., 1997). In this previous study, there was a 19% rate of Hickman line thrombosis, which has been reduced to 6% (three out of 45 patients) by low-dose warfarin anticoagulation. Other Hickman line problems including shoulder pain and lines becoming dislodged occurred in four patients. These problems lead to the discontinuation of 5-FU as a PVI and the use of the 1 h infusion of 5-FU on days 1 and 15. Previous endocrine therapy was continued to ensure that any tumour clone has been well documented, giving better subjective responses in terms of improvements in pain score and performance status, and similar PSA responses to antiandrogen therapy (Fossa et al., 2001). The beneficial but confounding effects of steroids on tumour response have been demonstrated in two steroid-naïve patients treated in our institution with ECARBoF subsequent to the current series (Figure 1A and B). The administration of dexamethasone for spinal cord compression in these two patients was followed by a prompt fall in PSA, which may not have been seen with chemotherapy alone.

This study confirms the efficacy and manageable toxicity of the ECARBoF regime in selected patients with hormone refractory prostate cancer receiving treatment as outpatients. The number of dose reductions and treatment delays illustrate that this is an aggressive regime. It would, therefore, not be suitable for the majority of patients, but should be considered for the sizeable minority in whom combination chemotherapy is appropriate. The encouraging response rate from ECARBoF implies that combination chemotherapy is superior to single-agent cytotoxic treatments. This conclusion would require a randomised study, however, where factors such as quality of life and overall survival would additionally need to be compared.

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