

Letter to the Editor

Metronomic chemotherapy with cyclophosphamide and dexamethasone in patients with metastatic carcinoma of the prostate

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Sir,

We read with interest the article by Khan *et al* (2011), which found that combined metronomic therapy with low-dose cyclophosphamide and methotrexate, combined with celecoxib, did not demonstrate significant activity in patients with advanced cancer. These conclusions are in contrast to our own findings that show clinical and biochemical response to metronomic low-dose cyclophosphamide and dexamethasone in patients with castration refractory metastatic carcinoma of the prostate.

We performed a retrospective audit of 28 patients with metastatic castration refractory carcinoma of the prostate who received cyclophosphamide 50 mg and dexamethasone 2 mg daily, until

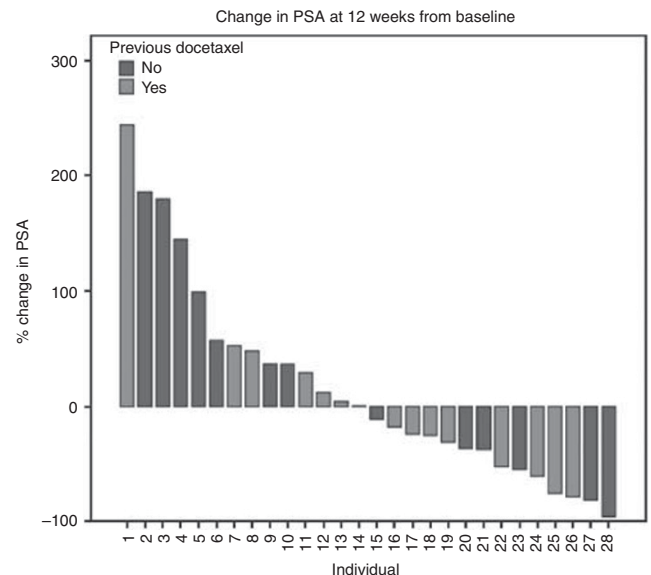
disease progression. Patient characteristics are provided in Table 1. Almost all patients had been exposed to previous continuous corticosteroid therapy, either as part of standard chemotherapy regimens, or as an independent hormonal treatment.

Response to treatment was determined according to recognised end points in patients with prostate cancer (Scher *et al*, 2008). A total of 13 out of 28 (46%) patients achieved a nadir PSA response below the baseline value (Figure 1). At 12 weeks, 12 out of 28 (43%) patients had a PSA reduction of $\geq 25\%$, 11 out of 28 (39%) had a PSA rise of $\geq 25\%$ and 5 out of 28 (18%) had a PSA within 25% of the baseline value. There was no significant association between disease response and the previous use of docetaxel chemotherapy (Student's *t*-test $P=0.314$). The median time to progression (25% increase above PSA nadir value (Scher *et al*, 2008)) was 16 weeks. Four patients had clinical improvement of symptoms.

Treatment was generally well tolerated in a heavily pre-treated group of castration refractory prostate cancer patients, such that

Table 1 Patient characteristics

	Number of patients
Mean age (years)	75
Gleason score	
● 5	1
● 6	1
● 7	1
● 8	2
● 9	10
● 10	2
● Biopsy not performed	11
Number of previous lines of hormone therapy	
● 2	2
● 3	15
● 4	8
● 5	3
Number of previous lines of chemotherapy	
● 0	14
● 1	12
● 2	2
Median baseline PSA at commencement of treatment	123.5 (range 16–3448)

**Figure 1** Change in PSA from baseline 12 weeks after the introduction of treatment with cyclophosphamide and dexamethasone.

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toxicities were mild or potentially attributable to the disease process. During treatment, four patients had myelosuppression, defined as anaemia requiring transfusion, and one patient had a suspected myocardial infarction. Two patients died during treatment. The treatment of two patients was interrupted for 8 and 12 weeks because of surgical procedures.

Previous work has also shown treatment response to metronomic cyclophosphamide and dexamethasone in castration refractory prostate cancer; Glode *et al* (2003) published PSA responses according to the PCWG1 guidelines (Bubley *et al*, 1999), showing that 29% of patients had a PSA reduction of $\geq 80\%$, 39% a reduction of 50–79%, 6% a $<50\%$ decrease and 26% of patients had a progressive disease (two consecutive PSA rises). Median time to progression was 9 months (36 weeks). As in our series, treatment was well tolerated. In contrast, our patients were more heavily pre-treated and the patients reported here had higher Gleason scores (9 vs 8.2).

It is possible that response to metronomic chemotherapy is, in part, influenced by the histology of the primary tumour. The study

by Khan *et al* (2011) contained patients with breast, gastrointestinal, renal, melanoma, ovarian, prostate (9 out of 69 patients) and unknown primary tumours. Our work, which shows response to metronomic chemotherapy, alongside the work by Glode *et al* (2003) shows benefit in patients specifically with prostate cancer. We believe that further investigation into the use of metronomic chemotherapy is warranted in prostate cancer, but acknowledge that may not be appropriate in all histological tumour subtypes.

The use of dexamethasone concurrently with cyclophosphamide could have contributed to the response demonstrated in our patients. However, as stated above, virtually all of our patients had been treated previously with corticosteroids, and so we believe the use of cyclophosphamide was responsible for most of the clinical benefit seen.

In conclusion, we believe that metronomic treatment with cyclophosphamide is a well tolerated and useful treatment in heavily pre-treated patients with metastatic castration refractory carcinoma of the prostate, and warrants further investigation.

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