LETTER TO THE EDITOR

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Comment on 'The efficacy and toxicity of gemcitabine, carboplatin and bevacizumab in metastatic breast cancer'

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Sir,

As pointed out in the excellent article by Miles *et al* (2013), the identification of patients benefiting most from bevacizumab remains elusive. The activity of the gemcitabine and platinum combination in a variety of neoplasms is well described. In metastatic breast cancer, it has often been used as a standard regimen in patients with triple-negative disease, despite a lack of comparative phase 3 data, especially in anthracycline and taxane pre-treated individuals (Perez, 2004; Heinemann *et al*, 2006; Sanchez-Escribano Morcuende *et al*, 2007; Maisano *et al*, 2011). The role of gemcitabine and carboplatin in this setting has been highlighted by its use in the control arm in randomised trials of PARP inhibitors (Foulkes *et al*, 2010; Stebbing *et al*, 2010; O'Shaughnessy, 2012).

The use of bevacizumab in breast cancer has been associated with controversy and it has been combined with a wide variety of cytotoxics (Jones and Ellis, 2011), some combinations thought to have more benefits than others (Miller *et al*, 2007; O'Shaughnessy and Brufsky, 2008; Brufsky *et al*, 2011; Hamilton and Blackwell, 2011; Brufsky *et al*, 2012; Kesikli and Kilickap, 2012). To the best of our knowledge, the activity and toxicity of gemcitabine, carboplatin and bevacizumab has not been described in women with metastatic breast cancer.

The oncology cohort at the Leaders in Oncology Care (LOC) clinic in London includes over 11 000 patients with data prospectively recorded for the period between May 2005 and September 2011, as previously described (Kitchen *et al*, 2012). When patients attend the clinic for treatment, their toxicities are recorded electronically on the MOSAIQ electronic medical records package (Elekta, Stockholm, Sweden) using the Chemotherapy Toxicity Criteria (CTCAE3.0) scale. We identified during this time, any patients with metastatic breast cancer regardless of histology, who received treatment with gemcitabine, carboplatin and bevacizumab.

Patients received bevacizumab (15 $mgkg^{-1}$ on day 1), gemcitabine (1000 mg/m^2 on days 1 and 8) and carboplatin (AUC 5 on day 1) for up to eight 3 weekly cycles. A total of 14 patients were identified who received this combination; the median progression-free survival (PFS) measured 5.1 months (95% CI 2.2–8.0 months) with a median overall survival (OS) of 8.3 months (95% CI 6.5–10.0 months); 71% were alive at 6 months. Their median age was 45 years old (range 31–66 years). A total of 10 patients (71%) in the cohort had triple-negative breast cancer, with the entire cohort being negative for HER-2. The liver, lung and bone metastases were the commonest metastatic sites, with six individuals (43%) having metastases at all these locations. The median number of treatments received for metastatic disease prior to commencing treatment with gemcitabine, carboplatin and bevacizumab was 2 (range 0–4), with nine patients (64%) having received either an anthracycline, taxane or both in their previous metastatic regimens prior to receiving therapy; gemcitabine, carboplatin and bevacizumab was first-line treatment in three individuals (21%).

The most common grade III/IV toxicities (Table 1) were fatigue in six patients (43%) and pain in five patients, though this latter side effect was probably related to the cancer itself (36%). Alopecia and bleeding were not reported. Figure 1 demonstrates the OS and PFS curves for this single cohort.

The median number of cycles of gemcitabine, carboplatin and bevacizumab administered was 5 (range 1–8). An objective partial

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Table 1. Grade III/IV toxicities

Side effects	*N* (%)
Fatigue	6 (43)
Diarrhoea	2 (14)
Pain	5 (36)
Dry skin	1 (7)
Nausea	1 (7)
Vomiting	1 (7)
Severe anaphylaxis	1 (7)
Hand–foot reaction	1 (7)
Cough	1 (7)
Insomnia	2 (14)
Mucositis	1 (7)
Hot flushes	1 (7)
Nerve pain	1 (7)
Hypertension	1 (7)
Taste changes	1 (7)

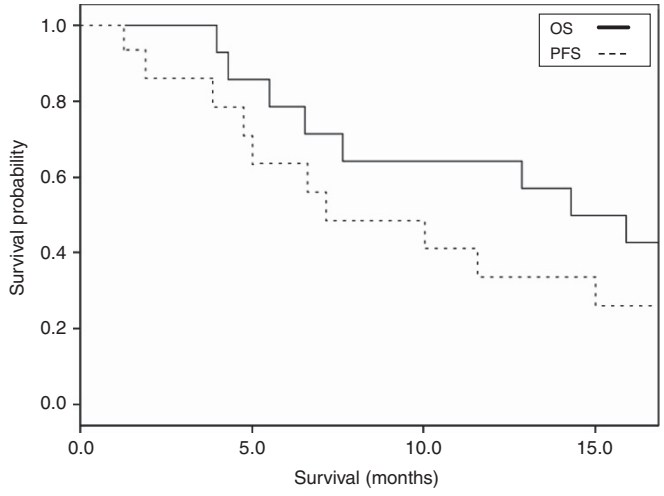

Figure 1. Kaplan–Meier curves showing overall (OS) and progression-free survival (PFS).

response was observed in nine patients (64%). Interestingly, nine patients (64%) in the cohort had shown disease progression on their previous treatment protocols and six of these (66%) then went on to have a response to the gemcitabine, carboplatin and bevacizumab; one individual (7%) developed brain metastases following commencement of gemcitabine, carboplatin and bevacizumab.

To the best of our knowledge, this is the first-line treatment with gemcitabine, carboplatin and bevacizumab described in metastatic breast cancer. It is difficult to make comments on efficacy from a single arm study, but the PFS appears to be comparable with other regimens in late-stage disease.

Bevacizumab combined with paclitaxel has been shown to improve PFS when compared with first-line taxane therapy alone in individuals with HER-2-negative metastatic breast cancer (Miller *et al*, 2007), although its benefits in combination with other cytotoxics has been questioned particularly when cost-effectiveness is considered (D'Agostino, 2011). In one study in which bevacizumab was administered as a second-line treatment protocol in triple-negative breast cancer, the median PFS was 6.0 months (Brufsky *et al*, 2012), similar numerically to the results observed here, though any comparison between studies should be interpreted with caution. In our cohort a further two women were treated with gemcitabine, cisplatin and bevacizumab, and data were similar to those observed here, but we did not include these in the primary analysis.

In summary, gemcitabine, carboplatin and bevacizumab is a well-tolerated regime that may provide an attractive treatment option in patients whose disease is continuing to progress despite ongoing interventions, who are not eligible for clinical trials. As suggested by Miles *et al* (2013), plasma VEGF-A and VEGFR-2 levels may be potential predictive biomarkers in this patients too.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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