OPEN

Do Not Give Up

To the Editors:

Most women with advanced ovarian cancer undergo cytoreductive surgery and chemotherapy, enter a period of follow-up, and ultimately relapse. Although there are a number of therapeutic interventions in this situation with at least 7 active chemotherapy or biological agents and the possibility of secondary cytoreductive surgery, long-term survival after relapse is rare and most women succumb to their disease.[1]

We present a woman diagnosed with an advanced ovarian cancer who had a total of 22 relapses, 19 systemic treatments, and 6 localized palliative interventions for over a 14-year period, which, to the best of our knowledge, to more therapy than has been described before. She had no previous significant medical history but did have a positive family history of ovarian cancer; her sister died from the disease at the age of 48 years and a paternal cousin developed ovarian cancer in her 60s. On the basis of this, she elected to undergo prophylactic oophorectomies at the age of 46 years but imaging before surgery revealed an ovarian mass, which led to a pelvic clearance and omentectomy, and she was diagnosed with a stage 3 grade 3 endometrioid carcinoma of the ovary. After surgery, she had adjuvant chemotherapy in the context of the SCOTROC3 study.[2] She relapsed 7 months later rendering her only partially platinum sensitive. Despite this, she went on to receive platinum-containing chemotherapy on 10 separate occasions, and each time, this resulted in a Ca125 marker and clinical response (Fig. 1). In between and during most treatments, she was fit and enjoyed a good quality of life.

Interestingly, genetic screening on the basis of her family history and her repeated responses to platinum-based chemotherapy did not reveal a BRCA mutation when initially performed around the time of diagnosis or when repeated several years later with the assumption that improved molecular techniques would identify a mutation. It is quite possible, however, that she will have had an as yet unidentified mutation conferring "BRCAness" that may have responded to Poly (ADP-ribose) polymerase inhibitors. Drugs used (Table 1) in combination with platinum in her case include etoposide, paclitaxel, and gemcitabine. Drugs used as single agents included oral altretamine, pegylated liposomal doxorubicin, oral cyclophosphamide, and tamoxifen. Nodal relapses were treated with palliative radiotherapy to good effect and she participated in 4 different clinical trials. Her first relapse was 7 months after primary treatment and most of her subsequent treatment free intervals were between 4 and 6 months except after 2 clinical trials involving vascular disruptive agents (VDAs) where the intervals were much longer (18 months for combretastatin[3] and 9 months after OXI4503[4]). The monoclonal antibody, bevacizumab, and other antiangiogenic agents have been investigated and have a role in the treatment of ovarian cancer, but this is 1 class of drugs to which she was not exposed. The funding approval

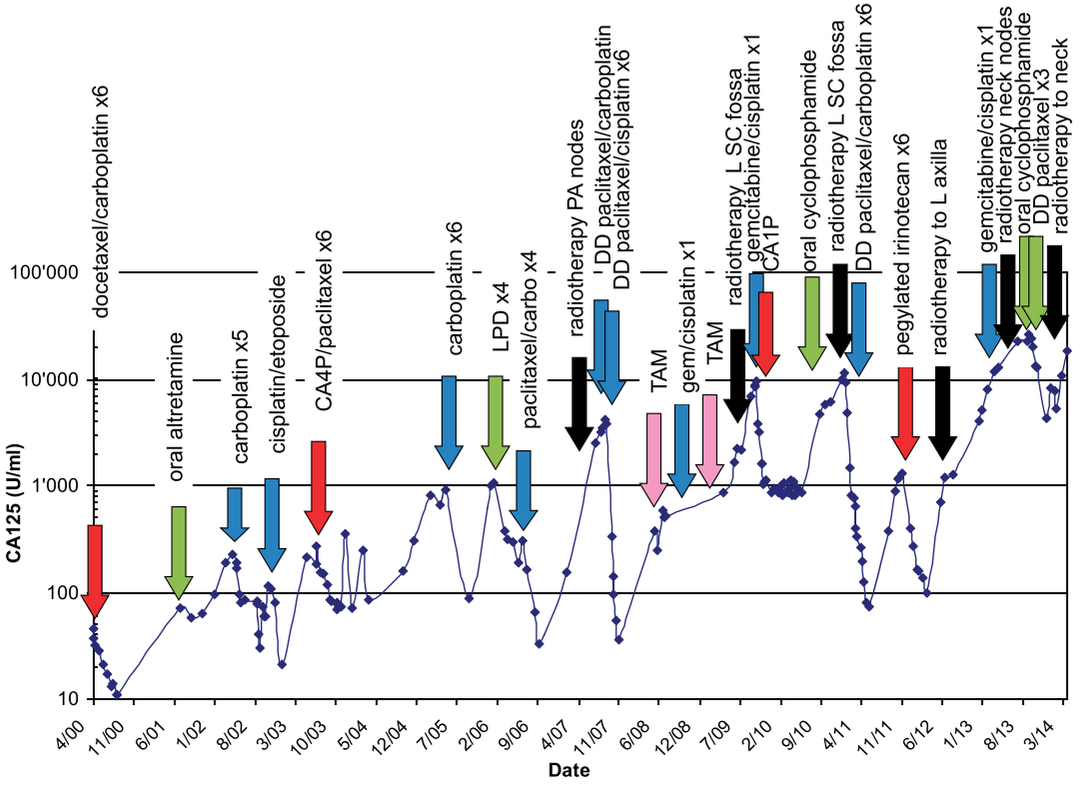

FIGURE 1. Change in CA125 levels is response to therapy.

TABLE 1. Treatment given for each line of therapy

Relapse	Relapse Date	Treatment and No. Cycles Given
First line	April 2000	Docetaxel/carboplatin (SCOTROC 3)
First relapse	July 2001	Oral altretamine
Second relapse	March 2002	Carboplatin × 5
Third relapse	September 2002	Cisplatin/etoposide (DD) × 6 wk
Fourth relapse	July 2003	CA4P/paclitaxel (combretastatin study) × 6
Fifth relapse	April 2005	Carboplatin × 6
Sixth relapse	January 2006	Pegylated liposomal doxorubicin × 4
Seventh relapse	June 2006	Carboplatin/paclitaxel × 4
Eighth relapse	February 2007	Radiotherapy to para-aortic nodes
Ninth relapse	August 2007	DD carboplatin/paclitaxel × 3
		Allergic reaction, switch to DD cisplatin/paclitaxel × 6
10th relapse	March 2008	Tamoxifen
11th relapse	July 2008	Gemcitabine/cisplatin × 1 (stopped because of sickness and good response), continued on maintenance tamoxifen
12 relapse	May 2009	Radiotherapy to left SCF nodes (20Gy in 5#)
13th relapse	July 2009	Gemcitabine/cisplatin × 1
14th relapse	October 2009	OXI4503 phase 1 trial (CA1P, vascular disrupting agent) × 6 (18 infusions OXI4503)
		Oral cyclophosphamide × 2
15th relapse	September 2010	Radiotherapy to right SCF nodes
16th relapse	November 2010	DD carboplatin/paclitaxel × 6
17th relapse	January 2011	Pegylated irinotecan × 6 (NEKTAR study)
18th relapse	November 2011	Radiotherapy to left axilla (20Gy in 5#)
19th relapse	July 2012	Gemcitabine/cisplatin × 1
20th relapse	February 2013	Gemcitabine/cisplatin × 1
21st relapse	June 2013	Radiotherapy to left neck nodes (20Gy in 5#) and oral cyclophosphamide × 1
22nd relapse	October 2013	DD weekly paclitaxel × 3 interrupted by fractured humerus, further radiotherapy to neck
Date of death	November 06, 2014	

DD indicates dose dense; SCF, supraclavicular fossa.

for bevacizumab in the United Kingdom was in the first-line[5] and platinum-sensitive[6] settings and did not apply to this patient. It had been hoped that she would remain well enough to enter another VDA trial in combination with pazopanib, an antiangiogenic tyrosine kinase inhibitor (PAZOFOS, UKCRN 88145142), but sadly she died before the study opened.

This case demonstrates that platinum resistance by conventional definition does not mean that patients with ovarian cancer will never respond to platinum in the future and the role of VDAs, alongside conventional antiangiogenics in the management of this disease, is looked to with interest.

René Lynnette Roux, MRCP
Marcia Rosalind Hall, MB, BS, PhD, FRCP
Mount Vernon Cancer Centre
Northwood, Middlesex
United Kingdom

Gordon John Sampson Rustin, MD
Mount Vernon Cancer Centre
Northwood, Middlesex
United Kingdom
grustin@nhs.net

Martin Zweifel, MD, PhD
Division of Medical Oncology
Bern University Hospital
Bern, Switzerland

The authors declare no conflicts of interest.

REFERENCES

1. Jayson GC, Kohn EC, Kitchener HC, et al. Ovarian cancer. *Lancet*. 2014;384:1376–1388.
2. Vasey PA, Jayson GC, Gordon A, et al. Scottish Gynaecological Cancer Trials Group. Phase III randomized trial of docetaxel-carboplatin *versus* paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. *J Natl Cancer Inst*. 2004;96:1682–1691.

3. Zweifel M, Jayson GC, Reed NS, et al. Phase II trial of combretastatin A4 phosphate, carboplatin, and paclitaxel in patients with platinum-resistant ovarian cancer. *Ann Oncol*. 2011;22: 2036–2041.
4. Patterson DM, Zweifel M, Middleton MR, et al. Phase I clinical and pharmacokinetic evaluation of the vascular-disrupting agent OXi4503 in patients with advanced solid tumors. *Clin Cancer Res*. 2012;18: 1415–1425.
5. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365: 2473–2483.
6. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol*. 2012;30:2039–2045.