family history. Clearly, more detailed studies, which are epidemiologically-based are required to examine this in more detail but these findings already suggest that somatic *BRCA1* mutations may not be that important and that mutations in other genes may circumvent the necessity of *BRCA1* mutations during tumorigenesis.

One of the clearest conclusions from the linkage consortium analysis was that there was at least one more gene for breast cancer [5]. While almost all of the families with predisposition to breast cancer and ovarian cancer were due to *BRCA1*, this gene did not explain those families in which a male also had breast cancer, or a number of large families with breast cancer the only cancer in obvious excess. A number of groups (led by scientists from the Institute of Cancer Research, Sutton, England and the University of Utah, U.S.A.) embarked on a genome-wide search for *BRCA2* taking those families clearly not attributable to *BRCA1*. Chronologically, the first of the three papers to be published reported the mapping of *BRCA2*, in this case to 13q12-q13 and in the proximity of the retinoblastoma gene (*RB1*) (although this clearly is not *BRCA2* since recombination events exclude it) [3]. The evidence for this location is impressive with a LOD score of 11.65 and a clear definition of a region encompassing *BRCA2* of 5 cM. Examination of sporadic breast tumours shows loss of heterozygosity to be common around *BRCA2* which suggests again that *BRCA2* is a tumour suppressor gene (or, possibly close to another tumour suppressor gene). Interpretation of these results is again complicated (as was the interpretation of such studies for *BRCA1*) by the presence of a known tumour suppressor gene in the region (*RB1*).

Unlike *BRCA1*, a mutation in *BRCA2* does not appear to confer such a dramatically increased risk of ovarian cancer [3]. It does, however, seem to produce an increased risk of breast cancer in men. Crude calculations suggest that *BRCA1* and *BRCA2* explain approximately equal proportions of breast cancer families (perhaps 40% each) and that therefore at least one more gene (*BRCA3*?) is required to explain dominantly inherited susceptibility to breast cancer. Watch this space . . .

1. Miki Y, Swensen J, Shattuck-Eidens D, *et al.* A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. *Science* 1994, **266**, 66–71.
2. Futreal PA, Liu Q, Shattuck-Eidens D, *et al.* BRCA1 mutations in breast and ovarian cancers. *Science* 1994, **266**, 120–122.
3. Wooster R, Neuhausen SL, Mangion J, *et al.* Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 1994, **265**, 2088–2090.
4. Hall JM, Lee MK, Newman B, *et al.* Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990, **250**, 1684–1689.
5. Easton DF, Bishop DT, Ford D, Crockford GP and The Breast Cancer Linkage Consortium. Genetic linkage analysis in familial breast and ovarian cancer; results from 214 families. *Am J Hum Genet* 1993, **52**, 678–701.
6. Ford D, Easton DF, Bishop DT, *et al.* Risks of cancer in BRCA1 mutation carriers. *Lancet* 1994, **343**, 692–695.
7. Smith SA, Easton DF, Evans DGR, *et al.* Allele losses in the region 17q12-21 in familial breast and ovarian cancer involve the wild-type chromosome. *Nature Genet* 1992, **2**, 128–131.
8. Kelsell DP, Black DM, Bishop DT, *et al.* Genetic analysis of the BRCA1 region in a large breast/ovarian family; refinement of the minimal region containing BRCA1. *Hum Molec Genet* 1993, **2**, 1823–1828.
9. Easton DF, Narod SA, Ford D, *et al.* The genetic epidemiology of BRCA1. *Lancet* 1994, **344**, 761.

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Second-line Chemotherapy in Epithelial Ovarian Carcinoma: Platinum Again? Taxanes? How to Choose?

J.P. Guastalla

ALTHOUGH ADVANCED stage ovarian cancers are sensitive to chemotherapy, the prognosis remains poor. Thus despite an 80% clinical response rate for platinum-based first-line chemotherapy, with an almost 50% complete clinical response and a 10–30% pathological complete response (PCR), the overall survival rate is only of the order of 20% at 5 years [1]. Although patients in PCR have the best prognosis, 50% relapse after 5 years. Patients in partial response have a 10% survival rate at 5 years, and all patients who are stable or progress , die within 3 years [2]. It is, therefore, appropriate to consider second-line chemotherapy in the majority of cases of ovarian cancers.

Second-line chemotherapy has not improved survival, but its aim is palliative and improvement of the quality of life of patients is the priority [3]. Bolis and coworkers, in a paper in this issue of the *European Journal of Cancer* (pp. 1764), confirm, as has been reported by other authors [4,5], that in a large number of cases the disease remains sensitive to second-line platinum-based

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chemotherapy, there being a higher response rate with a longer interval without progression after initial treatment. In the study of Bolis and colleagues, first-line chemotherapy was varied (cisplatin alone, carboplatin alone or platinum in combination with cyclophosphamide with or without doxorubicin), but this did not seem *a priori* to influence the results reported. Second-line chemotherapy was also varied (cisplatin–epirubicin or cisplatin–eteposide or cisplatin–carboplatin associations), but no comparison was made of the different protocols, although the response rates were very similar. The principal results were that, of 72 patients, 70% responded to second-line platinum at the time of recurrence, 60% responded when recurrence was after 4–18 months, 66% when it was after between 18 and 36 months, and 88% when it was after 36 months. The higher response rate than that reported by Markman and coworkers (43%) [4] or by van der Burg and coworkers (32%) [5] may be explained by the selection of patients with good responses after first-line chemotherapy, defined by a complete histological response or a residual tumor of $\leq$ 5 mm during second-look surgical evaluation. The conclusion of these observations is that in patients having responded initially to platinum, recurrent cancer cells may remain sensitive to platinum-based chemotherapy, and the best predictive factor of response is the length of the interval before progression of the disease.

Recurrent cancers of the ovary respond to a number of second-line chemotherapeutic treatments. The response rate in phase II studies of monochemotherapy rarely exceeds 20%, and it has also been noted, in these studies, that the response rate is correlated to the initial response to platinum treatment and on the interval without treatment (rarely indicated in publications). When the tumour is refractory to platinum, responses to other anticancer agents are rare; with ifosfamide, for example, a response of 19% was found in patients who had responded to platinum, whilst only 12% of 42 patients, who did not show a partial response responded [6]. The taxanes appear to be among the most efficient drugs in the treatment of recurring ovarian cancers with a 35% response rate with docetaxel [7] and a 21–30% response rate with paclitaxel [8–10]. In patients who were refractory to platinum after two or more lines of chemotherapy, a 22% response rate (4% complete response) was seen among 652 evaluable patients following a 24-h perfusion with 135 mg/m^2 paclitaxel [11]. The haematological toxicity, which is severe when paclitaxel is administered as a 24-h perfusion, was significantly reduced when 175 mg/m^2 were administered safely in a 3-h perfusion in patients who had already received two lines of chemotherapy and there was no observable decrease in efficiency [12, 13]. It is interesting to note that diseases not refractory to platinum, treated with paclitaxel can, at the time of progression, respond again to platinum-based chemotherapy whether or not there was a response to paclitaxel [14, 15]. There is therefore a choice of palliative second-line treatment at the time of recurrence between a resumption of platinum chemotherapy or treatment with taxanes. The best guide for this decision is the length of the interval before progression: platinum-resistant tumours should be treated with taxane but recurrences after 36 months, which have a probability of response above 80%, should receive platinum. No rule can be set for recurrences between these two extremes, and it should be remembered that there does not appear to be a cross-resistance to paclitaxel–platinum.

However, questions still remain concerning drug resistance and the number of lines of chemotherapy. It has been shown that the best first-line chemotherapy is platinum-based [1], and that the response to second-line chemotherapy is influenced by the results of the initial chemotherapy. In this regard, it should be noted that the term 'refractory' to platinum has been defined differently by authors: as either tumour progressing during treatment, tumour not having responded at least partially, stable disease or 'early' recurrence, after an interval without progression considered to be 'brief' (after 4, 6 or 12 months, depending on the study). Moreover, a description of resistance to platinum after polychemotherapy is not clear since resistance concerns each of the drugs administered and not just platinum. In addition can we definitively attribute the response to a second-line chemotherapy association to platin compound when the agent combined to platinum is different from those combined to platinum in the first-line association, could not the non-platinum compound be the only active factor at that time? On this point, the response rate of phase II studies of monochemotherapy are less equivocal. Moreover, there is no precise definition of the term 'line' of chemotherapy: one could agree that six courses of cisplatin–cyclophosphamide as an induction treatment represents a line of therapy. However, does a patient with a partial response at second look, after six courses of cisplatin–cyclophosphamide, who receives three identical complementary courses, receive a sole line? If carboplatin replaces cisplatin for the three complementary courses because of toxicity, is this still just one line? If the three complementary courses are of intraperitoneal cisplatin? If cyclophosphamide is replaced by etoposide or an anthracycline? If the patient receives not three but four, five or six complementary courses? Such cases are numerous and may influence the results of so-called second-line studies, especially the cumulative toxicity.

In conclusion, because of the poor prognosis with ovarian carcinoma, prospective studies must be the rule in recurrent disease. Priority should be given to the research of active treatments on drug-resistant tumours, defined as progressing during chemotherapy with the drug. In particular agents showing activity in platinum-resistant tumours should be further investigated in first-line chemotherapy trials (as, for example, are the taxanes). If the studies include tumours whose resistance to platinum has not been demonstrated, the length of the interval before progression should be used to estimate the possible benefit of the new treatment, and the response rate must be compared with that which could be obtained with platinum-based chemotherapy over the same time. Finally, the number of lines of chemotherapy in patients does not appear to be informative, but more useful is the knowledge of clear drug-resistance of the tumour and of cumulative doses of drugs previously received which could influence the toxicity of the study treatments.

1. Advanced Ovarian Cancer Trialits Group. Chemotherapy in advanced ovarian cancer; an overview of randomised clinical trials, *BMJ* 1991, **303**, 884–893.
2. Neijt JP, ten Bokkel Huinink WW, van der Burg MEL, *et al.* Long term survival in ovarian cancer, *Eur J Cancer* 1991, **27**, 1367–1372.
3. Ovarian cancer, screening, treatment and followup. NIH Consensus Development Conference, Bethesda, 5–7 April, 1994.
4. Markman M, Rothman R, Hakes T, *et al.* Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991, **9**, 389–393.
5. Van der Burg MEL, Hoff AM, van Lent M, *et al.* Carboplatin and cyclophosphamide salvage therapy for ovarian cancer patients relapsing after cisplatin combination chemotherapy. *Eur J Cancer* 1991, **27**, 248–250.
6. Markman M, Hakes T, Reichman B, *et al.* Ifofamide and Mesna in

previously treated adanced epithelial ovarian cancer: activity in platinum-resistant disease. *J Clin Oncol* 1992, **10**, 243–248.
7. Aapro MS, Pujade-Lauraine E, Lhomme C, *et al.* EORTC Clinical Screening Group: Phase II study of Taxoter[R] (docetaxel) in ovarian cancer. *Proc Am Soc Clin Oncol* 1993, **12**, 256.
8. Einzig AI, Wiernik PH, Sasloff J, *et al.* Phase III study and long term follow-up of patients treated with Taxol for advanced ovarian adenocarcinoma. *J Clin Oncol* 1992, **10**, 1748–1753.
9. WcGuire WP, Rowinsky EK, Rosenshein NB, *et al.* Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med* 1989, **111**, 273–279.
10. Thigpen T, Blessing J, Ball H, *et al.* Phase II trial of Taxol as second line therapy for ovarian carcinoma: a Gynecologic Oncology Group Study, *Proc Am Soc Clin Oncol* 1990, **9**, 156.
11. Trimble EL, Adams JD, Vena D, *et al.* Paclitaxel for platinum-refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. *J Clin Oncol* 1993, **11**, 2405–2410.
12. Ten Bokkel Huinink WW, Eisenhauer E, Swenerton K, for the Canadian–European Taxol Cooperative Trial Group. Preliminary evaluation of a multicenter randomized comparative study of Taxol[R] (paclitaxel) dose and infusion length in platinum-treated ovarian cancer. *Cancer Treat Rev* 1993, **19** (suppl.C), 79–86.
13. Guastalla JP, Lhomme C, Dauplat J, *et al.* Taxol[R] (paclitaxel) safety in 99 patients pretreated by platinum chemotherapy for ovarian carcinoma. *Proc Am Soc Clin Oncol* 1994, **13**, 270.
14. Vermorken JB, Huijskes RVHP, van Rijswik REN, *et al.* "Paclitaxel or no paclitaxel in second line, that's the question" in ovarian cancer patients who relapse after a prolonged platinum-free interval. 8th NCI-EORTC symposium on new drugs in cancer therapy. Amsterdam, 1994 abstract no. 497 p. 199.
15. Kukelda A, Tresukosol D, Edwards C, *et al.* Post taxoid carboplatin reinduction in patients with platin refractory epithelial ovarian cancer. *Proc Am Soc Clin Oncol* 1994, **13**, 276.

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Papers

Local Injection of OK-432/Fibrinogen Gel into Head and Neck Carcinomas

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Immunotherapy with biological response modifiers (BRM) is a possible strategy against head and neck solid tumours. However, the rapid disappearance of BRM from the tumour area is one of the reasons for its limited clinical application. In this pilot study, fibrinogen gel containing OK-432 (a compound composed of attenuated *Streptococcus pyogenes*), an inducer of natural killer cells and T-cell cytotoxity, was injected directly into head and neck solid tumours of 15 patients. A dose of 5 Klinische Einheiten (KE) of OK-432 was reconstituted in 1 ml aprotinin and mixed with fibrinogen, the latter to maintain the OK-432 locally. 3 patients showed tumour regression, and in addition, we observed histological changes in the injected tumour of all patients. These results suggest that OK-432/fibrinogen gel generates a local immune response, leading to tumour regression.

Keywords: immunotherapy, head and neck carcinoma
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INTRODUCTION

OK-432, A LYOPHILISED powder prepared from a penicillin G-treated Su strain of Type III Group A *Streptococcus pyogenes*, has been shown to manifest a tumoricidal effect not only directly, but also by potentiating the host's immunity [1, 2]. Talmadge and Herberman reported that OK-432 is a potent biological response modifier (BRM), which can augment natural killer (NK) cell activity, macrophage-mediated cytotoxity and T-cell function [3]. In Japan, the subcutaneous systemic injection of OK-432 is considered to be an effective clinical treatment in a substantial proportion of patients with various tumours, resulting in improved survival [4, 5].

Recent interest in OK-432 has focused on its effect when administered locally. However, the duration of response is limited and local intratumoral administration of OK-432 does not always provide the desired effect on solid tumours, unless it is repeatedly administrated in large doses [6, 7]. One reason for

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