Table 1. Cumulative risk of a hypersensitivity reaction with cycle number of carboplatin

Cycle no.	No. of patients receiving cycle	No. of patients with hypersensitivity	Cumulative risk of hypersensitivity (%)
6	34	2	6
7	32	8	25
8	24	13	54
9	20	12	60
10	12	8	67

No difference in total dose, total dose per metre squared or overall time from first exposure to carboplatin was seen during repeated courses of carboplatin between those patients developing and not developing a hypersensitivity reaction.

However, the cumulative risk of a reaction increased from 6% (2 out of 34) at cycle six to 67% (8 out of 12) by cycle 10 of carboplatin (Table 1) ($P<0.01$, χ^2 test). This high incidence compares well to the occupational setting, where repeated exposure to platinum salts can cause hypersensitivity reactions in 60% of people [6]. The low incidence of hypersensitivity reactions to carboplatin in oncological settings is mainly derived from studies using carboplatin either as a first-line agent or following cisplatin at relapse [3–5].

In 14 patients with hypersensitivity reactions, further carboplatin was given safely. In 10/11 patients, prophylactic chlorpheniramine [10 mg i.v. (intravenous) prior to carboplatin and 4 mg orally three times daily for 24 h postinfusion] prevented further hypersensitivity reactions. This is similar to the experience with cisplatin [7], and suggests further carboplatin can be safely given following hypersensitivity reactions with prophylactic chlorpheniramine. However, we did not attempt further platinum therapy in the 1 patient with anaphylactic shock.

The mechanism of hypersensitivity reactions to carboplatin is unclear. The prolonged period of sensitisation and rapid onset of symptons during carboplatin infusions would support a role for a type I IgE-mediated mechanism. In the occupational setting, there is good evidence to support this mechanism for platinum salt hypersensitivity [8, 9]. However, in the treatment setting, other mechanisms may operate, such as non-immunological histamine release, as suggested by the absence of evidence for IgE type I hypersensitivity in two cases of cisplatin hypersensitivity [7].

Whatever the mechanism, hypersensitivity reactions to carboplatin appear to be increasingly common with repeated prolonged use, and easily avoidable with chlorpheniramine. This permits the continued use of carboplatin in patients where mild or moderate hypersensitivity symptoms have occurred.

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Phase II Study of Mitomycin C Plus 5-fluorouracil in Patients with Refractory Ovarian Cancer

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PATIENTS WITH advanced ovarian cancer refractory to cisplatin-containing combinations have an extremely unfavourable prognosis [1]. One of the highest response rates obtained in this group of patients was reported by Alberts and colleagues who used a combination of mitomycin C and 5-fluorouracil (5-FU) in patients with advanced disease refractory to cisplatin with a 40% remission rate [2]. These impressive results prompted us to start a phase II study to confirm these data.

Eligibility criteria were pathological proof of epithelial ovarian cancer, prior platinum chemotherapy, measurable disease, no central nervous system metastases, performance status (WHO)$\leq$ 2, leucocytes $\geq$ 3500/mm^3, platelets $\geq$ 100 000/mm^3 and serum creatinine $\leq$ 1.2 mg/dl. Informed consent was obtained in all cases. Patients were treated as follows: mitomycin C 10 mg/m^2 intravenously (i.v.) on day 1 every 6 weeks and 5-FU 500 mg/m^2 i.v. on days 1 to 3 every 3 weeks. Routine laboratory analysis and CA-125 were performed on days 1 and 21 of each course. Response on therapy was assessed after two courses and WHO criteria were followed to evaluate both response and toxicity.

From October 1990 to December 1992, 18 consecutive patients entered this study, 15 of them being fully evaluable, 2 only for response (because of rapid progression and death) and 1 for toxicity (insufficient treatment due to grade 3 diarrhoea).

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Table 1. Patients' characteristics

	No. of patients
Total no. of patients	18
Age (years)	
Median (range)	59.5 (49–69)
Histology	
Serous	9
Mucinous	2
Clear cell	2
Endometrioid	2
Undifferentiated	3
WHO performance status (range)	1 (0–2)
No. of prior chemotherapy regimens (range)	1 (1–4)
Response to previous chemotherapy*	
Primary platinum-resistant	10
Secondary platinum-resistant	3
Potentially platinum-sensitive	5

*According to Markman classification [3].

Patient's characteristics are shown in Table 1. Median number of courses received per patient was two (range 0.5–11) at a dose intensity (mg/m^2/week delivered versus planned) of 94.20% for mitomycin C and 93.34% for 5-FU. Evaluation of response was made by computed tomography scan in 8, physical examination in 8, and by tumour marker (CA-125) in 1. There were no objective remissions with 2 patients with stable and 15 with progressive disease. Median time to progression was 10 weeks (range 3–37) and median survival time was 29 weeks (3–118+). Toxicity grade 3–4 (WHO) during the whole treatment period (% of patients) was leucopenia 12%, stomatitis 12%, diarrhoea 12%, nausea and vomiting 6% and alopecia 6%. No toxic deaths occurred.

Two additional studies using these drugs have been published since Alberts report and remission rates of 24 and 29%, respectively, were noted [4, 5]. Compared to the other series, our patients were less heavily pretreated with similar performance status and better dose intensity. In conclusion, we could not confirm the activity of the combination of mitomycin C and 5-FU as second-line therapy in patients with refractory ovarian cancer.

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Serological and Molecular Study on the HLA Phenotype of Female Breast Cancer Patients

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THE STUDY of susceptibility to breast cancer is clinically relevant because women may be helped by screening or by prevention advice; it is also biologically interesting because patients provide means of identifing genes of the histocompatibility complex (MHC) that may have a significant influence on immune response against this tumour, which, when faulty, can predispose to malignancy.

Over the past 10 years, tissue typing has demonstrated an alteration of MHC antigen expression of breast carcinomas, which is usually related to prognosis [1, 2]. Instead, blood cell typing has so far provided little and contradictory information regarding the association of HLA phenotypes and breast carcinoma [3, 4]. We report here a study aimed at re-evaluating, on the basis of serological and molecular techniques, data on HLA phenotype expression in peripheral blood lymphocytes (PBL) of female breast cancer patients.

From 1987 to 1992, we studied 62 patients with breast cancer, stage I or II, who were referred to our institutes. Tumours were classified histologically as infiltrating ductal carcinomas (IDC) and staged according to AJC/UICC criteria. Among the cases evaluated, HLA phenotype for 32 patients was performed concomitantly with the diagnosis; for the other 30 women, it was performed some years after the diagnosis of breast cancer and consequently after surgery and therapy.

The PBLs of these patients were typed and the HLA antigens frequencies were compared with a local control group of bone marrow donors. Using the standard cytotoxicity test to analyse HLA antigens, we detected a slightly significant decrease in the frequency of HLA-B7 and HLA-DR4 in the patients: 2/62 versus 34/269 in the control group ($P < 0.03$, according to Fisher's test), and 2/62 versus 29/242 ($P < 0.02$), respectively. Comparison for DR phenotype between patient group and control population, which was in Hardy–Weinberg equilibrium for DR antigens, showed serological homozygosity in the tumour cases (55 versus 12.3% of the controls). There was no relationship between the findings and the period of the analysis for these patients.

Molecular typing was carried out in 8 serological homozygote patients by means of restriction fragment length polymorphism (RFLP) method for DR locus [5]. We analysed *Taq* polymor-

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