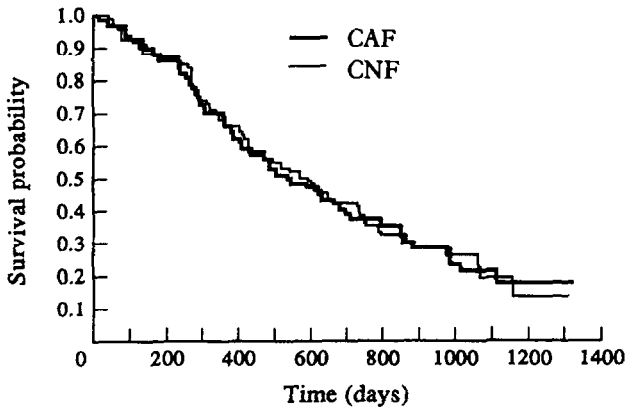

Figure 1. Survival in days as a proportion of all randomised patients surviving from date of entry to date of death.

was defined as the time from randomisation to the last observation or death. Time to disease progression was from randomisation date to the first sign of relapse. Time to event analyses were performed using the Kaplan–Meier method [3,4].

A total of 142 patients were enrolled at 12 sites in France between June 1983 and December 1984. 69 patients were randomised to CNF, and 73 to CAF. As previously reported [1], the two treatment groups showed similar distributions of pretreatment characteristics. For evaluable patients, the overall response (complete + partial response) for CAF was 42% (28/66) with 9 complete responses, and 42% (30/71) for CNF with 6 complete responses, $P > 0.99$ Fisher's exact two-tailed [5].

Both regimens caused myelosuppression, with approximately 45% of patients requiring a reduction and/or delay of therapy dosage. The types, severities and frequencies of the adverse events were similar for both CNF and CAF groups. However, CNF-treated patients had a lower incidence and severity of alopecia, with reports in 51% (222/439) of treatment cycles, 12% (53/439) of these at grade 4, compared to 78% (339/432) for CAF with 44% (189/432) at grade 4 ($P<0.01$). Similarly, nausea and vomiting in the CNF patients were observed in 43% of cycles, with 23% of cycles grade 3 or 4, compared to an incidence of 60%, with 39% grade 3 or 4, in the CAF group ($P< 0.02$). During the treatment phase, moderate and clinically non-significant reduction of left ventricular ejection was observed in 6 of the patients treated with CAF and in 2 of the patients treated with CNF [1].

The survival times for all randomised patients in both treatment groups are shown in Figure 1. There were no statistically significant differences in survival (log rank test, $P = 0.93$). The median survival for CNF was 600 days [95% confidence interval (CI) 426–738] and for CAF 551 days (95% CI 410–743). The estimated hazard ratio was 1.02 (95% CI 0.69–1.49). These survival times are consistent with, or somewhat higher than, previously published reports of these agents in combination therapy in patients with advanced breast cancer [6–8].

For all randomised patients, the median time to disease progression was 233 days (95% CI 147–272) for CNF and 182 days (95% CI 145–294) for CAF, with no statistically significant difference (log rank test $P = 0.43$), and an estimated hazard ratio of 0.86 (95% CI 0.61–1.23).

The long-term follow-up requested reports of severe adverse events and their relationship to protocol therapy. A total of 20 adverse events were reported, 12 on CNF and eight on CAF. Four cardiovascular events were reported during the follow-up phase for patients initially randomised to CAF with two reported on CNF. A case of thrombocytopenia was thought to be possibly related to CNF treatment, and one case of pulmonary oedema to CAF. All other reported severe adverse events were related to therapy administered subsequent to completion of the study.

The survival data from this clinical trial indicates that mitoxantrone is equally as effective as doxorubicin in combination with cyclophosphamide and 5-fluorouracil in the treatment of women with advanced breast cancer.

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Detection of Platinum–DNA Adducts in Cord Blood Lymphocytes Following *In Utero* Platinum Exposure

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ASSESSING THE impact of chemotherapy on the fetus of patients treated for a malignant disease during pregnancy has been limited to epidemiological analysis of clinical outcomes.

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Irradiation and chemotherapy are known to induce abortions and fetal malformations when given during the first trimester, whereas the risk is less during the second or third trimester. Cisplatin-based treatment of ovarian cancer during pregnancy has been reported [1, 2], however, fetal exposure to platinum compounds has not been evaluated. Platinum compounds act by directly binding to DNA, resulting in platinum–DNA adducts. The level of platinum–DNA adducts correlates with tumour cell kill *in vitro* and with clinical disease response *in vivo* [3]. The presence of persistent platinum–DNA adducts was measured in the newborn baby of a woman treated with carboplatin during pregnancy to determine the level of exposure of the fetus to platinum compounds.

A pelvic mass was found at 18 weeks gestation in a 41-year-old gravida 1, para 0 female with a history of infertility. She underwent left salpingo-oophorectomy, right ovarian wedge biopsy, omentectomy and lymph node dissection. Pathological review showed an 8 × 10 cm endometroid ovarian carcinoma with an intact capsule, histological grade 2. The patient received three cycles of adjuvant chemotherapy which included administration of carboplatin 400 mg/m^2 beginning at 22 weeks gestation and given without complications every 4 weeks. The last therapy was given 9 weeks prior to delivery. The fetus was delivered by primary Caesarean section at 37 weeks, yielding a normal appearing 3245 g male infant with Apgar scores of 9 and 9. The infant showed no myelosuppression and had normal renal function. Total abdominal hysterectomy and right salpingo-oophorectomy was performed and did not reveal any residual neoplasm. The infant continues to develop normally. Platinum–DNA adducts were measured by absorbance spectroscopy method described by Reed and colleagues [4]. Measurements were made on blood lymphocyte preparations from the mother prior to the third cycle of chemotherapy and on fetal cord blood lymphocytes at delivery (Table 1). Platinum adducts were found in each sample, and were similar at delivery in maternal and fetal lymphocyte samples.

Data on the *in utero* effects of platinum compounds in humans is limited. Cisplatin treatment during pregnancy has not been associated with adverse maternal or fetal effects. However, Kai and colleagues, using pregnant crJ:CD rats, showed that carboplatin was embryolethal when given on days 6 to 9 of gestation and produced a variety of fetal anomalies. These changes were not observed when carboplatin was given later in gestation, suggesting that gestational age at time of exposure is critical to outcome [5]. Diwan and colleagues treated pregnant SENCAR mice with single intraperitoneal doses of cisplatin and observed significantly higher initiation of skin tumours in the offspring treated with topical TPA (12-0-tetradecanoylphorbol-13-acetate). There was also high incidence of preneoplastic and neoplastic lesions in these mice, suggesting transplacental carcinogenicity of cisplatin in mice [6].

Since we found detectable levels of platinum DNA adducts in cord blood lymphocytes 9 weeks after the last dose of therapy, we can assume that fetus tissues were exposed to carboplatin, starting with the first course of therapy at the 22nd week of pregnancy, and that fetal exposure to carboplatin resulted in persistent platinum–DNA adducts. It is of interest that the level of adducts was similar in cord blood and maternal lymphocytes, indicating little protective effect of the placental/blood barrier for a small chemotherapeutic compound such as carboplatinum. While there was no clinical sequela in this infant, it is unclear how well fetal cells in general process and repair platinum adducts. Their presence indicates the need for caution in the use of platinum compounds during pregnancy, and the need for ongoing surveillance to detect the late sequela of chemotherapy; including carcinogenesis, sterility, retarded physical and/or mental growth, and development and teratogenicity in second generations, all of which are potential complications [7].

Table 1. Platinum (Pt)–DNA adducts in material and fetal lymphocytes

Lymphocyte sample	Total μg DNA	Pt–DNA adducts pg/μg DNA	Pt–DNA adducts fmol/μg DNA	Lesions/kb
Maternal, week 30 (Prior to 3rd cycle)	22.0	66.7	342.1	0.068
Maternal, week 37 (at delivery)	39.0	14.5	74.4	0.015
Newborn cord blood	32.0	14.1	72.2	0.014

fmol/μg was converted to lesions per kilobase (kb) using 195 as the molecular weight (MW) of elemental platinum, and 300 as the average MW of a DNA nucleotide.

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