Phase II study of esorubicin (4'-deoxydoxorubicin) in advanced epithelial carcinoma of the ovary:
A Gynecologic Oncology Group study

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Summary
Twenty-six patients with advanced, measurable epithelial carcinoma of the ovary were treated with 76 courses of esorubicin at doses ranging from 20–30 mg/m2 every 3 weeks. All patients are evaluable for toxicity and response. All patients had received prior therapy including radiation therapy in 9, non-anthracycline chemotherapy in 25, and surgery in 25. All patients were GOG performance status 0, 1 or 2. Two partial responses were seen. Severe (grade 3 or 4) leukopenia, thrombocytopenia, and anemia were seen in 13, 1 and 4 patients, respectively. Moderate gastrointestinal toxicity was also noted. Alopecia and mucositis were rare. Phlebitis was not seen. Neither clinical congestive cardiomyopathy nor decrement in left ventricular ejection fraction was observed. We conclude that using this dose and schedule of esorubicin as second-line chemotherapy in ovarian epithelial neoplasms lacks significant activity and is associated with moderate toxicity.

Introduction
Esorubicin (4'-deoxydoxorubicin) is a new analog of doxorubicin synthesized by Arcamone [1]. The compound is identical to doxorubicin with the exception of reduction of the 4' position of the aminosugar. Both in vitro and animal studies suggested that esorubicin was twice as potent as doxorubicin [2–4] on a molar basis and, more importantly, animal models failed to demonstrate any cardiotoxicity [5]. Phase I trials defined the maximally tolerated dose (MTD) as 30 mg/m2 using a bolus every 21 day schedule. Dose-limiting toxicity was granulocytopenia [6,7]. Phlebitis, alopecia and nausea were noted but appeared to be less common and severe than with doxorubicin. Chronic cardiotoxicity was not seen. Phase II trials demonstrated some activity for esorubicin in colorectal cancer, breast cancer and multiple myeloma [8–10]. No activity was noted in trials of non-small cell lung cancer, melanoma, hypernephroma, prostate cancer, or head and neck cancer [11–15]. As more experience with the drug was accumulated, evidence of cardiotoxic effects were noted [16]. Since adriamycin is an active drug in ovarian epithelial neoplasms, it seemed appropriate to evaluate this potentially less toxic analog in this patient population [17].

Material and methods
Patients were entered into this Gynecologic Oncology Group (GOG) study from January, 1985 to July, 1987. All patients had histologically documented epithelial ovarian malignancies of various
cell types. The patients were no longer candidates for curative intent therapy but were not allowed to enter this trial if they had received prior anthracycline therapy or more than one prior chemotherapeutic regimen. Other eligibility requirements included: WBC $\geq 3,000$/mm$^3$; platelets $\geq 100,000$/mm$^3$; creatinine $\leq 2.0$ mg%; bilirubin, SGOT, and alkaline phosphatase $\leq 2 \times$ upper normal limit; GOG performance grade of 0–2; one or more lesions measurable in perpendicular diameters by physical examination or radiographic study; a gated cardiac scan with a left ventricular ejection fraction within the normal range; and no surgical or radiation therapy within the four weeks prior to study entry.

Pretreatment evaluation included: assessment of performance grade; measurement of the indicator lesion(s); physical exam; complete blood count and differential; serum electrolytes, bilirubin, SGOT, alkaline phosphatase, creatinine and BUN; chest x-ray and gated cardiac scan. Complete blood count and differential was repeated weekly and hematologic toxicity was based upon nadir counts. The pretreatment evaluation was repeated every three weeks with the exception of the chest x-ray (unless for indicator lesion measurement) and gated cardiac scan which were performed after every 2–3 courses of therapy. The patient was removed from study if there was any clinical evidence of congestive heart failure or the left ventricular ejection fraction fell below the normal range.

E sorubicin was started at a dose of 25 mg/m$^2$ (all patients were considered poor risk due to prior chemotherapy). Dose escalation was allowed in increments of 5 mg/m$^2$ if there was no hematologic toxicity. De-escalation to 20 mg/m$^2$ was allowed for grade 3 or 4 hematologic toxicity. Further significant hematologic toxicity after dose reduction to 20 mg/m$^2$ required removal of the patient from study. Standard criteria of response of the indicator lesion(s) were utilized.

Results

Twenty-six patients were entered on this study. Patients' characteristics are detailed in Table 1. A total of 76 courses of treatment were administered (median 2; range 2–12).

Eight patients received only a single course of treatment followed by disease progression, seven patients had subsequent courses without dose modification, seven patients required dose reductions for hematologic toxicity, one patient had dose escalation, and three patients had escalation and de-escalation.

Prior chemotherapy was exclusively cisplatin-based except for a single patient who received melphalan. Prior radiation therapy consisted of external beam to the pelvis in six and to the whole abdomen in two. Surgery varied from laparotomy and biopsy only to total abdominal hysterectomy, bilateral salpingo-oophorectomy, and debulking surgery.

A partial response to therapy was noted in two patients. Thirteen patients had stable disease lasting two to four months while 10 patients experienced rapid disease progression.

Leukopenia was the most frequent and significant adverse effect observed in 20 (77%) patients with four (14%) having grade 4. The median WBC nadir for the 20 patients experiencing toxicity was