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Original Article

# Possible surrogate marker for an effective dose-dense chemotherapy in treating ovarian cancer

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ABSTRACT

*Objective:* To dissect the correlated hematologic markers that reflect the clinical outcome or treatment response in patients receiving dose-dense chemotherapy with a combination of platinum (cisplatin or carboplatin) and paclitaxel.

*Materials and Methods:* From 2009 to 2014, we enrolled 55 ovarian cancer patients (total 67 courses) including first-line, persistent, platinum-sensitive, or platinum-resistant disease in MacKay Memorial Hospital, Taipei, Taiwan. Weekly pretreatment complete blood counts and calculated ratios [platelet/neutrophil ratio, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), neutrophil/monocyte ratio, platelet/monocyte ratio, lymphocyte/monocyte ratio] during dose-dense chemotherapy were collected. By grouping these hematologic biomarkers into three different response subgroups (responsive, stable, and nonresponsive) according to CA125 trend, the data were analyzed using one-way analysis of variance, and using *post hoc*-Tukey test for comparing each other. A $p$ value $< 0.05$ was considered to be statistically significant.

*Results:* Absolute counts of lymphocytes and platelets, PLR, platelet/neutrophil ratio, platelet/monocyte ratio (all $p < 0.001$), and NLR ($p = 0.013$) had statistically significant differences. Moreover, using box-and-whisker plot, absolute count of lymphocyte, PLR, and NLR showed most remarkable discrepancy in responsive, stable, and nonresponsive patients. Subgroup analysis for primary, platinum-sensitive, and platinum-resistant patients further revealed that PLR and NLR were significantly correlated to the outcome of dose-dense chemotherapy.

*Conclusion:* Lower PLR or lower NLR had better treatment response for dose-dense chemotherapy and are possible markers for representing treatment response in dose-dense chemotherapy. For a clinician, this is useful for timing when to switch to another chemotherapy regimen.



## Introduction

Epithelial ovarian cancer is the fifth leading cause of cancer-related death among women. Evidence has established tumor debulking surgery followed by a platinum-based chemotherapy as the first-line therapy for advanced ovarian cancer, yielding response rates of > 80%. However, for platinum-resistant ovarian cancer, second-line cytotoxic agents only achieve a 15–20% response rate. Nowadays studies are still seeking another possible mode, schedule, or regimen of chemotherapeutic strategies. Chemotherapy refinement and optimization might be the other focus to overcome the development of drug resistance and improve the survival of the patients. The standard regimen of chemotherapy for advanced ovarian cancer is combination of platinum (cisplatin or carboplatin) and paclitaxel and response rates have been reported in 73% of those receiving cisplatin/paclitaxel and in 60% of those receiving cisplatin/cyclophosphamide combinations [1].

The concept of dose-dense therapy was defined by the Norton–Simon regression hypothesis, which was proposed in the 1970s and suggests that the rate of tumor regrowth between

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**Table 1**
Patient demographics.

| | |
|---|---|
| Patient number | 55 |
| Course number | 67 (1–3 courses) |
| First | 11 (16%) |
| Persistent disease | 4 (6%) |
| Platinum-sensitive | 26 (39%) |
| Platinum-resistant | 26 (39%) |
| Age (y) | 54.8 (33–81) |
| Treatment duration | 194.6 (45–1122) |

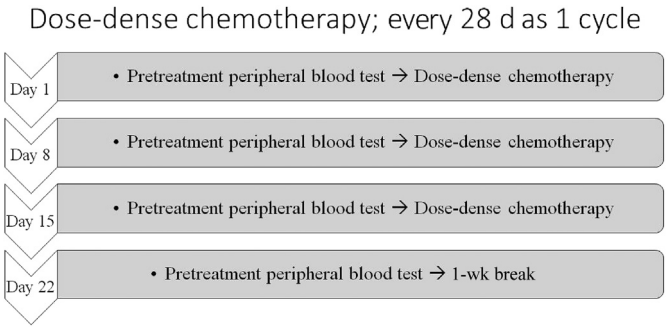


**Figure 1.** Schedule for dose-dense chemotherapy. The patients had pretreatment peripheral blood tests on the mornings of Day 1, Day 8, and Day 15. If the result of blood test was acceptable, dose-dense chemotherapy with paclitaxel (60–80 mg/m$^2$) plus platinum [carboplatin (area under the curve = 1.2–2) or cisplatin (25–30 mg/m$^2$)] was performed. If not, chemotherapy is delayed until bone marrow recovery. One cycle is dose-dense chemotherapy continuing for 3 weeks followed by a 1-week break.

treatments will be proportional to the rate of tumor growth. It means that tumors given less time to regrow between treatments are more likely to be destroyed [2]. Despite the uncertain mechanism, clinically, we have found therapeutic efficacy of dose-dense chemotherapy in treating ovarian epithelial cancer including first-line or salvaged settings. Moreover, it is noteworthy that dose-dense chemotherapy is effectively applied even for platinum-resistant disease. Many researchers have reported that the patients receiving dose-dense chemotherapy have better tolerance and a higher response rate (about 43–60%) [3,4].

Recently, many studies have investigated the mechanism of dose-dense chemotherapy, either the cytotoxic or immunogenic effect. Previously we have documented a correlation between the induction of serum interferon-γ and interleukin-2 and the efficacy of chemotherapy by weekly low-dose carboplatin and paclitaxel in the patients having platinum-resistant ovarian cancer, indicating a role of antitumor immunity in dose-dense chemotherapy [5].

Cancer patients who receive multiple chemotherapies are usually immunocompromised. They are relatively difficult to be induced strong antitumor immunity. Clinically there is a need to evaluate which patient would benefit from this mode of dose-dense treatment. We conducted this study in order to determine if there were hematological markers [neutrophil count, lymphocyte count, platelet count, monocyte count, and ratios, such as platelet/neutrophil ratio (PNR), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), neutrophil/monocyte ratio (NMR), platelet/monocyte ratio (PMR), and lymphocyte/monocyte ratio (LMR)] in patients with ovarian cancer receiving dose-dense chemotherapy.

## Materials and methods

### *Patient selection*

From 2009 to 2014 (Table 1), primary or recurrent epithelial ovarian cancer patients who had received dose-dense chemotherapy as adjuvant or salvage chemotherapy in MacKay Memorial Hospital, Taipei, Taiwan were enrolled in our retrospective study.

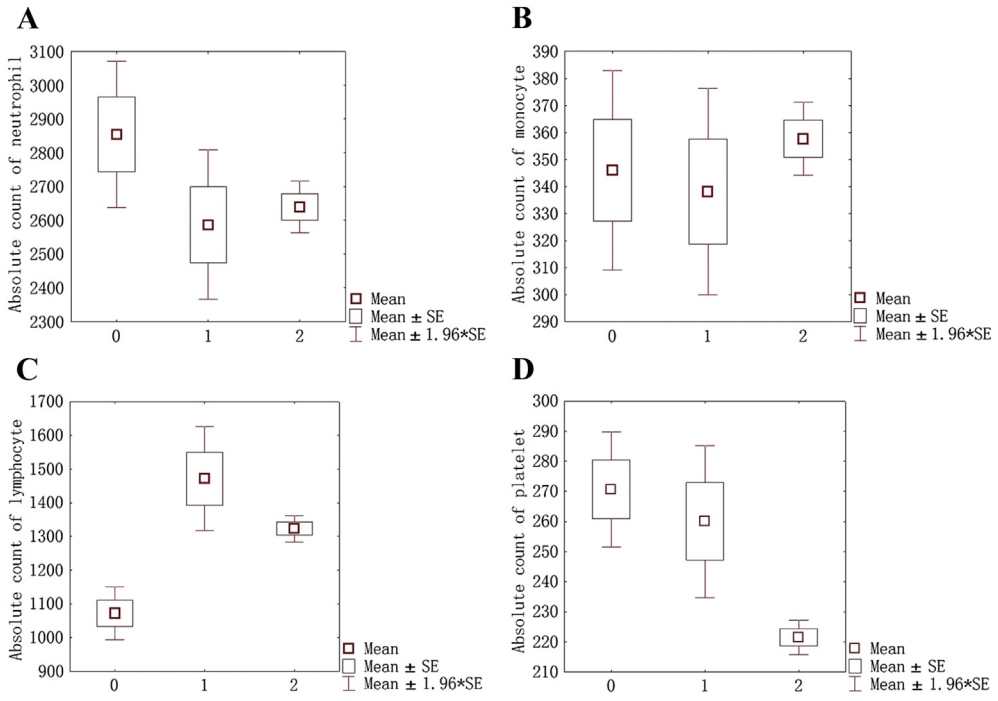


**Figure 2.** The distribution of blood cell count [(A) neutrophils; (B) monocytes; (C) lymphocytes; (D) platelets] in nonresponsive, stable, and responsive groups: using box-and-whisker plot. Absolute count of lymphocytes showed remarkable difference in the three subgroups. 0 = nonresponsive; 1 = stable; 2 = responsive; Mean ± 1.96 SE = 95% confidence interval; SE = standard error.