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ORIGINAL ARTICLE

Biweekly vinorelbine and gemcitabine as second-line and beyond treatment in ovarian cancer

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Abstract
Purpose To evaluate the activity and tolerance of vinorelbine (VRL) in combination with gemcitabine (GEM) in pre-treated patients with refractory ovarian cancer.
Patients and methods Seventeen patients with ovarian cancer who had disease progression after a carboplatin and taxane front-line regimen were treated with VRL 30 mg/m^2 IV over 10 min followed by GEM 1,200 mg/m^2 IV over 30 min on days 1 and 15 of each 28 days cycle. Chemotherapy was given in a initial prospective plan of six cycles, unless disease progression or unacceptable toxicity was seen, giving more cycles as consolidation therapy in the case of CR, PR or SD. The median age of patients was 67 years old, and the performance status (WHO) was 1 for 13 and 2 for 4 patients. The treatment was second-line for 11 (65%) and >third-line for 6 (35%) patients.
Results One complete and one partial response were observed (ORR:11%). Stable disease was seen in 4 (24%) patients and progressive disease in 11 (65%). The median time to tumor progression was 4 months (range 2–11), and the median survival has not yet been reached. Myelotoxicity was rare. Grade 1 neutropenia was observed just in one patient and grade 2/3 anemia in four patients (24%). Thrombocytopenia was absent. Non-hematologic toxicity was also predictable and easily manageable.
Conclusion The vinorelbine plus gemcitabine combination at the present doses and schedule is a safe but ineffective regimen, and therefore, is not recommended as second-line and beyond treatment in patients with refractory ovarian cancer.

Keywords Vinorelbine · Gemcitabine · Ovarian cancer · Second-line · Phase II

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Introduction

Currently, standard primary therapy for ovarian cancer involves a combination of cytoreductive surgery and chemotherapy with taxanes and platinum compounds. Despite initial high response rates, more than two-thirds of patients with advanced disease will develop recurrent tumors and die of chemoresistant disease, resulting in a long-term therapeutic challenge. Generally, the treatment of patients with recurrent ovarian cancer has been guided by the concept of platinum sensitivity (recurrence within 6 months considered platinum resistant disease, while recurrence after >6 months is considered platinum sensitive) [1]. Several agents, such as anthracyclines, camptothecins, etoposide, gemcitabine and vinorelbine, have been associated with substantial activity (response rates up to 20%) in patients with platinum resistant disease [2]. These promising results and high primary chemosensitivity are sufficient enough to justify consideration of second-line therapy trials with new

or older agents, in different combinations and schedules, especially in patients with good performance status and reasonable life expectancy.

Gemcitabine and vinorelbine have demonstrated clinical efficacy both as single agents and in combinations in patients with ovarian cancer [3, 4]. Vinorelbine (VRL) is a semisynthetic vinca alkaloid with a broad spectrum of anti-tumor activity. It is approved for the treatment of advanced NSCLC and breast cancer. The antitumor activity of vinorelbine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Myelosuppression is the most frequent cause of vinorelbine treatment delay or dose reduction. In phase II studies, this drug was administered on a weekly schedule with doses ranging from 25 to 30 mg/m^2, and up to 45% response rate has been reported as first-line treatment in a variety of solid tumors [5].

Gemcitabine (GEM) is a nucleoside analog of deoxycytidine with a unique mechanism of action, favorable toxicity and has been tested in a wide variety of malignancies, both as a single agent and in combination with other drugs [6]. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate and triphosphate nucleosides. Gemcitabine diphosphate facilitates the incorporation of gemcitabine triphosphate into DNA strands by inhibition of ribonucleotide reductase, which is responsible for generation of the deoxynucleoside triphosphates. Incorporation of gemcitabine nucleotide into growing strands results termination of DNA synthesis [7]. Mild myelosuppression, transaminases increase and flu-like syndrome are the most frequent toxicities of gemcitabine.

The combination of vinorelbine and gemcitabine has already been tested in several tumors, like lung and breast cancer, associated with an excellent toxicity profile [8, 9]. However, in most of these studies, efficacy was generally modest, which may partially depends on the sequence of the drug administration. In vitro and pharmacokinetic studies suggest that gemcitabine followed by vinorelbine may influence each other during liver elimination extraction and metabolism and finally decreasing plasma concentration of both drugs [10].

The role of the vinorelbine plus gemcitabine combination in patients with resistant or refractory ovarian cancer has not been clearly defined yet. We decided, therefore, to conduct a phase II study to evaluate the efficacy and toxicity of a gemcitabine plus vinorelbine combination administered every 2 weeks in pre-treated patients with refractory ovarian cancer.

Patients and methods

Eligibility criteria

Patients with histologically or cytologically confirmed ovarian cancer, who had measurable disease progression after a platinum and taxane-based regimen, were enrolled. Other eligibility criteria were: performance status (WHO) 0–2; age < 75 years; a life expectancy of at least 3 months; adequate hematologic parameters (absolute granulocyte count > 1,500/μl, hemoglobin level > 9 g/dl and platelet count >100,000/μl), adequate hepatic (serum bilirubin < 1.5 mg/dl, transaminases < 2 × the upper limit of normal) and renal function (serum creatinine <1.5 mg/dl); pre-existing peripheral neuropathy up to National Cancer Institute grade 1 and no other medical problems severe enough to affect patient's compliance to the protocol. Patients with brain metastases were eligible if they had been irradiated, the brain lesions were radiographically stable, and clinical improvement was evident. Patients with malnutrition (>15% loss of body weight), active infection, or a second primary tumor other than skin squamous cell carcinoma or in situ cervical carcinoma, were not eligible. All patients gave written informed consent to participate in the study, and the trial was approved by the Ethical and Scientific Committees of our Institution.

Treatment plan

Vinorelbine 30 mg/m^2 was administered as a 10 min IV infusion followed by GEM 1,200 mg/m^2 over 30 min IV infusion on days 1 and 15 of each 28 day cycle. Chemotherapy was given for six cycles unless disease progression or unacceptable toxicity was seen. Prophylactic administration of hematopoietic growth factors was not given.

Patients' evaluation

Baseline evaluations included the following: patient history, physical examination, chest X-rays, complete blood count (CBC) with differential and platelet count, blood chemistry, electrocardiograph (ECG), computed tomography (CT) scans of the chest, abdomen and pelvis, while whole brain CT scans were performed when clinically indicated. CBCs with differential and platelets count were performed twice weekly or daily in patients with severe myelosuppression. Whole blood chemistry and physical examination, as well as a detailed toxicity questionnaire, were performed before each cycle. Toxicities were recorded according to standard WHO criteria. Day 1 and day 14 treatments were administered on scheduled dates without any delay or dose reduction if the laboratory inclusion criteria were met; otherwise, treatment of day 1 and 14 was postponed for up to 7 days until resolution of the prohibitive toxicity. If the prohibitive toxicity had not resolved after a 7-day treatment postponement, the scheduled treatment was missed and upon resolution of the toxicity, treatment was continued as a new cycle with a 20% dose reduction in both drugs. All patients had tumor

measurements (by physical examination, CT or MRI) performed within 14 days of registration and subsequently after every three cycles of treatment. Response was assessed according to the standard RECIST criteria for those who did [11]. In case of a partial response, patients received three additional cycles of chemotherapy after the criteria of partial response were first met. Patients with stable disease were treated for a maximum of six cycles. Patients were withdrawn from the study at any evidence of progressive disease. Tumor responses had to have been confirmed 4 to 6 weeks after their initial documentation.

Statistical considerations

The primary objective of this phase II study was to explore the toxicity and efficacy (objective response rate, time to progression and survival) of the regimen. A Simon two-stage accrual design was employed for the study [12]. Initially, 17 evaluable patients were entered into the study. If three or more objective responses were seen in this initial sample, the study was to enroll 20 additional patients for a total number of 37 patients. Analysis was performed on an intent-to-treat basis provided that the main inclusion criteria were satisfied. The duration of response was measured from the day of the first documentation of response to chemotherapy until disease progression. Overall survival time was measured from the first day of treatment until death or last contact. The probability of survival was estimated by the Kaplan–Meier method [13] and tested for differences by using the log-rank test. The 95% confidence intervals (CI) for response rates were calculated using methods for exact binomial confidence intervals [14]. Progression-free survival was measured from the first day of treatment to the date on which disease progression was documented. On completion of protocol therapy, patients were seen in the clinic every 3 months for 1 year and subsequently every 6 months. The follow-up time was measured from the day of first treatment administration to last contact or death. Differences of the nadir hematological parameters between cycles (cycle 1 versus cycle 3 or 4) were examined by a two-way analysis of variance; this allowed also the assessment of an interaction effect between cycles.

Results

Patients' characteristics

Between October 2003 and July 2009, 17 patients with refractory ovarian cancer were enrolled in the study (Table 1). The median age of patients was 67 years, and the performance status (WHO) was 1 for 13 and 2 for 4 patients. For 11 (65%) patients, the treatment was a second-line chemotherapy regimen and for the rest 6 (35%) it was >third-line. The median interval between the end of the previous treatment and study entry was 2 months (range 0–9 months). All patients were assessable for toxicity and response.

Table 1 Patients characteristics

Patients enrolled	17
Assessable	17
Median age (range)	67 (41–75)
Performance status 1/2	13/4
Line of treatment 2nd/>3rd	11/6
Median 1st line response duration (range)	2 months (0–9)

Compliance to treatment and toxicity

A total of 81 chemotherapy courses were administered. The median number of courses per patient was 4 (range 2–12 cycles). No dose modification was required for vinorelbine. Gemcitabine dose reduction was required in 3 patients because of transaminases elevation. The median delivered dose intensity for vinorelbine was 15 mg/m^2/week (100% of the protocol planned dose) and for gemcitabine 600 mg/m^2/week (87% of the protocol planned dose). Ten patients discontinued the treatment before the completion of the planned six cycles due to disease progression. Two patients received more than 6 cycles because of partial response and stable disease, respectively, at the final evaluation. Toxicity was mild (Table 2). Anemia grade 2 was observed in three patients (18%) and grade 3 in one patient (6%). Mild anemia (grade 1) was more frequent (6 patients, 35%). One patient (6%) developed neutropenia grade 1. Thrombocytopenia was absolutely absent. The most frequent serious non-hematologic adverse events were transient hepatotoxicity grade 2 in three patients (18%), asthenia grade 1 in six patients (35%) and grade 2 in two patients (12%), flu-like syndrome grade 1 in three patients (18%), nausea/vomiting grade 3 in one patient (6%) and grade 1/2 in two patients (12%) and vein irritation in two patients (12%). No treatment-related deaths were reported.

Response and survival

There were one partial and one complete response among the 17 evaluable patients on the study. Therefore, the study was closed to further accrual, as per the initial statistical consideration. Four (24%) patients had stable disease, and 11 (65%) had disease progression. In two patients we did not have CT confirmation of the disease's progression, and evaluation was based on clinical examination. The median time to tumor progression for patients with disease stabilization was 4 months (range 2–6 months). After a median

Table 2 Major toxicities during chemotherapy

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%
Neutropenia	1	6	–	–	–	–	–	–
Febrile neutropenia	–	–	–	–	–	–	–	–
Anemia	6	35	3	18	1	6	–	–
Thrombocytopenia	–	–	–	–	–	–	–	–
Nausea/vomiting	1	6	1	6	1	6	–	–
Flu-like syndrome	3	18	–	–	–	–	–	–
Asthenia	6	35	2	12	–	–	–	–
Phlebitis	1	7	1	7	–	–	–	–
Hepatotoxicity	–	–	3	18	–	–	–	–

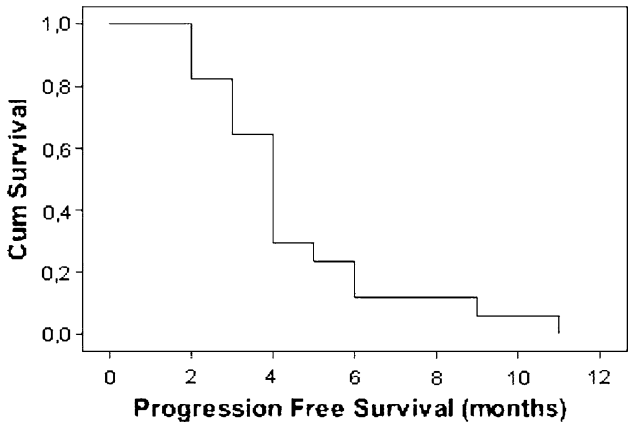

Fig. 1 Kaplan–Meier for progression-free survival

follow-up period of 6 months (range 2–23 months), all patients have progressed. The median progression-free survival (Fig. 1) was 4 months (range: 2–11 months; 95% CI: 3.4–4.6 months). At the end of follow-up period, five patients have died. The median survival has not yet been reached (Fig. 2). The 1- and 2-year Kaplan–Meier survival probability were 87 and 69%, respectively.

Discussion

Owing to the advances made in the last decade with platinum-based therapies, more patients are surviving long enough, with good performance status and could be offered second-line and beyond chemotherapy courses. Especially, for the patients with platinum-sensitive ovarian cancer re-challenge to a second-line platinum-based regimens seems to improve survival [15] and progression-free survival [16] compared with conventional platinum-based monotherapy. In contrast, in patients with resistance or refractory disease non-platinum topotecan combinations did not provide any survival advantage over topotecan alone, as have been

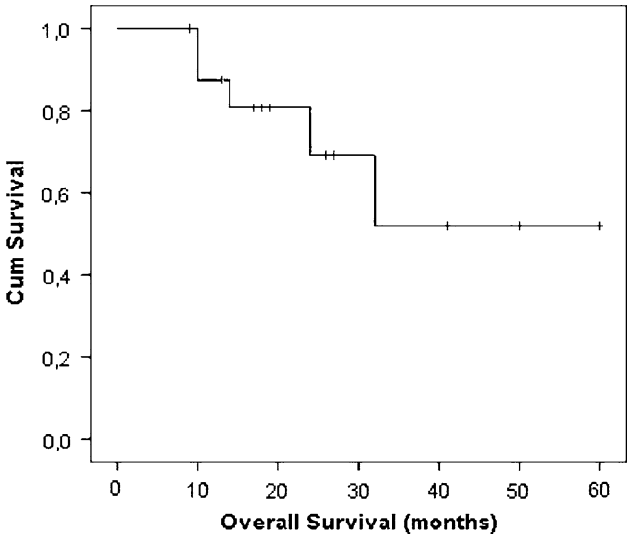

Fig. 2 Kaplan–Meier for overall survival

shown in a large phase III trial [17]. Reasonable aims of therapy in women with recurrent or resistant ovarian cancer are to achieve a balance between a likely benefit (in terms of both prolonging survival and improving quality of live) and the chemotherapy side effects. Cumulative toxicities, especially myelotoxicity, limit the treatment options available for subsequent therapeutic regimens. Therefore, effective but less toxic therapy is needed for patients with recurrent or resistant disease after failure of first-line chemotherapy.

Both, vinorelbine [4] and gemcitabine [18], have shown moderate activity as monotherapy in refractory ovarian cancer. To our knowledge, the combination of the two drugs has not been tested in the treatment of ovarian cancer. However, it seems to be a well-tolerated chemotherapy regimen when tested in several other malignancies [19, 20]. Nevertheless, when the combination was given at significantly higher doses, severe myelotoxicity was reported [21]. Pre-clinical data on the efficacy of VRL/GEM combination over the last years have been contrasting. There are reports advocating that the two drugs act synergistically [22], and others concluding that the combination has an antagonistic effect in cancer treatment [23]. These conflicting results may be indicative of the heterogeneity in chemosensitivity of tumor cell lines and reflect the high variability that exists within primary human tumors.

We conducted a phase II study with a VRL plus GEM combination given in a biweekly schedule, following the recommended sequence of drug administration, to further explore its toxicity, activity and palliation potential in patients with refractory ovarian cancer. The present regimen showed a favorable toxicity profile, which can be explained by the mild and non-overlapping toxicities of the individual agents [5, 24]. Indeed, hematologic toxicity was

infrequent and never exceeded that of grade 2, except in one case of anemia grade 3. Moreover, there were no episodes of febrile neutropenia. Similarly, non-hematologic toxicity was rare, mild and reversible. Dose reduction was required only for gemcitabine in three patients with transaminases elevation, which subsequently resolved.

Regarding efficacy, the current schedule of gemcitabine and vinorelbine, although well tolerated, was found to be ineffective. Although the progression-free survival was moderate, the lack of relevant clinical efficacy (only one complete and one partial response) was the reason for the early termination of the study, as per the initial statistical consideration. There may be several explanations for the lack of objective responses shown in the present trial, and the treatment schedule may be the most important. Dosing consecutively on days 1 and 8 or on days 1, 8 and 15 may achieve a dose threshold that the present dose and schedule could not reach. The biweekly schedule with our dose choice may allow time for either tumor regrowth between doses or promote development of resistant cell clones in the tumor cell population by not taking advantage of the sequential therapy. Additionally, although from the review of the literature, efficacy and survival may be impacted by the sequence of drug administration, this was not seen in the present study. Moreover, GEM was administered in fixed-dose infusion rate allowing more drug amount to be phosphorylated and activated by deoxycytidine kinase.

In conclusion, the vinorelbine plus gemcitabine combination at the present doses and schedule is a safe but ineffective regimen, and therefore, is not recommended as second-line and beyond treatment in patients with refractory ovarian cancer.

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