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SHORT COMMUNICATION

Phase II study of sodium valproate in combination with oral etoposide in platinum-resistant ovarian cancer

Thejeswar Nakka[1] · Luxitaa Goenka[1] · Biswajit Dubashi[1] · Smita Kayal[1] · Jayanthi Mathaiyan[2] · Deepak Barathi[3] · Narendran Krishnamoorthy[1] · Divya Bala Thumaty[1] · Sindhu Dahagama[1] · Prasanth Ganesan[1]

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Abstract

Patients with platinum-resistant ovarian cancer (PROC) have limited therapeutic options and poor survival. There is a need for the development of newer therapies. Sodium valproic acid (VPA) is a short-chain fatty acid histone deacetylase (HDAC) inhibitor with antitumor activity in preclinical models of PROC. Synergism with conventional cytotoxic agents like etoposide has been demonstrated. In this prospective, single-arm, open-label, phase 2 study, we included patients ≥ 18 years with histologically or cytologically confirmed PROC and Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–3. Patients received oral VPA 60 mg/kg/day in three divided doses for 3 days (D1–D3), followed by oral etoposide 50 mg once daily for two consecutive weeks (D4–D17). Serum samples were collected to assess peak VPA drug levels. The primary endpoint was the overall response rate (ORR). The secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity. We sought to show an improvement in response rate from 25% (historically with oral etoposide) to 40% with the addition of VPA. 27 patients were enrolled in the study, and 18 [median age: 52 (45–59) years; serous histology:17 (94%); ECOG-PS 2 or 3: 14 (78%)] were evaluable for the response after 4 months. Nine patients were lost from follow-up before achieving the primary endpoint (mainly due to Covid-related lockdown issues). The median number of prior lines of treatment was 2 (1–3). ORR was 0% according to GCIG criteria. The disease was stable in two patients [clinical benefit rate (CBR) of 11%]. The median OS and PFS were 7 months and 2 months, respectively. Grade ≥ 3 adverse events were reported in 6 (33%) patients. The addition of valproic acid to oral etoposide in patients with PROC and poor general condition was not helpful and failed to improve responses compared to those historically achieved with single-agent etoposide. However, further phase 2 randomized controlled trials with larger sample size can be done to confirm the findings.

Keywords Advanced ovarian cancer · Platinum resistance · HDAC inhibitors · Valproic acid · Oral etoposide

Introduction

Epithelial Ovarian Cancer (EOC) is one of the deadliest cancers affecting women. Most patients present with advanced disease (stages III and IV in 70–80%). After initial treatment with chemotherapy and surgery, the majority recur. Retreatment is with platinum-based chemotherapy in relapsing patients. At some point in their natural history, most of the relapsing patients reach a state of platinum-resistant/ refractory ovarian cancer (PROC). Progression within 6 months of the last platinum-based treatment is defined as PROC [1]. There are few effective treatment options for these patients. Conventional chemotherapy agents produce responses in 10–25% of patients, and trials with newer agents (Bevacizumab, Olaparib) have been disappointing [2]. Many patients with PROC present with a poor general condition,

✉ Prasanth Ganesan
pg1980@gmail.com; p.ganesan@jipmer.edu.in

[1] Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), 3rd Floor, Super Speciality Block, Dhanvantari Nagar, Puducherry 605006, India

[2] Department of Pharmacology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

[3] Department of Radiodiagnosis, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India

further limiting the use of intense chemotherapy. These factors may also lead to inferior survival outcomes in these patients (median survival of about 1 year). Thus, there is an urgent need to understand platinum-resistance mechanisms to help us plan specific therapies to overcome this problem.

PROC cell lines exhibit reduced drug uptake, increased efflux, decreased apoptosis, increased deoxyribonucleic acid (DNA) repair, cellular detoxification of platinum by adding glutathione, and epigenetic changes [3–6]. Preclinical studies have demonstrated the expression of histone deacetylases in ovarian cancer, and their inhibition can reverse platinum resistance [6, 7]. Sodium valproic acid (VPA) is a histone deacetylase inhibitor (HDACi) that has independent antitumor activity in ovarian cancer cell lines [8]. VPA has selective action against the HDAC1 isoform, expressed in ovarian cancer cell lines [9]. Inhibition of HDAC1 has been demonstrated to control the growth of ovarian cancer in vivo [7]. Oral Etoposide is one of the standard agents used in PROC [10]. Preclinical studies in glioblastoma, neuroblastoma, and melanoma cell lines show that VPA enhances the cytotoxicity of etoposide [11–13]. Recently, VPA was used in a clinical lymphoma study as a sensitizer before each cycle [14]. We hypothesized that combining VPA with etoposide could synergistically improve PROC outcomes. We included patients with PROC up to ECOG PS 3 as the toxicity was expected to be manageable.

Methodology

This phase II study was conducted at a single institution from January 2020 to July 2021 after Ethics Committee approval (JIP/IEC/2019/182) and registration at the www.ctri.nic.in (CTRI/2020/01/022781). Patients (≥ 18 years) with PROC (ECOG PS 0–3 at time of enrollment) were enrolled. Patients with previous exposure to etoposide or VPA and any severe illness precluding treatment administration were excluded.

Study intervention and follow-up

Patients received oral etoposide and oral VPA as 21-day cycles. They received drugs for 17 days as follows: VPA 60 mg/kg/day by mouth in three divided doses for 3 days (D1–D3) followed by oral etoposide 50 mg once daily for two consecutive weeks (D4–D17) (Fig. 1). Serum samples were collected from all participants to assess peak VPA drug levels 4 h after the 1st dose of VPA. Patients were reviewed before each cycle with serum CA-125, and a contrast-enhanced computed tomography (CECT) thorax and abdomen were done after two cycles. Toxicity assessment was done during follow-up visits and whenever patients presented with toxicity.

Endpoints

The primary endpoint was the overall response rate at 4 months [complete response (CR)+ partial response (PR)] assessed by the investigator as per the GCIG criteria with a combination of CA-125 and imaging [15]. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and adverse events according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. PFS was defined as the time from enrollment to disease progression or death due to any cause. OS was the time from enrollment to death due to any reason.

Sample size and statistical analysis

We estimated the sample size based on Fleming's two-stage design. The expected response rate with single-agent oral etoposide ORR was 25%, and an improvement to 40% with the addition of VPA was considered clinically relevant. To prove this, we required 68 patients, with 33 in the first stage. If there are nine or few responses (out of 33 patients), the study would be stopped for futility. If there were 14 or more responses in 33 patients, the null hypothesis would be rejected. If responses were between 10 and 13, additional patients would be accrued in the second stage. After the second stage, the null hypothesis would be rejected if 24 or more responses were observed in 68 patients. This design yields a type I error rate of 0.05 and a power of 0.8 when the actual response rate is 40%. However, the study was stopped after 18 eligible patients were enrolled due to expected futility.

Responses and toxicities were summarized as frequencies and percentages. The chi-square test measured the strength of association between baseline characters and responses. Kaplan Meier survival analysis method was used to estimate the PFS and OS. For this analysis, survival data were censored on Aug 31, 2021. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Thirty-seven patients with PROC were screened during the study period, and 27 were enrolled (Fig. 1a shows the reasons for exclusion). Of these 27 patients, two withdrew consent after 2 days of treatment. In 25 patients, response assessment at 2 months was available in 20 patients. Response assessment at 4 months (primary endpoint) was available for 18 patients (the reasons for not assessing

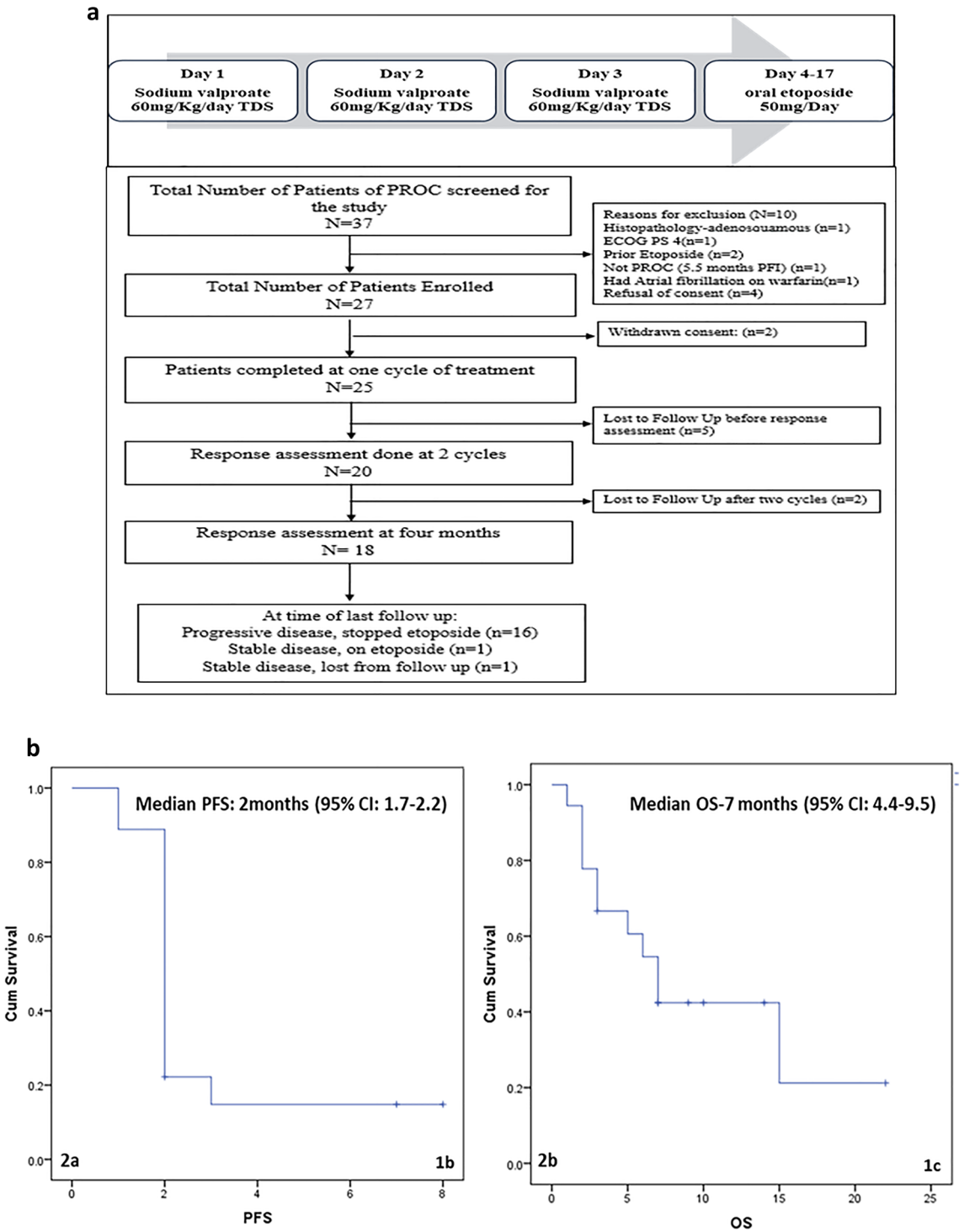

Fig. 1 **a** Schedule of therapy and patient disposition in the study. **b** shows PFS **c** shows OS of the patients treated in the trial by the Kaplan–Meier method

responses in the other seven patients is shown in Fig. 1a). The median age was 55 years (34–71), and 14 (78%) had ECOG PS ≥ 2. At presentation, nine patients (50%) had ascites, and 16 (89%) had disease extension beyond the pelvis. The median CA-125 was 605.7 U/mL (4-5190). In our study, mean serum VPA level achieved was 607.5 uM. The median duration from the initial diagnosis to enrollment was 19.4 months (12–22). The median number of prior lines of treatment was 2 (1–3). Nine patients were considered platinum-refractory (progressed during

or within 4 weeks of previous platinum therapy) (Supplementary Table 1).

Efficacy

Overall response rate

The mean value of the "peak" VPA level was 658.8 µM. The median number of cycles administered was 2 (1–9). After two cycles, 20 patients were evaluated for ORR by CA 125 assessment. Among them, two patients (10%) responded. These two patients were lost to follow-up during the covid-19 pandemic lockdown and their response at 4 months was unknown. One patient presented later with progressive disease, and the other patient died at home. At 4 months, 18 patients had been evaluated for ORR, and no one had achieved either CR or PR. The disease was stable in two patients at 4 months [clinical benefit rate (CBR) of 11% at 4 months], while the rest (89%) progressed. Among the patients whose condition was stable, one was lost from follow-up after 9 months of treatment, and another was on follow-up and had completed 6 months of therapy (Table 1). The median change in CA125 value was 223 IU/mL (9.75–841).

Survival

After a median follow-up of 6 months, 11 patients had died due to disease progression. The estimated OS at 6 months was 50% [median OS: 7 months (95% CI 4.4–9.5)]. The estimated progression-free survival at 3 months was 11% [median PFS: 2 months (95% CI 1.7–2.2)] (Fig. 1b, c). At the last follow-up, only one patient was continuing primary treatment. Among the 16 patients with disease progression, 11 (61%) received subsequent lines of therapy. The agents used in subsequent lines were gemcitabine ($n=4$), oral cyclophosphamide ($n=4$), and liposomal doxorubicin ($n=3$). The remaining five patients were advised best supportive care.

Adverse events

All 18 patients received at least two sodium valproate and oral etoposide doses and were included in the adverse event analysis. Adverse events of any grade were seen in 17 patients (94%). No patient died because of toxicity. Serious adverse events occurred in two patients, both were attributed to progressive disease. Grade ≥ 3 adverse events were reported in 6 patients. The most common Grade ≥ 3 toxicities were gastrointestinal events. Toxicities with > 10% incidence were CINV, fatigue, anorexia, abdominal pain, constipation, anemia, and mucositis. Adverse events led to treatment interruption and dose modification in one patient. VPA-specific adverse events like giddiness were seen in one patient. There were no toxic deaths (Supplementary Table 2).

Discussion

We found that the addition of VPA to oral etoposide did not improve response rates in PROC. The ORR was 10% after two therapy cycles, which is less than expected with single-agent etoposide. After four cycles of treatment, there were zero responses. Because of this, trial enrollment was stopped with only 18 evaluable patients. The survival of these patients was dismal, with only 50% alive at 6 months. Only 11 patients (61%) received subsequent lines of treatment, and 11 patients (61%) died at the last follow-up. The

Table 1 Response evaluation

Response assessment	$N=20$	%
After two cycles		
Complete response	0	0
Partial response	2	10
Stable disease	2	10
"Clinical Benefit" (Partial response + Stable disease)	4	20
Progressive disease	16	80
	$N=18$	%
At 4 months		
Complete response	0	0
Partial response	0	0
Stable disease	2	11
Progressive disease	16	89

outcomes in PROC continue to be dismal, and there is an urgent need to identify novel drugs to manage these patients.

The overall response rate in our study was lower than the 26% reported by Hoskins et al. with single-agent etoposide in PROC [16]. However, in their study, patients had better performance status (ECOG-PS ≤ 2, with an expected life expectancy of more than 12 weeks). Patients with stable disease (SD) or partial response to platinum therapy were also included. Excluding the patients with PR/SD on the last platinum-based therapy response rate was 18%. The higher dose of etoposide used in their study might have contributed to a better response. A similar result was obtained in the gynecologic oncology group study, where the ORR in PROC was 27% [17]. This study used a higher dose of etoposide (50 mg per m^2 per day) and reported higher hematological toxicities rates. Our study included patients with ECOG-PS 2 and 3; hence, we chose to use a lower dose of etoposide (50 mg flat dosing for 14/21 days). Other prospective studies have also used the 50 mg dose of etoposide combined with novel agents [18, 19]. Oral absorption of etoposide is variable, affecting outcomes due to variable pharmacokinetics and drug exposure. Adequate systemic exposure to etoposide is required for efficient antitumor activity [20]. VPA achieves antitumor activity in ovarian cancer cell lines by decreasing proliferation, increasing apoptosis, and preventing metastasis [21]. In our study, the serum mean peak VPA level achieved was 658.8 uM which may be sufficient for increasing the acetylation of H3K9ac [22]. However, we did not directly histone acetylation status.

The median PFS was 2 months (95% CI 1.7–2.2), and the median OS was 7 months (95% CI 4.4–9.5), which is lower than reported earlier [10, 17]. The "poorer-than-expected" survival may be due to several factors: a higher proportion of patients with adverse features (ECOG-PS 3, ascites, higher grade, extensive disease, refractory disease, and inclusion with patients with a life expectancy of < 12 weeks) and differences in dosing, schedule of etoposide, and response assessment timing difference compared to other studies. After two cycles, we found early progression in seven asymptomatic patients. Though grade ≥ 3 toxicities were reported in 39% of patients, they were mostly manageable. Hematological toxicities were rare (compared to schedules of etoposide of 50 mg/m^2/day for 3 weeks and 100 mg/day for 2 weeks), and the combination was feasible to administer in the clinic. Our study was a nonrandomized, single-center effort with a small sample size significantly impacted by the Covid-19 pandemic. Since there were no responses after 18 patients, further recruitment was unlikely to show benefit, and the study was stopped. However, further phase 2 randomized controlled trials with larger sample size can be done to confirm the findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12032-022-01833-6.

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Declarations

Conflict of interest None of the authors have any relevant conflicts of interest to declare.

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