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Comparison of the effectiveness of liposomal doxorubicin and gemcitabine in patients with platinum-sensitive recurrent ovarian cancer receiving third-line chemotherapy

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Abstract. – OBJECTIVE: In this retrospective study, we compared the effectiveness and reliability of the third-line chemotherapies gemcitabine and liposomal doxorubicin, in patients with platinum-sensitive ovarian cancer (OC).

PATIENTS AND METHODS: The retrospective study included platinum-sensitive epithelial ovarian cancer patients who had previously received paclitaxel and carboplatin therapy. Between 2013-2021, cross-matched 45 patients who received gemcitabine and 48 who received liposomal doxorubicin as third-line therapy were compared based on clinicopathological characteristics, biomarkers, and blood cancer antigen (CA) 125 levels. Time to treatment failure, survival, and quality of life were additional objectives.

RESULTS: The study included a total of 93 patients. The reported mean survival durations for treatments, 19.45 months for gemcitabine and 17 months for liposomal doxorubicin, did not statistically significantly differ (p=0.398). The mean CA 125 levels for the liposomal doxorubicin and gemcitabine groups after treatment were 54.4±11.4 U/ml and 54.7±11.1 U/ml, respectively. There was no noticeable difference between the treatments when comparing the postop CA 125 value (p=0.37).

CONCLUSIONS: For both pegylated liposomal doxorubicin (PLD) and gemcitabine as single agents in the third line, our data revealed comparable effectiveness results, and there was no substantial difference in progression-free survival (PFS) for recurrent ovarian cancer. These therapies were tolerated with an expected incidence of hematological toxicities.

Key Words:
Ovarian cancer, Liposomal doxorubicin, Gemcitabine.

Introduction

Ovarian cancer is the second most common gynecological cancer with the highest mortality rate. It is a heterogeneous disease with varying clinicopathological characteristics and prognosis[1]. The important genetic risk factors for ovarian cancer are germline breast cancer gene 1 (*BRCA1*) and breast cancer gene 2 (*BRCA2*) mutations[2]. Due to the absence of apparent symptoms and the lack of a screening approach, the disease is diagnosed late, negatively affecting treatment response and increased mortality. Generally, cytoreductive surgery is followed by chemotherapy for treatment[3].

Response rates are comparable and limited despite significant advancements in treatment. Although most ovarian cancer patients have complete clinical remission following the first treatment, relapses can be seen in most cases[4,5]. Due to disease progression and multidrug resistance, the frequency of treatment may change once the disease relapse. Changes in anti-apoptotic signals, immune system regulatory mechanisms, and mutations that induce the excretion or inactivation of cytotoxic medications can all cause treatment resistance and a poor prognosis[6,7].

Platinum is the key component of systemic therapy for ovarian cancer, and the emergence of platinum resistance is linked to a poor prognosis; platinum resistance can occur as a consequence of disease recurrence. Recurrent ovarian cancer can be divided into platinum-sensitive (relapsing 6-12 months after receiving platinum-based chemotherapy) and platinum-resistant (relapsing within six months after receiving platinum-based chemotherapy)[8].

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Deoxycytidine analog gemcitabine (2', 2'-difluoro deoxycytidine) inhibits deoxyribonucleic acid (DNA) synthesis and has been shown[9] to have antitumor effects in both *in vitro* and *in vivo* tumor models. Presently, metastatic pancreatic cancer, bladder, breast, and different malignancies, including ovarian cancer, can be treated with gemcitabine either alone or in combination with other chemotherapeutics[9]. In the treatment of recurrent ovarian cancer, gemcitabine is active as a single agent. However, there are certain side effects (fever, vomiting, peripheral edema, fatigue, proteinuria, etc.). It is a medication that can be administered as a quick infusion and is simple to use, often has mild toxicity, and is well tolerated[10].

Pegylated liposomal doxorubicin (PLD) is one of the therapeutic drugs delivered in vesicles called liposomes. Anthracycline doxorubicin hydrochloride is the main ingredient of pegylated liposomal doxorubicin. Pegylated liposomal doxorubicin was as effective as topotecan or gemcitabine in patients with platinum-sensitive or resistant ovarian cancer, according to the data from multicenter randomized studies[11,12].

The mechanism of drug resistance in ovarian cancer is the focus of the research. Increased DNA repair is just one of several mechanisms. Genes, for instance, Matrix metallopeptidase 9 (*MMP-9*), phosphatase and tensin homolog (*PTEN*), multidrug resistance protein 1 (*MRP1*), adenosine triphosphate (ATP)-binding cassette subfamily C member 2 (*ABCC2*), and neurogenic locus notch homolog protein 1 (*NOTCH1*) are associated with metastasis and tumorogenesis and cause treatment resistance. They have been identified as a result of next-generation sequencing technology, and targeted drugs, and drug combination studies are being conducted. Studies[13-15] on folate receptor targeting, polyadenosine diphosphate-ribose polymerase (*PARP*) inhibitors, tyrosine kinase inhibitors, and different combinations with platinum-based medications are a few examples of these. Access to new procedures for ovarian cancer patients was also necessary due to the latest advances in treatment[13,16].

Patients and Methods

Participants

Ninety-three patients who did not respond to second-line therapy and were being monitored by the Department of Gynecology at the Cukurova University's Faculty of Medicine were included in the study retrospectively between June 2013 and June 2021. A thorough medical history was taken, and a radiological assessment of tumor and metastatic sites was performed.

Inclusion Criteria

1. Patients who are at least 18 years of age or older.
2. Patients who previously received and failed at least two lines of standard systemic therapy for their cancer, such as chemotherapy or targeted therapy.
3. Patients with adequate organ function, as determined by laboratory tests and medical evaluation.
4. Patients who are willing and able to comply with study requirements, including regular follow-up visits and assessments.

Exclusion Criteria

1. Patients who have a history of severe or uncontrolled medical conditions, such as uncontrolled diabetes, uncontrolled hypertension, or severe renal or hepatic impairment, that would make them ineligible for treatment.
2. Patients with active, uncontrolled infections or known active viral hepatitis.
3. Patients with significant psychiatric or cognitive disorders that would impair their ability to provide informed consent, comply with study requirements, or complete study assessments.

Study Design

The patients were separated into groups receiving PLD and gemcitabine. Forty-five patients received gemcitabine (Gemko®, Kocak Farma, Istanbul, Turkey), whereas 48 received PLD (Caelyx, GlaxoSmithKline Manufacturing S.p.A, San Polo, Torrile, Italy). Every four weeks, PLD 50 mg/m^2 was administered to the PLD group. Other patients received intravenous infusions of gemcitabine at a fixed dosage rate of 1,000 mg/m^2 on days 1, 8, and 15 of a monthly cycle. At the beginning of each chemotherapy cycle, patients underwent a thorough physical examination, any side effects were reported, and a complete blood count was performed. CA 125 levels were measured on day 10 of treatment, every 4 weeks thereafter, and at the end of treatment. Toxicity, response rate, overall survival, and progression-free survival were assessed.

The Scientific Research and Publication Ethics Committee of Cukurova University in the Field of Health Sciences approved the study, and each

participant signed an informed consent form after being informed of its details.

Statistical Analysis

SPSS 22 program (IBM Corp., Armonk, NY, USA) was used in the analysis of the data. The propensity score was used for crossmatching. Kolmogorov Smirnov test was used as the normal distribution test. Kaplan Meier survival analysis, Log-rank, Cox regression analysis, Mann-Whitney, and Chi-square tests were used in the analyzes. A value of $p<0.05$ was considered statistically significant.

Results

Patient Characteristics

Between June 2013 and June 2021, a total of 93 patients were enrolled. Demographic information about research participants is shown in Table I. Twelve of 93 patients (12.9%) were aged over 65 years. Socio-demographic and clinicopathological traits were similar across treatments, and statistically significant differences between the groups were not detected (Table I).

The mean age was 54.4±11.48 in the PLD group and 54.7±11.10 in the gemcitabine group

Table I. Sociodemographic variables of patient groups.

		Platine sensitive thirdline CT n (%)		
		Liposomal doxorubicine	Gemcitabine	p
Age groups	<50	15 (31.3)	13 (28.9)	0.760
	50-65	28 (58.3)	25 (55.6)	
	>65	5 (10.4)	7 (15.6)	
Menopause	Premenopausal	14 (29.2)	13 (28.9)	0.976
	Postmenopausal	34 (70.8)	32 (71.1)	
Parity	Nulliparous	2 (4.2)	5 (11.1)	0.136
	1 birth	1 (2.1)	4 (8.9)	
	≥2 birth	45 (93.8)	36 (80.0)	
WHO obesity classification	<18.5	0 (0.0)	0 (0.0)	0.228
	18.5-24.9	7 (15.9)	4 (9.3)	
	25-29.9	24 (54.5)	18 (41.9)	
	30-39.9	12 (27.3)	17 (39.5)	
	≥40	1 (2.3)	4 (9.3)	
Infertility	No	46 (95.8)	39 (86.7)	0.115
	Yes	2 (4.2)	6 (13.3)	
Comorbidities	No	31 (64.6)	25 (55.6)	0.374
	Yes	17 (35.4)	20 (44.4)	
Debulking type	Primary	42 (87.5)	35 (83.3)	0.575
	Interval	6 (12.5)	7 (16.7)	
Resection	R0	28 (58.3)	22 (48.9)	0.361
	R1-2	20 (41.7)	23 (51.1)	
Stage	1	2 (4.2)	2 (4.4)	0.489
	2	4 (8.3)	1 (2.2)	
	3	38 (79.2)	40 (88.9)	
	4	4 (8.3)	2 (4.4)	
Lenfovascular invasion	No	4 (8.9)	6 (15.0)	0.383
	Yes	41 (91.1)	34 (85.0)	
Lymph node dissection (LND)	No	28 (58.3)	24 (53.3)	0.722
	Only pelvic	2 (4.2)	1 (2.2)	
	Pelvic paraaortic	18 (37.5)	20 (44.4)	
Seccytoreduction	No	41 (85.4)	38 (84.4)	0.896
	Yes	7 (14.6)	7 (15.6)	

Table II. Comparison of age and postoperative CA 125.

	Platine sensitive thirdline CT	Mean	Std. Deviation	p
Age	Liposomal doxorubicine	54.4	11.48	0.914
	Gemcitabine	54.7	11.10	
Postop CA125	Liposomal doxorubicine	278.2011	410.68099	0.370
	Gemcitabine	416.2739	932.82309	

(p=0.914). After comparing the treatments, it was discovered that there was no discernible variation in the postop CA 125 value (p=0.370) (Table II).

Resection and stage were revealed to be significant factors when the lifespans of the patients were compared. It was discovered that patients with complete resection (R0) and patients in the early stages have longer average life expectancies (Table III).

It was revealed that the Cox regression model designed to predict life expectancy is significant; the probability of mortality increased by 2.42 times in patients who did not accomplish R0 resection and by 2.11 times in patients who underwent interval surgery (Table IV).

Following the third-line treatment, the patient's overall survival was compared (Figure 1). There was no statistically significant difference between the mean survival times for liposomal doxorubicin and gemcitabine (p=0.398), which was reported to be 19.45 months for gemcitabine and 17 months for liposomal doxorubicin (Table V).

The survival rates of patients for prognosis were compared after treatment was complete (Figure 1). Gemcitabine's average survival time was 14.74 months and liposomal doxorubicin was

Table III. Comparison of the median life expectancy based on sociodemographic and clinicopathological characteristics.

		Median	95% Confidence Interval		p
			Lower Bound	Upper Bound	
Age range	<50	44.7	35.8	53.6	0.291
	50-65	48.091	42.550	53.632	
	>65	37.167	27.017	47.316	
Parity	Nulliparous	48.833	37.333	60.334	0.481
	1 birth	52.000	10.988	93.012	
	≥2 birth	44.789	40.348	49.230	
WHO obesity classification	18.5-24.99	42.700	34.441	50.959	0.826
	25-29.99	46.056	39.341	52.770	
	30-39.99	46.480	37.944	55.016	
	≤40	45.750	14.756	76.744	
Comorbidities	No	45.479	39.699	51.260	0.950
	Yes	45.394	38.663	52.125	
Debulking type	Primary	46.809	41.931	51.686	0.055
	Interval	36.000	26.811	45.189	
Cytoreduction optimation	R0	51.585	44.456	58.715	0.004
	R1	42.800	35.811	49.789	
Lenfovascular invasion	No	50.750	37.437	64.063	0.610
	Yes	45.092	40.289	49.896	
Seccyto reduction	No	44.648	39.991	49.305	0.433
	Yes	51.100	38.610	63.590	
Platine sensitive third-line CT	Liposomal doxorubicin	48.927	42.759	55.095	0.197
	Gemcitabine	41.875	35.832	47.918	
Stage	Early stage (1-2)	67.429	47.227	87.630	**0.006**
	Advanced stage (3-4)	43.365	39.241	47.488	

Table IV. Cox regression results.

	B	*p*	HR	95.0% CI for HR	
				Lower	Upper
Resection	0.886	**0.001**	2.425	1.440	4.085
Stage	0.787	0.092	2.197	0.880	5.482
Platine sensitive third-line CT	0.311	0.185	1.364	0.862	2.159
Debulking type	0.750	**0.035**	2.117	1.053	4.256

15.24 months; there was no statistically significant difference between the two groups (p=0.992).

The total stable disease (SD) for all patients was 21.5%, the partial response (PR) was 3.2%, and the majority of patients (74.1%) showed progression. Among 45 patients who received gemcitabine as a third-line treatment, 35 (77.7%) presented with progressive and 9 (20%) with stable

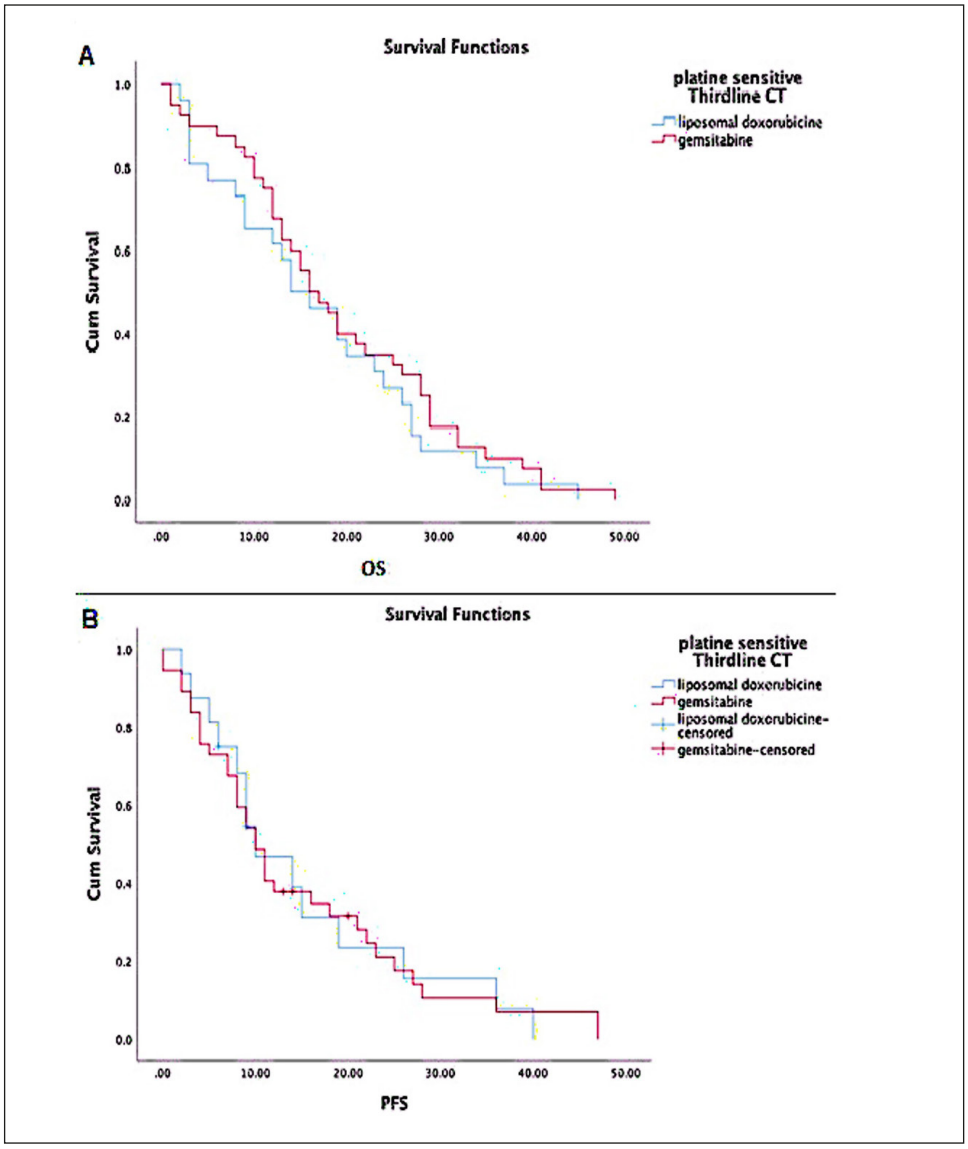

Figure 1. **A**, Overall survival (OS) analysis of groups. **B**, Progression-free survival (PFS) analysis of groups.

Table V. Means for survival time.

Platine sensitive third-line CT	Mean			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Liposomal doxorubicin	17.038	2.287	12.556	21.520
Gemcitabine	19.450	1.881	15.762	23.138
Overall	18.500	1.449	15.659	21.341

disease. Among 48 patients who received PLD as a third-line treatment, there were 34 (70.8%) progressive disease (PD), 11 (22.9%) SD, and 2 (4.1%) PR observed. In the gemcitabine group, thrombocytopenia was seen more frequently than in the other group (42.2% for gemcitabine, 12.5% for PLD) (Table VI).

Discussion

In this retrospective study, we compared progression-free survival, effectiveness, and toxicity in patients with platinum-sensitive recurrent ovarian cancer who received gemcitabine and liposomal doxorubicin as third-line therapy. The lifespans of the patients were compared, and it was found that resection results and stage were important determinants. The reported mean survival durations for treatments were 19.45 months for gemcitabine and 17 months for doxorubicin. However, there was no significant statistical difference in their comparative effectiveness (p=0.398). No statistically significant difference existed between the average survival times after liposomal doxorubicin (15.24 months) and gemcitabine (14.74 months) treatments. The mean CA 125 levels for the liposomal doxorubicin and gemcitabine groups were 54.4=11.4 U/ml and 54.7=11.1 U/ml, respectively. There was no noticeable difference between the treatments when comparing the postop CA 125 value (p=0.37). Grade 2/3 side effects and hematologic toxicities had comparable frequency in the gemcitabine and PLD; neutropenia, anemia, and fatigue were the predominant toxicity.

Ovarian cancer has the highest mortality rate among gynecological cancers. Because recurrent ovarian cancer (ROC) is a heterogeneous disease with varying clinicopathological characteristics and prognosis, it affects therapeutic success, and

Table VI. Side effects and clinical response.

	Gemcitabine group (%)						PLD group (%)					
Side effects	G1	%	G2	%	G3	%	G1	%	G2	%	G3	%
Fatigue	6	13.3	14	31.1	2	4.4	4	8.3	12	25.0	2	4.1
Nausea-vomiting	3	6.6	10	22.2	4	8.8	3	6.2	10	20.8	2	4.1
Constipation	2	4.4	6	13.3	1	2.2	3	6.2	4	8.3	1	2.0
Rash	3	6.6	7	15.5	1	2.2	1	2	3	6.2	1	2.0
Thrombocytopenia	11	24.4	6	13.3	2	4.4	1	2	3	6.2	2	4.1
Anemia	13	28.8	5	11.1	1	2.2	15	31.2	6	12.5	1	2.0
Neutropenia	7	15.5	9	20.0	1	2.2	3	6.2	15	31.2	1	2.0
Clinical Response												
			n	%					n	%		
PD			35	77.7					34	70.8		
SD			9	20.0					11	22.9		
PR			1	2.2					2	4.1		
CR			0	0					1	2.0		

PLD: pegylated liposomal doxorubicin; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

managing it is challenging[17,18]. Therefore, studies[8] focused on the use of less toxic and, better therapeutic approaches.

The application of genomic profiling in the treatment of patients has been advanced by the development of next-generation sequencing. Individualized precision medicine enables the prioritization of clinical trials of current treatments and increases the number of patients who will benefit from chemotherapy, and targeted agents[15,19,20], but traditional treatments are still utilized and are still important in nations with limited or no access to these technologies.

The time of platinum-free exposure affects how recurrent ovarian cancer is treated in a clinic. While individuals with a shorter platinum-free interval (PFI) are routinely treated with a single non-platinum agent, patients with more than six months since their last dose of platinum are typically given a platinum agent or dual therapy containing platinum.[21] Gemcitabine and liposomal doxorubicin, the third-line chemotherapy alternatives for patients with platinum-sensitive ovarian cancer, revealed no statistically significant difference in our study.

A permanent and practically relevant parameter in ovarian cancer trials is progression-free survival[22] and the serum level of CA 125 is used to assess treatment response[23]. After comparing the treatments, it was discovered that there was no discernible variation in the postop CA 125 value. Liposomal doxorubicin and gemcitabine both had comparable efficacy based on these criteria. As response might not be sustained over the long term in patients with OC, it is necessary to choose a treatment with low toxicity. Neutropenia, anemia, and fatigue were the predominant toxicity, as confirmed by the literature[10,11,24].

There are not many single-agent comparisons as third-line therapy, the clinical activity of these agents can be used for research. The development of cytotoxic drugs with better features, such as PLD, and gemcitabine, has made it possible to use disease management approaches more effectively than in the past. New studies[25] aim to use currently available agents to administer treatments with better safety profiles, thereby reducing the need for combination therapies.

Even while genetic profiling enables the use of personalized and targeted drugs more conveniently, the use of these next-generation therapeutics is constrained in developing countries due to the difficulty in accessing molecular tests, economic and sociocultural health policies, and a lack of infrastructure. Even if patients have the opportunity to access the tests, their access to these drugs is very limited, depending on their state. Due to this, countries like Turkey still prioritize traditional medical practices. A comparison of frequently utilized therapeutic agents was conducted in this research.

Clinical research[12,24] suggests that PLD and gemcitabine as a single agent, have modest efficacy in patients with well-defined platinum-sensitive ovarian cancer. Even though research[26] examining the efficiency and safety of bevacizumab combination therapy has produced favorable outcomes, by comparing patients who had received a single agent, we were able to observe both the differences in treatment options and the differences in toxicity from combination therapies in this study.

International and national health organizations, the pharmaceutical business, and employees should take steps to ensure that all patients have access to molecular diagnostics and novel therapeutics. Existing agents will remain important and in use until every patient can access novel drugs.

Limitations

The limitations of this study are that patient selection bias exists because the study was retrospective. The patient's earlier chemotherapy regimens and durations may have differed since the drugs were selected based on adverse effects or the patient's treatment plan.

Conclusions

This is a rare retrospective study examining a third-line single-agent therapy for recurrent ovarian cancer, comparing PLD with gemcitabine. This research contains important recommendations for treatment alternatives in patients with recurrent OC who have limited access to novel therapeutics. The overall cost of care per month for the PLD group was 250 Euros. Alternative options for treatment are assessed, especially if they are more cost-effective and effective. When a treatment option is more effective than the alternative but also more expensive, its efficacy should be worth the cost. According to the unit cost data shared by Cukurova University Hospital and most public hospitals, the cost of treatment per patient for the drugs used in the gemcitabine group is 224 Euros.

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None.

Conflict of Interest
The authors have no conflicts of interest.

Ethics Approval
This study was approved by the Cukurova University Health Sciences Research Ethics Committee (04/02/2022).

Informed Consent
Each participant signed an informed consent form after being informed of its details.

Data Availability
All relevant data are within the manuscript.

Authors' Contributions
Ertugrul Bayram, Ghanim Khatib, Semra Paydas, conception and design of the study; Ertugrul Bayram, acquisition of data; Ertugrul Bayram, Ghanim Khatib, Mehmet Ali Vardar, analysis and interpretation of data; Ertugrul Bayram, Umran Kucukgoz Gulec drafting the article; Ertugrul Bayram, Ghanim Khatib, Semra Paydas, making critical revisions.

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References

1) Kossaï M, Leary A, Scoazec JY, Genestie C. Ovarian cancer: A heterogeneous disease. Pathobiology 2018; 85: 41-49.
2) Alsop K, Fereday S, Meldrum C, deFazio A, Emmanuel C, George J, Dobrovic A, Birrer MJ, Webb PM, Stewart C, Friedlander M, Fox S, Bowtell D, Mitchell G. Brca mutation frequency and patterns of treatment response in brca mutation-positive women with ovarian cancer: A report from the Australian ovarian cancer study group. J Clin Oncol 2012; 30: 2654-2663.
3) Pisano C, Cecere SC, Di Napoli M, Cavaliere C, Tambaro R, Facchini G, Scaffa C, Losito S, Pizzolorusso A, Pignata S. Clinical trials with pegylated liposomal doxorubicin in the treatment of ovarian cancer. J Drug Deliv 2013; 2013: 898146.
4) Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin 2000; 50: 7-33.
5) Matsuo K, Lin YG, Roman LD, Sood AK. Overcoming platinum resistance in ovarian carcinoma. Expert Opin Investig Drugs 2010; 19: 1339-1354.
6) Runnebaum IB, Stickeler E. Epidemiological and molecular aspects of ovarian cancer risk. J Cancer Res Clin Oncol 2001; 127: 73-79.
7) Ottevanger PB. Ovarian cancer stem cells more questions than answers. Semin Cancer Biol 2017; 44: 67-71.
8) McMullen M, Madariaga A, Lheureux S. New approaches for targeting platinum-resistant ovarian cancer. Semin Cancer Biol 2021; 77: 167-181.
9) Mini E, Nobili S, Caciagli B, Landini I, Mazzei T. Cellular pharmacology of gemcitabine. Ann Oncol 2006; 17: v7-v12.
10) Lorusso D, Di Stefano A, Fanfani F, Scambia G. Role of gemcitabine in ovarian cancer treatment. Ann Oncol 2006; 17 Suppl 5: v188-v194.
11) Lyseng-Williamson KA, Duggan ST, Keating GM. Pegylated liposomal doxorubicin: A guide to its use in various malignancies. BioDrugs 2013; 27: 533-540.
12) Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, Wang Y, Scribner DR, Jr., Marciniack M, Naumann RW, Secord AA. Randomized phase iii trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol 2007; 25: 2811-2818.
13) De Leo A, Santini D, Ceccarelli C, Santandrea G, Palicelli A, Acquaviva G, Chiarucci F, Rosini F, Ravegnini G, Pession A, Turchetti D, Zamagni C, Perrone AM, De Iaco P, Tallini G, de Biase D. What is new on ovarian carcinoma: Integrated morphologic and molecular analysis following the new 2020 world health organization classification of female genital tumors. Diagnostics (Basel) 2021; 11: 697.
14) Colak B, Cansaran Duman D, Yilmaz E. The role of molecular mechanisms in targeted therapy strategies in ovarian cancer. Turk Hij Den Biyol Derg 2022; 79: 153-162.
15) Grunewald T, Ledermann JA. Targeted therapies for ovarian cancer. Best Pract Res Clin Obstet Gynaecol 2017; 41: 139-152.
16) George A, Riddell D, Seal S, Talukdar S, Mahamdallie S, Ruark E, Cloke V, Slade I, Kemp Z, Gore M, Strydom A, Banerjee S, Hanson H, Rahman N. Implementing rapid, robust, cost-effective, patient-centered, routine genetic testing in ovarian cancer patients. Sci Rep 2016; 6: 29506.
17) Tortolero-Luna G, Mitchell MF. The epidemiology of ovarian cancer. J Cell Biochem Suppl 1995; 23: 200-207.

18) Kajiyama H, Shibata K, Mizuno M, Umezu T, Suzuki S, Yamamoto E, Fujiwara S, Kawai M, Nagasaka T, Kikkawa F. Long-term clinical outcome of patients with recurrent epithelial ovarian carcinoma: Is it the same for each histological type? Int J Gynecol Cancer 2012; 22: 394-399.

19) Borad MJ, LoRusso PM. Twenty-first-century precision medicine in oncology: Genomic profiling in patients with cancer. Mayo Clin Proc 2017; 92: 1583-1591.

20) Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: Evolution of management in the era of precision medicine. CA Cancer J Clin 2019; 69: 280-304.

21) Monk BJ, Coleman RL. Changing the paradigm in the treatment of platinum-sensitive recurrent ovarian cancer: From platinum doublets to non-platinum doublets and adding antiangiogenesis compounds. Int J Gynecol Cancer 2009; 19 Suppl 2: S63-S67.

22) Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ, Wagner U, Stähle A, Stuart G, Kimmig R, Olbricht S, Le T, Emerich J, Kuhn W, Bentley J, Jackisch C, Luck HJ, Rochon J, Zimmermann AH, Eisenhauer E. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: An intergroup trial of the ago-over, the ncic ctg, and the eortc gcg. J Clin Oncol 2006; 24: 4699-4707.

23) Gupta D, Lis CG. Role of ca125 in predicting ovarian cancer survival - a review of the epidemiological literature. J Ovarian Res 2009; 2: 13.

24) Takahashi Y, Takei Y, Machida S, Taneichi A, Takahashi S, Yoshiba T, Koyanagi T, Tamura K, Saga Y, Fujiwara H. Efficacy and toxicity of pegylated liposomal doxorubicin as therapy for recurrent ovarian cancer in relation to the number of previous chemotherapy regimens: Comparison with gemcitabine. J Obstet Gynaecol Res 2021; 47: 551-559.

25) Guth U, Huang DJ, Schötzau A, Wight E. Is the current concept of recurrent ovarian carcinoma as a chronic disease also applicable in platinum resistant patients? Arch Gynecol Obstet 2010; 281: 339-344.

26) Nasu H, Nishio S, Park J, Yoshimitsu T, Matsukuma K, Tasaki K, Katsuda T, Terada A, Tsuda N, Ushijima K. Platinum rechallenge treatment using gemcitabine plus carboplatin with or without bevacizumab for platinum-resistant ovarian cancer. Int J Clin Oncol 2022; 27: 790-801.